THE STUDY OF EXECUTIVE FUNCTIONS IN DISORDERS OF INHIBITORY CONTROL DYSFUNCTION: AUTISM SPECTRUM DISORDER AND NEUROFIBROMATOSIS TYPE 1.

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ABSTRACT

Aim: Previous literature indicates that executive functioning is altered in both Autism Spectrum Disorder (ASD) and Neurofibromatosis Type 1 (NF), having an impact on response inhibition although it is not yet established to what extent. The primary aim of this dissertation is to study executive functions (EFs), with focus on response inhibition, in disorders with inhibitory dysfunction (ASD and NF1), allowing us to understand phenotype specificities. **Method:** A total of 60 participants, forming two experimental groups (ASD vs. NF1) and their respective control groups (CTASD vs. CTNF1) participated in the study. Participants were matched in age, sex and handedness with their respective control groups. A battery of 4 CANTAB tests, Trail Making (A and B) and Stroop tests were administered to fully evaluate EF in our groups. **Results:** Significant differences were found in the ASD group which take longer to react (latency is higher) to achieve a good performance (not making errors) in comparison to controls. In the NF1 vs. CTNF1 comparison, there were no significant differences, except on the screening test, where NF1 were faster than CTNF1, although this did not have a negative influence on performance. **Conclusion:** These findings reveal different patterns of performance in both ASD and NF1 groups although they predominantly indicate spared EF as they were measured in the current study. Further exploration of the results and practical implications are discussed, highlighting the need to conduct large-scale studies in adults using more ecological tasks that better represent the daily-life experiences of the participants.

Keywords: Autism Spectrum Disorder, Neurofibromatosis Type 1, Inhibitory dysfunction, Executive functions

RESUMO

Objetivo: A literatura sugere que o funcionamento executivo está alterado na Perturbação do Espetro do Autismo (PEA) e na Neurofibromatose Tipo 1 (NF1), tendo um impacto na resposta inibitória, embora ainda não seja claro em que magnitude. O principal objetivo desta dissertação consiste em estudar as funções executivas (FEs), com incidência na inibição de resposta, em perturbações com disfunção inibitória, (PEA e NF1) permitindo-nos compreender as suas especificidades. **Método:** Um total de 60 participantes, formando dois grupos experimentais (PEA vs. NF1) e os seus respetivos grupos de controlo (CTPEA vs. CTNF1) participaram neste estudo. Os participantes tinham a mesma idade, lateralidade e sexo que os seus respetivos controlos. Foram administrados 4 testes da CANTAB, Trail Making Test (A e B) e o teste Stroop, a fim de avaliar as FEs nos grupos. **Resultados:** Foram encontradas diferenças significativas no grupo PEA que demorou mais tempo a reagir (maior latência) para alcançar um bom desempenho (sem erros) em comparação com o seu grupo de controlo. Na comparação NF1 vs. CTNF1, não houve diferenças significativas, exceto no teste de rastreio, onde NF1 foi mais rápido do que CTNF1, embora isto não tenha tido uma influência negativa no desempenho. **Conclusão:** Estes resultados revelam padrões diferentes de desempenho dos grupos PEA e NF1, embora indiquem FEs preservadas, tal como foram medidas neste estudo. São discutidos aprofundadamente os resultados e as implicações práticas, destacando-se a necessidade de estudos futuros, em adultos, utilizando tarefas mais ecológicas que representem melhor as experiências da vida quotidiana dos participantes.

Palavras-chave: Perturbação do Espetro do Autismo, Neurofibromatose Tipo 1, Disfunção inibitória, Funções executivas

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INTRODUCTION

The term "executive functions" (EFs) is a catch-all term for the mental operations or cognitive processes, such as planning, working memory, cognitive flexibility and inhibitory control, that allow a person to direct behavior by means of mental models or long-term objectives (Hughes et al., 1994). Neuropsychological theories postulate that executive dysfunctions impair one's capacity to manage behavior, contributing to impulsivity, inattention, and poor planning (Brophy et al., 2002).

Early-life inhibitory control seems to be a good indicator of outcomes throughout life, especially in adulthood (Diamond, 2013), which seems to indicate that EFs are one of the most important features of the human brain. Hence, the characterization of executive functioning in disorders of impaired neurodevelopment, such as Autism Spectrum Disorder (ASD) and Neurofibromatosis Type I (NF1), reveals particular relevance.

Clinically, it is apparent that EF deficiencies play an important role in NF1, contributing to neurodevelopmental outcomes that have an impact on quality of life. The effects of impaired EFs are felt throughout many areas of functioning, from social interaction to economic independence, and are not only limited to academic success (Smith et al., 2020).

Similarly, in ASD, neurocognitive processes are also crucial to the basic behaviors, in addition to genetic and neurobiological factors that influence the ASD phenotype. EF data collected since ASD was first recognized as a psychiatric diagnostic were included in the meta-analysis conducted by Demetriou et al., 2017, which consistently showed that executive dysfunction in ASD has a moderate overall effect size. The average EF performance of people with ASD was substantially lower than that of neurotypical controls and this seems to be stable across the development.

According to Demetriou et al., 2017, although authors have dedicated a great effort exploring this topic, with numerous meta-analyses and reviews included, the function of EF in ASD is still unknown. The same pattern is found in the NF1 literature regarding the severity of EF deficiencies in this condition and their effects on cognition, behavior, and academic achievement (Smith et al., 2020).

Thus, and in need to complement research in this field, with a view to a better understanding of this theme, the primary aim of this dissertation was to study the executive functions in disorders with inhibitory control alterations, such as ASD and NF1. This paper is divided into four sections, one addressing the relevant literature review, another outlining the

methodology used to conduct the study, another addressing the results obtained and, lastly, a full discussion on the topic.

LITERATURE REVIEW

Autism Spectrum Disorder Characterization

Since its restrictive definition and rarity in childhood, Autism Spectrum Disorder (ASD) has become a well-known, supported, and studied lifelong condition that is now understood to be extremely common and heterogeneous (Lord et al., 2018). The enormous expansion in research evidence has contributed to increased knowledge, and awareness of autism in recent decades (Elsabbagh et al., 2012).

ASD is primarily defined as a lifelong neurodevelopmental condition that involves impairments in communication and social interaction (Elsabbagh et al., 2012). Since its inception, the description of the core features of ASD has remained mostly unchanged: along with reciprocal communication and social interaction difficulties, an essential characteristic remains as the repetitive and atypical sensory-motor behaviors (Lord et al., 2018). In addition to these core features, co-occurring psychiatric or neurological illnesses such as attention deficit hyperactivity disorder (ADHD), anxiety, depression, and epilepsy, are common in ASD. The diagnosis is based on clinical criteria and performed through clinical observation along with the use of well-stablished assessment instruments. The gold-standard procedures include a full developmental history, parents' reports and the clinical observation of the child (Lord et al., 2020).

As reported by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) (American Psychiatric Association, 2017), the diagnostic criteria of ASD are the following:

Table 1.

Diagnostic criteria of ASD

	Autism Spectrum Disorder
Diagnostic Criteria	
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive; see text):	
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.	

2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures: to a total lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for ex ample, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behavior

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note. Adapted from American Psychiatric Association. (2017). Diagnostic and statistical manual of mental disorders: Dsm-5.

Some associated features that support the ASD diagnosis include intellectual and/or language impairments (e.g., slow talk, language comprehension behind the production, echolalia). In addition, the gap between cognitive and adaptive functioning skills is frequently wide (Campisi et al., 2018). Despite the fact that ASD is not strictly related to severe motor deficits, it is common to find unusual gait, clumsiness, deficits in gross and fine motor movement and other atypical motor symptoms (e.g., walking on tiptoes). Self-injury (e.g., head pounding, biting the wrist) and inappropriate behavior can also manifest in this diagnosis (Ming et al., 2007). Additionally, some ASD children may exhibit excessive sensitivity to certain noises, lights, or odors as well as hyposensitivity to pain, indicating either a hyper or hyposensitive state to sensory stimuli (Campisi et al., 2018). In adulthood, a great percentage of ASD individuals with intellectual disability are able to communicate to some extent and meet their basic needs although requiring daily assistance (Lord et al., 2018).

The clinical expression of ASD is highly variable, not only among different individuals, but also within the same person over time. It is usually present from birth, but the age at which it manifests itself varies. When the symptoms correspond to classic autism or when there is a delay in the child's development, they appear in the first two years of the child's life and in most

cases, the diagnosis is made at the age of 3 (Monteiro et al., 2014). A change in the early ability to coordinate attention with a social interlocutor in response to any object/event (called "joint attention"), is one of the main manifestations of autism (Alessandri et al., 2005).

Relatively to High Functioning Autism Spectrum Disorder (HFASD) traits initially appear to be the same as those linked to a diagnosis of classic autism. However, individuals with HFASD often exhibit cognitive abilities in the ordinary to above-average range, and occasionally they may even show superior intellectual abilities. In addition, these individuals with HFASD frequently have spared language abilities, particularly in what refers to grammar and syntax. As a result, many HFASD individuals are able to conclude their educational trajectory (Sansosti & Sansosti, 2012). For the present study, only individuals diagnosed with HFASD were illegible to participate, as the presence of severe learning disabilities was an exclusion criterion.

The World Health Organization (WHO) estimates that one in 160 children worldwide has an ASD diagnosis, although its prevalence reported in various studies is variable - values that are significantly higher have been discovered by numerous controlled trials. It is unclear how common ASD is in various low- and middle-income countries. In a lone epidemiological study published in 2005, Oliveira evaluated the prevalence of ASD in Portugal, finding that 1 in every 1000 individuals (1:1000) were affected. Males outnumbered females by a ratio of 3:1, confirming the well-described male predominance.

Significant harm is caused to numerous facets of adaptive functioning, including basic personal and domestic activities to financial autonomy. To be somewhat independent, people with ASD need varying degrees of psychosocial support, and in certain cases, they may need continuing care (Campisi et al., 2018).

Neurofibromatosis Type 1 Characterization

Neurofibromatosis (NF), firstly defined in 1882 by Frederich von Recklinhausen, is described as a genetic disorder affecting the nervous system. The two most prevalent types of NF are type 1 (NF1) and type 2 (NF2), with NF2 assuming more severe manifestations (Levine et al., 2006).

NF1 is one of the most prevalent nervous system single-gene diseases. It is an autosomal dominant disorder that affects about one in every 4,000 individuals, and has equal sex incidence (North, 2000). The disorder, which can impact both the central and peripheral nervous systems, is characterized by abnormal cell proliferation and tissue development (Ozonoff, 1999). The majority of patients who have NF1 experience neurocutaneous symptoms such *café-au-lait*

macules (CALMs), axillary freckling, iris hamartomas (Lisch nodules) and cutaneous neurofibromas (North, 2000). Neurofibromas and CALMs can range in quantity from a few to several thousand. Many of the symptoms that are helpful in diagnostics – besides neurofibromas – have no clinical side effects (Levine et al., 2006). Over the course of a person's lifetime, the illness progresses gradually, however the precise symptoms, rate of development, and severity of problems can all vary greatly (Gutmann et al., 2017). The diagnosis is performed on a clinical basis following the criteria defined by the National Institutes of Health Consensus Development Conference (1988). For a better comprehension, the most recent NF1 revised diagnostic criteria is presented below on Table 2:

Table 2.

