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TESTING VISUO-SPATIAL MEMORY AND EXECUTIVE FUNCTION DURING NAVIGATION IN CHILDREN WITH ADHD:

THE VIRTUAL CITY™

Settore Scientifico Disciplinare MED/39

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Introduction

1.1 Attention Deficit Hyperactivity Disorder

1.1.1 Clinical presentation and aetiopathogenesis

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with persistent inattention and/or hyperactivity/impulsivity, present for more than six months in at least two life contexts, associated with significant social and academic impairment and with onset before 12 years of age (American Psychiatric Association, 2013). Inattention can be expressed as poor focused and sustained attention skills, easy distractibility and disorganization, determining avoidance of activities requiring a prolonged mental effort. It is important to highlight that inattention is present in different contexts, not only at school or during schoolwork but also in sports, games, and daily activities. Hyperactivity is instead characterized by an excessive motor activity, together with an internal feeling of tension and instability. Impulsivity, often associated with hyperactivity, can be defined as the difficulty of inhibiting the automatic motor or cognitive response to a target stimulus, derived from the need for immediate gratification. According to the Diagnostic and Statistical Manual of Mental Disorders – Fifth edition (DSM-5; American Psychiatric Association, 2013) there are three ADHD presentations depending on the prevalent symptoms: predominantly inattentive, predominantly hyperactive/impulsive, and combined.

ADHD is one of the most prevalent childhood disorders, with problems often persisting into adolescence and adulthood (Faraone et al., 2021). In its frequent chronic course, ADHD is associated with significant impairment in multiple areas, including academic achievements, employment and interpersonal relationships, increasing also the risk of problematic substance abuse and psychiatric disorders in comorbidities (Cuffe et al., 2020; Diamantopoulou et al., 2007; Klein et al., 2012). Whereas some patients with ADHD show a seemingly partial or full remittance of symptoms by adolescence or early adulthood, many continue to present impairing cognitive symptoms (Biederman et al., 2011; Sibley et al., 2012) and it is as yet unclear how cognitive impairments relate to changes in symptom expression with age (Biederman, et al. 2000; Larsson et al. 2011). Regarding epidemiology, the prevalence of ADHD in children and adolescents has varied according to differences in methodological approaches (as ascertainment, case definition and study design). The meta-analytic analysis including the largest number of studies (Polanczyk et al., 2007) indicated a pooled prevalence rate of 5,29%. Data on sex differences has consistently reported a male preponderance with a ratio of M: F of 4:1 in clinical samples (Faraone et al., 2015). The literature on sex differences according to ADHD presentation is still inconclusive, however, females in general show fewer symptoms of hyperactivity/impulsivity while gender differences may be less pronounced for the prevalently inattentive presentation (Arnett et al., 2015).

The multifaceted nature of ADHD is expressed by the heterogeneity of its clinical presentations. One of the aspects of this heterogeneity of ADHD is the comorbidity with other psychiatric disorders, which contribute to the functional impairment of the patient, such as oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders, sleep disorders (Biederman et al. 2005; Pliszka et al., 2006; Reale et al., 2017). Furthemore, ADHD is frequently associated with other neurodevelopmental disorders, particularly Autism Spectrum Disorder (ASD) (Antshel and Russo, 2019) but also Intellectual Disability (McClain et al., 2017). ADHD and Specific Learning Disorder (SLD) are also commonly co-occurring with an estimated 45% of children with ADHD meeting criteria for an SLD (DuPaul et al., 2013).

On the cognitive level, neuropsychological difficulties and/or impairments which have been frequently documented are within the realm of executive functions although there is no unanimous consensus on the neuropsychological signature of ADHD. Even in the presence of average intelligence, cognitive functioning in ADHD is highly heterogeneous, with some patients exhibiting no neuropsychological deficits, and others, only in some cognitive domains.

Finally, the co-occurrence of emotional dysregulation in at least 40% of the patients has meaningful implications not only in clinical expression, but also in comorbidities (both psychiatric and non-psychiatric), and in response to treatments (Masi et al., 2020). As for the pathogenesis, ADHD is considered as a multifactorial disorder, with both genetic, neurophysiologic and environmental factors, their interactions leading to the disorder. The study of the neurobiology underpinning ADHD, on the structural level, has identified a disruption of fronto-striatal volumes and white matter tracts as a possible pathway to the disorder, which hold, however still dubious clinical utility (Konrad et al., 2018). On the level of functional brain imaging, there is ample convergence of data of a reduced activation in inferior fronto-striatal regions in children and adolescents (Hart et al., 2012). However, beyond the lateral prefrontal cortex and the basal ganglia, also more wide-ranging dysfunctions involve the cingulate, orbitofrontal regions and networks involving frontal regions and their connections to the parietal cortex, the limbic system and the cerebellum (Rubia, 2018, Rubia et al., 2014). Structural MRI evidence based on multi-center data (ENIGMA-ADHD study- 2.246 patients with ADHD both children and adults) has recently revealed lower surface area values in frontal, cingulate and temporal regions as well as reduced thickness of the fusiform gyrus and temporal pole only in children with ADHD (Hoogmann et al., 2019). In summary, ADHD is highly heterogeneous at the clinical, genetic, brain, cognitive and environmental levels, mediated by complex causal pathways. The understanding of the different pathophysiological mechanisms and their interrelations is unfortunately not yet complete.

1.1.2. Models of cognitive functioning in ADHD

The heterogeneity of cognitive functioning in ADHD is probably due to different pathophysiological pathways underpinning the disorder (Sonuga-Barke et al., 2010).

Two models of the relationships between cognitive and ADHD symptoms have been proposed. The first, the *trait liability hypothesis*, posits that neurocognitive impairments are directly related to the aetiology of the disorder, are markers for ADHD regardless of disease status, and persist over time independent of changes in symptoms (Barkley, 1997; Castellanos & Tannock, 2002). Alternatively, a *cognitive maturation hypothesis* suggests that improvement in neuropsychological functioning (namely, executive functioning) during middle childhood and adolescence contributes to ADHD symptom improvements observed during this same time period for some children (Doehnert et al., 2010; El-Sayed et al., 2003).

Cognitive impairments are potential endophenotypes, that is, relatively objective features, part of disease liability or mechanisms of symptom change, which can potentially clarify how neurodevelopmental disorders progress and might be better prevented or treated. Yet resolving their role has been difficult, in part because of the unclear association with developmental changes. The abundant literature on the cognitive/neuropsychological endophenotypes of ADHD have led to a series of single deficit models the most prominent being Barkley's (1997). It was the first to put forward executive dysfunction, in terms of inhibitory control as the core neuropsychological impairment. According to the model's predictions, the inability to withhold or delay a response interfered with optimal performance on other four executive functions defined as working memory, internalization of speech, emotional and motor self-regulation, motivation and arousal reconstitution.

Throughout the decades, other data derived from group level comparison of children with ADHD and typically developing peers has revealed deficits in a variety of executive functions thus reducing the primacy of inhibitory control and issues have been raised as to the centrality of executive functions to the pathophysiology of ADHD, especially regarding their role in explaining symptom expression changes over time. Children with ADHD have been found to display deficits in both executive and non-executive task (memory, visuo-perceptual tasks) and no single executive deficit characterized all children with ADHD with a minority of children displaying no executive function deficits (Rhodes et al., 2005; Niggs et al., 2005). These data led to a conceptualization of ADHD with neuropsychologically defined subtypes that can predict disorder course, comorbidity patterns and treatment outcomes, with multiple pathways leading to ADHD. Sonuga-Barke and collegues' dual pathway model, suggested that executive dysfunction (especially inhibitory control) or a shortened delay gradient (delay of gratification) may be two possible pathways for ADHD manifestation (Sonuga-Barke et al., 2003). The dual pathway model was further expanded to include a third pathway (Castellanos and Tannock, 2003) that included executive dysfunctions (working memory), shortened delayed gradient as well as temporal processing deficits. Multiple pathway models have conceptualized ADHD as heterogeneous in terms of neuropsychological functioning with however consistent and large effect sizes for working memory, delay aversion and moderate effects for impulsivity, decision making and timing (Coghill et al., 2014). Consistent are also the findings that a portion of children (up to 25%) show no deficits on any neuropsychological domains, a minority show deficits in any one of the domains (from 18-36%) and no individual child is impaired across all domains. At the level of model predictions, it may be the case that a neuropsychological pathway to ADHD behaviors may not be the only path and that and integrated theory of ADHD pathophysiology should be envisaged. Models of neuropsychological functioning should also make predictions on symptom emergence and symptom changes over time and fit with corroborated and consistent neurobiological findings.

