# Examination of cognitive impairment in Hereditary Spastic Paraplegia

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**Abstract**

Hereditary spastic paraplegia (HSP) is a disorder which belongs to a heterogeneous group of inherited diseases, where the main clinical symptoms include progressive spasticity and lower-extremity weakness. Although HSP is believed to mostly impair the corticospinal tract and leave the cognitive domain unaffected, some studies suggest that this is not the case. The aim of this particular research, is to attempt a more apparent and valid inspection of the specific disease. According to our results, almost all participants present cognitive impairment. A dysexecutive syndrome seems to be the most distinguished finding among the patients. with an intercurrent impairment in social cognition as well. In a neuroanatomic level, this specific decline, might suggest a dysfunction localized in the frontal area of the brain in HSP patients.

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## *Overview*

Hereditary spastic paraplegia (HSP) is a disorder which belongs to a heterogeneous group of inherited diseases, in which the main clinical symptoms include lower-extremity weakness and progressive spasticity. Approximately, 80 types of HSP are known, which differ genetically. They are most certainly classified according to the mode of inheritance, the gene responsible for the mutation, and the clinical symptoms that are present. It is well – known, however, that HSP is usually transmitted in an autosomal dominant way. Most frequently, autosomal dominant HSP is due to the mutation of the SPAST gene, which is responsible for the encoding of spastin protein, located on the 2p chromosome (SPG4 locus). This specific protein is notorious for its microtubule-severing qualities (D¨urr et al., 1996).

## *Historical Context*

The first case of HSP is considered to be published in 1880 by Strümpell. In his report, he described two brothers from the same family, who seemed to be affected by the disease at issue. After examination, it became known that their father was also experiencing some of the disorder's main symptoms, verifying the transmission pattern that is now thought to be the most common (Strumpell, 1880). In the following years, numerous reports of HSP started to appear in the academic literature. However, it was not until a hundred years later when Harding, after closely evaluating a respectable amount of families, suggested that according to the symptoms,

HSP could be classified into two different forms. Those were afterwards adopted by the community, and we now speak of “pure” and “complicated” HSP (Harding, 1981).

### *Clinical Characteristics*

**Pure Hereditary Spastic Paraplegia.** The pure form of HSP is characterized by neurological impairment limited in the symptoms examined below. The vast majority of patients present a gait or walking disturbance. The affection is spread across both legs in a similar degree. Delay in walking can be present in the cases of childhood onset. Generally, the age of onset is not specific and can occur from infancy till the eight decade of life. Amongst common symptoms, patients present leg stiffness, disturbances pertaining to urination, as well as lower-extremity paresthesias. However, as Harding suggests, a detailed clinical evaluation needs to take place in the affected families, as almost a quarter of the overall patients, tend to be asymptomatic. (Harding, 1981)

The main abnormalities observed in patients with the pure form include spasticity, hyperreflexia and a pyramidal weakness in the lower limbs. The spasticity on the lower limb is most common in the hamstrings, quadriceps, and ankles. In addition, when muscle weakness is present, it can be found in the anterior tibialis, as well as in the iliopsoas and the hamstrings (Bickerstaff, 1950).

Individuals with uncomplicated spastic paraplegia most often experience the following features as well: subtle sensory disturbance in the lower limbs, mild upper limb ataxia, pes cavus and absent ankle jerks (D¨urr et al., 1994). Sensory impairment is present in approximately 40% of cases of pure HSP and it usually includes an impaired vibration sense in the lower limbs. Schady and his colleagues (1990), noticed that when put under nerve conduction

studies, patients had normal results, meaning that nerves could successfully send impulses to the desired muscles. This finding led to the suggestion that central axonopathy, and not peripheral association, is responsible for the disturbances observed during the clinical evaluation.

Although the symptoms described above have a disabling character, HSP patients do not experience a shortened life span (Hedera , 2000).