Diagnostic criteria of NF1

Revised diagnostic criteria for NF1
A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present: • Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[a] • Freckling in the axillary or inguinal region[a] • Two or more neurofibromas of any type or one plexiform neurofibroma • Optic pathway glioma • Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging • A distinctive osseous lesion such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone • A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

[a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.

[b]Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

Note. Adapted from "Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation" by E. Legius, L. Messiaen, P. Wolkenstein, P. Pancza, R.A. Avery, Y. et al., International Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC), S.M. Hudson, D.G. Evans and S.R. Plotkin, 2021, *Genetics in Medicine, 23(8),* 1506–1513. Copyright 2021 by The Author(s).

The majority of people diagnosed with NF1 experience moderate symptoms and minimal complications; however, some cases are more complex and are characterized by significant cognitive impairments, physical abnormalities, and serious life-threatening medical issues (Levine et al., 2006). The most frequent consequence in children diagnosed with NF1 is the possible cognitive impairment, which lead to a significant impact on future academic achievement (Hyman et al., 2006). Nearly 40% of children with NF1 meet the diagnostic criteria for attention-deficit/hyperactivity disorder (ADHD), and up to 81% of them exhibit moderate to severe impairment in one or more cognitive areas (Hyman et al., 2005). The prevalence of intellectual disability (full-scale IQ < 70) ranges from 4% to 8%, which is higher than in the overall population (North et al., 1997).

Connection between ASD and NF1

The co-occurrence of ASD in NF1 has recently gained significant study interest (Garg et al., 2014), being the reason for choosing these two disorders specifically in the current study. As seen before, ASD is a widespread developmental disease that typically manifests in early childhood and is characterized by limitations in reciprocal social interaction, social communication, and restricted interests or rigid, repetitive activities (Garg et al., 2013). Recent years have seen a rise in interest in the social outcomes for individuals with NF1, and a growing amount of material has been published detailing a variety of social and behavioral challenges.

Only a few studies have looked at social cognition in NF1, but the results show that this population has both perceptual and higher-level abnormalities in this domain (Chisholm et al., 2018). In a study conducted by Chisholm et al., in 2018, the results show that social functioning abnormalities are significantly more common in NF1 and offer strong support for that similar ASD symptoms and behaviors are present in the NF1 profile, with a significantly higher prevalence than what has been reported concerning the general population (Garg et al., 2013). Smith et al., (2020) assert that there is no standard profile for the diagnosis of ASD in NF1

individuals and that this may vary greatly from the expression of ASD in non-NF1 samples. Interestingly, a common pathophysiological basis associated with the dysfunction of inhibitory GABAergic circuits has been reported in both NF1 and ASD (Ramamoorthi & Lin, 2011; Bernardino et al., 2021). In both pathologies alterations in the inhibitory neurotransmission (GABA levels), as assessed by magnetic resonance spectroscopy (MRS), have been reported and have been hypothesized as the mechanisms underlying cognitive impairments in these patients.

Executive Functions

Although there are many different definitions of executive function (EF), generally speaking, EF refers to cognitive processes that are necessary for the conscious, top-down control of action, thinking, and emotion that are connected to brain systems involving the pre-frontal cortex (Zelazo & Müller, 2010 cit in., Lerner et al., 2015). These top-down processes are needed when we have to pay attention and focus, making it impossible to rely on our automatic instinct/intuition (Diamond, 2013). Considering that daily contexts and demands are always changing, we may understand that a diverse variety of behaviors are associated with the executive functioning. These processes are present when, for example, we actively change from one activity to another, resist temptation, or establish a long-term goal; in other words, whenever we carry out a number of actions that enable us to lead autonomous and goal-directed behaviors (Gilbert & Burgess, 2008).

The study of EFs is particularly relevant since these are necessary for maintaining a good mental and physical health, succeeding in school and in life, and fostering cognitive, social, and psychological growth (Diamond, 2013). Table 3 summarizes the importance of the EFs in our daily life:

Table 3.

Executive functions (EFs) relevance

Aspects of life	The ways in which EFs are relevant to that aspect of life	References
Mental health	EFs are impaired in many mental disorders, including:	
	- Addictions	Baler & Volkow, 2006

	- Attention deficit hyperactivity (ADHD)	Diamond 2005, Lui & Tannock 2007
	- Conduct disorder	Fairchild et al., 2009
	- Depression	Taylor-Tavares et al., 2007
	- Obsessive compulsive disorder (OCD)	Penadés et al., 2007
	- Schizophrenia	Barch, 2005
Physical health	Poorer EFs are associated with obesity, overeating, substance abuse, and poor treatment adherence	Crescioni et al., 2011, Miller et al., 2011, Riggs et al., 2010
Quality of life	People with better EFs enjoy a better quality of life	Brown & Landgraf 2010, Davis et al., 2010
School readiness	EFs are more important for school readiness than are IQ or entry-level reading or math	Blair & Razza, 2007, Morrison et al., 2010
School success	EFs predict both math and reading competence throughout the school years	Borella et al. 2010, Duncan et al., 2007, Gathercole et al. 2004
Job success	Poor EFs lead to poor productivity and difficulty finding and keeping a job	Bailey, 2007
Marital harmony	A partner with poor EFs can be more difficult to get along with, less dependable, and/or more likely to act on impulse	Eakin et al., 2004
Public safety	Poor EFs lead to social problems (including crime, reckless behavior, violence, and emotional outbursts)	Broidy et al., 2003, Denson et al., 2011

Note. Adapted from "Executive Functions" by Adele Diamond, 2013, *Annual Review of Psychology*, *64*(1), 135–168. Copyright 2013 by Annual Reviews. All rights reserved.

Due to this evidence, studying the EFs seemed of a high-importance, especially associated with ASD and NF1, as this to our knowledge has not been profoundly analyzed.

When we consider EF, we mainly focus on three core functions: inhibition, working memory (WM) and cognitive flexibility. Inhibition mainly refers to the aspect of inhibitory control, which involves not acting towards an impulse or in a premature manner, suppressing context-inappropriate automatic reactions to adopt more adaptive voluntary responses. WM

concerns the act of keeping in memory and utilizing knowledge cognitively (e.g., relating one thing to another, using information to solve a problem). On the other hand, there is cognitive flexibility, which in simple terms is the ability to switch between tasks; finding different or alternative perspectives with flexibility (Diamond, 2013).

EFs and Inhibitory Control

Inhibitory control, one of the fundamental EFs, refers to the capacity to restrain one's attention, behavior, thoughts, and/or emotions in order to thwart a potent internal urge or an enticing external force and act in accordance with what is more suitable or required. We would be at the whim of impulses, entrenched habits, and/or outside cues that urge us in one direction or another if we lacked inhibitory control. As a result, inhibitory control allows us to change and choose our actions rather than becoming mindless automatons. The ability to sustain emotional and behavioral control in order to retain behavioral control is known as self-control: the ability to restrain oneself from acting on impulse and to resist temptation (Diamond, 2013). There are numerous sources of information competing for our attention at any given time, making interaction with the outside world complex. Thus, a key component of effective performance in many contexts is the capacity to manage our attention, keeping it away from irrelevant information so that we may focus on what is crucial (Lustig et al., 2001). Response inhibition and attentional inhibition are two important cognitive processes that have been studied under the umbrella of inhibitory control. Response inhibition refers to the capacity to control an overactive motor reaction, whereas attentional inhibition refers to the capacity to withstand interference from distracting stimuli (Tiego et al., 2018).

Many individuals diagnosed with developmental disorders suffer from impairments in response inhibition, leading to executive function impairments, in particularly those with ADHD, obsessive compulsive disorder (OCD), and ASD (Sweeney et al., 2004). Despite not being classified as an inhibitory dysfunction disorder, there is evidence that it is disrupted in ASD. Executive dysfunction has been linked to autism's inability to actively cease repetitive activities (Lopez, Lincoln, Ozonoff, & Lai, 2005; South, Ozonoff, & McMahon, 2007 cit in., O'Hearn et al., 2008). In a study conducted by Luna et. al. in 2007, authors attempted to clarify the developmental course of response inhibition in ASD from adolescence to adulthood and the results indicate that voluntary response inhibition of participants with ASD was compromised. Participants diagnosed with ASD, at all ages, exhibited worse response inhibition abilities that never caught up to that of typically developing individual although they showed an improvement throughout the development that was similar to the one observed in the control

group. In another study, Christ et al., (2007), found that children with ASD performed poorly on a go/no-go task as well as in a flanker task, when compared with controls but achieved a comparable performance on both computer and card versions of the Stroop task. In this study individuals with ASD made more errors on the go-trials suggesting difficulties in the sustained attention rather than an inhibitory control dysfunction (more characterized by increased number of errors in the no-go trials). In accordance with these results, Zhou & Wilson (2020), found no significant differences between children with ASD and typically developing children in a Stroop-like laboratory task suggesting spared cognitive inhibition skills. These results highlight the importance of testing different aspects of executive dysfunction in population which reveals a heterogeneous pattern of performance.

As we have seen previously, there are several different types of cognitive abnormalities associated with NF1. Executive dysfunction and impaired response inhibition have been described as relevant features of the NF1 cognitive phenotype (Ribeiro et al., 2015). In the study conducted by Ribeiro et al., in 2015, brain correlations of weakened inhibitory control in children and teenagers with NF1 were examined. In terms of behavior, individuals diagnosed with NF1 displayed more errors of commission (false alarms) and quicker reaction times in go trials, which suggested an impulsive response style. Additionally, in a study conducted by Rowbotham et al., in 2009, with the main goal of definitely establishing the NF1 cognitive profile, results showed that NF1 patients exhibit poorer performance than controls in visuospatial encoding (perception), executive functioning, and visuomotor coordination tasks and, more importantly, this varies in accordance to the level of cognitive control demands. In a meta-analysis performed to explore the magnitude of the alteration of each EF in children with NF1, Beaussart et al., (2018), showed that planning/problem-solving and working memory exhibited greater impairment than inhibitory control and cognitive flexibility, revealing a different pattern of dysfunction according to the EF in appreciation.

Study Aims

Taken together, the aforementioned scientific evidence indicates that executive functioning is altered in both ASD and NF1, although it is not yet established to what extent. Additionally, the literature has mainly focused on investigating executive functioning in children, turning out difficult to draw a conclusion on the progression of these difficulties across age. Given the fact that both disorders have been associated with deficits in the inhibitory control, it is relevant the characterization of executive functioning of both ASD and NF1, in the same study and using the same methodological procedures.

Thus, the primary aim of this dissertation is to study the EFs, with a particular focus on response inhibition, in disorders with inhibitory control alterations, such as ASD and NF1. This will allow us to understand phenotype specificities. A comprehensive understanding of the executive functioning in these neurodevelopmental disorders is pivotal for the implementation of more effective rehabilitation strategies.

This aim is reflected throughout the dissertation as a range of topics is discussed by firstly defining each disorder, relating them and describing the impact of executive functions in each one, more specifically in inhibitory control. In order to do this, the Stroop Color Word Test (SCWT), the Trail-Making Test (TMT) and four tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered to each participant of this study. Comparisons were made between them, to acknowledge possible significant differences. Given the previous review of literature, we hypothesize that both ASD and NF1 groups would exhibit deficits in selected neuropsychological measures, although we expect a disease-related pattern of performance.