1.1.3 Neuropsychological functioning in ADHD

Before analyzing the available recent literature on the neuropsychological functioning in ADHD, the profiles at the Wechsler scales will be briefly outlined. Intellectual functioning is generally preserved in such a neurodevelopmental disorder, although the cognitive profile as assessed by multi-componential standardized tests is uneven (Mayes et al. 2012, Styck et al. 2017). At the WISC- IV, the Wechsler Intelligence Scale for children, fourth edition (Wechsler, 2003) children with ADHD consistently show lower scores on the Processing Speed Index (PSI) and Working Memory Index (WMI) than the Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI), a pattern observed also on previous versions of the WISC (Mayes et al., 2006; Naglieri et al., 2003). The ADHD inattentive presentation is specifically associated with slowed processing speed expressed by lower scores on the PSI with respect to the combined type (Thaler et al., 2013). When ADHD is comorbid with SLD, the WMI is significantly lower than in ADHD with no SLD comorbidity (Parke et al., 2020).

Children and adolescents with ADHD present with deficits in higher-level cognitive functions, the so-called executive functions (EFs). Among the ‘‘cool’’ EFs, motor response inhibition, working memory (WM), sustained attention, response variability and cognitive switching are prevalently involved (Pievsky & McGrath, 2018). There is a vast literature on the neurobiological underpinnings of EF deficits in ADHD which suggests that this disorder is associated with a delay in functional brain maturation. This is supported by indirect evidence that the reduced regional activations in ADHD patients, relative to their age-matched peers, during inhibition (Hart et al., 2012; McCarthy et al., 2014; Norman et al., 2016), attention (Hart et al., 2013), working memory (McCarthy et al., 2014) and timing tasks (Hart et al., 2012) are in brain regions that have shown to increase in activation progressively between childhood and adulthood. Among the brain regions are the inferior frontal cortex, basal ganglia, anterior cingulate cortex and supplementary motor area for motor response inhibition, dorsolateral prefrontal cortex, parietal lobe and basal ganglia for sustained attention, dorsolateral prefrontal cortex for working memory and left inferior frontal cortex for timing (for review see: Rubia, 2013). This evidence suggests that the activation pattern in ADHD patients is analogous to that of younger relative to older children. A delay in brain function maturation would parallel evidence for a maturational delay in brain structure (Shaw et al., 2007, 2013) and in functional connectivity (Sripada et al., 2014). Meta-analyses of structural volumetric studies in ADHD have shown deficits most prominently in subcortical regions such as the basal ganglia and insula (Nakao et al., 2011; Norman et al., 2016). The largest recent meta- and mega-analysis of subcortical structural imaging studies across 23 sites including more than 1713 ADHD patients and over 1500 controls, found additional volume reductions besides the basal ganglia in limbic areas such as amygdala and hippocampus (Hoogman et al., 2017). Abnormalities in ventromedial frontal regions, however, have also been observed in large-numbered meta-analyses (Norman et al., 2016) and there is evidence for a delay in cortical thickness maturation in frontal, temporal and parietal regions (Shaw et al., 2007, 2012). In addition to the grey matter structural alterations, abnormalities of white matter tracts have also been found, most prominently fronto-striato-cerebellar as well as fronto-posterior and interhemispheric tracts (Chen et al., 2016).

Among deficits in the several cognitive areas previously mentioned, impairment/weaknesses in working memory have received much attention. Working memory (WM) is the function of actively holding in mind and manipulating information relevant to a goal. The active maintenance of visual information serves the needs of ongoing tasks, which includes not only the part responsible for information maintenance, but also the central executive system related to the active control process, which is closely related to the attention process (Aben et al., 2012; Luck and Vogel, 2013; Kofler et al., 2010). Clinical studies report that working memory impairment in ADHD patients may be mainly manifested as a deficit of attention-related processes (Chacko et al., 2013; Gibson et al., 2011; Lenartowicz et al., 2014). It is estimated that 81% of children with ADHD have a deficit in the *working* component (central executive) of WM (Rapport et al., 2013), in contrast to the less impaired *memory* component (phonological and visuospatial storage/rehearsal).

The neurobiological underpinnings of the spatial working memory deficit in ADHD are not yet fully understood, with studies reporting inconsistent results (Lenartowicz et al., 2014, 2016; Liu et al., 2016). These inconsistencies may be attributed to the multidimensional nature of working memory (consisting of encoding, and storage and retrieval processes) and the clinical heterogeneity of ADHD (Pincham, 2014).

Visual-spatial working memory maintenance (VWM), which processes spatial information, involves the ability to actively maintain visual information in the focus of attention (Baddeley, 1996; Engle, 2002; Kane et al., 2007; Unsworth & Engle, 2007). Studies on clinical and non-clinical ADHD samples have reported a deficit in VWM, (Dowson et al., 2004; Kim et al., 2014; Mattfeld et al., 2015; Bollmann et al., 2017) when measured with standardized neuropsychological measures delivered in the reaching space, such as the Corsi Block Tapping test. It has been suggested that visual-spatial working memory impairment may be a leading candidate endophenotype for ADHD. Better scores on VWM tasks have been associated with more efficient top-down control mediated by the dorsal lateral prefrontal cortex (Arnsten, 2009; Arnsten & Rubia, 2012). Furthermore, development of VWM was related to improvement in symptoms of inattention across early and middle childhood as confirmed in both parent and teacher reports (Karalunas et al., 2017). Determination of the importance of VWM in ADHD from cross sectional data must be qualified by careful consideration of children's age and supported by repeated assessment over time to evaluate change in cognitive effects with development (Karalunas et al., 2017). Cross-sectional meta-analytic findings indicate that ADHD effect sizes on working memory tasks decrease as children get older (Kasper et al., 2012), suggesting that a relevant proportion of individuals with ADHD may have impairments in working memory at some point in development, although there also exists a large group of children cognitively unimpaired. However, these findings suggest that VWM improvements may contribute to symptom remission for some children.

Response inhibition is fundamental when alternative courses of thoughts or actions (planned or already initiated) have to be inhibited to allow the emergence of goal-directed behavior (Bari & Robbins, 2013). Controlled and sustained inhibitory processes strongly affect everyday life, and their deficit is associated with impulsive behaviors, a core DSM-5 diagnostic feature of ADHD. Impulsivity is a multidimensional construct, resulting from both rapid-response impulsivity, and reward-delay impulsivity (or choice-impulsivity), with proneness to sensation-seeking and at-risk-behaviors and negative prognostic implications (i.e., behavioral addictions, impulsive eating, substance abuse) (Ortal et al., 2015; Cortese et al., 2016).

The reward-delay impulsivity has been explored with a meta-analytic method to examine differences in children and adolescents with and without ADHD (Patros et al., 2016). Twenty-eight tasks from 26 studies, including 4320 total children (ADHD=2360, normal controls = 1960) were examined, with a medium-magnitude between-group effect size (d=.47), suggesting that children and adolescents with ADHD exhibit moderately increased impulsive decision-making compared to controls.

Boundaries between WM and inhibition are not always clearly defined and may be both involved in cognitive processes. The Stop-signal Paradigm (Logan & Cowan, 1984) is the most frequently used measure of behavioral inhibition in ADHD subjects. It involves inhibiting a prepotent response when a cue precedes the stimuli (for example, avoid pressing the right button when one sees an arrow pointing right on the screen when a sound precedes the visual stimulus). However, the stop-signal paradigm's choice-reaction time component markedly involves working memory processes (e.g., controlled-focused attention), compared to inhibition (as in go/no-go tasks). Firm conclusions on the prevalence of inhibition vs. working memory deficits in the performance on the stop signal task in children with ADHD are still lacking. This possible overlap between working memory and inhibition (or the insufficient specificity of the stop-signal paradigm) was explored in 55 children (8-12 years) with and without ADHD using phonological and visuospatial working memory measures, as well as stop-signal and go/no-go (GNG) tasks varying with respect to demands on controlled-focused attention (Tarle et al., 2019). Although working memory and GNG performance each uniquely predicted children's inattention, stop-signal task performance was not a significant predictor of unique variance in inattention, above and beyond variance associated with working memory. Collectively, these findings suggest that performance on the stop-signal task, compared to the GNG task, is confounded by greater demands associated with working memory and consequently reflects an impure estimate of the inhibition construct.

