Executive dysfunction in Spinocerebellar Ataxia type 3 – SCA3

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List of Abbreviations

SCAs Spinocerebellar ataxias
SCA3 Spinocerebellar ataxia type 3
CAG cytosine, adenine and guanine
IGT Iowa Gambling Task
FDT Five Digit Test
BAI BECK Anxiety Inventory
BDI BECK Depression Inventory
Abstract

The objective of this research was to evaluate the executive functions by means of neuropsychological tests in patients with spinocerebellar ataxia type 3 (SCA3). It is a neurodegenerative disease with autosomal dominant genetic transmission. SCA3 is part of the Ataxias group, today with more than 49 classified types. The symptoms of the disease arise around the third to the fifth decade of life, they are different neurological alterations such as motor impairment, cognitive and emotional symptoms. In the study, we evaluated 27 genetically confirmed patients with the diagnosis of SCA3 and 21 participants in the control group matched by age and years of education. The neuropsychological evaluation included instruments to measure aspects of cognitive functions and inventories of depression and anxiety. The results showed that patients with SCA3 had statistically significantly lower scores in verbal fluency, cognitive flexibility and inhibitory control compared to the control group, in addition to significantly higher levels of Anxiety. There were inverse correlations between the number of cytosine, adenine and guanine (CAG) repeat expansions and scores in inhibitory control and cognitive flexibility. No statistically significant correlations were found between the results of the neuropsychological tests and the disease duration. Executive dysfunctions in patients with SCA3 are associated with degeneration in several cortical and subcortical structures of the brain and cerebellum, ruptures in the closed cortico-ponto-cerebello-thalamo-cortical loops and prefrontal cortico-striato-thalamo-cortical loops.

Keywords: spinocerebellar ataxia type 3, executive dysfunction, cerebellum, cognitive flexibility, inhibitory control.
Título em português: Disfunção Executiva na Ataxia Espinocerebelar tipo 3 - SCA3

Resumo expandido

A pesquisa teve como objetivo avaliar as funções executivas por meio de testes neuropsicológicos em pacientes com ataxia espinocerebelar tipo 3 (SCA3). Trata-se de uma doença neurodegenerativa, com transmissão genética, autossômica dominante. A SCA3 faz parte do grupo das ataxias, hoje com mais de 49 tipos classificados. Os sintomas da doença surgem por volta da terceira à quinta década de vida, são eles alterações neurológicas diversas como comprometimento motor, sintomas cognitivos e emocionais. Foram avaliados 27 pacientes geneticamente confirmados com o diagnóstico de SCA 3 e 21 participantes sem desordens neurológicas, pareados por idade e escolaridade. A avaliação neuropsicológica incluiu testes de fluência verbal (FAS - fonêmica e semântica), span de dígitos ordem direta e inversa, teste de Iowa- IGT, teste dos cinco dígitos- FDT e inventários BECK de depressão e ansiedade. Os resultados mostraram que os pacientes com SCA3 tiveram escores estatisticamente significativamente mais baixos em fluência verbal, flexibilidade cognitiva e controle inibitório comparados ao grupo controle, além de níveis significativamente mais altos de ansiedade. Houve correlações inversas entre o número de repetições Citosina, Adenina, Guanina (CAG) e os resultados nos testes de controle inibitório e flexibilidade cognitiva. Não foram encontradas correlações estatisticamente significativas entre os resultados dos testes neuropsicológicos e o tempo de sintomas. As disfunções executivas em pacientes com SCA3, em estudos anteriores, estão associadas às degenerações em diversas estruturas corticais e subcorticais do cérebro e cerebelo, rupturas nos circuitos fechados córtico-ponto-cerebelo-tálamo-cortical e córtico pré-frontal – estriado-tálamo-cortical.
1. Introduction

Spinocerebellar ataxias (SCAs) comprise a heterogeneous group of neurodegenerative diseases, of genetic inheritance, autosomal dominant transmission, that is, when one parent is affected, the chance of transmission to their children is 50% (Shulz et al., 2010 Tamura et al., 2018). The word Ataxia means instability and incoordination (Giocondo & Curcio, 2018) and the same name is given to the set of diseases, ataxias, which present as one of the first symptoms, gait ataxia. Other symptoms such as nystagmus / visual changes, dysarthria, dysphagia, cognitive and psychiatric symptoms are also present (Schols et al., 2004). SCAs are rare genetic diseases, the prevalence is 1-4 in 100,000 individuals, and SCA type 1, 2, 3, 6 and 7 are the most common subtypes corresponding to 50% of all dominant autosomal ataxias (Castilhos et al., 2014; Giocondo & Curcio, 2018; Shakkottai & Fogel, 2013; Sullivan, Yau, O'Connor, Houlden, 2018). Recent advances have identified new genes implicated in SCAs, and today more than 49 subtypes of ataxias have been classified (Yuan et al., 2019).

Among the types of ataxias, spinocerebellar ataxia type 3 (SCA3), or Machado Joseph disease, is the most common type worldwide, although it is considered a rare disease. Some types of ataxias are more common in certain regions of the world (Yuan et al., 2019). In Brazil, SCA3 is the most common type (Shakkottai & Fogel, 2013).

SCA3 is a disease caused by an abnormality in the ATXN3 gene on chromosome 14q (increased CAG repeats - cytosine, adenine and guanine). The disease is diagnosed by molecular genetic testing to detect abnormal repetition in CAG trinucleotide expansion in ATXN3 (Chuang
et al., 2019). Most affected individuals have CAG trinucleotide repeats alleles between 52 and 86, although manifestations of disease in smaller numbers of repetitions. In normal chromosomes the number of repeats is less than 44 (Padiath, et al., 2005; Ramos et al., 2018).

In ataxias areas of the cerebellum and brain such as frontal, parietal and temporal lobes, temporal gyrus, cingulate gyrus, putamen and pale globe are affected by the disease (Wang et al., 2015). Degenerations in the dentate nucleus, spinocerebellar tract, extrapyramidal system are described as substantia nigra, red nucleus and subthalamic nucleus (Chuang et al., 2019). The change in brain complexity is observed throughout the disease, with the most substantial changes in the later stages of the disease (Wang et al., 2015).

1.1. Manifestations of the disease

The clinical manifestations of SCA3 are diverse and some of these symptoms are common to other types of ataxia. Symptoms such as motor incoordination, peripheral neuropathy, ophthalmoparesis, pyramidal symptoms, dystonia, sleep disorders and parkinsonism may be present. In addition to the symptoms described, there are other symptoms such as speech, swallowing, cognitive and psychiatric disorders (Mass et al., 2015; Yan et al., 2019). Symptoms and severity of the disease, as well as the age of onset of symptoms, are widely varied and may vary within the same family.