Evaluating EFs

There are many ways to evaluate EFs, and depending on the EFs that are being evaluated, specific tests are administered. As mentioned before, we focused on inhibitory control in this study and so selected tests of the CANTAB were used, as well as SCWT and the TMT (A and B).

The use of computerized versions of neuropsychological and cognitive tests to evaluate EFs, such as CANTAB, has grown in popularity recently and offers many benefits over more conventional practices. For instance, computerized tasks can increase data collection accuracy and allow researchers to regulate a variety of unimportant variables, allowing for more accurate measurement of particular cognitive processes (Brophy et al., 2002). Numerous clinical populations, including school-aged autistic children, have undergone this test battery (Hughes et al., 1994). By using a computer, it is possible to record accuracy and speed in great detail and verify that the test is administered in a standardized manner with standardized feedback (Fray et al., 1996). The current study also intends to evaluate the sensitivity of this computerized test battery in detecting subtler deficits in these neurodevelopmental disorders, as compared to more classical approaches.

Stroop (1935) asserts that the SCWT evaluates the capacity to inhibit cognitive interference, which happens when the simultaneous processing of one characteristic of a stimuli is impacted by the processing of another attribute of the same input. According to O'Hearn et

al., (2008), the SCWT is a well-known task for studying EFs, more specifically, response inhibition. In addition, Spieler et al., 1996 suggested that an age-related decrease in the effectiveness of inhibitory mechanisms is the cause of a rise in the Stroop effect (West & Alain, 2000).

Furthermore, one of the tests that neuropsychologists use most commonly is the TMT. Executive function-serving brain areas have been linked to cognitive deficits discovered using TMT error analysis (Mahurin et al., 2006).

STUDY METHODOLOGY

Participants

The present study included two clinical groups (ASD and NF1) and their respective control groups, CTASD and CTNF1. ASD and NF1 participants were enrolled in a large-scale research project investigating the GABAergic dysfunction in these conditions (Bernardino et al., 2022a, 2022b). Healthy volunteers were recruited for this research study, taking into consideration the demographic characteristics of the clinical groups.

ASD Group

A total of 17 high-functioning ASD participants were recruited, all of them male, aged between 17 and 30 years old (mean = 20.59, SE = 0.84), from a database used in previous studies (Bernardino et. al., 2022a) and in collaboration with local ASD associations. All ASD participants obtained positive results on the gold standard diagnostic instruments, namely parental or caregiver interview [Autism Diagnostic Interview-Revised, ADI-R (Lord et al., 1994)] and direct structured proband assessment [Autism Diagnostic Observation Schedule, ADOS (Lord et al., 1999)], and met the current diagnostic criteria for ASD as assessed by the Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5 (2017)]. Exclusion criteria included genetic syndrome, neurological or psychiatric comorbidities, history of traumatic brain injury, epilepsy, contraindications to MR scanning or TMS and severe learning disabilities (full-scale intellectual quotient < 85). None of the participants were diagnosed with Attention deficit hyperactivity disorder (ADHD), Obsessive compulsive disorder (OCD), anxiety or mood disorders. Three ASD participants were under chronic medication for ASD-related symptomatology (methylphenidate n = 2; risperidone n = 1) and were instructed to maintain the treatment as usual.

NF1 Group

A total of 15 NF1 patients, 6 males and 9 females, aged between 26 and 55 years old (mean = 39.2, SE = 2.10), were enrolled in this study. NF1 patients were recruited in collaboration with the Portuguese Association of Neurofibromatosis. All patients met the National Institute of Health (NIH, Consensus Development Conference 1988) diagnostic criteria for NF1 and some of them underwent genetic testing. Exclusion criteria were as follows: other neurological or psychiatric disorders, history of traumatic brain injury, epilepsy, substance abuse and severe learning disabilities (WAIS-III, IQ < 70). None of the participants were taking medication that could affect the central nervous system.

Control Groups

The healthy control participants formed the control groups of this experiment and were recruited from the local population. Control participants had no known history of psychiatric or neurological conditions and were not currently taking any medications that could implicate with the study.

The control samples were matched by age, sex and handedness with their respective experimental groups, forming two control groups, CTASD (N=17) and CTNF1 (N=14). ASD and CTASD were IQ-matched but the same was not verified between NF1 and CTNF1 groups. However, it is worth mentioning that the mean IQ of the NF1 group was within the mean range. Level of education differed between clinical and control groups as was expected given the learning difficulties associated to the ASD and NF1 diagnostics.

Demographic characteristics are summarized below in the Tables 4 (ASD comparison) and 5 (NF1 comparison):

Table 4.

ASD and CTASD demographic characteristics

	ASD (N = 17)			**CTASD (N = 17)**		
	Mean	**SE**	**Range**	**Mean**	**SE**	**Range**
Age	20.59	0.84	17 – 30	20.77	0.81	17 - 30
IQ	104.71	2.61	86 – 119	106.24	2.36	92 - 128
Level of Education*	12.35	0.38	11 – 17	14.29	0.60	10 - 19
Sex (M - F)		17 – 0			17 – 0	

Handedness (R - L)	14 – 3	14 – 3

Note. ASD = Autism Spectrum Disorder Group, CTASD = Control Autism Spectrum Disorder Group, IQ = Intellectual Quotient, SE = Standard Error, M = Male, F = Female, R = Right, L = Left, N = Number of participants: * $p < .05$;

Table 5.

NF1 and CTNF1 demographic characteristics

	NF1 (N = 15)			**CTNF1 (N = 14)**		
	Mean	**SE**	**Range**	**Mean**	**SE**	**Range**
Age	39.20	2.10	26 - 55	38.93	2.26	26 - 55
IQ*	102.80	3.50	76 - 128	113.57	3.61	84 - 133
Level of Education*	12.47	0.83	4 - 17	16.29	0.58	9 - 18
Sex (M - F)		6 – 9			5 – 9	
Handedness (R - L)		14 – 1			12 – 2	

Note. NF1 = Neurofibromatosis Type 1, CTNF1 = Control Neurofibromatosis Type 1 Group, IQ = Intellectual Quotient, SE = Standard Error, M = Male, F = Female, R = Right, L = Left, N = Number of participants; * $p < .05$;

Instruments

For the present study, six different instruments were used along with an informed consent. These six instruments served different purposes in order to fully evaluate the participants in the relevant domains for the study. This evaluation took approximately 1 hour and 15 minutes to complete, involving different types of engagement in each task. The instruments applied were: Sociodemographic Questionnaire, Edinburgh Handedness Inventory, Wechsler Adult Intelligence Scale - Third Edition (adapted short-version), Trail Making Test, Stroop Color Word Test and the Cambridge Neuropsychological Test Automated Battery (four selected tests).

The following instruments will be further explained:

Sociodemographic Questionnaire. The purpose of applying a sociodemographic questionnaire (see Appendix A), apart from characterizing the sample in relation to: date of birth; sex; nationality; level of education; profession; medication intake; presence or diagnosis of neurological or neuropsychiatric disorder; health issues and relevant observations, was to make sure the participant was eligible for the study, i.e., if it met the inclusion criteria – no

neurological/neuropsychiatric disease or medication intake that could implicate with normal cognitive functioning.

Edinburgh Handedness Inventory. The Edinburgh Handedness Inventory (EHI) served the same purpose as the sociodemographic questionnaire, used as a means to characterize the population, not being a part of the future statistical analysis. The EHI is beneficial because it is a simple and quick way to rate laterality on a quantitative scale. This inventory is based on a 10-question questionnaire, questioning the participant on with which hand it prefers to perform certain activities (Oldfield, 1971). The EHI was administered as part of a neuropsychological battery and took approximately 5 minutes to complete by each participant.

Trail Making Test. The Trail Making Test (TMT) is a well-known neuropsychological screening tool for identifying neurological disorders and cognitive impairment. This test can also be used as a component of a wider battery of tests, as in the present study. It took approximately 5 minutes to complete by each participant.

Parts A and B make up the TMT version that was utilized. In part A, a sequence of 25 ringed numerals is connected in numerical order by the subject using a pencil. In section B, the subject connects 25 ringed numbers and letters in a mixture of numerical and alphabetical order. As an illustration, the first number "1" is followed by the first letter "A," then the second number "2," followed by the second letter "B," and so on. In order to prevent the examinee's lines from crossing, the numbers and characters are placed in a semi-random arrangement. Part A is typically assumed to assess motor speed and visual search abilities, whereas part B is also thought to test higher-level cognitive abilities including mental flexibility (Bowie & Harvey, 2006). The number of errors as well as the time of execution (in sec) were used as performance measures.

Stroop Color Word Test. The Stroop Color Word Test (SCWT) test was administered with the objective of evaluating the participants' executive functions. This is a neuropsychological test which was proposed by Stroop in 1935, that is widely used to examine the capacity to inhibit cognitive interference, named the "Stroop Effect", which happens when the processing of one sensory attribute interferes with the simultaneous processing of another (Scarpina et al., 2017).

All the participants performed the standard SCWT (Golden, 1978) composed of two congruent conditions [word (W) and color (C)] and one incongruent (interference) condition

[color-word (CW)]. Participants had 45s to complete each task condition. An Interference Index was calculated according to the method proposed by Golden (1978): Incongruent Score (IG) = CW- [(W x C) / (W + C)].

Wechsler Adult Intelligence Scale - Third Edition. An adapted short-version by Sattler & Ryan (1999) of the Wechsler Adult Intelligence Scale - Third Edition (WAIS-III) (Wechsler, 2008) was used as a means to characterize the population and make sure that intellectual deficits were excluded in order to confirm the exclusion criteria. A combination of 3-sub-tests were used: Picture Completion to evaluate performance, more specifically, perceptual organization; Vocabulary to evaluate verbal comprehension; and lastly, Arithmetic to evaluate working memory. Full-scale IQ was calculated using the reference values obtained by Sattler et al., 1999 that showed high reliability and validity coefficients.

Cambridge Neuropsychological Test Automated Battery. The Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks are known to be the most reliable and popular computerized assessments of cognition. To assess particular features of cognitive performance in various therapeutic contexts, tasks can be ordered individually or as a battery. These cognitive tasks can be divided into four different batteries that incorporate various tests: Attention and Psychomotor Speed, Memory, Executive Function and Emotion and Social Cognition (Cambridge Cognition, 2019). For the purpose of this study, a short-version of the CANTAB was used, including Motor Screening Task (MOT), Multi-Tasking Test (MTT), Reaction Time (RTI) and Rapid Visual Information Processing (RVP).

In total, the admission and completion of this version took approximately 20 minutes for each participant.

Motor Screening Task (MOT)

MOT is a user-friendly way of introducing the CANTAB tests to the participant. It consists in a screening test since it provides a broad evaluation of whether sensorimotor deficits or lack of comprehension will limit the collection of valid data from the participant. This task takes 2 minutes to complete. During the task, colored crosses are presented in different locations on the screen one at a time and the subject is requested to select the cross as soon as it turns green, as quickly and accurately as possible. The outcome measures assess the participant's speed of response and the accuracy of pointing (selecting the cross). MOT measure descriptions are present in Table 6:

Table 6.