**Complicated Hereditary Spastic Paraplegia.** This form is characterized by the symptoms that are present in the pure form of HSP, but it also presents additional impairments involving other system dysfunctions. It must be noted that some certain types of complicated HSP are extraordinarily rare and they might just involve individual families.

The complicated form has been associated with many other conditions. Dementia, seizures, ataxia, retinopathy, mental retardation, deafness and epilepsy are some of the most prominent ones among them.

Dementia seems to be present in family members who also have additional features such as dysarthria, ataxia and epilepsy. Studies suggest that dementia can be found in both autosomal dominant and recessive families, in a form of a supplementary symptom to spastic paraparesis. In these cases, patients show similar patterns of cognitive impairment. More specifically, they present deficits in attention, short - term memory, processing speed, and in visuomotor abilities. According to the above symptoms, subcortical dementia seems to be the main characteristic of the phenotype of HSP's complicated form with dementia (McDermotta et al., 2000).

Recently, several reports have been published, in which scientists suggest that there is a connection between epilepsy and HSP. The type of inheritance seems to be both recessive and autosomal dominant and the type of seizure is not specific (Heinzef et al.,1998).

***Neuropathology***

As previously mentioned, HSP patients generally reach the normal life expectancy, most frequently dying old, from other circumstantial diseases. Depending on the time of the onset and the availability of treatment methods, it is not unusual that a vast amount of the overall patients do not need to be under routine inspection by a neurologist.

The most prominent feature in the pathology of pure HSP is axonal degeneration, which seems to be maximal in the terminal portions of the longest ascending and descending tracts across the spinal cord. In addition, gliosis and demyelination are frequently part of the findings. Other pathways that are affected, and actually critically, are the crossed and uncrossed corticospinal tracts that travel to the lower limbs. Other reports suggest that as far as it concerns the V layer of the brain's motor cortex, there are fewer numbers of pyramidal cells of Betz. Neuronal loss has also been reported in the basal ganglia and the cerebellum by some authors (Schwartz & Liu, 1956 )

***Genetic Factors***

The heterogeneity of HSP is not limited in the clinical symptomatology, but it is also visible in the genetic area. As previously mentioned, the type of inheritance is well – known and is classified into autosomal dominant, recessive and X-linked.

The autosomal dominant type of inheritance, which we will examine in this particular study, is the most common one, and it has been linked to loci SPG4 on chromosome 2p ( Webb, 1998), SPG3 on chromosome 14q ( Hentati, 1994), SPG6 on chromosome 15q (Fink , 1995), SPG8 on chromosome 8q (Hedera, 1999), SPG9 on chromosome10q (Seri, 1999), and locus SPG10 on chromosome 12q (Reid, 1999).

Below, we will examine the loci of interest, in accordance to our patients' genetic mutation type.

**Chromosome 2P locus (SPG4)**. This particular locus is actually promptly connected with 40% of the overall HSP cases reported. Even though most SPG4 pedigrees have the pure form of HSP, there have been a few families with complicated symptoms, also linked to this locus.

The gene responsible is called spastin, and has been spotted with the use of positional cloning strategy. Spastin is located on chromosome 2p22-p21 and it belongs to a group of ATP proteins (AAA) (Confalonieri & Duguet, 1995).

As it has been reported, certain mutations occur regarding spastin, and they include missense, nonsense, and splice site mutations in discrete exons, causing extensive changes in the sequence of amino acids in the AAA domain. This finding suggests that SPG4 is caused by a function loss, making it obvious that the expression level of spastin is crucial for the normal activity of the axons across the corticospinal tract (Hazan, 1999).

There seems to be a variability regarding the age of onset in chromosome 2p linked families. According to the reports, the mean age at onset of symptoms ranges from 12 to 43 years, indicating once again interfamilial alteration (White et al., 2000).

**Chromosome 12Q locus (SPG10)**. This is the latest locus that has been discovered, and it belongs to chromosome 12q13. The mean age at onset of symptoms in patients was at approximately 10 years. This gene is connected with the pure form of HSP, and although some of them present severe symptoms, others remain almost asymptomatic at the age of 40 years (Reid et al., 1999).