1.1.1. Cognitive manifestations

In the past, studies with patients with SCA3 did not consider cognitive and emotional aspects as symptoms of the disease, but without the systematization of the application of formal evaluations to support this impression. In recent years, studies have described impaired cognitive
functions in various types of ataxias, and SCA3 is among the group that, besides motor aspects, suffers cognitive impairments (Moriarty et al., 2016). Despite the occurrence of cognitive changes, the evolution of deficits to dementia is less frequent in SCA3 and more frequent in other ataxias such as SCA 1 or SCA 2 (Tamura et al, 2018). Therefore, the most recent focus of scientific studies has therefore been on the cognitive and emotional aspects that may also be affected with the disease. Changes in attention, memory, visuospatial skills and executive functions are cited, although there is no consensus regarding cognitive domains, between these and their correlations with compromised brain structures in SCA3 and, how the process of cognitive decline occurs over the years (Braga -Neto et al., 2014; Burk et al., 2003; Kawai et al., 2004; Klinke et al., 2010; Lopes et al., 2013, Maruff et al., 1996; Radvany, Camargo, Costa, Fonseca, & Nascimento, 1993; Roeske et al., 2013; Tamura et al., 2018; Zawacki, Grace, Friedman & Sudarsky, 2002). Some aspects make comparisons between studies difficult, such as small samples, with no paired control individuals and the inappropriate selection of tests in which symptoms of the disease may interfere with test performance (Lopes et al., 2013).

Among the cognitive functions affected by the disease, we highlight the executive functions, considered extremely important for self-management and engagement in situations that promote safety or that, in case of dysfunction, may expose the individual to risk situations. Therefore, executive functions can be considered essential for the adaptation of the individual to the demands of daily life and for the development of new skills (Diamond, 2013).

Lezak, Howieson, Bliger & Tranel (2012) hypothesized that four domains make up executive functions, which are volition, planning, intentional action and effective performance, which are related in some way, and impairment in one of these domains, would lead to executive dysfunction. According to Diamond (2013) executive functions can be understood as complex cognitive skills
that allow the identification of goals, mental goal planning and behavioral organization to achieve these goals. As reported by the same author, there are three centers of executive functions: inhibition (inhibitory control and interference control), working memory and cognitive flexibility (mental flexibility) and, from these, others are built as reasoning, problem solving and planning. Executive functions can then be considered important in all aspects of life, for physical and mental health, social life, for success in academic and professional life.

1.1.2. Psychiatric manifestations

As stated by McMurtay, Clark, Flood, Perlman & Mendez (2006), in a study of patients with ataxias of various subtypes (SCA1, SCA2, SCA3 and SCA6), depressive symptoms were more frequent in SCA3 (60%) compared to the other ataxia subtypes. Based on the authors, depressive symptoms may occur due to dysfunction in the frontal-subcortical circuits and basal nuclei. In addition to cerebellar degeneration, lesions in other areas such as the dentate nucleus, substantia nigra, subthalamic nucleus, pale globe, and striatum may be responsible for psychiatric symptoms. Zawacki et al. (2002) found depressive symptoms considered moderate to severe in emotional self-analysis scales. Kilke et al. (2010) identified depressive symptoms in 15 SCA3 patients assessed using the BECK Depression Inventory. In another study (Pedroso et al., 2011), 40 patients with SCA3 were evaluated for psychiatric manifestations using the Hamilton Anxiety Scale and the BECK Depression Inventory and showed a strong correlation between these symptoms and sleep behavior disorder.
1.2. The role of the cerebellum in cognition and emotion

The cerebellum is among the regions that undergo SCA3 degeneration and, previously related mainly to the role of motor coordination, balance and articulation of speech, clinical data have shown that cerebellar functions go beyond the motor domain, adding to the cerebellum the cognitive domain (Marvel & Desmond, 2010). The cerebellum has been the subject of neuroanatomic studies that have revealed its connection with areas of association of the cerebral cortex involved in higher cognitive functioning. In addition to the cerebral cortex, the cerebellum has connections to the medulla and brainstem, and by analyzing these areas to which the cerebellum connects, it is possible to understand the functional organization of the cerebellum in advance (Stoodley & Schmahmann, 2010). The cerebellum, according to the same authors, is connected to the brain by two connecting pathways (forward and backward). Information from cortical regions of the brain ends in the nucleus at the base of the pons which in turn transmits information to the cerebellum. On the other hand, projections of the cerebellum leave the cerebellar cortex via the cerebellar nucleus and end up in the thalamus, which then sends projections back to the cerebral cortex. Thus, this brain-cerebellar organization indicates that information on motor sensory cortex versus association is processed in different regions of the cerebellum.

Rammani (2006) reviewed some aspects of cerebellar information processing by understanding its anatomy and connections. Anatomical studies have revealed not only the connections between cerebellum regions and motor areas, but also between associative areas involved with superior mental functions and functional studies have shown cerebellum activation in non-motor tasks, which corroborates the thought that the cerebellum is involved not only with the control of movements, but also with the control of cognitive functions, such as executive functions (Bugalho, Correa & Vianna Baptista 2006).
In accordance with Teive and Arruda (2016), the improvement of functional neuroimaging methods has shown that cerebellum activities go beyond motor functioning. Functional neuroimaging studies then demonstrated which areas of the cerebellum are activated when the individual performs cognitive tasks. More systematic and sensitive neuropsychological tests, applied to patients with cerebellar lesions, have helped to broaden the understanding of cerebellar functions, as well as attributing cognitive and emotional functions to motor functions (Baillieux, Smet, Paquier, Deyen & Mariën, 2008).

According to Damiani, Gonçalves, Kuhk, Aloi & Nascimento (2016), the cognitive-affective cerebellar syndrome, proposed by Schmahmann & Sherman (1998), reports the evidence of cognitive and emotional changes in patients with cerebellar diseases. Cognitive changes (deficits in executive function, such as abstract thinking, verbal fluency, working memory and planning, visual and spatial impairments), and personality disorders (affective blunting, depressive symptoms, inappropriate behavior, uninhibited or psychotic symptoms, with similarities between cognitive-affective cerebellar syndrome and frontal lobe lesions. Neuroanatomic evidence supports the communication circuits between the cerebellum and frontal lobe (Marvel & Desmond, 2010).

1.3. Progression of disorder

The large variation between the onset date of symptoms may in part be attributed to the difference between the size of the expansion of CAG repetitions. The size of the expansion has been inversely correlated with the onset of symptoms, the larger the size of the expansion, the earlier the symptoms appear (Klockgether, 2008). Other factors cited as related to the onset of
symptoms are the origin, environmental factors, and others that are not yet clear (Mattos et. Al, 2019).

The progression of the disease usually occurs slowly and progressively, and the worsening of the gait evolves to the need for wheelchair use 10 to 15 years from the onset of symptoms. Dysarthric speech becomes more incomprehensible, worsening dysphagia, dystonic posture and ophthalmoparesis (Paulson, 2015). Death usually occurs after 6 to 29 years of onset of symptoms due to respiratory complications and cachexia.

Genetic tests in asymptomatic people are available, so that, relatives of affected people can know, even without the symptoms of the disease, if they have the mutation of the disease gene. There are several reasons for seeking predictive tests, such as family planning, financial, professional and psychological preparation to face the onset of symptoms. If having the disease mutation gene may raise concerns about the future, the individual who does not carry the disease mutation may also not experience a lighter burden, as the person often considered the “healthy family member”, who is responsible for caring for family members already in a situation of dependence by the progression of the disease.