CANTAB Measure Descriptions – Motor Screening Task (MOT)

Task	Measure Name	Measure Description
MOT	Mean latency	The mean latency from the display of a stimulus to a correct response to that stimulus during assessment trials.
MOT	Total correct	The total number of assessment trials on which the subject made a correct response.

Note. Adapted from CANTAB® [Cognitive assessment software]. Cambridge Cognition (2019). All rights reserved. www.cantab.com

Multi-Tasking Test (MTT)

The MTT was administered, taking up a total of 8 minutes to complete. The purpose of this task is to test the participants' ability to manage contradictory information offered by an arrow's direction and its position on the screen, while ignoring information that is not important to the job at hand.

Regarding the task format, the test shows an arrow that may appear on the right or left side of the screen and may point in either direction (to the right or to the left). At the top of the screen, a cue is displayed for each trial, instructing the participant to choose the right or left button depending on the "side on which the arrow appeared" or the "direction in which the arrow was pointing". This criterion may apply to only one component of the task in certain trials (single task), while in other trials it may vary from trial to trial in a randomized order (multitasking). A single rule is less cognitively demanding than the flexible application of both rules. Congruent stimuli, such as an arrow pointing in the appropriate direction, are displayed in some trials, whereas incongruent stimuli, which involve a higher level of cognitive effort, are displayed in other trials (e.g., arrow on the right side of the screen pointing to the left).

Outcome measures for this task involve response latencies and error scores that reflect the participant's ability to manage multitasking and the interference of incongruent task-irrelevant information on task performance, similarly to a Stroop-like effect. MTT measure descriptions are present in Table 7:

Table 7.

CANTAB Measure Descriptions – Multi-tasking Test (MTT)

Task	Measure Name	Measure Description
MTT	Median Incongruency cost*	The difference between the median latency of response (from stimulus appearance to button press) on the trials that were congruent versus the trials that were incongruent. Calculated by subtracting the median congruent latency (in ms) from the median incongruent latency. A positive score indicates that the subject is faster on congruent trials and a negative score indicates that the subject is faster on incongruent trials. A higher incongruency cost indicates that the subjects takes longer to process conflicting information.
MTT	Median Reaction latency*	The median latency of response (from stimulus appearance to button press). Calculated across all correct, assessed trials.
MTT	Multitasking block errors	The number of trials in assessed block(s) in which both rules are used and the trial outcome was an incorrect response.
MTT	Median Multitasking cost*	The difference between the median latency of response (from stimulus appearance to button press) during assessed blocks in which both rules are used versus assessed blocks in which only a single rule is used. Calculated by subtracting the median latency of response during single task block(s) from the median latency of response during multitasking block(s). A positive score indicates that the subject responds more slowly during multitasking blocks, and indicates a higher cost of managing multiple sources of information.
MTT	Commission errors	The number of trials for which the trial outcome was a commission error (response when no stimulus present).
MTT	Total incorrect*	The number of trials for which the outcome was an incorrect response (subject pressed the incorrect button within the response window). Calculated across all assessed trials.

MTT	Omission errors	The number of trials for which the trial outcome was an omission error (no response).

Note. *Key measures considered by CANTAB

Reaction Time (RTI)

RTI covers measurements of movement time, reaction time, response accuracy, and impulsivity in addition to assessments of motor and mental response speeds. The administration of this test takes 3 minutes in total and consists in asking the participant to select and hold a button at the bottom of the screen. Then, five circles are presented above and, in each case, a yellow dot will appear in one of the circles. The participant must react as soon as possible by releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared, and so on until the end of the task.

The outcome measures are divided into reaction time and movement time. RTI measure descriptions are present in Table 8:

Table 8.

CANTAB Measure Descriptions – Reaction Time (RTI)

Task	Measure Name	Measure Description
RTI	Five-Choice Error Score (premature)	The total number of trials where the subject made a response before the presentation of the target stimulus. Calculated across all assessment trials in which the stimulus could appear in any one of five locations.
RTI	Median Five-Choice Movement Time*	The median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.

RTI	Median Five-Choice Reaction Time*	The median duration it took for a subject to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.
RTI	Five-Choice Total Error Score	The total number of trials where the subject made any form of response error. This measure is calculated through summing the inaccurate, incorrect location, omission and premature errors, alongside two other possible errors not individually output. These two additional errors are the use of multiple fingers and dragging a finger outside of a response box. Calculated across all assessment trials in which the stimulus could appear in any one of five locations. Please note that this outcome measure combines multiple, separate cognitive functions (i.e. an omission error is not psychologically the same as a premature error) and is therefore not a recommended measure for standard practice.

Note. *Key measures considered by CANTAB

Rapid Visual Information Processing (RVP)

Regarding the RVP, this is a measure of sustained attention and the administration of this task takes 7 minutes to complete. Concerning its format, the task is presented with a white box in the middle of the screen, inside of which numbers from 2 to 9 arrive in a seemingly random order at a rate of 100 numbers per minute. The subject is asked to detect a target sequence of digits, 3-5-7, and when this target sequence is seen, the participant must respond by selecting the button on the screen as fast as possible, only clicking when the last number, in this case 7, is seen.

In relation to the outcome measures, these cover latency (speed of response), probability of false alarms and sensitivity. RVP measure descriptions are present in Table 9:

Table 9.

CANTAB Measure Descriptions – Rapid Visual Information Processing (RVP)

Task	Measure Name	Measure Description
RVP	A prime*	The signal detection measure of a subject's sensitivity to the target sequence (string of three numbers), regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences.
RVP	Median Response Latency*	The median response latency on trials where the subject responded correctly. Calculated across all assessed trials.
RVP	Probability of False Alarm*	The number of sequence presentations that were false alarms divided by the number of sequence presentations that were false alarms plus the number of sequence presentations that were correct rejections: (False Alarms ÷ (False Alarms + Correct Rejections))
RVP	Total False Alarms	The total number of stimulus presentations during assessment blocks that were false alarms.
RVP	Total Misses	The total number of target sequences that were not responded to within the allowed time during assessment sequence blocks.

Note. *Key measures considered by CANTAB

Procedure

Informed consent was obtained from the participants before beginning the testing, both from the control groups and the experimental groups. A complete participation required approximately a 1 hour and 15 minutes session with each participant. Both control groups and the clinical groups were obtained using a convenience sample. The measures were administered in a consistent order: Sociodemographic Questionnaire, EHI, TMT, SCWT, WAIS-III and ended with the CANTAB sub-tests.

Data Analysis

For the data analysis, the IBM SPSS Statistics version 28.0.1.0 (142) was used. The normality of the variables was tested using the Shapiro-Wilk value and it was found that the majority of the variables did not follow a normal distribution. For this reason, non-parametric tests for comparison between independent samples, the Mann-Whitney U test, was used for the CANTAB and the TMT results analysis. The only variable that followed a normal distribution for all groups was the Stroop Interference Index measure and, for this reason, the Independent Samples *T*-test was used for these comparisons. An exact p value < 0.05 was considered significant.

The outliers analysis was performed according to the criteria defined by SPSS for extreme outliers: any data value is considered to be an extreme outlier if it lies outside of the following ranges: 3rd quartile + 3*interquartile range and 1st quartile – 3*interquartile range. However, after visual inspection, it was possible to verify that this criterion was removing the biological variability expected within groups. For this reason, these values were not excluded from the analysis of the results.

For the sake of clarity, all graphs referring to the variables where statistically significant differences were obtained are shown in the text while the others are presented in the Appendixes section in a table form.

RESULTS

In order to create a better organization of the findings and to make the reading of the obtained results as perceptible as possible, these will be explained by comparing them between groups in three stages: ASD vs. CTASD; NF1 vs. CTNF1 and ASD vs. NF1. Although it is not the main purpose of the study to compare the NF1 and ASD groups because they are not matched with respect to age and sex, there is a third section where this direct comparison will be addressed.

The graphs of the results which were statistically significant ($p < 0.05$) will be displayed in the Results section, whereas the remaining results that were not significant ($p > 0.05$), can be found in the Appendixes section, divided accordingly into different tables.

ASD vs. CTASD Comparison

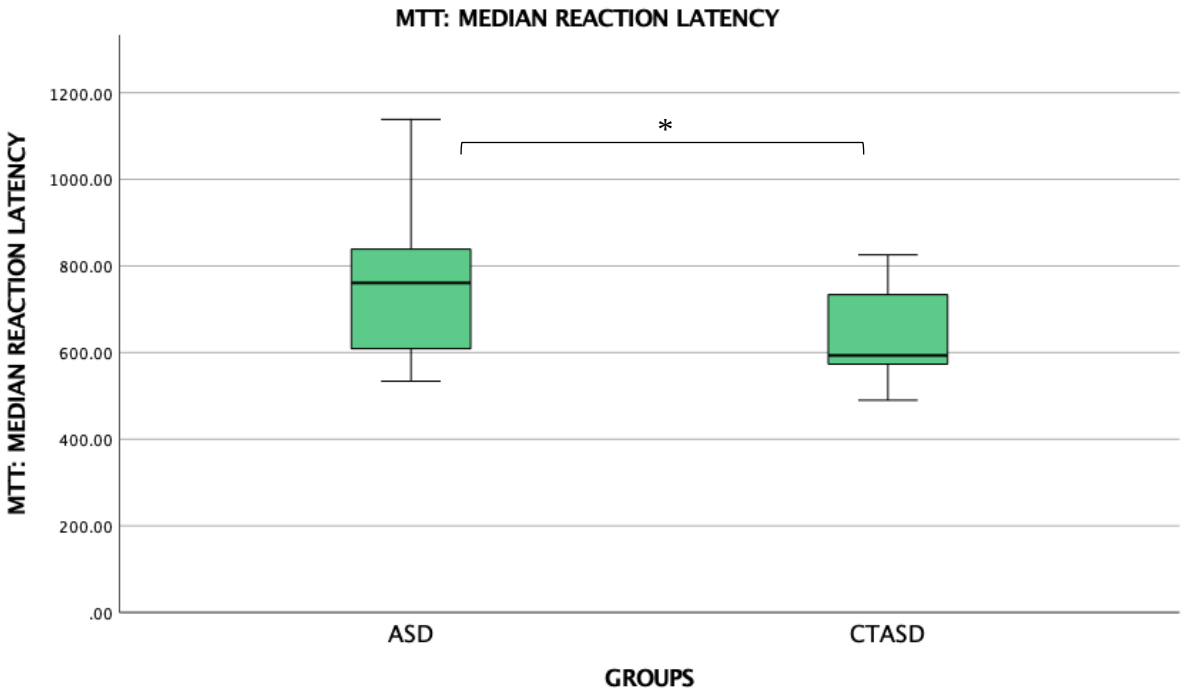
In the screening test (MOT), ASD participants did not significantly differ from the CTASD group for both Mean Latency (ASD *Mdn* = 765.60, CTASD *Mdn* = 815; *U* = 137.0, *z*

= -0.258, p = 0.812) and Total Correct Measures (ASD *Mdn* = 10, CTASD *Mdn* = 10; U = 144.0, z = 0.042, p = 1.000). Regarding the Total Correct Responses, both groups were able to perform correctly in all the test trials (10 correct responses) revealing good sensorimotor and comprehension abilities.