**Chromosome 15q locus (SPG11) .** Time of symptom onset varies from infancy till adulthood. Only a few families have been linked to the SPG11 locus, as well. The symptoms that the patients presented were pretty acute and more than half of them required the use of a wheelchair. (Hedera et al., 1999).

***Treatment***

Until today, there exists no specific treatment towards the prevention of the common degeneration symptoms in HSP. All the available therapies aim at reducing symptoms by improving strength, balance and agility. In addition, the prescription of drugs that reduce muscle spasticity (e.g tizanidine, dantrolene) and urinary need (e.g., oxybutynin, solifenacin), is a frequent pharmaceutical measure (Hedera, 2000)

***Indication of Cognitive Impairment in HSP***

Although Hereditary Spastic Paraplegia is considered to mostly impair the corticospinal tract causing mainly motor deficits with no damage in cognition, a handful of studies suggest that this is not the case. According to Tallaksen and his colleagues (2003), an asymptomatic cognitive impairment is observed, mostly affecting executive functions in SPG4 mutation carriers and has actually more frequently been observed in families with missense mutations. This dysexecutive syndrome has also been reported by Chamard et al. (2016), who suggested that patients present additional deficits in concentration and, interestingly, social cognition impairment. As the authors proposed, this specific impairment might suggest a dysfunction of the motor / mirror neuronal activity and of the frontal lobe in general, in SPG4 patients.

In another study conducted by Byrne et al (1998), it has been suggested that there is a connection of an autosomal dominant HSP family and cognitive impairment

to a locus on chromosome 2p. As it was previously mentioned, pedigrees linked to this locus, present the ‘pure’ symptoms of HSP. The most prominent deficit in this particular family was. mainly observed in visuo-spatial functions.

Additionally, in a different study Webb administered the Cambridge Cognition Examination battery and noticed that compared with the control group, HSP patients presented a considerable impairment on the total score, especially in the subdomains of language expression and comprehension, but also memory. However, the authors reported that when the overall sample was divided by taking into consideration the age factor, there was no difference between the younger groups. That did not apply to the older age group, where a consequential difference between the affected and control groups concerning their cognitive function, still remained. This might suggest that a late onset cognitive impairment is among the clinical features of pure HSP ( Webb, 1998)

In another study conducted by Uttner, Baumgartner, Sperfeld and Kassubek (2007), the results showed that in comparison with the control group, only patients with the complicated form of HSP presented a significant worse performance. On the contrary, pHSP patients scored almost similar to the control group. The authors mention that they used a comprehensive neuropsychological battery measuring working and declarative memory, attention and executive functions. CHSP patients, although younger than the control group, presented a considerable cognitive impairment in all those subdomains.

Due to the ambiguity of the results, especially pertaining to the specific amount of the overall cognitive impairment, and because of the relatively small sample sizes used in the studies (ranging from 8 to 19 patients), even the respective authors encourage a more detailed investigation, which will give prominence to the nature of the cognitive decline, with even more

credibility. Consequently, studies including a more thorough neuropsychological assessment which will attempt to measure a wider range of cognitive abilities seems necessary in order to clearly understand whether this neurological cohort presents cognitive deficits and specifically in which domains. Additionally, more substantial sample size would certainly add liability to the results.

The aim of this particular study is to attempt a more thorough and valid inspection of the disease under review, leading to better understand cognitive parameters of the disorder.

## Methods

### *Participants*

For current study's aims, ten patients (2 women) with HSP were recruited from Department of Neurogenetics at Eginition Hospital in Athens, 35–71 years old (mean: 53.7, SD: 12.7). Participants diagnosis was conducted based on the commonly accepted criteria for the HSP, including genetic testing as well. A control group consisted of 30 participants (13 women), 35–65 years old (mean: 51.33, SD: 9.2), derived from the project "Investigation of cortical surface patterns and their relation with speech metrics and performance in neuropsychological assessment in healthy participants," conducted at Eginition Hospital in Athens, School of Medicine, Greece (research protocol approval ID: ΩΟΞΛ46Ψ8Ν2-7PN, July 2017). The two groups were matched for age and years of education, control group had no history of neurological or psychiatric disorders (see Table 1 for demographics). All participants were right-handed, monolingual Greek speakers. Informed consent was obtained from all participants prior to participation according to Ethics Committee of Eginition Hospital.