Deficits in planning abilities are frequently reported in ADHD and measured by planning task as the well-known Tower of London task (Shallice, 1982). A meta-analysis examined performance and latency metrics in five tower planning task variants in 41 studies including ADHD, to calculate between-group effect sizes, applying meta regression techniques to examine potential moderating effects. A moderate-magnitude planning deficit was found, ranging from Hedge's *g* of 0,36 to 0,59. Analysis of latency metrics revealed small- to moderate-magnitude between-groups differences (Hedge's *g* ranging from -0,42 to 0,41). Children with ADHD responded more quickly on planning tasks when compared with normal peers. Age, percentage of females, solution presentation (e.g., pictorial vs. physical display), and task complexity (beads vs. disks) were significant moderator variables.

1.2 Navigation

Spatial navigation is certainly one of the most complex neural functions in humans and one that is absolutely vital to everyday life. Retrieving locations and paths, planning routes to distant destinations, ascertaining one's location in space, drawing and reading maps, are all daily navigational tasks. To perform accurate spatial navigation, individuals must identify their current position and destination in the environment and trace the best path between the starting position and the destination. These activities involve higher cognitive processes, including visuo-spatial working memory, planning and problem solving (Bocchi et al., 2017), which are based on perceiving, integrating and interpreting the multisensory environmental signals as well as signals from individual movements to generate, update and transform cognitive maps of the environment (Piccardi et al., 2008; Mirino et al., 2022). A lack of navigation skills may impair one's ability to find things, reach targets, avoid obstacles, and return home. It may lead to complete dependence on others, or even to death, if experienced in a dangerous environment. In spite of a large amounts of studies on navigation deficits in patients with neurological deficits (Tedesco et al., 2017; Piccardi et al., 2010a; Guariglia et al., 2010; Boccia et al., 2018; Piccardi et al., 2010b), the availability of validated diagnostic tools for navigation disorders is still extremely limited.

Traditionally, spatial navigation has been assessed by means of paper mazes, in manual space and not requiring locomotion. Some hypotheses have inspired recently the creation of new paradigms for studying visuo-spatial abilities also in the navigational space. In fact, neuropsychological evidence allows distinguishing, as discussed by Berthoz & Zaoui (2014), five networks corresponding to five different space frameworks: body space, reaching space (such as a table), near out of reach and near locomotor space (such as a room), far environmental space (such as a city) and imaginary space. These “action spaces”, as supported by several neurological and brain imaging studies, probably require different processing strategies and furthermore involve different brain networks (Ladavas et al., 1998, Nemmi et al., 2013). Near space is also called peri-personal or reaching space and refers to “the portion of space within the grasping distance” (Nemmi et al. 2013). Far space is also called extra-personal or navigational space and extends beyond our reach and has been called the space “within walking distance” (Halligan and Marshall, 1991). Studies on primates (Rizzolatti et al., 2003, Caggiano et al., 2009) and on lesional patients with neglect (Ladavas et al., 1998) demonstrate a double dissociation of information processing deficits in near and far space, suggesting the existence of two independent or only partially overlapping systems. Initially, this dissociation was considered to be limited only to perception and action, while some evidence has subsequently suggested how much this can also extend to the memory system. Some evidence (Piccardi et al., 2010, 2011) in fact revealed the existence of two independent modes of memory processing of visual-spatial information, demonstrating that coding, storage and retrieval of such information are subserved by different neural system depending on the space frame. Nemmi and co-workers (2013) investigated whether the dissociation described for near and far space in the perceptual and visuo-motor domains also applies to memory processes through an fMRI study. The results support the idea of a partial segregation between neural circuits for reaching and navigational space also in spatial learning and long-term memory.

Therefore, the evidence supports that navigation requires a different processing of spatial data from reaching. Whereas reaching locations are coded relative to the body, more options are available when navigating: updating egocentric locations or switching to an allocentric reference frame. A fundamental cognitive challenge facing the brain during navigation is the changing spatial relationship between one's own body and external space. This is referred to as the *reference frame problem* (Galati et al., 2010). Sensory stimuli are first encoded in spatial reference frames centered on the sensory organs, to be then integrated by posterior parietal cortex into more global, but still *egocentric* reference frames centered on different body parts (Buneo and Andersen, 2006), and finally in an *allocentric* reference frame, i.e., one that is consistent with some environmental features and is independent of body motion (Berthoz, 1999; Galati et al., 2010). The egocentric frame leads to the creation of body centered representations, based on subject-to-object relations (Colombo et al., 2017). This is fundamental in visuo-motor control as the planning and execution of actions require the representation of the target position in space in relating to the body (Milner & Goodale, 1993). The allocentric reference frame leads instead to a representation independent from the subject's point of view, based on object-to-object relationship (Figure 1). This cognitive strategy is supposed to be acquired later in life and is important to develop mature navigation skills, introducing a substantial computational simplification, but requiring, in the meanwhile, the maturation of specific brain networks. In real life, more than one strategy is often available and can be successful in many situations. People choose their strategy on the basis of task demands, environmental features, and individual characteristics. Convergent evidence points to a crucial age, around 10-11 years, for the achievement of adult-like navigation strategies, that are based on allocentric spatial representation (Belmonti et al., 2015). However, some studies show that children around the age of 3 have already been shown to use allocentric encoding in a spatial judgment task, differently from what has been observed in other studies and from the Piagetian theories.

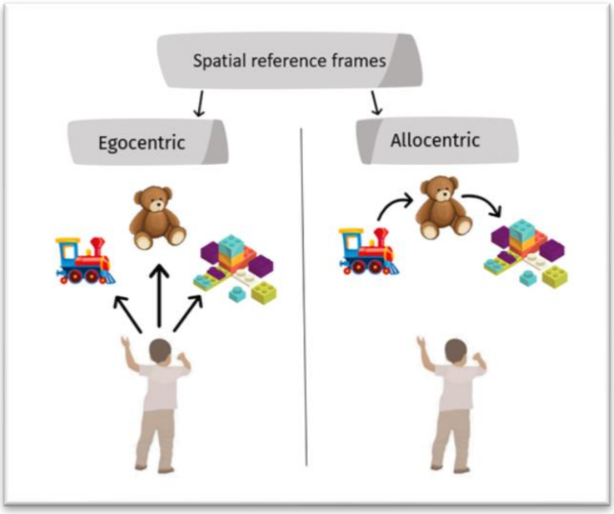

Figure 1. The image shows stimulus encoding in the two spatial reference frames, egocentric and allocentric

Therefore, a more complex picture has been proposed by Burgees (Burgees, 2006): both egocentric and allocentric strategies could be available from an early stage, but the two may act in a complementary way. A lack of strategy-switching from egocentric to allocentric frames rather than a lack of allocentric strategies per sè could be the basis of incomplete spatial abilities in children under 10. In fact, before 10 years children may have difficulty in inhibiting egocentric frames of reference, seemingly lacking allocentric strategies (Bullens et al., 2010). This latter hypothesis is confirmed by several studies, pointing to the key role of executive functions in navigation.