On the MTT Test, by comparing these 2 groups, we only found significant differences on the variable Median Reaction Latency (ASD *Mdn* = 761.08, CTASD *Mdn* = 593.50; U = 79.0, z = -2.256, p = 0.024), represented on Figure 1. The median reaction latency (median latency of response from stimulus appearance to button press measured in milliseconds) for the ASD group is 761.08 milliseconds and for the CTASD group it is 593.50.8 milliseconds which indicates that the ASD group takes longer to acknowledge the stimulus appearance until the actual button press in comparison with its control group.

Figure 1.

MTT Median Reaction Latency compared in between ASD and CTASD groups



Note. ASD = Autism Spectrum Disorder Group
CTASD = Control Autism Spectrum Disorder Group
MTT = Multi-Tasking Test
* p < 0.05

The remaining MTT variables, namely Median incongruency cost*; Multitasking block errors; Multitasking cost*; Commission Errors; Total incorrect* and Omission errors, did not

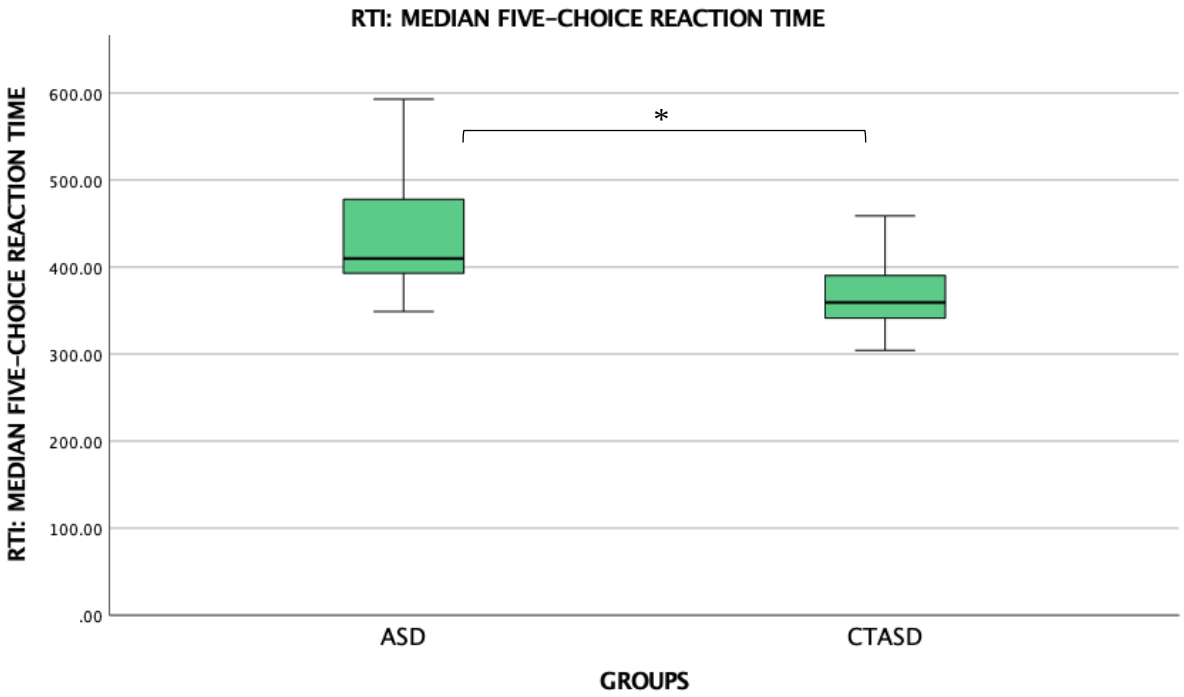
present significant differences between ASD and CTASD ($p > 0.05$). Results for the non-significant variables can be found on Appendix B, Table B.1.

On the RTI Test, ASD and CTASD groups significantly differed on the RTI Median Five-Choice Reaction Time* (ASD *Mdn* = 410.00, CTASD *Mdn* = 359.50; $U = 53.5$, $z = -3.135$, $p = < 0.001$), and on the RTI Five-Choice Total Error Score (ASD *Mdn* = 0, CTASD *Mdn* = 1; $U = 74.0$, $z = -3.024$, $p = < 0.003$), represented on Figures 2 and 3, respectively.

A significant difference is pictured on Figure 2, where the median reaction time (median duration it took for a subject to release the response button after the presentation of a target stimulus, measured in milliseconds) in the ASD group is greater than in the CTASD group, suggesting that the ASD group takes more time to release the button after stimulus presentation in comparison to its control group (CTASD).

Figure 2.

RTI Median Reaction Time compared in between ASD and CTASD groups



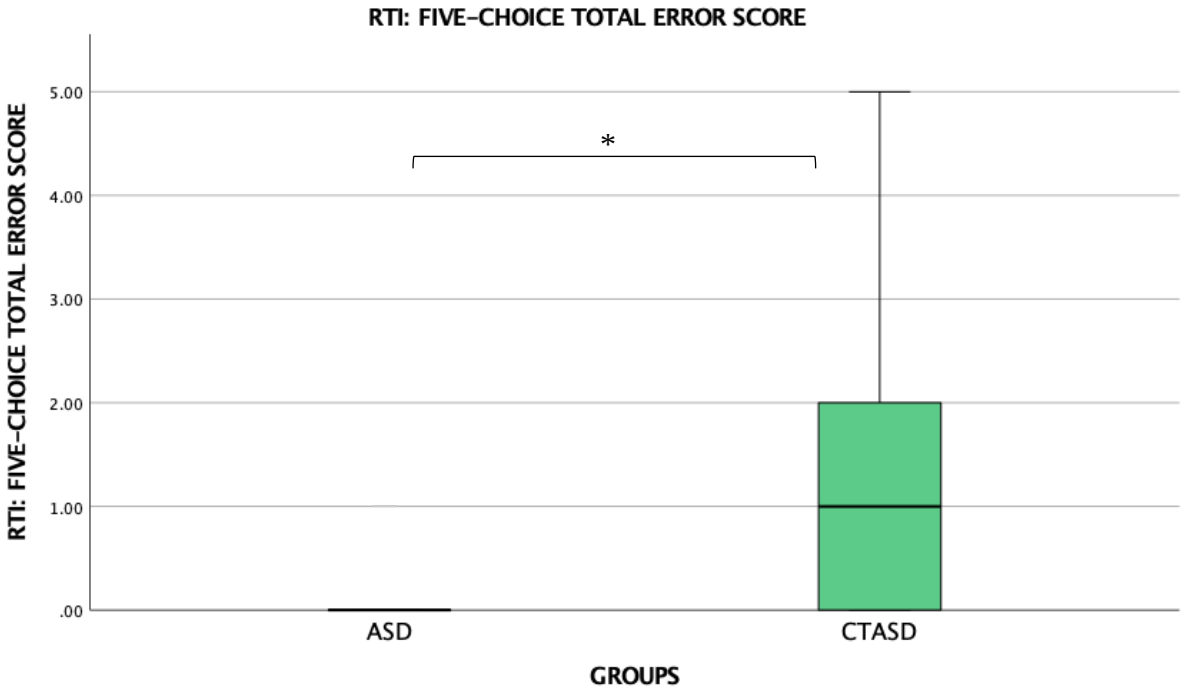
Note. ASD = Autism Spectrum Disorder Group
CTASD = Control Autism Spectrum Disorder Group
RTI = Reaction Time
* p < 0.05

We can also find a significant difference portrayed on Figure 3, where the total error score is measured and the ASD obtains a median value of 0 errors and the CTASD group a

median value of 1. The total error score refers to the total number of trials where the subject made any form of response error, meaning that the CTASD group made more errors than the ASD group.

Figure 3.

RTI Five-Choice Total Error Score compared in between ASD and CTASD groups



Note. ASD = Autism Spectrum Disorder Group
CTASD = Control Autism Spectrum Disorder Group
RTI = Reaction Time
* $p < 0.05$

The two remaining RTI variables, RTI Five-Choice Error Score (premature) and RTI Median Five-Choice Movement Time*, did not present significant differences between ASD and CTASD ($p > 0.05$), although results can be found in Appendix B, Table B.2.

Regarding the RVP Test, no significant differences were found for any variable ($p > 0.05$), namely RVP A prime*; RVP Median Response Latency*; RVP Probability of False Alarm*; RVP Total False Alarms and RVP Total Misses. Results can be found on Appendix B, Table B.3.

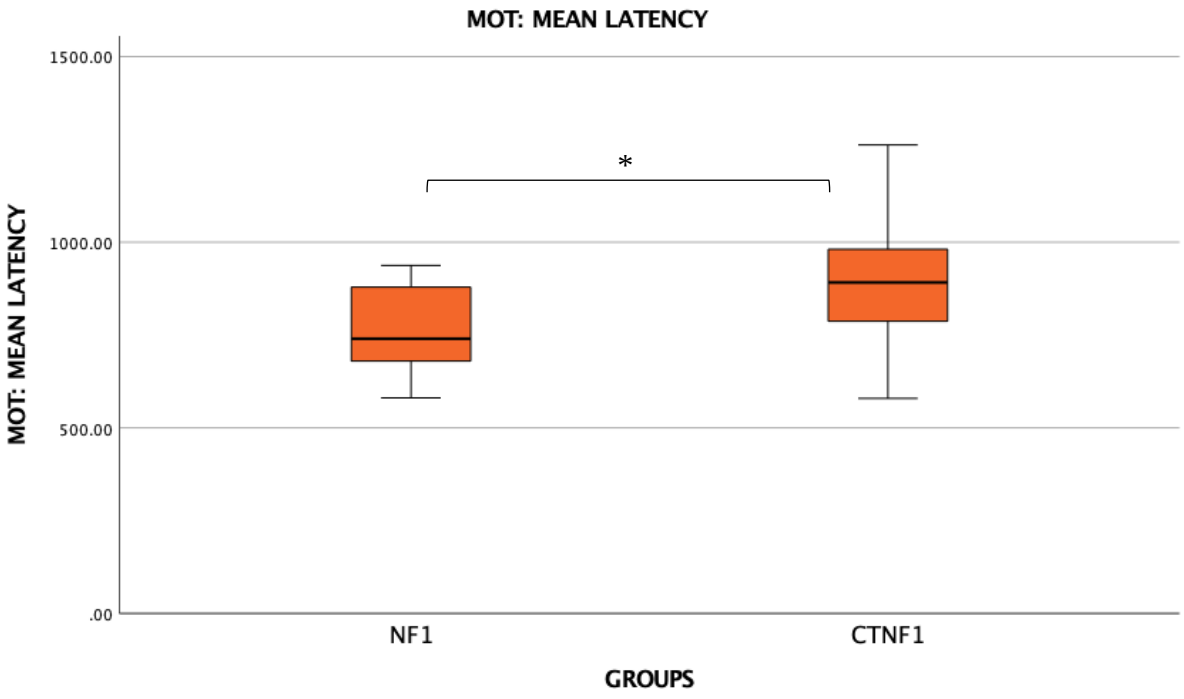
In relation to the SCWT and the TMT, no significant differences were found for either test, each giving a p value > 0.05. Results are presented in Appendix B, Tables B.4 and B.5, respectively.