Table 1

*Descriptive Statistics For Hsp Patients and the Control Group, including T- test's P-values for Age and Education Variables*

| Group | N | Men | Women | Mean age | Std Dev | Education | Std Dev | P-values Age | P-values Education |
|---|---|---|---|---|---|---|---|---|---|
| HSP | 10 | 8 | 2 | 53.70 | 12.70 | 12.90 | 5.40 | .526 | .419 |
| Controls | 30 | 17 | 13 | 51.33 | 9.19 | 14.13 | 3.65 | .526 | .419 |

***Neuropsychological Assessment***

All participants (patients and healthy controls) were assessed according to standard administration procedures described in the corresponding normative studies (please see below for a detailed description of neuropsychological tests).

**Auditory Verbal Learning Test**. AVLT is a neuropsychological assessment created to evaluate verbal memory in patients and it can be utilized in order to evaluate the severity of memory dysfunction and to track changes in memory function over time (Bean, 2011), adjusted in Greek (Constantinidou, Zaganas, Papastefanakis, Kasselimis, Nidos, & Simos, 2014).

**Boston Naming Test.** BNT short form consists of 20 black and white drawings of various objects, and it constitutes a measure of confrontation naming (Kaplan et al., 1983), standardized in Greek (Simos, Kasselimis, and Mouzaki, 2011a; 2011b).

**Peabody Picture Vocabulary Test**. This is a multiple-choice vocabulary test aiming to examine one-word receptive language skills in children, as well as adults. Participants are requested to match a word the examiner says with one of four pictures that best describes that word (Dunn & Dunn, 2007). The test was standardized in Greek (Simos, Kasselimis, and Mouzaki, 2011a; 2011b).

**Comprehension of Instructions in Greek.** A variant of the Token Test assessing the ability to preserve for a short period of time, comprehend and execute complex commands related with visual stimuli (Simos, Kasselimis, Potagas, & Evdokimidis, 2014)

**Controlled Oral Word Association Test.** COWAT (Benton, Hamsher, Rey & Sivan, 1994) adjusted in Greek (Kosmidis, Vlahou, Panagiotaki & Kiosseoglou, 2004) is a test

that measures verbal fluency and it constitutes a subcategory of the Multilingual Aphasia Examination Test. The COWAT uses a three-letter group in order to examine phonemic fluency and a three category subset (animals, fruits, objects) to assess semantic fluency. Participants should utter as many words as they can that they fall into each of the aforementioned categories, within one minute.

**Word and pseudoword reading fluency measures**. The reading fluency task consists of a list of 112 high-frequency words in order of increasing length. The pseudoword fluency task consists of a list of 70 pseudowords in order of increasing length. For both tasks, the patient is asked to read items aloud with a time limit of 45 seconds, as fast as possible. Total number of correctly read items within the given time limit, is the final score of the patient in each task (Simos, Sideridis, Kasselimis, and Mouzaki, 2013)

**Digit Span Test.** This task attempts to measure the capacity of working memory, a cognitive system with a narrow size, which has the responsibility of making information available for processing, but for a limited time. In every trial, the examiner recites a list of numbers (e.g., 2, 4, 3, 2, 6, 9). There are two categories in this test: forward-span and backward-span. In the forward-span version, at the end of each trial, participants attempt to recall the digits in the exact order that they were read. In the backward-span version, at the end of each trial participants need to recall the digits in the reverse order. In each task, the number of items gradually increases (Simos, Papastefanakis, Panou and Kasselimis, 2011).