Different brain activation patterns seem to be associated with egocentric and allocentric strategies, as revealed by animal and human studies. An increasing number of studies have investigated the neurobiological correlates of egocentric and allocentric reference frames, pointing out that the latter are not restricted to the dorsal visual stream but extend to ventral, medio-temporal and prefrontal areas (Galati et al., 2010, Zaehle et al., 2007, Carrieri et al., 2018). In particular, the egocentric frame relies primarily on the caudate nucleus and more generally on the medial parietal lobe (Cook & Kesner, 1988), with a significant involvement of the posterior parietal area in the integration of different egocentric representations (Burgees, 2008). As for the allocentric frame, on the other hand, this is mainly supported by hippocampus place cells (Ekstrom et al., 2003), which fire in specific spatial locations independently from the subject's orientation, by the parahippocampal gyrus (Zhang & Ekstrom 2013) and the medial temporal lobe. The retrosplenial cortex (Zhang & Ekstrom 2013, Mao et al., 2017) is also involved, performing translations between egocentric and allocentric coordinate frames and allowing aligning the current “map” in the medial temporal lobe with the current viewpoint in the parietal cortex (Byrne et al., 2007). Some studies support the involvement of the hippocampus in both strategies. In particular, while allocentric navigation relies more on the right hippocampus, the left hippocampus supports sequential egocentric navigation (Iglòi et al., 2010). Recent studies highlight an important role of cerebellum in developing, storing and retrieving cognitive maps of the environment, allowing placing a set of spatial positions in the correct sequence (Tedesco et al., 2017). Considering this evidence, it is has become evident that to assess visuo-spatial memory existing standardized tests are not sufficiently informant for disentangling the different processes that underly this complex function. The Corsi Block-tapping Test (CBT) (Corsi, 1972) is one of the most widely used measure of visuo-spatial memory, evaluating the ability to retrieve a previously seen sequence of blocks by finger-tapping. It analyses only visuo-spatial memory in the reaching space and not in the navigational space. For this reason, novel tests for the assessment of navigation have been created and recently validated in adults and children (Belmonti et al., 2015a; Berthoz et al., 2015a). The Magic Carpet (MC) is such a test and has been validated both in typically developing children and in children with cerebral palsy (Belmonti et al., 2015b). It is derived from the Walking Corsi Test (WCT) (Piccardi et al., 2008; Piccardi et al., 2013, 2014; Faedda et al., 2021) and assesses locomotor navigation via the same procedure of the CBT for short-term visual-spatial memory, but translated from manual into locomotor space. The MC test relies on a new electronic device (Figure 2). It consists of 10 square tiles (30 x 30 cm), covered with white plexiglass, each containing four pressure sensors along the sides and a blue LED at the centre. Nine tiles are embedded within a dark-grey carpet (310 x 260 cm) with the same spatial layout as the CBT.

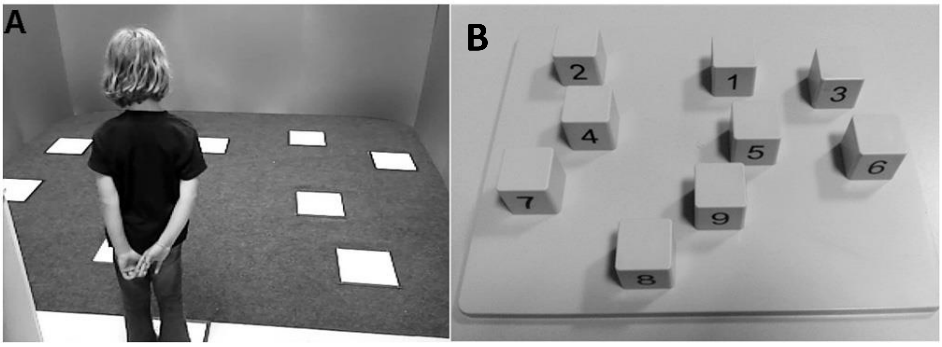

Figure 2. Belmonti et al., 2015b (A) experimental Magic Carpet setup, (B) Corsi block tapping test from BVS (Mammarella et al., 2008) (experimenter's view)

The tenth tile, representing the starting point, is placed just outside the carpet, at the midpoint of one of its long sides. All tiles are connected via an electronic controller to a laptop, receiving input from pressure sensors and delivering output to LED switches. The procedure of the MC is very similar to the one of the CBT. While standing in the starting position, the subject looks at the sequence of tiles that light up at the at the same pace of one per second as in the CBT. When the computer delivers the acoustic start signal, the subject reproduces the sequence by walking on the tiles, instead of tapping blocks. The sequence length increases across trials and a span level is then identified. The entire pool of stimuli consists of 40 pseudo-randomly generated sequences, five per level. A level is passed when at least three of its sequences are correctly reproduced. If, on the contrary, three or more errors are made at a level, the test is terminated. The span score is given by the highest level passed.

By analysing the errors made on the MC (Perrochon et al., 2014; Belmonti et al., 2015a; Belmonti et al., 2015b) it has been possible to gain insight into the cognitive strategies used by different clinical and control groups at different ages and to formulate hypotheses on the development of human navigation. The authors identified four different types of errors:

1. Omission: the subject misses a tile that has been presented in the sequence and overall, the number of correct locations (tiles) reproduced is lower than the ones presented;
2. Substitution: the subject replaces a location present in the sequence with a different one;
3. Insertion: the subject inserts a location which is not present in the sequence and overall the number of tiles reproduced is higher than the number presented in the sequence;
4. Permutation: the subject inverts the order of two locations when he/she reproduces the sequence.

Permutation errors were by far the most frequent type of error both on MC and on CBT and at all ages. Considering also the location coordinates, the errors were then further classified into global error patterns. When challenged by difficult sequences, subjects have to choose between retaining the highest possible number of correct locations in any order (place-sparing) or trying to approximate the global path (path-sparing). The presence of permutation errors could in fact distinguish error patters as either place-sparing (preserving locations, not order) or path sparing (preserving order but losing some spatial information). As expected, place-sparing errors have been found to be far more frequent than path-sparing ones on both tests and at all ages, just as permutations are the most frequent point errors. However, and importantly, path-sparing patterns are relatively favoured on the MC compared to the CBT, which further supports a different treatment of spatial data. Moreover, the frequency of path sparing patterns follows a developmental trend on the MC, whereas no such trend can be observed on the CBT.

Further analyses were carried out in order to investigate which characteristics of the task most influence the performance of the subjects, studying a set of geometric parameters of stimulus sequences (Belmonti et al., 2015a). The geometric parameters considered were:

- Distance travelled: the total distance travelled along the path;
- Distance ratio: distance travelled divided by the shortest theoretical path;
- Inversions: defined as the number of times a right rotation is followed by a left one or viceversa;
- Crossing: as the number of crossings between two path segments;
- Occlusions: number of locations still to be touched and lying behind the subject;
- Updating angles as the sum of absolute rotations.

Results showed that the only parameter that correlated with success rate on the CBT was distance travelled, and thus could be considered as a measure of sequence difficulty when applying the CBT protocol. Considering the MC task, all geometric parameters (except inversions) correlated with the probability of success. Further analyses support the importance of updating angles in determining performance at the MC, underlining the need to treat spatial data differently than in the reaching space. However, the influence of updating angles decreased with age, becoming no longer significant in adults, supporting the hypothesis that allocentric navigation is increasingly activated, reducing the disorienting effect of body rotation.

Taken together, all these findings coherently support the hypothesis that a navigation mode is increasingly adopted by older subjects when facing the MC task, while younger subjects seem to assimilate it to a locomotor reaching task. Furthermore, these results seem to converge towards a dissociation between a reaching mode and a navigational mode, each involving specific cognitive strategies and brain networks.

These navigation tasks revealed that different cognitive strategies are called for in memory tasks in a locomotor space with respect to a reaching space gaining new insights on the developmental course of navigation skills. A limitation of the MC and WCT was that it did not allow measuring the kinematics of the trajectory, nor the head direction as an index of gaze direction. A new test was thus needed to better quantify how the child approached a complex spatial memory navigation task, in a more playful “gaming” format, where the child was asked move around a city environment projected on the ground with houses and streets: the Virtual City paradigm (VC™).