NF1 vs. CTNF1 Comparison

Regarding the MOT test, a significant difference was found for the Mean Latency (NF1 *Mdn* = 740.20, CTNF1 *Mdn* = 815; *U* = 58.0, *z* = -2.051, *p* = 0.041), when comparing NF1 with the CTNF1 group (Figure 4) whereas the Total Correct measure (NF1 *Mdn* = 10, CTNF1 *Mdn* = 10; *U* = 105.0, *z* = 0.000, *p* = 1.000), did not significantly differ between groups. ($p > 0.05$). As it is possible to observe, on Figure 4, the NF1 group obtained a mean latency value of 740.20 milliseconds, whereas the CTNF1 group obtained a value of 815 milliseconds. The mean latency refers to the time taken from the display of a stimulus to a correct response to that stimulus during the assessment trials, which means that the control group (CTNF1) took longer to answer in comparison to the experimental group (NF1). Despite this difference, it is possible to observe that both NF1 and CTNF1 groups performed correctly in all the test trials, suggesting adequate task comprehension and motor skills to interact with CANTAB demands.

Figure 4.

MOT Mean Latency compared in between NF1 and CTNF1 groups



Note. NF1 = Neurofibromatosis Type 1
CTNF1= Control Group Neurofibromatosis Type 1
MOT = Motor Screening Task
* p < 0.05

Regarding the MTT Test, there were no statistically significant differences on any variable, namely: MTT Median Incongruency cost*;* MTT Median Reaction Latency; MTT

Multitasking block errors; MTT Multitasking cost*; MTT Commission Errors; MTT Total incorrect* and MTT Omission errors. Nevertheless, results can be found on Appendix C, Table C.1.

In the RTI Test, likewise to the MTT Test, there were no differences found on any variable, namely: RTI Five-Choice Error Score (premature); RTI Median Five-Choice Movement Time*; RTI Median Five-Choice Reaction Time* and RTI Total Error Score (Five-Choice). However, results for these variables are presented on Appendix C, Table C.2.

Lastly for the RVP Test, the same situation happened. No differences were found for any variable at test, specifically: RVP A prime*; RVP Median Response Latency*; RVP Probability of False Alarm*; RVP Total False Alarms and RVP Total Misses. Even so, results can be found on Appendix C, Table C.3.

Regarding the SCWT and the TMT, no significant results were found for either test, each giving a p value > 0.05. Anyhow, results are presented in Appendix C, Tables C.4 and C.5, respectively.

ASD vs. NF1 Comparison

We decided to perform a direct comparison between the clinical groups as an exploratory approach. It takes caution to discuss these results since, as referred above, these groups were not matched for age and gender.

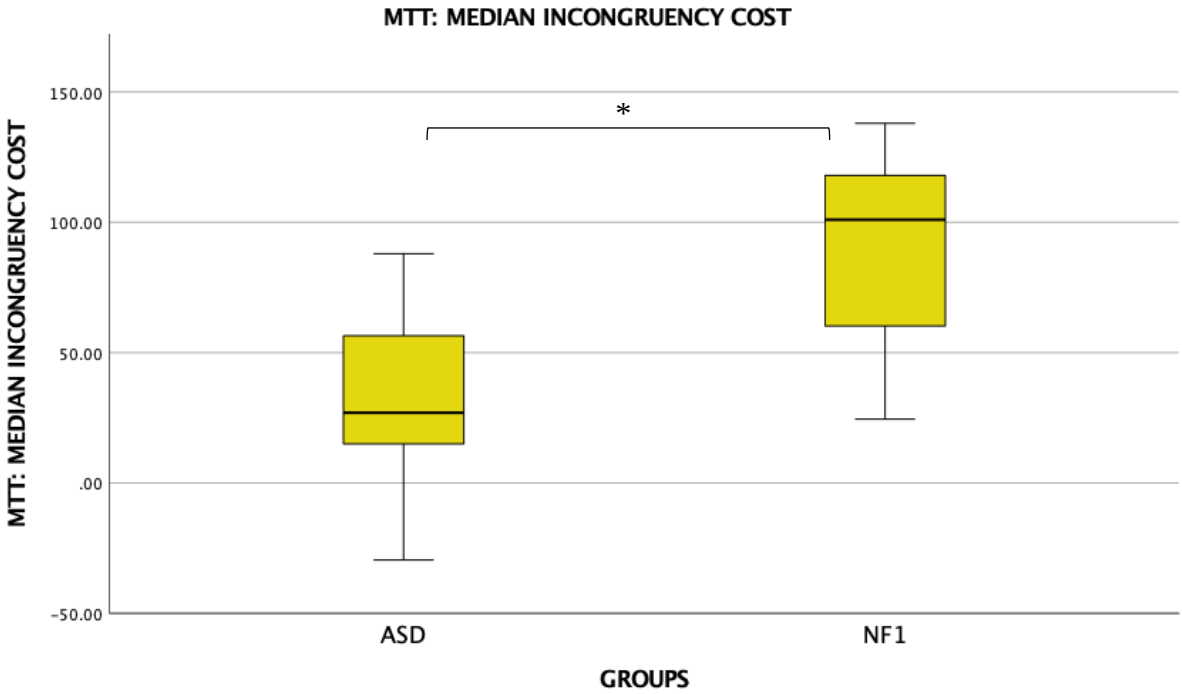
In the MOT screening test, ASD participants did not significantly differ from the NF1 participants for both MOT Mean Latency (ASD *Mdn* = 765.60, ASD *Mdn* = 740.20; U = 126.0, z = -0.057, p = 0.970) and MOT Total Correct Measures (ASD *Mdn* = 10, NF1 *Mdn* = 10; U = 120.0, z = 0.939, p = 1.000), being matched for the motor and comprehension abilities.

On the MTT Test, by comparing these two groups, we found significant differences on the variables: MTT Median Incongruency cost* (ASD *Mdn* = 27, NF1 *Mdn* = 101; U = 43.5, z = -3.172, p = 0.001), represented on Figure 5 and on MTT Multitasking cost* (ASD *Mdn* = 147, NF1 *Mdn* = 227; U = 75.0, z = -1.983, p = 0.049), represented on Figure 6.

On Figure 5, it is possible to observe significant differences on the median incongruency cost, where the NF1 group obtained a value of 101 milliseconds and the ASD group a value of 27 milliseconds. A higher incongruency cost indicates that the subjects take longer to process conflicting information, which means that the NF1 group takes significantly more time (measured in milliseconds) than the ASD group to process information that is not consistent.

Figure 5.

MTT Median Incongruency Cost compared in between ASD and NF1 groups

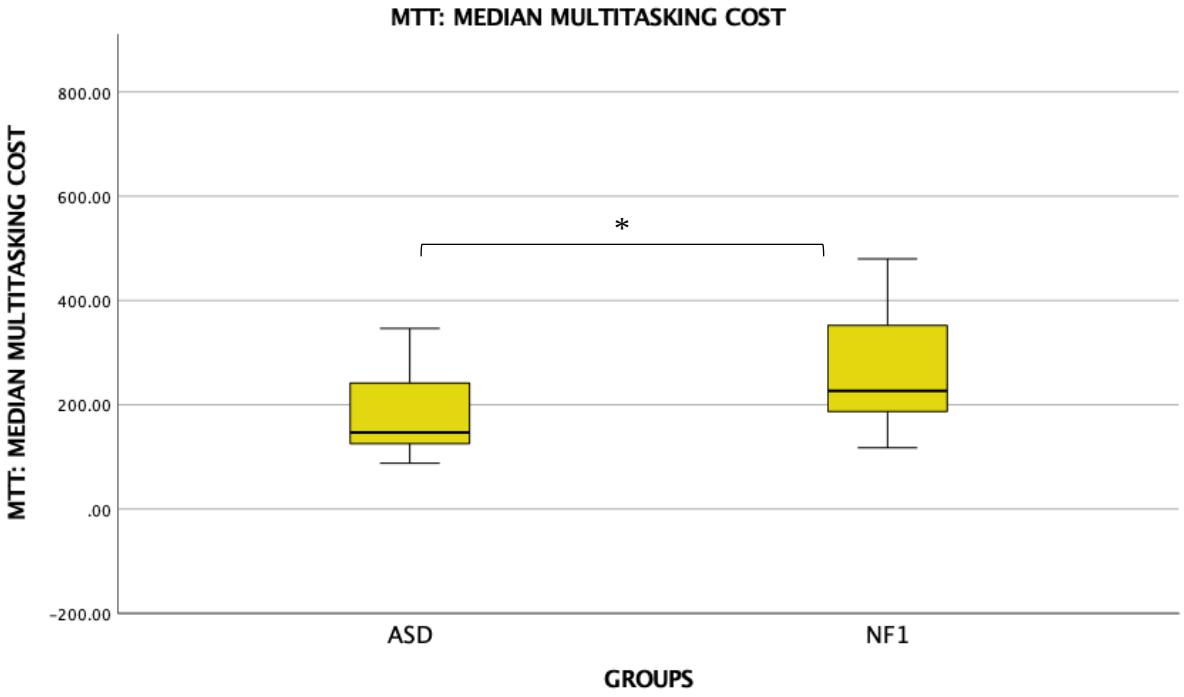


Note. ASD = Autism Spectrum Disorder Group
NF1= Neurofibromatosis Type 1
MTT = Multi-Tasking Test
* $p < 0.05$

It is also possible to observe on Figure 6 significant differences on the median multitasking cost, where the NF1 group obtained a value of 227 milliseconds and the ASD group a value of 147 milliseconds. A positive score on this measure indicates that the participants respond slower during multitasking blocks, and indicates a higher cost of managing multiple sources of information. Both groups obtained a positive score, although the NF1 achieves a higher score than the ASD group, translating in an increased difficulty to manage multiple sources of information at the same time

Figure 6.

MTT Median Multitasking Cost compared in between ASD and NF1 groups



Note. ASD = Autism Spectrum Disorder Group
NF1= Neurofibromatosis Type 1
MTT = Multi-Tasking Test
* p < 0.05

The remaining of the MTT variables, namely: MTT Median Reaction Latency; MTT Multitasking block errors; MTT Commission Errors and MTT Total incorrect*, did not present significant results ($p > 0.05$). Nonetheless, results for these variables can be found on Appendix D, Table D.1.

Concerning the RTI Test, no significant results were found for any of the variables ($p > 0.05$), namely: RTI Five-Choice Error Score (premature); RTI Median Five-Choice Movement Time*; RTI Median Five-Choice Reaction Time* and RTI Total Error Score (Five-Choice). Even so, results for these variables can be found on Appendix D, Table D.2.

As for the RVP Test, the same results were obtained ($p > 0.05$) for every variable in test, more specifically: RVP A prime*; RVP Median Response Latency*; RVP Probability of False Alarm*; RVP Total False Alarms and RVP Total Misses. Still, results for these variables can be found on Appendix D, Table D.3.

Lastly, for the SCWT and the TMT, no significant results were found for either test, each giving a p value > 0.05. Results are presented in Appendix D, Tables D.4 and D.5, respectively.