There is still no effective drug treatment capable of preventing the progression of the disease. Existing drug treatments are to relieve present symptoms such as spasticity, sialorrhea, sleep disorders and mood disorder (Paulson, 2015).

2. Research Objective

The proposed research aimed to evaluate the executive functions, by neuropsychological tests, of patients with confirmed diagnosis of SCA3, correlate the CAG repetitions and disease duration and the performance in the neuropsychological tests.
2.1. Research Justification

Understanding the cognitive deficits of individuals with SCA3, mainly the executive dysfunction, is extremely important to broaden the knowledge of the disease, improve patient and family orientations while minimizing the risks in their daily lives, taking into consideration their safety and well-being. The hypothesis is that there is a significant difference between patient and control group performance in tests that evaluate executive functions, indicating impairment of these functions.

3. Manuscript

The results of this research are presented in manuscript form which was submitted for publication in the Journal of Clinical and Experimental Neuropsychology.
Executive dysfunction in Spinocerebellar Ataxia type 3 – SCA3

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Introduction

Spinocerebellar ataxia type 3 (SCA3), known as Machado Joseph disease, represents the most common form of ataxia worldwide (Sequeiros, Martins & Silveira, 2012; Schols, Bauer, Schmidt, Schulte & Riess, 2004). To date, a total of 49 subtypes of SCAs have been classified (Yuan et al., 2019). The SCA3 type is an autosomal dominant neurodegenerative disease characterised by progressive cerebellar dysfunction, associated with other symptoms of the central and peripheral nervous systems involving predominantly the cerebellar, pyramidal, extrapyramidal, motor neuron and oculomotor systems. As SCA3 shares some features with other types of SCAs, it is important the identification of more specific signs for its differential diagnosis (Tamura et al., 2018). In the early stages of the symptoms a clinical diagnosis of SCA3 may not be easy to establish. The mean age at onset is around 40 years, with a mean survival time of 21 years (ranging from 7 to 29 years). Gait ataxia and diplopia are cited as first symptoms in 92.4% and 7.6% of cases, respectively (Castilhos et al., 2014). The identification of the causative gene of SCA3 allowed the detection of the mutation making possible the molecular diagnosis of the disease and its subtypes.
Based on the nature of the underlying causative mutations, the SCAs in general can be divided into three major categories: 1) “polyglutamine” ataxias, caused by CAG repeat expansions that encode a pure repeat of the amino acid glutamine in the corresponding protein; 2) non-coding repeat ataxias, caused by repeat expansions falling outside of the protein-coding region of the respective disease genes; and 3) ataxias caused by conventional mutations in specific genes, such as deletion, missense, nonsense, and splice site mutations. (Bettencourt & Lima, 2011).

Several SCAs, including the SCA3 type, are caused by CAG repeat expansions (CAGexp). The causative mutation of SCA3 consists in an expansion of an unstable CAG tract in exon 10 of the ATXN3 gene, located at chromosome 14q32.1. In normal chromosomes, the CAG repeat length is smaller than 44 repeats, and most affected individuals have between 52 and 86 repeats, although shorter repeats have been associated with disease manifestations (Ramos et al., 2018). SCA3 onset and CAG repeat expansion size are inversely correlated (Coarelli, Bruce & Durr, 2018), but the expansion of CAG length determines approximately 50% of the variability observed in the age of symptoms onset (Mattos et al., 2019). Additional unknown factors should explain the clinical variability of SCA3 that is not explained by the size of the CAG tract (Ramos et al., 2018).

Patients with SCA3 present a wide phenotypic heterogeneity that is the reason for the classification into three main clinical types. The SCA3 type I is characterised by spasticity, rigidity and bradykinesia without prominent ataxia, typically of young to mild-adult onset. Type II, the commonest one, is mainly characterised by symptoms of ataxia, pyramidal signs, and has its onset in young to mid-adult individuals. Type III is marked by symptoms of ataxia and peripheral neuropathy/amyotrophy, and usually has its onset in middle to late middle age. Lately, a fourth type, named type IV, was proposed to accommodate patients with a marked parkinsonian symptoms (Lindsay & Storey, 2017).
Genetic tests are available for SCA3, and genetic counseling programs have been created to better assist the affected families, namely on what concerns the possibility of pre-symptomatic testing. There is currently no preventive or curative treatment, but different therapeutic approaches are being tested (Coarelli et al, 2018).

**Epidemiology**

SCAs are considered rare disorders, with prevalence estimates from 0.3 to 2.0 per 100.000 (Van de Warrenburg et al., 2002). SCA3 is considered the most common form of SCA worldwide (Sequeiros et al., 2012; Schols et al., 2004). A recent systematic review showed that the global prevalence of SCA3 is 3 in 100,000 (Ruano, Melo, Silva & Coutinho, 2014). Among SCAs, the relative frequency of SCA3 is higher in countries such as Brazil, 69-92% (Teive, Munhoz, Raskin & Werneck, 2008), Portugal, 58-74% (Jardim et al., 2001), Singapore, 53% (Zhao et al., 2002), China, 48-49% (Tang et al., 2000), the Netherlands, 44% (Van de Warrenburg et al., 2002), Germany, 42% (Schols et al., 1997), and Japan, 28-63% (Shibata-Hamaguchi, Ishida, Iwasa & Yamada, 2009).

Although constituting the most prevalent subtype of SCA, in Portugal, for example, SCA3 is relatively rare in the mainland (1/100,000), with few exceptions such as a small area of the Tagus River Valley (1/1,000), but highly prevalent in the Azores Islands, where the highest worldwide prevalence occurs in Flores Island (1/239) (Bettencourt, Santos, Kay, Vasconcelos & Lima, 2008).

**Clinical Presentation**

A broad range of clinical manifestations characterise SCA3, including cerebellar ataxia, spasticity, parkinsonism, dystonia, hyperreflexia, and ophthalmoplegia. A clinical report notes that
dementia is less frequent in SCA3 than in SCA1 or SCA2 (Schols et al., 2004). The neuropathological findings of SCA3 consist of degeneration in cerebellar areas such as the dentate nucleus, spinocerebellar tracts, extrapyramidal system, the substantia nigra, red nucleus, globus pallidus and subthalamic nucleus, and cerebral cortices including frontal, parietal, temporal and occipital lobes (Braga-Neto, Dutra, Pedroso & Barsottini, 2014; D´Abreu et al., 2012; Lopes et al, 2013; Murata et al., 1998). In SCA3 the cerebral cortex is not macroscopically involved although there is severe neuronal loss (Seidel et al., 2012; Rub et al., 2013).

The cognitive impairment and brain degeneration observed in patients with SCA3 is broader and more complex than previously thought. In recent decades clinical and experimental studies have shown a broader role of the cerebellum that goes beyond the motor aspects (Baillieux et al, 2008; Bugalho & Viana-Baptista, 2006; Damiani, Gonçalves, Kuhl, Aloi & Nascimento, 2016; Giocondo & Curcio, 2018).

The cognitive impairments in SCA3 might result from the degeneration of cortical and subcortical regions, such as frontal and temporal lobes (Murata et al., 1998), temporal gyrus, bilateral inferior temporal gyrus and cingulate gyrus (Goel et al., 2011), bilateral putamen and pallidum (Reetz et al., 2013), reduction of gray matter volume in the cerebellum, putamen, cingulum, precentral, and parietal lobe (Lopes et al, 2013), occipital and limbic lobes and cerebro-cerebellar loops degeneration (Braga-Neto et al., 2014).