**Corsi Block Tapping Task.** With this test, researchers attempt to measure visuo-spatial short – term and working memory. In each trial, the participant attempts to repeat the exact sequence of tapping movements, which the examiner previously demonstrated. The sequence becomes more complex in each trial (Kessels et al., 2000).

**Trail Making Test.** It constitutes a tool for examining visual attention and task switching. The participant's task is to accurately connect a set of 25 dots, as fast as he can (Parkington & Leiter 1949, adapted in Greek Zalonis, Kararizou, Triantafyllou, Kapaki, Papageorgiou, Sgouropoulos & Vassilopoulos, 2007). In addition, in order to eliminate the effect of motor aspect during the task we calculated the variables B-A and B/A as suggested by Christidi, Kararizou, Triantafyllou, Anagnostouli and Zalonis (2015).

**Symbol Digit Modalities Test.** This test belongs to the category of substitution tasks and it focuses mostly on attention, processing speed and visual scanning**.** With the help of a reference key, the participant has to pair specific numbers with certain geometric figures, within ninety seconds (Smith, 1982, adapted in Greek: Constantinidou, Christodoulou & Prokopiou, 2012).

**Faux Pas Test.** This test was created in order to examine the participant's social cognition level. The task consists of 10 short stories, which contain incidents of situations /where someone says something which they should not have (faux pas). These narrations are read to the person, who then has to answer some questions, which determine whether or not they detected the faux pas (Stone, Baron-Cohen & Knight, 1998).

## Results

All statistical configuration was performed with the SPSS's 23rd version software. Initially, group comparisons were made using the non-parametric Mann-Whitney U test, due to small sample of patients' group, in order to investigate possible differences between patients and controls group. More specifically, twenty-three Mann-Whitney U test were conducted, and p values were adjusted using FDR correction via Benjamini-Hochberg (BH) method. Table 2 presents median values for two groups, U values and adjusted p values for neuropsychological tests that remained significant after FDR correction.

Only 2 tests survived after FDR corrections, meaning that patients are significantly decreased compared with control group in semantic fluency and TMT-B, while performance in CIG, SDMT and TMT-A appeared to differ between the two groups marginally with adjusted p values 0.055. Regarding TMT performance, it should be reported that since the group of patients confronts motor deficits, we should rely on TMT B/A and TMT B-A variables which are considered to reduce the motor effect (see Tasks description in Methods section). Since this variable is not presented significantly different between the two groups, we chose not to take under consideration the significant difference of TMT B.

Table 2

*U and P Values for Mann-Whitney (U) Test*

| | HSP | Controls | | |
|---|---|---|---|---|
| | Median | Median | U | P adjusted |
| FLUENCY_SEM | 8.35 | 24.55 | 28.50 | .000759 |
| CIG | 12.60 | 23.13 | 71.00 | .055 |
| SDMT | 12.25 | 22.67 | 67.50 | .055 |
| TMT A | 26.10 | 18.63 | 38.00 | .055 |
| TMT B | 19.60 | 20.80 | 58.50 | .023 |