1.3 Aims

The primary aim of the study was to create a new motivating task, called the Virtual City (VC™ paradigm), simulating real-life situations in a gaming format, in order to assess locomotor navigation in a controlled laboratory space and under specific experimental conditions, tapping different degrees of task difficulty and cognitive processes as executive functions and visuo-spatial memory. The child is asked to reach houses within a city projected on the floor. As these cognitive processes are particularly challenging for children with neurodevelopmental disorders, a group of school-aged children diagnosed with ADHD was therefore recruited and assessed with a protocol of standardized neuropsychological tests and with the VC™ paradigm. Such neuropsychological protocol allowed to investigate the cognitive profile and the neuropsychological functioning of the ADHD sample, by focusing in particular on executive functions and visuo-spatial memory, therefore comparing our results with the existing literature. Concerning the VC™ paradigm, this study was also aimed at assessing its acceptability and usability for children diagnosed with ADHD, by means of a feasibility checklist and an ad-hoc tailored questionnaire administered to the clinicians. Performance of ADHD children in VC™ paradigm was examined by analyzing quantitative measures and comparing them with the standardized neuropsychological tests outcomes, in order to understand the cognitive processes involved in such a navigation task. VC™ quantitative parameters of ADHD children and those of a small control group of aged - matched typically developing children were compared**,** in order to investigate performance differences in such a navigation task, as expected according to the neuropsychological functioning assessed. A final aim of this study was to provide preliminary data on cognitive strategies, such as egocentric and allocentric reference frames, necessary for successful completion of the locomotor navigation task. To this end data on the trajectories the child made to reach the houses (obtained by the computerized motion capture system of the VC™) were qualitatively analyzed, comparing typically developing and ADHD children of the same age.

2. Method

2.1 Participants

A clinical group of drug-naïve children with a diagnosis of ADHD was recruited in the third-level hospital of Child and Adolescent Neurology and Psychiatry of IRCCS Fondazione Stella Maris. All participants underwent a multi-dimensional assessment, and diagnoses were made according to the DSM 5 (American Psychiatric Association, 2013), based on clinical history and a structured interview, Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997). ADHD severity was assessed with ADHD-Rating scale (IV and V version) (ADHD-RS) (George et al., 1998; DuPaul et al., 2016), an 18-item questionnaire consisting of two subscales, Inattention (9 items) and Hyperactivity-Impulsivity (9 items), completed by the parents, that measured ADHD symptoms according to the DSM-5. Higher scores indicate the presence of more symptoms. Inclusion criteria were: 1) diagnosis of ADHD; 2) Drug naïvité for stimulant treatment and any other pharmacotherapy; 3) Absence of intellectual disability; 4) Absence of comorbid conditions, except for Specific Learning Disabilities-SLD- (DSM 5); 5) Verbal intelligence of 85 or above (Wechsler Scales) to ensure full comprehension of the verbal instructions of the VC^{TM} paradigm; 6) absence of any visual (non-corrected) or gait problems.

Thirty-one patients aged 7-13 years were recruited (mean 9,3 years; sd 1,68 years) and were eligible to be included in the study. In accordance to the literature on sex differences in ADHD (Faraone et al., 2015), there was a male preponderance, with a ratio of M:F of about 3:1 (males n= 24; 77,4%; females n=7; 22,6%). ADHD presentation was 77,4% combined (n= 24) and 22,6% inattentive (n= 7), 41% displaying comorbid SLD (n= 13). Demographic and clinical data for the entire sample of 31 participants is presented in Table 1.

A control group of 19 typically developing children matched for age was also recruited (mean 9,1 years; sd 1,5 years). Similarly to the ADHD group, there was a male preponderance, with a ratio of M:F of about 2:1 (males n=12; 63,2%; females n=7; 36,8%). The Covid-19 emergency undermined the recruitment of a control sample at primary and secondary schools, resulting in a reduction of the number of participating children compared to the initial project. The typically developing children sample was therefore recruited through an informative flyer delivered to the Stella Maris Foundation employees. Interested families were invited to contact the research team in order to discuss their children eligibility, according to the following inclusion criteria: 1) age between 7-13 years 2) absence of any documented neuropsychiatric disorders, 2) no learning difficulties as reported by parents or teachers, 3) absence of any visual (non-corrected) or gait problems.

The entire study complied with the Declaration of Helsinki and was approved by the Regional Pediatric Ethical Committee (n.175/2019). Parents and children signed a written consent form (for children, in a child friendly format).

Table 1. Demographic and clinical data of the ADHD sample

n.	Age (yrs;mo)	Sex	Adhd presentation	Specific Learning Disability	Intelligence (WISC-IV Indices)			
					VCI	PRI	WMI	PSI
1	7;11	M	combined		104	98	82	68
2	7;3	F	combined		116	93	82	56
3	9;6	M	combined		120	106	121	123
4	12;8	M	inattentive	yes	112	119	103	123
5	13;1	M	inattentive		108	104	94	88
6	8;0	M	combined		100	91	61	53
7	8;2	M	combined		104*	96**	NA	NA
8	9;5	M	combined		120	93	97	94
9	7;10	M	combined		90	80	79	82
10	12;3	M	inattentive		120	122	103	79
11	8;11	M	combined	yes	108	100	94	94
12	9;8	F	combined	yes	98	89	79	94
13	13;8	M	combined	yes	122	108	112	74
14	12;10	M	combined	yes	96	102	82	94
15	8;5	M	combined		100	91	70	85
16	8;8	F	inattentive	yes	128	91	85	82
17	8;0	F	combined		112	126	94	79
18	10;3	M	inattentive	yes	108	91	82	109
19	10;7	M	combined		114	124	103	118
20	9;3	M	combined		132	113	94	88
21	8;9	F	combined	yes	114	100	91	71
22	10;7	M	combined		106	124	94	79
23	8;5	F	inattentive	yes	90	93	70	NA
24	11;3	M	inattentive		112	130	85	76
25	9;11	M	combined	yes	126	115	91	126
26	8;6	M	combined		114	106	61	85
27	11;2	M	combined		102	126	88	97
28	9;7	M	combined		122	115	97	103

29	9;6	F	combined	yes	98	82	70	76
30	9;11	M	combined	yes	108	102	109	88
31	8;0	M	combined	yes	94	104	94	82

Legend: VCI Verbal Comprehension Index; PRI Perceptual Reasoning Index; WMI Working Memory Index; PSI Processing Speed Index; *Verbal intelligence quotient and **Performance intelligence quotient WPPSI-III at 6;8 years: NA not applicable/available

2.2 Procedure and measures

2.2.1 The Virtual City paradigm™

The Virtual City paradigm (VC™) has been developed during this PhD project in collaboration with Alain Berthoz's research team in Paris. It was implemented using the Virtual Carpet™ experimental design (Berthoz et al., 2015, Perrochon et al., 2018; Kronovsek et al., 2021).

The VC™ is a virtual town projected on the floor, consisting of 20 colored houses, street lanes and crossings (Figure 3), created on Unity 5.5.1© platform. The houses to be reached flickered to designate those which were the targets of the locomotor navigation. Houses flickered either: a) in a sequence, or b) all together (Del Lucchese et al., 2021).

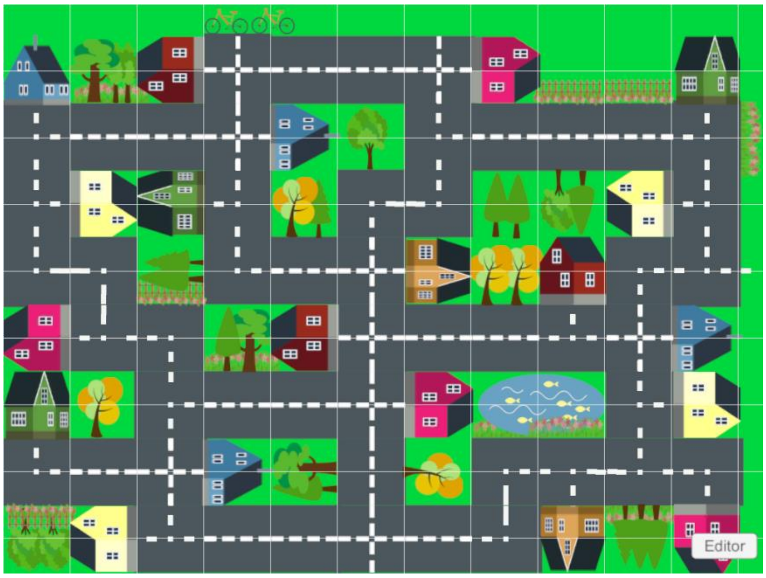

Figure 3. VC™ projection on the ground, consisting of 20 houses, created on Unity 5.5.1 platform ©.