GENERAL DISCUSSION

Discussion

The overarching purpose of the present study was to explore EFs in disorders with inhibitory control alterations, such as ASD and NF1, by evaluating our samples with a comprehensive battery of neuropsychological tests: SCWT, TMT and four sub-tests of the CANTAB, to obtain a well-found conclusion. We hypothesized that both ASD and NF1 groups would exhibit deficits in selected neuropsychological measures, although we expected a disease-related pattern of performance. Indeed, we found differential patterns of response from both ASD and NF1 groups, with ASD participants exhibiting slower approaches to the tasks execution and NF1 participants performing similarly to the control group in all tasks administered.

Based on the results obtained when comparing the ASD and the CTASD groups, as we referred in the results section, we will not be discussing the screening task (MOT) as we did not expect significant differences between groups. This task served the main purpose of demonstrating that both groups had good motor capacities to interact with the tablet and that they were able to understand the instructions by fully completing the task with no errors.

Differently, on the MTT we observed that the ASD group takes longer to acknowledge the stimulus appearance until the actual button press in comparison with its control group, meaning they take more time to react to the stimulus. However, they do not make more errors in comparison to their control group. Therefore, for ASD participants to achieve a "perfect" performance, they spend more time accomplishing the task. In this case, it is possible to make the connection to the fact that one of the characteristics of the autistic population is to have interest in following rules and restricted routines. Thus, in the context of performing a task, from the moment they understand the instructions, they follow the rules to the end with effort and dedication. The fact that we do not observe significant differences on the Incongruency and Multi-tasking costs means that although they take longer to complete the proposed task, they are capable of processing conflicting and multiple source information. As shown, they are capable of dealing with these interferences, making no errors, although they take longer to respond. This also stands against the idea of an impulsive response style in this clinical group.

As for the RTI what we observe is that, once again, ASD participants are slower at answering in comparison to their control group. However, this time, comparatively, they make less mistakes, which leads us to believe, once again, that for them to have an intact performance they take more time to react to the stimulus. Complementarily, premature answers are not

found, which in other words means they do not make errors by answering ahead of time, which demonstrates a good capacity of response inhibition. In a study conducted by Sinzig et al., 2008, they found that children with ASD without ADHD comorbid symptoms performed better than those diagnosed with ADHD only, suggesting that ADHD symptoms weaken the capacity of response inhibition. This finding brings us a great point of discussion, leading us to believe that our ASD participants did not significantly differ from their control groups in response inhibition because none of them presented a formal diagnosis of ADHD and on the contrary, presented a relatively high IQ.

Regarding the RVP, what we observe once more, is that there are no significant differences between groups. As aforementioned, RVP measures sustained attention, which translates in the ASD participants being able to maintain sustained attention as well as their control group. In accordance to these findings, a recent study exploring sustained attention and working memory abilities in ASD found a highly variable attention profile in ASD (Alloway & Lepere, 2019). However, these authors concluded that the attention difficulties in these patients are not due to a primary deficit in sustained attention, being instead better explained by motivational factors. The same pattern was previously found in a study demonstrating that ASD children were not impaired in most conditions of the Continuous Performance Test. The authors concluded that the difficulties found in ASD children were result of developmental delays and of motivational contingencies of the administered tasks (Garretson et al., 1990). Additionally, the fact that our ASD participants do not have comorbid ADHD symptoms may help to explain the lack of differences between groups found in our study.

As a result of the substantial overlap in EFs between ADHD and ASD, along with concomitant symptoms of inattention and hyperactivity, the research concludes that investigations relating to ASD should consider symptoms of ADHD (Sinzig et al., 2008). Additionally, in a study conducted by Corbett et al., 2009, results have shown that across a wide range of tasks that evaluate EFs, children with ASD showed an extensive impairment in comparison with the typical group specifically in tasks that involved response inhibition, working memory, flexibility/shifting and vigilance. Importantly, in this study, authors did not exclude ADHD symptoms from the ASD participants, but did exclude autism symptoms from the ADHD group and ADHD and ASD symptoms from the typical development group, leading to the conclusion that the bulk of the ASD participants could have comorbid ADHD symptoms as well, which will, as expected, lead to a significant impairment on response inhibition. Over and above that, in a study conducted by Goldberg et al., 2005, results demonstrated that there were no differences between groups in response inhibition. This study included a sample of

ADHD, HFA (excluding ADHD symptoms) and typical development participants to posteriorly compare them between groups. Interestingly, neither the ADHD participants nor the HFA participants differed significantly in response inhibition from their control groups. However, despite this study having a similar sample to our study, authors only used the SCWT to evaluate response inhibition, which leaded the authors to consider the construct validity of the SCWT when applied to ADHD. Interestingly, in our study we found the same pattern of spared performance in the ASD group when tested with the SCWT.

On the other hand, on the NF1 and CTNF1 comparison, significant results were not found in any variable measured except for the screening task (MOT) mean latency, where the NF1 group took less time to recognize the display of a stimulus to a correct response to that stimulus during assessment trials. This may indicate a more impulsive style of response, which is in agreement with the disease profile, however, this had no negative influence on performance because the groups did not differ in errors. The fact that the NF1 group answers faster is not affecting their performance on the proposed task.

On the other tasks, the fact that we are not able to observe significant differences can make us think of two possible reasons. The first being that these measures may not be sensitive enough to assess more subtle deficits, in other words, deficits that are not so severe may not be noticeable by these tests. Even though it is a computerized measure that intends to be more sensitive and captures deficits more easily than a more classical approach, this may depend on the more ecological nature of the tasks, that is, tasks that better resemble the everyday tasks that people encounter on a daily basis. Here, we may question if these specific tasks performed on a computer are inserted into a normal everyday context. Taking into consideration the aforementioned aspects, these measures may not rate exactly the difficulties of executive functioning experienced on a daily basis, namely decision-making, planning, etc. (Table 3). We can also draw on the fact that we have a sample in NF1 that has no intellectual deficits, with an average IQ of 102, leading us to believe that executive function deficits may be slightly masked by this higher cognitive ability and also possibly there may be some more subtle difficulties that these tests are not able to capture. This aspect may be linked to the limitations of our study, which is having very homogeneous samples that do not capture the diversity of the spectrum and the diversity of NF1 as well.

Thus, derived from the results we obtained, what we are able to conclude is that there are no significant differences in the way the NF1 group performs the CANTAB tests in comparison with its control group, which leads us to believe that there are no impairments, or at least significant impairments, in the EFs of our participants diagnosed with NF1. On the other

hand, a study conducted by Beaussart-Corbat et al., 2021, in a sample of 33 children diagnosed with NF1 aged 3 to 5 years old, used the Hand Game to evaluate motor response inhibition. Results showed that children with NF1 had a higher percentage of uncorrected errors than control children, indicating an early disruption on the evaluated task. Also, in a study conducted by Payne et al., 2012, where investigators used a sample of 49 children aged 7 to 15 to compare on measures of spatial working memory and response inhibition, results demonstrated that both NF1 groups (one with comorbid ADHD symptoms and one without) showed impaired response inhibition.

Although these results demonstrate opposite findings to our study, these cannot be generalizable to our target population. Our sample consisted of 15 participants aged between 26 and 55 years old diagnosed with NF1, whereas these two studies only focused on children under 15 years old. To our knowledge, and according to Miguel et al., 2015, there is a dearth of understanding about adults with NF1 due to the little number of studies that have been done on their cognition. We can hypothesize that with the development trajectory, discrepancies between individuals diagnosed with NF1 and healthy control children could disappear, especially when EF structures mature (Lee et al., 2013 cit in. Beaussart et al., 2018).

Furthermore, when we compared the ASD and NF1 groups, we found significant differences on two aspects of the MTT, Incongruency and Multi-tasking costs. Here we understood that the NF1 group has decreased performance when compared with the ASD group regarding both variables. This way, they show a greater difficulty in dealing with conflicting and multiple source information.

On the other hand, we need to acknowledge that we have not found differences in the number of errors made on the Total error score, neither on the Omission and Commission errors, which means that although the NF1 group does take more time in answering correctly, they are also able to maintain an intact performance, having a greater interference.

Our results may suggest that measures like reaction times or latencies may be more sensitive in detecting modest differences than the overall number of errors because the majority of the measures where we observed differences were connected to the response time. Additionally, the selected tasks do not have a high level of difficulty, making it such that there are no disparities in the level of errors. Instead, they wind up being more repetitious and monotonous because they are not very challenging. In some tasks, we got outcomes measures that were on the called ceiling effects, meaning that participants are able to complete all trials correctly, without making any mistakes, due to the level of difficulty of the task proposed. As a result, response time measures appear to be more sensitive to detect more subtle variations.

Regarding the SCWT and the TMT, significant differences were also not found between experimental groups and their respective control groups. In a study conducted by Goldberg et al., 2005, they hypothesized that a key executive function characteristic that sets ADHD apart from autism would be response inhibition. However, the outcomes demonstrated that neither HFA nor ADHD children substantially deviated from controls on the SCWT. Likewise, Losh et al., (2009) found no significant differences between ASD and control groups in the time required to complete the TMT. Once again, we may hypothesize that both these tests do not have enough sensitivity to measure subtle differences between groups.

Study Limitations

There are some limitations associated with the current study that should to be taken into consideration whilst overlooking the obtained results. Firstly, the outcome of convergent research showing that ADHD is highly prevalent in ASD and in NF1 including a variety of studies demonstrating they found differences on response inhibition when participants had comorbid ADHD symptoms, makes us believe that our results do not represent the entire autism spectrum.

Another limitation of our study was the fixed order of test administration which can lead us to believe that order effects may have played a part in the test and domain effects. Additionally, the experimental groups were evaluated in a more controlled environment (laboratory), whereas the control group were evaluated in different environments (participants' homes) in order to facilitate each participants' collaboration.

Additionally, when we discuss that the CANTAB battery might not be sensitive enough to measure more subtle differences, this can also be related to the fact that some people might touch the screen in a lighter manner and the touch screen, itself being a highly reliable instrument, does also have its disadvantages. In these circumstances, it is important to take into account, although we do not consider this factor determinate for the present results, especially because this aspect has only been studied in children (Luciana & Nelson, 2002), that the response latency data can be distorted and may not portray the reality.

Several articles mentioned above in the discussion section found alterations in the executive functions in studies involving children, but these findings are not comparable to our study because our population were constituted by young adults and adults. In fact, the comprehension of the current results turns out complex since there is limited evidence in adults.

The lack of differences found in the majority of the tests used may possible be explained by the maturation of the executive functions as described by Lee et al., 2013.

Finally, the traits of our ASD and NF1 groups (adults, high functioning autism, the lack of intellectual disabilities, no DSM-V comorbidity with ADHD, and above average IQ level) limit the generalization of these findings, due to a very high level of homogeneity in our sample.

FINAL CONSIDERATIONS

The current study explored EFs in two developmental disorders associated with inhibitory dysfunction (ASD and NF1) using a computerized approach (CANTB sub-tests) and more classical measures (TMT and Stroop). The main findings revealed increased latencies in ASD when compared to controls in tasks requiring cognitive flexibility and rapid reactions that do not impair the performance accuracy. Regarding the NF1 performance, we observed a similar pattern of response when compared to matched controls. When considering the more classical testing, the selected measures did not capture differences in our group comparisons. These findings seem to reveal different patterns of performance in ASD and NF1 and more spared abilities than those typically reported in studies involving children. Indeed, few studies have focused on the adult populations and, for this reason, the present study becomes relevant as it fills in a gap giving some insight on executive functioning in HFA and NF1 adults.