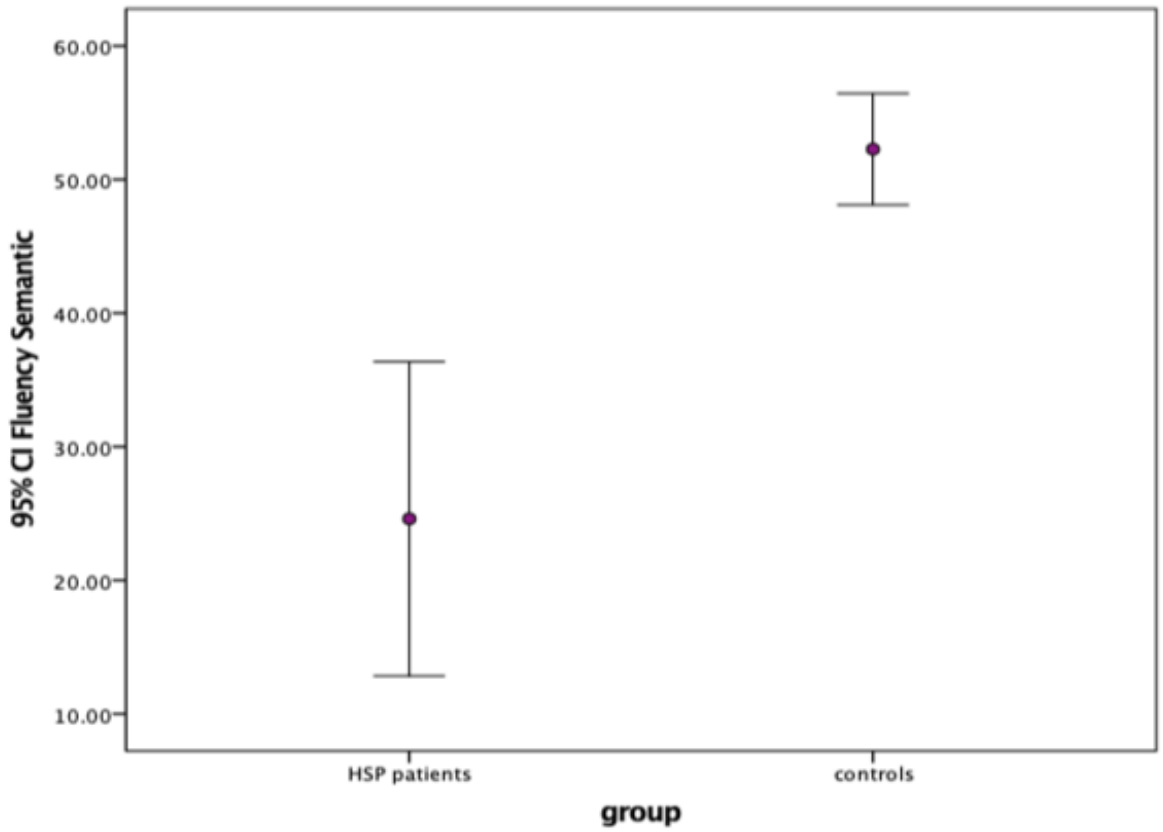


*Figure 1.* Error bar chart with mean scores of HSP patients and the control group in Semantic Fluency Task.

We then transformed patients' raw scores to Z scores, based on the equivalent norms for each of the tests. A case-by case examination revealed that several patients displayed cognitive deficits in specific domains (See Figure 2).