In SCA3 cognitive changes, psychiatric symptoms, and motor neuron degeneration have been reported as part of the classical clinical spectrum. A majority of non-ataxia symptoms appear insidiously and are usually underestimated in clinical practice (Yuan et al., 2019).
The Cerebellar Affective Syndrome

The clinical features of many of the cerebellar arise from degeneration of both cerebellar and extra cerebellar structures (Lindsay & Storey, 2017). The role of the cerebellum in the coordination of movement was well known, but less attention has been directed to the cognitive and behavioral disorders that occurred in association with cerebellar diseases. Cortico-ponto-cerebello-thalamocerebellar projections that form part of a closed loop system with the cerebral cortex, in which the cerebellum returns projections to the prefrontal cortex via the thalamus and which in part seems to explain the role of the cerebellum in cognition (Lindsay & Storey, 2016; Rammani, 2006).

Schmahmann & Sherman (1998) brought evidence for the proposition that the cerebellum itself plays a role in cognition. It was known as the “cerebellar cognitive affective syndrome” (CCAS), that describes a range of impairments including executive dysfunction (deficits in planning, set shifting and abstract reasoning), language (semantic category fluency), spatial cognition (visual organization and visual memory) associated with posterior cerebellar lobe lesions, and not well determined changes in personality (blunting and disinhibition) associated with posterior vermis lesions. The lesions of the anterior cerebellum only produced motor impairment. Researchers attribute the CCAS to disruption of neural circuitry linking different regions of the posterior cerebellar cortex with cerebral association areas and paralimbic regions involved in higher cognitive processing (Lindsay & Storey, 2017).

Executive Functions in the Degenerative Ataxias

The Executive Functions (EF) can be considered the most complex system, the basis of many cognitive, emotional and social skills, necessary for appropriate and socially responsible conduct. Four components compound de EF: volition; planning and decision making; purposive action; and
effective performance (Lezak, Howieson, Bliger & Tranel, 2012). Patients with injury or disease of prefrontal regions present behavioral and personality changes associated with executive functions (Lezak et al., 2012).

The Executive Functions can also be associated with the Prefrontal Cortico-Striato-Thalamo-Cortical Loops, which project circuits from the dorsolateral and orbitofrontal prefrontal cortex to the basal ganglia via the ventral anterior and dorsomedial regions of the thalamus. Disruption in this circuitry is typically associated with cognitive deficits such as impaired set shifting and spatial working (Lindsay & Storey, 2017; Maruf et al., 1996; Robins et al., 1994).

Previous studies demonstrated cognitive impairments in SCA3, however, there is no consensus about the cognitive domains affected and the correlation with structural brain abnormalities (Lopes et al., 2013). Impairments in domains such as attention, executive function, nonverbal abstract reasoning, visual ability and memory have been reported (Braga -Neto et al., 2014; Burk et al., 2003; Kawai et al., 2004; Klinke et al., 2010; Lopes et al., 2013, Maruff et al., 1996; Radvany, Camargo, Costa, Fonseca, & Nascimento (1993); Roeske et al., 2013; Tamura et al., 2018; Zawacki, Grace, Friedman & Sudarsky (2002) However, most of the prior studies evaluated small samples of patients and applied neuropsychological tools which usually neglected the motor difficulties presented by these patients, what compromises the validity of the results. Moreover, some studies did not assess a control group matched for age, gender and educational level (Burk et al., 2003, Maruff et al., 1996; Zawacki et al., 2002).

Another difficulty faced by some studies is the lack of standardized neuropsychological tests, what makes results difficult to compare. The non-cognitive symptoms like speech, visual and motor confounders that may cause a worse performance in tests may also act as confounding factor (Lindsay & Storey, 2017).
Several studies have shown cognitive impairments associated with SCA3 patients. Radvany et al. (1993) assessed cognitive function of 35 participants, 12 with the diagnosis of SCA3 and 23 at risk. The results in the neuropsychological tests showed scores below normal in verbal memory in the affected group. Both groups scored below normal in identifying silhouettes, constructional praxis, visual memory, attention span and in vision aspects.

Maruff et al. (1996) examined cognitive function in 6 patients with genetically confirmed SCA3 and 15 age and ethnically matched control. SCA3 patients had deficits in visual attention function, with slowed processing of more complex visual information and impaired extradimensional attention set.

Zawacki et al. (2002) examined 6 patients that had impairments on fluency, timed verbal attention and executive tasks. Burk et al. (2003) tested 11 patients with SCA3. The results showed SCA3 patients had significant impaired performance mainly on verbal memory tasks. Kawai et al. (2004) evaluated 16 genetically confirmed SCA3 patients and 20 control subjects. Patients scored significantly lower than controls in verbal and visual memory, visuospatial and constructional tasks and in phonemic and semantic fluency tasks, all unrelated to CAG repeat length.

In another study (Klinke et al., 2010) with 15 SCA3 patients and 14 matched healthy control subjects, SCA3 patients presented mainly attentional and executive dysfunctions while semantic and episodic memory functions were preserved. Attentional and executive functions were partly correlated with ataxia severity. Depressive symptoms were assessed by the Beck Depression Inventory and all patients exhibited mildly depressed mood. Braga-Neto et al. (2012) evaluated 29 SCA3 patients and 25 control subjects and the results showed SCA3 patients had visuospatial system affect.
Roeske et al. (2013) assessed cognitive functions of 11 patients with SCA3 and compared with other SCA subtypes (1, 2 and 6) patients and with 14 age-matched and sex-matched control group subjects. The 11 SCA patients were re-evaluated 3.5 ± 0.4 years their first evaluation. The results indicated cognitive deterioration of verbal and figural memory.

Lopes et al. (2013) investigated cognitive domains of 32 patients with SAC 3 and 32 age-gender- and educational level matched healthy controls. Patients presented worse performance in episodic and working memory tests, they had mild impairment in the test that evaluate episodic memory-coding and inferior mild impairment in episodic memory-delayed recall; non-verbal abstract reasoning and working memory.

In a recent study (Tamura et al., 2018) it was assessed cognitive aspects of 15 SCA3 patients and 15 healthy control subjects. SCA3 patients showed impaired word recall with word recognition, episodic memory encoding and storage processes in short-term memory preserved.

The goal of the present study is to evaluate executive functioning of SCA3 patients using a neuropsychological battery that assessed short-term and working memory, verbal fluency, decision making, cognitive flexibility, inhibitory control and depressive and anxiety symptoms. The results were compared with a healthy control group. Furthermore, in the patients we investigated the influence of genetic markers, such as the CAG repeat length, and disease duration on the tests results.

Materials and methods

Participants

Participated in this study twenty-seven patients with genetically confirmed SCA3, from SARAH Networks Hospitals, Brasilia- DF and 21 healthy controls (HC), matched by age and years
of education and all of the participants were Brazilian. Participants were included if the total score in Mini-Mental Test (MMSE; Folstein, 1975) was within the established range of average for their education level.