This study also points out the need to address the presence of ADHD symptoms in both ASD and NF1 as well as the motivational factors which play an important role in maintaining sustained attention. Another relevant aspect is associated with the ecological dimension of the selected measures. Future studies should investigate the EF in both ASD and NF1 using ecologically valid measures that attempt to replicate real-world scenarios that better resemble the everyday challenges.

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APPENDIXES

Appendix A

Sociodemographic Questionnaire

Date of assessment: _____ Code: _____

Date of birth: _____ Age: _____years

Sex: Female _____ Male _____

Nationality: _____

Level of Education: _____

Profession: _____

Medication intake: Yes _____ No _____

If yes, what type: _____
_____

Presence or diagnosis of neurological or neuropsychiatric disorder: Yes _____ No _____

If yes, what type: _____
_____

Health issues: Yes _____ No _____

If yes, what type: _____
_____

Observations: _____
_____
_____
_____

Contact (e-mail/phone number): _____

Appendix B – Non-significant results for the ASD and CTASD comparison

Table B.1.

Non-significant CANTAB – MTT results between ASD and CTASD groups

Task	Measure Name	*U* value	*z* value	*p* value	ASD Mdn	CTASD Mdn
MTT	Median Incongruency cost*	101.0	-1.499	0.138	27,00	56,00
MTT	Multitasking block errors	129.5	-0.522	0.612	3,00	4,00
MTT	Median Multitasking cost*	133.5	-0.379	0.715	147,00	161,50
MTT	Commission errors	136.0	-1.000	1.000	0,00	0,00
MTT	Total incorrect*	140.0	-0.157	0.884	4,00	4,00
MTT	Omission errors	111.5	-1.413	0.191	0,00	0,00

Note. MTT = Multi-Tasking Test, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, CTASD Mdn = Control Autism Spectrum Disorder Group Median

Table B.2.

Non-significant CANTAB – RTI results between ASD and CTASD groups

Task	Measure Name	*U* value	*z* value	*p* value	ASD Mdn	CTASD Mdn
RTI	Five-Choice Error Score (premature)	127.5	-1.435	0.485	0,00	0,00
RTI	Median Five-Choice Movement Time*	110.5	-1.171	0.249	263,00	209,00

Note. RTI = Reaction Time, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, CTASD Mdn = Control Autism Spectrum Disorder Group Median

Table B.3.

Non-significant CANTAB – RVP results between ASD and CTASD groups

Task	Measure Name	*U* value	*z* value	*p* value	ASD Mdn	CTASD Mdn
RVP	A prime*	133.5	-0.380	0.714	0,99	0,99
RVP	Median Response Latency*	128.0	-0.568	0.580	337,00	350,00
RVP	Probability of False Alarm*	113.5	-1.076	0.290	0,00	0,00
RVP	Total False Alarms	106.5	-1.327	0.190	2,00	3,00
RVP	Total Misses	125.0	-0.682	0.505	3,00	1,00

Note. RVP = Rapid Visual Information Processing, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, CTASD Mdn = Control Autism Spectrum Disorder Group Median

Table B.4.

Non-significant SCWT results between ASD and CTASD groups

Stroop Test	*t* value	*p* value	ASD		CTASD	
			Mean	Std. Error	Mean	Std. Error
Incongruent Score	0.325	0.747	6.81	2.64	5.78	1.77

Note. ASD = Autism Spectrum Disorder Group, CTASD = Control Autism Spectrum Disorder Group, Std. Error = Standard Error

Table B.5.

Non-significant TMT results between ASD and CTASD groups

	***U* value**	***z* value**	***p* value**	**ASD Mdn**	**CTASD Mdn**
Trail Part A Error	144.5	0.000	1.000	0,00	0,00
Trail Part A Seconds	129.5	-0.517	0.615	32,00	28,00
Trail Part B Error	138.0	-0.318	1.000	0,00	0,00
Trail Part B Seconds	138.0	-0.224	0.832	57,00	63,00

Note. ASD Mdn = Autism Spectrum Disorder Group Median, CTASD Mdn = Control Autism Spectrum Disorder Group Median

Appendix C – Non-significant results for the NF1 vs. CTNF1 comparison

Table C.1.

Non-significant CANTAB – MTT results between NF1 and CTNF1 groups

Task	Measure Name	*U* value	*z* value	*p* value	NF1 Mdn	CTNF1 Mdn
MTT	Median Incongruency cost*	84.5	-0.895	0.382	101,00	70,75
MTT	Median Reaction latency*	64.0	-1.790	0.075	720,50	651,75
MTT	Multitasking block errors	103.5	-0.066	0.956	2,00	2,50
MTT	Median Multitasking cost*	96.0	-0.393	0.715	227,00	270,00
MTT	Commission errors	105.0	0.000	1.000	0,00	0,00
MTT	Total incorrect*	99.0	-0.265	0.803	3,00	3,00
MTT	Omission errors	95.5	-0.446	0.652	0,00	1,00

Note. MTT = Multi-Tasking Test, *Key measures considered by CANTAB, NF1 Mdn = Neurofibromatosis Type 1 Group Median, CTNF1 Mdn = Control Neurofibromatosis Type 1 Group Median

Table C.2.

Non-significant CANTAB – RTI results between NF1 and CTNF1 groups

Task	Measure Name	*U* value	*z* value	*p* value	NF1 Mdn	CTNF1 Mdn
RTI	Five-Choice Error Score (premature)	97.0	-0.662	0.598	0,00	0,00
RTI	Median Five-Choice Movement Time*	95.0	-0.437	0.675	253,00	244,50
RTI	Median Five-Choice Reaction Time*	65.5	-1.724	0.087	437,50	393,50
RTI	Five-Choice Total Error Score	103.0	-0.111	0.936	0,00	0,00

Note. RTI = Reaction Time, *Key measures considered by CANTAB, NF1 Mdn = Neurofibromatosis Type 1 Group Median, CTNF1 Mdn = Control Neurofibromatosis Type 1 Group Median

Table C.3.

Non-significant CANTAB – RVP results between NF1 and CTNF1 groups

Task	Measure Name	*U* value	*z* value	*p* value	NF1 Mdn	CTNF1 Mdn
RVP	A prime*	98.0	-0.306	0.772	0,99	0,99
RVP	Median Response Latency*	73.0	-1.397	0.168	364,00	374,50
RVP	Probability of False Alarm*	102.5	-0.110	0.921	0,00	0,00
RVP	Total False	103.0	-0.089	0.938	2,00	2,50

	Alarms					
RVP	Total Misses	98.0	-0.311	0.768	2,00	2,50

Note. RVP = Rapid Visual Information Processing, *Key measures considered by CANTAB, NF1 Mdn = Neurofibromatosis Type 1 Group Median, CTNF1 Mdn = Control Neurofibromatosis Type 1 Group Median

Table C.4.

Non-significant SCWT results between NF1 and CTNF1 groups

Stroop Test	***t* value**	***p* value**	**NF1**		**CTNF1**	
			Mean	**Std. Error**	**Mean**	**Std. Error**
Incongruent Score	0.944	0.354	5.13	3.13	1.67	2.00

Note. NF1 = Neurofibromatosis Type 1 Group, CTNF1 = Control Neurofibromatosis Type 1 Group, Std. Error = Standard Error

Table C.5.

Non-significant TMT results between NF1 and CTNF1 groups

	***U* value**	***z* value**	***p* value**	**NF1 Mdn**	**CTNF1 Mdn**
Trail Part A Error	84.0	-1.736	0.224	0,00	0,00
Trail Part A Seconds	83.5	-0.941	0.358	32,00	29,5
Trail Part B Error	83.0	-1.285	0.292	0,00	0,00
Trail Part B Seconds	69.5	-1.550	0.125	66,00	58,5

Note. NF1 Mdn = Neurofibromatosis Type 1 Group Median, CTNF1 Mdn = Neurofibromatosis Type 1 Group Median

Appendix D – Non-significant results for the ASD vs. NF1 comparison

Table D.1.

Non-significant CANTAB – MTT results between ASD and NF1 groups

Task	Measure Name	*U* value	*z* value	*p* value	ASD Mdn	NF1 Mdn
MTT	Median Reaction latency*	124.0	-0.132	0.904	761,08	720,50
MTT	Multitasking block errors	119.5	-0.305	0.772	3,00	2,00
MTT	Commission errors	127.5	0.000	1.000	0,00	0,00
MTT	Total incorrect*	111.0	-0.626	0.542	4,00	3,00
MTT	Omission errors	93.0	-1.590	0.119	0,00	0,00

Note. MTT = Multi-Tasking Test, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, NF1 Mdn = Neurofibromatosis Type 1 Group Median

Table D.2.

Non-significant CANTAB – RTI results between ASD and NF1 groups

Task	Measure Name	*U* value	*z* value	*p* value	ASD Mdn	NF1 Mdn
RTI	Five-Choice Error Score (premature)	119.0	-1.065	0.469	0,00	0,00
RTI	Median Five-Choice Movement Time*	122.5	-0.189	0.860	263,00	253,00

RTI	Median Five-Choice Reaction Time*	116.0	-0.434	0.675	410,00	437,00
RTI	Five-Choice Total Error Score	100.0	-1.644	0.115	0,00	0,00

Note. RTI = Reaction Time, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, NF1 Mdn = Neurofibromatosis Type 1 Group Median

Table D.3.

Non-significant CANTAB – RVP results between ASD and NF1 groups

Task	**Measure Name**	***U* value**	***z* value**	***p* value**	**ASD Mdn**	**NF1 Mdn**
RVP	A prime*	126.0	-0.057	0.963	0,99	0,99
RVP	Median Response Latency*	95.0	-1.228	0.227	337,00	364,00
RVP	Probability of False Alarm*	123.0	-0.171	0.873	0,00	0,00
RVP	Total False Alarms	120.0	-0.288	0.784	2,00	2,00
RVP	Total Misses	127.0	-0.019	0.993	3,00	2,00

Note. RVP = Rapid Visual Information Processing, *Key measures considered by CANTAB, ASD Mdn = Autism Spectrum Disorder Group Median, NF1 Mdn = Neurofibromatosis Type 1 Group Median

Table D.4.

Non-significant SCWT results between ASD and NF1 groups

Stroop Test	*t* value	*p* value	ASD		NF1	
			Mean	Std. Error	Mean	Std. Error
Incongruent Score	0.412	0.684	6.81	2.64	5.13	3.13

Note. ASD = Autism Spectrum Disorder Group, NF1 = Neurofibromatosis Type 1 Group, Std. Error = Standard Error

Table D.5.

Non-significant TMT results between ASD and NF1 groups

	U value	*z* value	*p* value	ASD Mdn	NF1 Mdn
Trail Part A Error	117.0	-0.630	0.645	0,00	0,00
Trail Part A Seconds	117.5	-0.378	0.716	32,00	32,00
Trail Part B Error	111.0	-0.792	0.498	0,00	0,00
Trail Part B Seconds	91.0	-1.379	0.173	57,00	66,0

Note. ASD Mdn = Autism Spectrum Disorder Group Median, NF1 Mdn = Neurofibromatosis Type 1 Group Median