The VC^{TM} paradigm included three different conditions in which the number of houses to be reached (span level), the sequence order, flicker duration, and the instructions varied.

1. City Pointing: While keeping the starting position, the child was asked to point (with a laser pointer) each house as it flickered (for 2,5 sec). The sequence of flickering houses was randomized and the houses' order was set so that no contiguous houses

flickered in a sequence. This procedure allowed assessing efficacy of visual search abilities in a large space and visuo-spatial span. If the child correctly pointed to at least 80% of the houses, the other conditions were administered.

2. City Following*:* A given number of houses was made to flicker in a sequence. The child was asked to remain in the starting position and observe each house as it flickered (for 2,5 sec). Then the child was asked to walk on the streets to reach each house in the same order he/she had seen them flickering. The sequences were randomized and the houses' order set with a mathematical algorithm to ensure both easy sequences (the houses are near to each other and not too many rotations are needed to reach the next one) and some difficult ones (i.e., more distant houses and more rotations). The classification into difficult and easy sequences was made taking into account the results obtained by Belmonti et al., 2015a, relative the geometric parameters that correlated with the success rate on the MC task (previously reported in detail). The rule of walking only on the street during locomotion and not crossing the houses had to be followed. Sequence length increased across trials and identified the level. There was a maximum of 5 span levels (from the starting level of 2 houses for all subjects up to level of 6 houses). The entire pool of stimuli consisted of 60 pseudo-randomly generated sequences, 10 per level. Criterion for success on any given level was 3 out of 5 trials correct and in case of failure, 5 additional trials for the same level were presented before proceeding with the third condition. Similarly to the CBT test, a span measure was obtained, as the longest sequence reached (but not passed) by the subject (even if the 3 out of 5 criterion was not met). The average execution time at the first three items of span level two in the following condition, performed by all subjects, was also considered as a measure of the efficiency of the neuropsychological processes involved in the task condition. Finally, according to literature data, detailed error analysis was conducted, also considering rule violations (as described in the "Results" section).

3. City Planning*:* The child was asked to observe the houses that were flickering simultaneously while keeping the starting position, and then to walk on the streets to reach the houses he/she had seen flickering. The specific instruction was to plan the shortest path. The rule of walking only on the street during locomotion and not crossing the houses had to be followed. There was a maximum of 5 span levels (from a span of 2 to a span of 6) each with 10 trials; each child performed two level and 20 trials: the span level reached in the second condition and the previous one. Flickering duration for each span level was respectively 7,4; 11,3; 13,1; 18,5; 22,2 seconds for ensuring that all houses flickering

simultaneously could be detected. Similarly to the following condition, the average execution time at the all items of span level three, performed by the majority of subjects, was considered as a measure of the efficiency of the neuropsychological processes involved in the present task condition, such as inhibition and planning. The mean execution time for all the items performed by each subject was also calculated. Considering that each subject performed different levels according to the following condition span, the number of houses was weighed. Finally, according to literature data, detailed error analysis was conducted, also considering rule violations (as described in the "Results" section).

The cognitive strategies needed to complete the VC^{TM} tasks could be the following: a first encoding phase in which the subject mentally encoded the spatial distribution of the houses and eventually the temporal sequence of their presentation. This encoding may be perturbed in ADHD due to a deficit in selective attention and/or spatial memory. For this reason, a control condition was added (City Pointing), to ensure that children do indeed pay attention to all houses in the town as they flicker; a second recall phase in which before starting the task, the subject had to mentally rehearse the encoded representation of the flickering houses' spatial distribution and to generate the trajectory. Both phases imply spatial short- and long-term memory and inhibition, intended, the latter, as the capacity to inhibit the prepotent response to start walking in the town before having generated a trajectory or the shortest path as in the City Planning condition; finally, when the subject navigated the town, he/she needed to update the mental trajectory of the houses he/she had generated. That is, he/she had to represent the position of the houses relative to his/her actual position in the town and no longer the one relative to the starting position in which he/she had originally encoded them. This phase could tax the updating component of spatial memory (working memory).

The projectors were installed so as to project the town on an off-white carpet (2,6 x 3,2 meters) in a dark laboratory space. The motion capture system included two sensors (HTC® Vive) applied on the head (fixed on a bike helmet) and on the trunk (fixed on a belt) of the participants and two infrared cameras registering the position of the two sensors, allowing tracking of body movement in 3D in real time (Figure 4). The system computed, for specific time frames (in ms), head and trunk sensor positions on X, Y and Z axes, and rotation angles with respect to the X, Y, Z axes direction. Each trajectory trial is saved individually as a TXT file. These raw data were treated using Matlab 2021 to yield the reconstruction of the trajectory, the kinematic behaviour and parameters such as trunk and head position and rotation in the horizontal plane, velocity, acceleration, and stops during the trajectory.

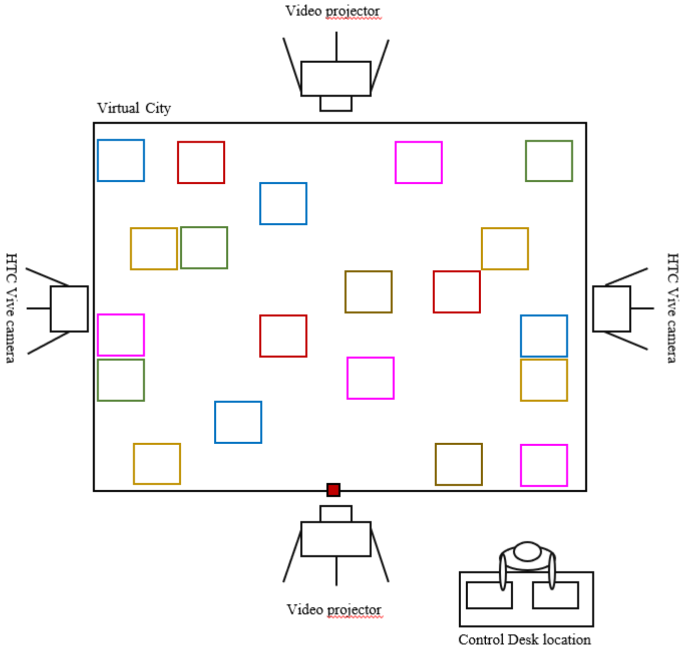

Figure 4. VC™ laboratory set-up (red square child's starting point).

The HTC® Vive system also included a headset that was only used during the calibration procedure to determine the navigational space and the position of each house in a cartesian coordinates system by triggering the 3D motion sensor. The calibration procedure was performed by the experimenter by placing himself over each target house following a standard order before starting the experimental procedure. Information about target location and spatial array coordinates were saved in a TXT file, used by Matlab during the software analysis procedure (Castilla et al., 2021).

The duration of the entire VC^{TM} paradigm ranged from 40 to 50 minutes in a single session although for some children, due to variability in collaboration, duration could be longer. The VC^{TM} paradigm and neuropsychological tests were carried out at different times of the same day or on two different days (no longer than a week apart), in order to reduce the fatigue effect as much as possible. Order of assessment was randomized with half of the participants starting with the VC^{TM} paradigm and the other half with the neuropsychological assessment, in the majority of cases.

2.2.2 Neuropsychological assessment

In order to understand the neuropsychological functions involved in the VC™ task, an assessment protocol was created by selecting standardized neuropsychological tests tapping functions believed to be recruited in the VC™ task.

To test visuo-spatial short-term memory/working memory in the reaching space the CBT task forward and backward and a computerized block tapping task, the Spatial Span Task (SSP)(CANTAB®) were selected. The CBT test was performed on a plastic board (28 x 22,5 cm), brown-coloured, containing nine blocks (2,9 x 2,9 cm x 3 cm high) (see Figure 2B). The blocks were numbered on the experimenter's side, while the remaining surface was blank. The material was part of a standardized package for paediatric visuo-spatial memory testing (BVS-Corsi; Mammarella et al., 2008). For each trial, the experimenter, seated in front of the subject, showed a sequence of blocks by tapping them with a stick, at a pace of one per second and moving the stick back to the starting position after each block. The subject had to wait for a verbal start signal, given 1 s after the last block, and then retrieve the sequence by tapping blocks with the preferred finger following the same order for the forward condition or reversing the order for the backward condition. Sequence length increased across trials from two up to nine blocks. Sequence length identified the span level. The entire pool of stimuli consisted of 40 pseudo-randomly generated sequences, five per level. A level was passed when at least three of its sequences were correctly retrieved. If, on the contrary, three or more errors were made at a level, the test was terminated. The span score was highest level passed.