SCA3 participants were selected through the electronic medical records database from the hospital. It was found 106 patients diagnosed with SCA3, the patients with severe motor disabilities, severe auditory and visual impairment or dementia were excluded. Patients from other states of Brazil without medical consultation schedule were also excluded. All the SCA3 participants that were invited accepted to participate. The HC participants selected had no history of neurological or psychiatric disease.

As showed in table 1, the age of SCA3 group ranged from 26 to 76 years (mean = 47.11, sd = 12.98), while the HC ranged from 21 to 72 years (mean = 51.19, sd = 14.10). The groups did not differ in terms of age (U = 338.0, p = 0.26). Regarding years of education, the SCA3 group ranged from 4 to 15 years (mean = 12.11, sd = 3.37), while HC group ranged from 6 to 15 years (mean = 12.38, sd = 2.94). Therefore, none of these variables were used as covariates in the analyses. Disease duration in years of the SCA3 participants varied from 1 to 15 years (mean = 7.33, sd = 4.33). Finally, the CAG repeat length varied from 54 to 73 (mean = 65.7, sd = 4.9).

The frequency of the sexes in the two groups was not equivalent, as revealed by a Fisher's exact test (Fisher = 0.15, p = 0.08). There were 37.02% of female participants in the SCA3, and 61.90% of female participants in the HC group.
Table 1 - Clinical characteristics of patients with spinocerebellar ataxia type 3 (SCA 3) and of healthy control (HC) subjects

<table>
<thead>
<tr>
<th></th>
<th>SCA 3 n= 27</th>
<th>HC n= 21</th>
<th>t- test /Fisher</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>47.11 (12.98) [26-76]</td>
<td>51.19 (14.10) [21-72]</td>
<td>t= 1.04</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 10; Male 17</td>
<td>Female 13; Male 8</td>
<td>F = 0.15</td>
<td>P= 0.08</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.11 (3.37) [4-15]</td>
<td>12.38 (2.94) [6-15]</td>
<td>t = 0.29</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Disease duration</td>
<td>7.33 (4.33) [1-15]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Procedure

CAG data were collected from the electronic medical record. One neuropsychologist administered the tests in one session of 1 hour and 30 minutes approximately. All participants in this study voluntarily signed informed consent forms. The research was approved by the Research Ethics Committee of the Association of Social Pioneers.

Neuropsychological examinations

All tests in the neuropsychological battery were selected with the aim to minimize the potential motor confounding factors, such as speech and motor impairments that are often observed in SCA3 patients (Lindsay & Storey, 2017; Tamura, 2018; Schols et al., 2004). The cognitive tests covered verbal fluency, verbal short-term and working memory, decision making, cognitive flexibility and inhibitory control. Inventories of depression and anxiety were also applied.

Verbal fluency task. The semantic and phonemic parts of the classical verbal fluency task (Esteves et al., 2015) were applied. In the semantic part, participants had to produce as many words as possible from the category “animals” in 60 seconds. In the phonemic part the participants
had to name words beginning with the letters F, A and S (60 seconds for each). Phonemic fluency is typically associated with left temporal region, related to language abilities and semantic fluency, with the left frontal cortex, with executive function (Julio-Costa, Moura & Haase, 2017).

Digit-span task. The forward and backward sequences from the Brazilian version of Wechsler Adult Intelligence Scale (Nascimento, 2004) were used to measure short-term and working memory abilities. Participants heard a sequence of numerical digits and were asked to recall the sequence in normal or reverse order. Structures such as right dorsolateral prefrontal cortex, bilateral inferior parietal lobule and anterior cingulate are related to these abilities (Gerton et al., 2014).

The Iowa Gambling Task (IGT). A computerized version of the IGT (Mueller & Piper, 2014) was used to assess decision making simulating real-life circumstances. The participants sat in front of a computer screen with four decks of cards equal in appearance and size. They were asked to choose a card each time and the computer button was pressed by the examiner. The decks differed from each other in the balance of reward versus penalty cards. Decks A and B were disadvantageous because they cost the most in the long term and decks C and D advantageous because they resulted in an overall gain in the long term. The goal of the game was to win as much money as possible. IGT scores reflected the overall money gain after 100 trials. Decision making function is associated with ventromedial prefrontal cortex, amygdala and insula (Lezak et al., 2012).

Five Digit Test (FDT). The instrument was used to assess Cognitive Flexibility and Inhibitory Control (Sedó, De Paula & Malloy-Diniz, 2015), typically known as associated with the dorsolateral prefrontal cortex and anterior cingulate (Lezak et al, 2012).
Beck Depression (BDI) and Anxiety (BAI) Inventories. The inventories were used to assess the presence and severity of symptoms of depression and anxiety (Cunha, 2001).

**Statistical analyses**

The results were analysed using SPSS version 18 for Windows. The patients with SCA3 and HC performances on neuropsychological tests were compared using the Mann-Whitney test. Differences were considered significant at $\alpha = 0.05$. The associations between the performance on cognitive tests and the disease duration and CAG repeat length were analyzed using Spearman's rho correlation coefficients.

**Results**

Table 2 shows descriptive statistics, significance levels and effect-sizes for all tests presented here. Verbal fluency tests: SCA3 patients had lower scores in all fluency tests, and significant differences were observed in the in semantic test and for the letters F, A and S tests (all p's < 0.05).

In short-term and working memory tasks: SCA3 patients showed lower scores in the forward span, but higher scores in the backward span, although no significant differences were observed between groups.

Decision Making Test: Both groups showed scores close to zero in the IGT task, with lower scores for the SCA3 group, although not statistically significant.

Inhibitory control and cognitive flexibility tests: In the inhibitory control and cognitive flexibility scores of the FDT task the SCA3 group showed significantly lower scores.
Anxiety and depression symptoms: According to the BECK Anxiety and Depression inventories, the presence of symptoms of anxiety was significantly higher in SCA3 participants, while both groups showed similar scores for depression symptoms.

In order to ensure that our results were not confounded by possible gender differences in the cognitive tests, we performed independent t-tests comparing male and female participants in all tests of the neuropsychological battery. Significant differences were observed in the S part of the verbal fluency task (U = 192.0, p = 0.05) and MMSE (U = 389.0, p = 0.03). We then performed an analysis of covariance (ANCOVA) on the scores of these two tasks, comparing SCA3 and HC participants and controlling for gender differences. Results revealed that both effects remained the same, that is, significant for the fluency test part S (F = 4.19, p = 0.05, $\eta^2_p = 0.09$), and non-
significant for MMSE (F = 0.50, p = 0.48, \( \eta^2_p = 0.01 \)). Therefore, we assumed that our results were not influenced by discrepancies in gender distribution across groups.

**Correlation analyses**

As presented in table 3, disease duration of SCA3 patients did not correlate with any of the measures used here. On the other hand, CAG repeat length correlated with inhibitory control (r = -0.45) and cognitive flexibility (r = -0.43) scores of FDT.