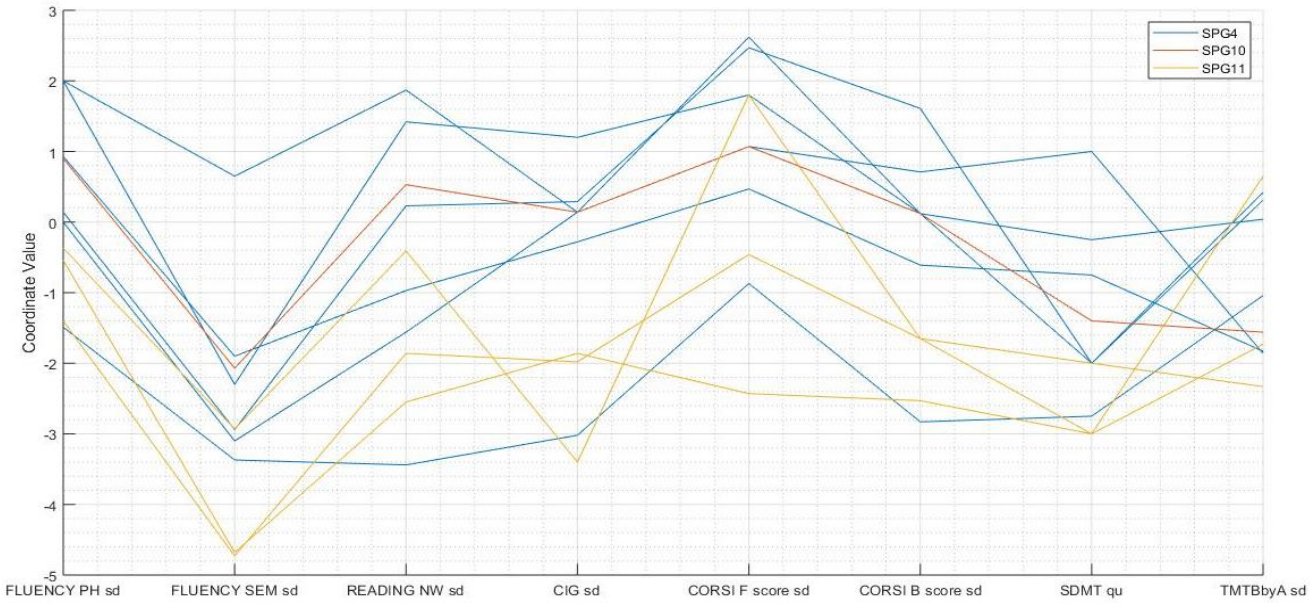


*Figure 2.* Chart of individual performance among all HSP patients, showcasing discrete cognitive profiles.

Finally, we categorized the patients into three groups, according to their gene mutation type (SPG 4/ SPG 10 /SPG 11) (See Figure 3). However, due to the small sample size, we didn't perform any statistical analysis. As presented in Figure 3, without exception, all groups demonstrated extended executive deficits, especially regarding the semantic fluency variable (at least 2 SD below mean healthy performance, with the SPG11 group reaching even 4 SD score below). Group 3, also demonstrated deficits in decoding written stimuli (as indicated by performance on the pseudoword fluency task, which was over –1.5 SD ), and also further executive impairment ( as indicated by performance on SDMT test and TMTBbyA, with respective scores 2,5 SD and 2 SD below the healthy group).

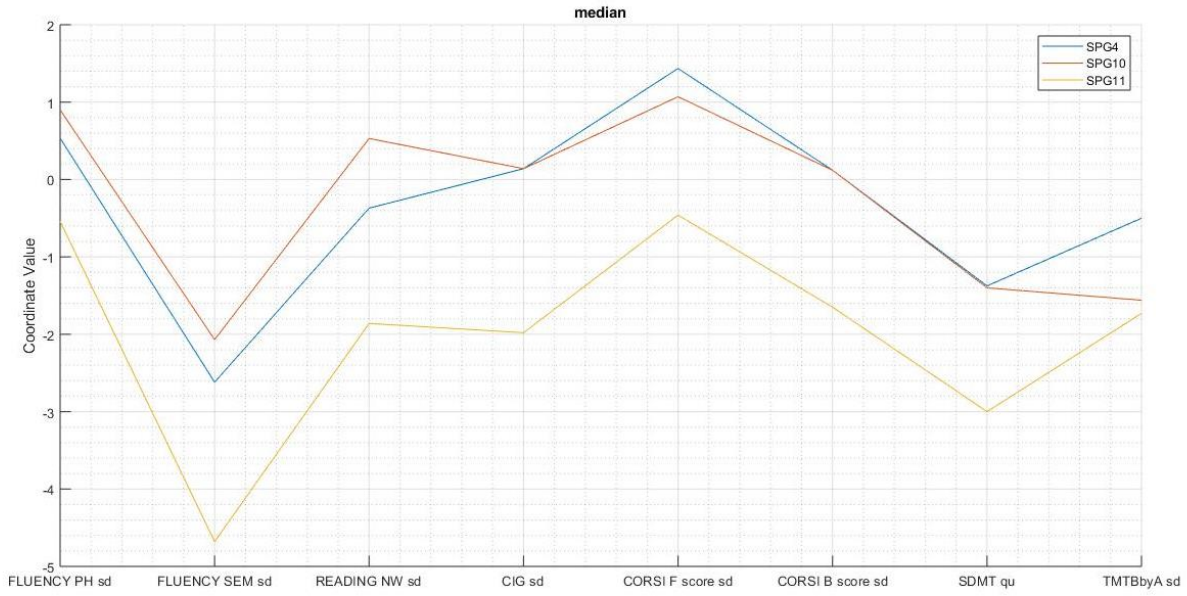


*Figure 3.* Chart of cognitive profile per genetic group. Investigation of the association between cognitive impairment and specific genetic mutations.