The Spatial Span Task (CANTAB ®) is the version of the previous task on a tablet (without the backward span condition). White squares were shown on the screen, some of which briefly changed colour in a variable sequence (Figure 5). The participant had to select the squares which changed colour in the same order that they were displayed (by touching them with the index finger of the preferred hand). The number of squares in the sequence increased from two at the start of the test, to nine at the end and the sequence and colour are varied through the test. Sequence length identified the span level. The entire pool of stimuli consisted of 24 pseudo-randomly generated sequences, three per level. A level was passed when at least one of its sequences were correctly retrieved. If, on the contrary, three errors were made at a level, the test was terminated. Italian verbal instructions were automatically given by the software. Among the outcome measures provided by the task, the following were selected:

- SSP Forward Span Length (SSPFSL): the longest sequence of boxes successfully recalled by the subject;
- SSP Forward Total Errors (SSPFTE): the total number of times a subject incorrectly touched a square which was not the next one in the sequence;
- SSP Forward Total Usage Errors (SSPFTUE): the total number of times a subject incorrectly selected a square which was not present in the target sequence.

Compared to the CBT Test (BVS), the Spatial Span Task yielded not a span measure, but also an analysis of the type of errors, allowing a better understanding of the performance, similarly to what was carried out in the studies through the MC paradigm (Belmonti et al., 2015b).

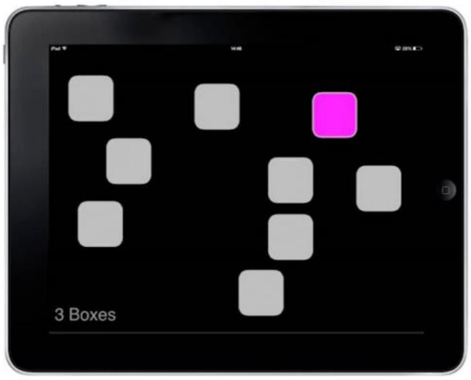

Figure 5. Spatial Span task (CANTAB®)

As a control verbal measure of spatial memory, the digit span, (WISC IV) (Wechsler, 2003) was administered. The subjects were asked to repeat a sequence of numbers, following the same order for the forward condition or reversing the order for the backward condition. Sequence length increased across trials. Sequence length identified the span level. The entire pool of stimuli consisted of 16 pseudo-randomly generated sequences, two per level. A level is passed when at least one of its sequences are correctly retrieved. If, on the contrary, three or more errors are made at a level, the test is terminated. The span score is given by the highest level passed.

To assess executive functions, the Stop Signal Task (SST) (CANTAB®) was administered as a measure of response inhibition and the Tower of London (Sannio Fancello et al., 2006) as a measure of planning. The Stop Signal Task is a computerized Go-No go test and consist of two different parts. In the first part, the participants were introduced to the task on a dark tablet screen and told to select the left-hand button when they saw a white left-pointing arrow and the right-hand button when they saw a white right-pointing arrow (Figure 6). There was one block of 16 trials for the participant to practice. In the second part, the participants were told to continue pressing the buttons when they saw the arrows but, if they heard an auditory signal (a beep), they should withhold their response and not select the button. The entire procedure lasted about 20 minutes. The task used a staircase design for the stop signal delay (SSD), allowing the test to adapt to the performance of the participant, narrowing in on the 50% success rate for inhibition. Verbal instructions were automatically given by the software. Among the outcome measures provided by the task, the following were selected:

- SST Stop Signal Reaction Time (SSTSSRT): the estimate of time where an individual can successfully inhibit their responses 50% of the time. This covert measurement is sampled from the length of time between the go stimulus and the stop stimulus at which the subject is able to successfully inhibit the response on 50% of the trials. Therefore, it is assumed that this is the time frame before which all actions become ballistic and the subject is no longer able to inhibit his/her action selection;
- SST Direction Errors - Go Trials (SSTDEG): the total number of trials where the subject pressed the wrong button to the direction of the arrow stimulus on a Go trial;
- SST Median RT - All Go Trials (SSTMRTG): the median reaction time taken across all the valid Go trials in the task;
- SST Missed Trials (SSTMT): the total number of trials which were missed by the subject.

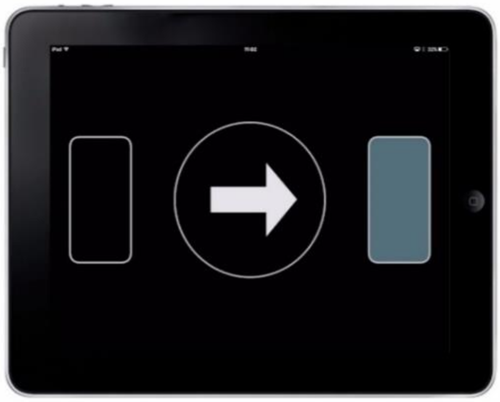

Figure 6. Stop Signal Task (CANTAB)

The Tower of London assesses executive skills such a strategic planning and problem solving, but the timed aspects of the task provide additional measures of speed and efficiency in problem solving. Moreover, the rule-violations score provides evidence of impulsivity and difficulties with rule-governed tasks. The task is performed on a wooden board consisting of three pegs of descending height, on which three balls (one green, one red, and one blue) can be arranged, three on the first peg, two on the second, and one on the third. In each of 12 different problems, the participant is asked to arrange the balls on the test board according to a bidimensional model shown as a picture. The board is always presented with the balls arranged in the same configuration, that is, with the green and blue balls placed on the first peg (the green ball under the blue one), and the blue ball on the second peg (starting position) (Figure 7). The participant is told that only one ball can be moved at a time, and that he or she should try to solve the problem with the fewest ball movements possible. For each problem, three points are assigned if the problem is solved in the first trial, two points if the problem is solved in the second trial, one point if it is solved in the third and, finally, zero if the problem is not solved within the three trials.

Outcomes provided by the task included: total score (i.e., the sum of the scores obtained for each problem), rule violation errors (i.e., total number of times a child breaks one of the previously established rules for task completion), total problem-solving time (i.e., the total time required to complete the 12 problems) and total decision time (i.e., the time between the stimulus presentation and the first subjects' move).

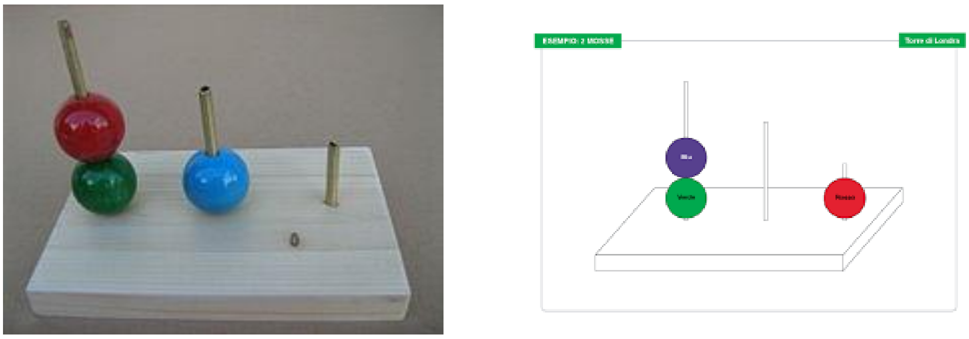

Figure 7. Tower of London test. On the left the starting position with the balls arranged in a fixed configuration; on the right the configuration to be executed in a total of two moves.

The duration of the neuropsychological assessment was one hour on average in one single session but varied as a function of degree of collaboration.

As an ecological measure of EFs, parents filled out the Behavior Rating Inventory of Executive Function - Second Edition (BRIEF-2) (Gioia et al., 2015). The BRIEF was constructed to evaluate everyday life behaviours that reflect the development of EFs in children and adolescents by means of parent and teacher reports (Gioia, et al., 2000; 2015).