**Table 3 - Correlation matrix (Spearman's Rho) between all measures**

<table>
<thead>
<tr>
<th></th>
<th>1</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Symptom duration</td>
<td>1.00</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>2 CAG repeat length</td>
<td>-0.15</td>
<td>1.00</td>
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<tr>
<td>3 MMSE</td>
<td>0.00</td>
<td>0.01</td>
<td>1.00</td>
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<td></td>
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<tr>
<td>4 FAS animals</td>
<td>-0.14</td>
<td>-0.21</td>
<td>0.47**</td>
<td>1.00</td>
<td></td>
<td></td>
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<tr>
<td>5 FAS F</td>
<td>-0.21</td>
<td>-0.25</td>
<td>0.51**</td>
<td>0.63**</td>
<td>1.00</td>
<td></td>
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<tr>
<td>6 FAS A</td>
<td>-0.21</td>
<td>-0.17</td>
<td>0.50**</td>
<td>0.56**</td>
<td>0.84**</td>
<td>1.00</td>
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<tr>
<td>7 FAS S</td>
<td>-0.24</td>
<td>-0.22</td>
<td>0.26</td>
<td>0.32*</td>
<td>0.59**</td>
<td>0.68**</td>
<td>1.00</td>
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<tr>
<td>8 Digit Span forward</td>
<td>-0.07</td>
<td>0.21</td>
<td>0.40**</td>
<td>0.34*</td>
<td>0.39**</td>
<td>0.33*</td>
<td>0.24</td>
<td>1.00</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>9 Digit Span backward</td>
<td>-0.13</td>
<td>-0.05</td>
<td>0.49**</td>
<td>0.46**</td>
<td>0.60**</td>
<td>0.27</td>
<td>0.02</td>
<td>0.47**</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 IGT</td>
<td>0.19</td>
<td>0.06</td>
<td>0.05</td>
<td>0.09</td>
<td>0.21</td>
<td>0.33*</td>
<td>0.24</td>
<td>-0.10</td>
<td>-0.26</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Cognitive Flexibility</td>
<td>0.08</td>
<td>-0.43*</td>
<td>0.24</td>
<td>0.26</td>
<td>0.38**</td>
<td>0.45**</td>
<td>0.42**</td>
<td>0.24</td>
<td>0.23</td>
<td>0.13</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Inhibitory Control</td>
<td>0.12</td>
<td>-0.45*</td>
<td>0.17</td>
<td>0.22</td>
<td>0.31*</td>
<td>0.25</td>
<td>0.04</td>
<td>-0.01</td>
<td>0.12</td>
<td>0.79**</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 BDI</td>
<td>0.11</td>
<td>-0.06</td>
<td>-0.30*</td>
<td>-0.15</td>
<td>-0.10</td>
<td>-0.09</td>
<td>-0.04</td>
<td>-0.27</td>
<td>-0.25</td>
<td>0.02</td>
<td>-0.18</td>
<td>-0.13</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>14 BAI</td>
<td>0.26</td>
<td>-0.08</td>
<td>-0.14</td>
<td>-0.23</td>
<td>-0.22</td>
<td>-0.14</td>
<td>-0.23</td>
<td>-0.17</td>
<td>-0.13</td>
<td>-0.13</td>
<td>-0.33*</td>
<td>-0.21</td>
<td>0.62**</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* p < 0.05  
** p < 0.01

We also observed significant correlations between BAI scores and FDT cognitive flexibility (r = 0.33). As we found significant differences between SCA3 and HC groups in FDT cognitive flexibility and in BAI scores, we ran an ANCOVA comparing FDT cognitive flexibility between groups controlling for BAI scores. Therefore, we can rule out the possibility that differences in cognitive flexibility were influenced by differences in the intensity of anxiety symptoms. The
ANCOVA revealed that the difference in FDT cognitive flexibility remained significant, with moderate effect-size ($F = 5.36, p = 0.03, \eta^2_p = 0.11$).

**Discussion**

The present study aimed to focus on the investigation of different aspects of executive functions in SCA3 patients by means of neuropsychological assessment. Previous studies demonstrated impairments in SCA3 in different cognitive domains, including executive functions (Maruff et al., 1996; Zawacki, Grace, Friedman & Sudarsky, 2002; Klinke et al., 2010; Tamura et al., 2018). However, there is still no consensus about how the different aspects of executive functions are affected and correlate with brain abnormalities in SCA3 (Braga-Neto et al., 2014; Burk et al., 2003; Kawai et al., 2004; Klinke et al., 2010; Lopes et al., 2013; Maruff et al., 1996; Radvany et al., 1993; Roeske et al., 2013; Tamura et al., 2018; Zawacki et al., 2002). Furthermore, many tasks for assessing executive functions rely on motor responses, which are moderately to severely impaired in SCA3 depending on the stage of the disease (Lindsay & Storey, 2017). In order to overcome these limitations, here we chose neuropsychological tasks that demand verbal responses only.

The results showed that SCA3 patients had significantly lower scores in verbal fluency, cognitive flexibility and inhibitory control, while preserved functioning was observed in working and short-term memory and decision making. CAG repeat length correlated with inhibitory control and cognitive flexibility, but no correlation was found with years of the symptoms and cognitive performance in neuropsychological tests. Furthermore, SCA3 patients showed significantly higher level of anxiety compared to HC group. In the following, these results are going to be discussed in more detail.
As previously reported by other studies (Kawai et al., 2004; Roeske, et al., 2013; Zawacki et al., 2002; Tamura et al., 2018) SCA3 patients showed significant difficulties in both phonemic and semantic parts of verbal fluency task, as compared to HC participants. Performance in verbal fluency tasks is associated with demands in the initiation of a rule-based retrieval of information from semantic memory and is related to dorsolateral prefrontal cortex and temporal lobes (Lezak et al., 2012).

Significant deficits in SCA3 patients were also observed in inhibitory control and cognitive flexibility components of executive functioning, which are associated with the dorsolateral prefrontal cortex, anterior cingulum and cerebellum (Akshoomoff & Courchesne, 1994; Kane & Engle, 2002; Lezak et al., 2012). The SCA3 patients showed significantly lower scores in both cognitive flexibility and inhibitory control tasks, indicating an important deficit in purposive action and online performance monitoring. These results are in accordance with the literature that found degeneration in frontal lobe and cerebellum in SCA3 patients (Braga-Neto et al, 2014; Lopes et al, 2013), although other previous study did not showed deficits in inhibitory control tasks (Tamura et al, 2018).

Despite the deficits described above, SCA3 patients exhibited preserved decision making and short-term and working memory skills. Poor performances in IGT would reflect deficits in decision making skills and is classically associated with lesions in ventromedial prefrontal cortex, amygdala and the insular cortex (Kane & Engle, 2002; Lezak et al., 2012). Digit Span forward and backward assessed the short-term and working memory and the results showed no significant differences between groups, in accordance with previous results reported by Lopes et al. (2013).

Regarding the results of the correlation analysis, CAG repeat length of SCA3 patients showed a moderate correlation with inhibitory control and flexibility scores of FDT. The CAG
repeat length has been usually associated with disease onset and variability on motor symptoms (Coarelli et al., 2018; Schols 2004; Schulz et al 2010) and, to our knowledge, previous research did not report significant associations between CAG repeat length and cognitive symptoms (Kawai et al, 2004; Lopes et al, 2013; Tamura et al, 2018). Nevertheless, Schulz et al. (2010) reported significant association between CAG repeat length and atrophy in striatum, which integrates the Prefrontal Cortico-Striato-Thalamo-Cortical loop, a network that integrates the dorsolateral prefrontal cortex. Because of small sample size, such result should be confirmed by future studies.