## Discussion

In this study we aimed to investigate the cognitive function of patients with HSP. According to our results, patients with HSP regardless of mutation type, presented a noticeable impairment in the variable of semantic fluency, as well as some minor deterioration in executive functions.

Until today, although there seems to be a sort of abnormal myelination in the CNS in some forms of the disease, however it is believed that the CNS is less likely to be involved with the syndrome per se. To our knowledge, limited studies including neuropsychological assessment focused on the investigation of the cognitive functions of these patients. In most of these studies, it is reported that cognitive impairment exists mostly in executive functions, while in others no significant deficits are observed. An interesting finding, which we also verify in this study, was a decline in social cognition.

Due to the ambivalence of the aforesaid results, especially pertaining to the specific amount of the total cognitive impairment, we implemented a more thorough neuropsychological assessment which attempted to measure a wider range of cognitive abilities compared to the past notable research endeavours.

The most intriguing discovery to emerge was the prominent deficit in the domain of the semantic fluency variable, which was common among all groups, independently of gene mutation type. The unexpectedly low scores in the semantic fluency tasks, might reflect an underlying dysfunction in frontotemporal network of especially dominant for language hemisphere. Previous studies suggested that semantic fluency task depends on a wider portion of the prefrontal cortex involving the left and right dorsolateral and the right ventromedial areas (Szatkowska et al., 2000). The impairment might also indicate a dysfunction in the right

ventrolateral pre-frontal cortex, which according to Petrides (2007), is responsible for the control of the semantic retrieval of a stimulus competing against similar verbal response options. Schmidt and her colleagues (2017), suggest that semantic fluency is mostly mediated by temporal brain areas, proposing that semantic verbal fluency is based on a serial search process, where according to the category, the first step is to inspect for sub-categories and then for parts of these specific sub-categories. In addition, the same study suggests that contrary to phonemic, semantic fluency establishes recruitment of working memory processes as well, and not only executive ones. Therefore, the impairment that was observed in the patients of our study, might indicate a further disturbance in the above mechanisms.

In addition, other impairments, mostly in the spectrum of the frontal area, might presage a dysexecutive syndrome among the patients. Low scores in the SDMT and CIG task, which were found marginally significant after the FDR corrections, may reveal a deficit in attention and speed processing abilities, thus confirming the dysexecutive pattern, mediated by frontal neural substrates.

Furthermore, taking into consideration Charmad's research in 2016, we attempted to assess social cognition as well, not only in SPG4 patients, but in all mutation types available in our registry. Our findings verify the aforesaid study, and further imply that an impairment in this domain, exists in patients with other mutation types of the disease. These findings seem to come in agreement with neuroimaging ones which have shown a frontotemporal hypoperfusion in the left hemisphere in some HSP patients (K. H. Scheuer et al., 2005)

In conclusion, this study suggests that almost all participants, present cognitive impairment. A dysexecutive syndrome seems to be the most prominent finding among the

patients. with an intercurrent impairment in social cognition as well. In a neuroanatomic level, this specific deterioration, might suggest a dysfunction localized in the frontal area of the brain.

Hence, it might be useful to regularly assess the preceding functions with an extensive neuropsychological evaluation, in order to enhance the clinical management of the HSP population.

At this point, we would like to assert a main limitation of the present study. Due to the recent COVID- 19 health measures, the patients that we were able to recruit were less than what we intended to, at the beginning of this study. However, due to the rarity of this specific disease, the relatively small sample size, comparable to similar studies, seems to be tolerable for the purpose of this research.

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