Cognitive impairments and emotional symptoms in SAC3 patients can be associated with the cerebellar cognitive affective syndrome, which describes a model for the cognitive and affective role of cerebellum (Schmahmann & Sherman, 1998), based on the presence of a range of executive, visual-spatial, linguistic and affective deficits in patients with cerebellar lesions (Braga-Neto et al., 2014; Lezak et al, 2012; Lopes et al., 2013; Schmahmann & Sherman, 1998). The wide range of deficits is usually associated with the disruption of the closed cortico-ponto-cerebello-thalamo-cortical loops, which link the prefrontal cortex, associated with executive function, with the cerebellar dentate nuclei and the associated posterolateral cerebellar cortex. Cerebellar output proceeds to the ventrolateral and medial dorsal nuclei of the thalamus, and then to the prefrontal cortex (Schmahmann & Pandya, 1997; Schmahmann & Sherman, 1998). In addition to the prefrontal cortex, associations were also demonstrated between areas of the cerebellum with areas involved in cognitive functioning, such as the parietal cortex and the limbic system (Schmahmann, 2000; Lindsay & Storey, 2017).

In the present study impairment in fluency, cognitive flexibility and inhibitory control can be associated with dorsolateral prefrontal cortex involved in the Prefrontal Cortico-Striato-Thalamo-Cortical Loops in accordance in accordance with previous studies that associated decline
in verbal fluency and impairment in response inhibition with lesions in these loops (Jahanshahi et al., 2000; Temel et al., 2005; Weintraub & Zaghloul, 2013).

Regarding the limitations of the study, the relatively small sample size should be highlighted, and no imaging exam was used to be related to the results. The objective of the study was to evaluate executive functions which cannot be ruled out the presence of cognitive impairment in other functions.

Some aspects should be highlighted in relation to this study as the fact that the chosen neuropsychological tests aimed to minimize the influence of the motor aspects of the disease that could confuse the results. Another aspect was the inverse correlation found between the number of CAG repetitions and the performance in cognitive flexibility and inhibitory control tests, which had not been found in previous studies.

The impairments in cognitive flexibility and inhibitory control favor risky attitudes on the part of patients and, they are most often, viewed by family members and caregivers as stubborn. For the rehabilitation team, the expansion of knowledge about the disease helps to improve the quality of information provided to family members and patients, thus increasing the safety and quality of life of these patients.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
References


4. General Discussion

The present study aimed to evaluate, through neuropsychological tests, executive functions in patients diagnosed with SCA3. There is no consensus in the literature about which cognitive functions are affected with the disease. Previous studies have evaluated distinct cognitive functions using different assessment tools, which makes it difficult to compare results (Braga-Neto et al., 2014; Burk et al., 2003; Kawai et al., 2004; Klinke et al., 2010; Lopes et al., 2013; Maruff et al., 1996; Tamura et al., 2018; Zawacki, Grace, Friedman & Sudarsky, 2002). It should be emphasized that the choice of the tests to evaluate executive functions should be cautious in order to reduce the interference of disease symptoms such as incoordination, dysarthria and visual alteration in the results (Lindsay & Storey, 2017). In this sense, the choice of tests was made in order to minimize this risk.

Study results showed that patients with SCA3 had statistically significantly lower scores on verbal fluency, cognitive flexibility, and inhibitory control when compared with the participants of the control group, as well as significantly higher anxiety levels. Previous studies have shown impaired verbal phonemic and semantic fluency (Kawai et al., 2004; Roeske, et al., 2013; Zawacki et al., 2002; Tamura et al., 2018), functions typically related to the dorsolateral prefrontal cortex and temporal lobe (Lezak et al., 2012).

Impairments in inhibitory control and cognitive flexibility, components of executive functions, in patients with SCA3 have also been found in previous studies (Braga-Neto et al. 2012; Roeske et al., 2013) associated with lesions in the dorsolateral prefrontal cortex, anterior cingulate gyrus and cerebellum (Akshoomoff & Courchesne, 1994; Kane & Engle, 2002; Lezak et al., 2012), although another study found no impairment in inhibitory control (Tamura et al, 2018).
There was no statistically significant difference between patient and control groups results regarding short-term and immediate memory, as in a previous study by Lopes et al. (2013). Regarding decision making, there was also no significant difference between the groups. Impaired performances in Iowa Gambling, that reflect poor decision-making, are typically associated with lesions of the ventromedial prefrontal cortex, amygdala, and insula (Kane & Engle, 2002; Lezak et al., 2012). There was no significant difference regarding the presence of depressive symptoms between groups.

Correlation analysis results showed a moderate inverse correlation between the number of CAG repeats and inhibitory control and cognitive flexibility in the Five Digit Test. Previous studies have not found significant correlations between the number of CAG repetitions with cognitive symptoms (Kawai et al., 2004; Lopes et al., 2013; Tamura et al., 2018). Schulz et al. (2010) reported a significant association between the number of CAG repeats and striatum atrophy that integrates the cortico-striato-thalamo-cortical circuit, which integrates connections between the striatum and prefrontal cortex.

Impaired executive functions in patients with SCA3 may be associated with cognitive-affective cerebellar syndrome, which refers to cognitive, emotional, and personality disorders in patients with cerebellar disease (Schmahmann & Sherman, 1998) like those seen in frontal lobe lesions. Neuroanatomic evidence underlies the communication circuits between the cerebellum and frontal lobe as the cortico-cerebellar-thalamic-cortical circuit (Braga-Neto et al., 2014; Lezak et al., 2012; Lopes et al., 2013; Marvel & Desmond, 2010).

The impairments in verbal fluency, cognitive flexibility, and inhibitory control that were found in the study may be associated with the dorsolateral prefrontal cortex involved in the cortico-striato-thalamo-cortical circuit and ruptures in the cortico-cerebello-thalamo-cortical circuit,
according to previous studies that showed impairment of these functions with lesions in these circuits (Jahanshahi et al., 2000; Temel et al., 2005; Weintraub & Zaghoul, 2013).

Regarding the study limitations, the sample size can be considered a limitation. One important aspect that can be highlighted was the focus on executive dysfunction which cannot be ruled out the presence of cognitive impairment in other functions.

Some important aspects in relation to this study are the fact that the chosen neuropsychological tests aimed to minimize the influence of the motor aspects of the disease that could confuse the results and the inverse correlation found between the number of CAG repetitions and the performance in cognitive flexibility and inhibitory control tests, which had not been found in previous studies.

The study of executive dysfunctions present in these patients can help the health team to plan a rehabilitation program more adequate to the demands of this population. Such approach proves to be even more important when it is considered that, so far, it is a disease without a cure, but adequate rehabilitation support plays a fundamental role in broadening patients' perception of quality of life. Future research will bring additional information to the findings in the present study.
General References


Termo de Consentimento Livre e Esclarecido

Você está sendo convidado a participar da pesquisa “Avaliação das funções executivas em pacientes com Ataxia Espinocerebelar Tipo 3 - SCA3”, de responsabilidade de Luciana de Figueiredo Pereira Freitas, psicóloga da Rede SARAH de Reabilitação e estudante de mestrado da Universidade de Brasília. O Objetivo dessa pesquisa é investigar as habilidades e as alterações em relação às funções executivas por meio de instrumentos de avaliação neuropsicológica em pacientes com o diagnóstico de ataxia espinocerebelar tipo 3 e em indivíduos sem o diagnóstico da doença.

Gostaria, então, de consultá-lo (a) sobre o seu interesse e disponibilidade de participar da pesquisa por ter o diagnóstico da Ataxia Espinocerebelar Tipo 3 – SCA3, participando da pesquisa no grupo clínico, ou seja, grupo de pacientes com a doença.

Você será esclarecido antes, durante e após o término da pesquisa a respeito dos procedimentos e resultados decorrentes da mesma. Eu lhe asseguro que o seu nome não será divulgado, garantindo o mais rigoroso sigilo com a omissão das informações que possam identificá-lo (a). Os dados resultantes da sua participação na pesquisa, tais como informações colhidas nas entrevistas e resultados dos testes aplicados ficarão sob a guarda e responsabilidade do pesquisador.

A sua participação na coleta de dados ocorrerá por meio da realização de testes neuropsicológicos que têm como principal objetivo a avaliação das funções executivas (atenção, planejamento, memória e sequenciação). Os testes serão aplicados em uma sala do Laboratório de Neuropsicologia do SARAH Lago Norte, localizado à QL 13, área especial C ou do SARAH Centro, localizado em SMHS 501. A avaliação acontecerá em uma sessão de cerca de 60 minutos. Os riscos decorrentes de sua participação na pesquisa são mínimos, um leve cansaço pode surgir com a testagem neuropsicológica. A aplicação dos testes neuropsicológicos é indolor, não invasiva e envolve respostas verbais ou escritas às tarefas cognitivas.
Com a realização da pesquisa espera-se conhecer melhor as habilidades e disfunções executivas em pacientes com o diagnóstico de ataxia espinocerebelar tipo 3, o que contribuirá para um melhor entendimento da doença e consequentemente um melhor acompanhamento e cuidados destes pacientes.

A sua concordância em participar da pesquisa estará contribuindo para que se possa conhecer melhor as possíveis alterações das funções executivas presentes na doença e para uma melhor assistência do profissional de saúde.

Sua participação é voluntária e livre de qualquer remuneração ou benefício financeiro. Você é livre para recusar, retirar o seu consentimento ou interromper a sua participação em qualquer momento. A recusa em participar não acarretará nenhum tipo de punição ou perda de benefícios quanto ao seu acompanhamento na Rede SARAH.

Caso você tenha alguma dúvida em relação à pesquisa, você pode entrar em contato com a pesquisadora responsável: Luciana de Figueiredo Pereira Freitas pelo telefone 61-33191010, pelo endereço SMHS 501, Brasília-DF ou pelo e-mail .

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa da Associação das Pioneiras Sociais, que poderá ser contactado em caso de questões éticas, pelo telefone: (61) 3319-1494 ou e-mail: .

Os resultados da pesquisa serão repassados aos participantes por meio de um relatório em uma entrevista posterior e poderão ser divulgados em veículos de comunicação de interesse da comunidade científica, preservado o sigilo quanto à identidade.

Este documento foi elaborado em duas vias, uma ficará com a pesquisadora responsável pela pesquisa e a outra com o senhor (a).

________________________________________________
Nome do participante em letra de forma.
________________________________________________
Assinatura do (a) participante.
________________________________________________
Luciana de Figueiredo Pereira Freitas CRP 01/10337 – Psicóloga e Pesquisadora Responsável

Brasília, ____________de ____________de _________________
Appendix 2 - Research Informed Consent Form for control group (in Portuguese)

Termo de Consentimento Livre e Esclarecido

Você está sendo convidado a participar da pesquisa “Avaliação das funções executivas em pacientes com Ataxia Espinocerebelar Tipo 3 - SCA3”, de responsabilidade de Luciana de Figueiredo Pereira Freitas, psicóloga da Rede SARAH de Reabilitação e estudante de mestrado da Universidade de Brasília. O Objetivo dessa pesquisa é investigar as habilidades e as alterações em relação às funções executivas por meio de instrumentos de avaliação neuropsicológica em pacientes com o diagnóstico de ataxia espinocerebelar tipo 3 e em indivíduos sem o diagnóstico da doença.

Gostaria, então, de consultá-lo (a) sobre o seu interesse e disponibilidade de participar da pesquisa por ser um indivíduo sem o diagnóstico da doença, participando então do grupo controle (sem a doença).

Você será esclarecido antes, durante e após o término da pesquisa a respeito dos procedimentos e resultados decorrentes da mesma. Eu lhe asseguro que o seu nome não será divulgado, garantindo o mais rigoroso sigilo com a omissão das informações que possam identificá-lo (a). Os dados resultantes da sua participação na pesquisa, tais como informações colhidas nas entrevistas e resultados dos testes aplicados ficarão sob a guarda e responsabilidade do pesquisador.

A sua participação na coleta de dados ocorrerá por meio da realização de testes neuropsicológicos que têm como principal objetivo a avaliação das funções executivas (atenção, planejamento, memória e sequenciação). Os testes serão aplicados em uma sala do Laboratório de Neuropsicologia do SARAH Lago Norte, localizado à QL 13, área especial C ou do SARAH Centro, localizado em SMHS 501. A avaliação acontecerá em uma sessão de cerca de 60 minutos. Os riscos decorrentes de sua participação na pesquisa são mínimos, um leve cansaço pode surgir com a testagem neuropsicológica. A aplicação dos testes neuropsicológicos é indolor, não invasiva e envolve respostas verbais ou escritas às tarefas cognitivas.

Com a realização da pesquisa espera-se conhecer melhor as habilidades e disfunções executivas em pacientes com o diagnóstico de ataxia espinocerebelar tipo 3, o que contribuirá para
um melhor entendimento da doença e consequentemente um melhor acompanhamento e cuidados destes pacientes.

A sua concordância em participar da pesquisa estará contribuindo para que se possa conhecer melhor as possíveis alterações das funções executivas presentes na doença e para uma melhor assistência do profissional de saúde.

Sua participação é voluntária e livre de qualquer remuneração ou benefício financeiro. Você é livre para recusar, retirar o seu consentimento ou interromper a sua participação em qualquer momento. A recusa em participar não acarretará nenhum tipo de punição ou perda de benefícios.

Caso você tenha alguma dúvida em relação à pesquisa, você pode entrar em contato com a pesquisadora responsável: Luciana de Figueiredo Pereira Freitas pelo telefone 61-33191010 pelo endereço SMHS 501, Brasília-DF ou pelo e-mail .

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Nome do participante em letra de forma.

________________________________________________
Assinatura do (a) participante.

________________________________________________
Luciana de Figueiredo Pereira Freitas CRP 01/10337 – Psicóloga e Pesquisadora Responsável

Brasília, _____________ de ____________ de __________________