The BRIEF-2 is comprised of 63 items, which form nine scales that evaluate inhibition (ability to control impulses and modulate behaviour in an appropriate way respecting to the context), self-monitoring (ability of keeping track of the effects of one's own behaviour), shifting (ability to move freely from one situation or aspect of one problem to another as required by the situation; ability to change the attentional focus and to be flexible in problem solving), emotional control (ability to modulate emotional responses appropriately), initiative (ability to independently initiate an activity and to complete it on time), working memory (ability to keep in memory the information needed to complete a task), planning and organization (anticipate future situations or consequences, set goals and develops a sequence of steps ahead of time to carry out a task or an action), task-monitor (check work; assess performance during or after finishing a task to ensure attainment of goals), and organization of materials (keep work space, play area and materials in an orderly manner). These executive domains are merged in three indices referring to cognitive, behaviour, and emotion regulation, and a global executive function score is also provided.

Furthermore, parents and children filled out a pilot questionnaire on visuo-spatial, orientation and navigation abilities (Santa Barbara Sense of Direction Scale-Parent and Child Version: p-SBSOD and c-SBSOD) adapted by Murias and co-workers (Murias et al., 2017). The SBSOD scale is a standardized, validated measure of subjective navigation abilities (Hegarty et al.,2002) with statements about real-life large-scale memory and navigation. Items were coded and averaged such that a high number indicated more orientation proficiency, or a better sense of direction. The child adapted SBSOD (c-SBSOD) and the parent adapted (p-SBSOD) scales included respectively 18 and 20 questions, ranked on a 7-point Likert Scale (strongly agree to strongly disagree) (See Appendix 1).

2.2.3 Feasibility assessment

The recent involvement of new technologies (i.e., robotic therapy, virtual reality interfaces and gaming strategies) for the assessment and rehabilitation of children with neurodevelopmental disorders has offered the possibility to enhance patients' participation and enjoyment, inserting health care in a more ecological contest, thus promoting generalization processes and a better understanding of the patient's daily life functioning. However, to develop new medical devices and technologies, characteristics of end-users and environment should be considered (Norman, 1986). The new technology could in fact be effective, but its use could be not feasible from the user’s point of view. This highlights the importance for the development of an innovative technological experimental paradigm, to firstly investigate end-user usability and acceptability, as the two main parameters according to the literature. However, even if the importance of these parameters is widely recognized, standardized measurement tools have not yet been developed for the use of technology in the field of assessment and rehabilitation in developmental age. Otherwise, it is important to consider that the evaluation of acceptability and usability of a new system cannot be carried out with a single tool, as it could be not very specific for the intrinsic characteristics of the system analysed. According to the literature, it is possible to create an ad hoc tool that considers these parameters, in order to increase the specificity and sensitivity of the measurement.

Firstly, a literature review allowed for the definition of usability and acceptability parameters and for the identification of the investigation criteria needed. The standard ISO 9241-11 (Guidance on Usability) defines usability as “the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use” (Jokela et al., 2003). The outcomes necessary for the assessment of the usability consist of the following: effectiveness “How well do the users achieve their goals using the system?”; efficiency “What resources are consumed in order to achieve their goals?” and satisfaction “How do the users feel about their use of the system?” (Abran et al.,2003; Wixon et al.,1997). Some standardized scales based on usability model, like the System Usability Scale (SUS) have already been developed and administered in different research contexts. These scales are available and easily accessible on the web and can be used to quickly collect a user subjective rating of the usability of a product or a service. Despite the existence of these tools, recent studies applied more frequently tailored questionnaires for usability assessment of specific devices, containing Likert Scales. In the healthcare field, the assessment questionnaire can be completed from someone other than the participant, such as a parent, a caregiver or a therapist. Acceptability is instead defined as the demonstrable willingness within a user group to employ technology for the task it is designed to support (Dillon et al., 1996. One of the most highly valued theory about is The Technology Acceptance Model (TAM) (Davis, 1985) which explores three main items: the perceived usefulness of the system (how the user thinks the system can improve their performance), the perceived ease of use (physical and mental effort) and the attitude towards using the system (Sgherri et al., 2020).

Considering this literature review, a feasibility questionnaire was created tailored for the VC™ (see Appendix 2), conformed to the standard definitions of usability and acceptability. According to the standard ISO 9241-11 and the Technology Acceptance Model, the questionnaire investigated the two feasibility domains, exploring the different main items previously described (effectiveness, efficiency and satisfaction for acceptability; perceived usefulness, perceived ease of use and attitude towards using the system for usability). The questionnaire consisted of 14 questions (6 for the usability assessment and 8 for the acceptability assessment) ranked on a 5-point Likert scale (1 most negative, 5 most positive), filled out by the two experimenters immediately after the VC™ assessment procedure. Items of usability and acceptability sections are reported in Table 2.

Table 2: Questionnaire items of each usability and acceptability section (Beani et al., 2020).

Domain	**Investigation criteria**	**Questions**
Usability	Satisfaction measures	In general, relative to this specific participant, how satisfied are you with the VC™ Paradigm (in terms of software, hardware and sensors- taken as a whole)?
		Your current knowledge of the system's functioning (software, hardware and sensors -taken as a whole-) is sufficient for use with this specific participant?
	Effectiveness measures	Do you believe that the system is suitable for this specific participant (in terms of carpet's size, sensors' size and wearability)?
		Were you able to achieve the goals you set for this specific participant?
	Efficacy measures	How dangerous is it to use this system with this specific participant?
		How easy was it to set the hardware for this specific participant?
Acceptability	Perceived ease of use	How easy was it to use this system with this specific participant?
		How often did you need to interrupt the paradigm with this specific participant due to technical issues arising during the system's utilization?
	Perceived usefulness and attitude toward the system	Did the VC™ Paradigm allow you analyse the skills that you intended to measure for this specific participant?
		How often did you have to interrupt the paradigm and provide a greater number of rests than established with this specific participant due to

		reduction in motivation or excessive mental or physical fatigue on the part of the participant?
		Do you believe the system needs to be modified to address this specific participant's needs?
		Do you believe that the system's data report is useful in clinical terms?
		Would you use this system as an intervention paradigm for this specific participant?
		Has the VC™ data stimulated your thinking on aspects of behavior that had not emerged from clinical evaluation?

There was also an introductory section with open and multiple-choice questions to collect information about the patient, the experimenter who filled out the questionnaire and on the assessment session just concluded.

Quantitative analysis of the data considered only scores assigned to the 14 questions ranked on a 5-point Likert scale. The minimum score was 14 (total number of questions for the minimum score on the scale) and the maximum score was 70 (total number of questions for the maximum score on the scale). For each session the following scores were obtainable: usability 6 min-30max; acceptability 8 min-40 max.

A feasibility checklist with criteria for success, based on a literature review (Beani et al., 2020a; 2020b), was also developed to understand how feasible the VC ™ assessment was as well as the entire study procedure. It consisted of 9 outcome measures grouped in 4 areas specific for the VC™ paradigm (accessibility, motivation, technical smoothness, and compliance) and 5 for the entire study design and procedures (participation willingness, participation rates, loss to follow-up, assessment timescale and assessment procedures) (Table 3). In particular, feasibility criteria and detailed measures were as follow:

Feasibility of the VC™ assessment

- Acceptability: intelligibility of activity rules in terms of execution measured recording the clarifications requested by the child to the psychologist;
- VC™ compliance: duration of the assessment with the VC™ device measured as the total time needed to complete the paradigm;
- Technical smoothness: functioning of VC™ (sensors and software), defined as the number of issues and malfunctioning experimented by the psychologist during the

session. It was measured as the number of participants that required stops during the VC™ assessment due to technical problems and the number of missing data recorded from the sensors;

- Motivation: motivation and reported effort in carrying out the VC™ assessment, measured as the number of participants that required stops due to subjects' loss of motivation and collaboration;

Feasibility of study design and procedures

- Participation willingness: rate of acceptance of the participation in the study, measured as the number of eligible participants that agreed to join the project;
- Participation rates: completion of the study measured the number of dropouts;
- Missing data from VC™ or neuropsychological assessment: possibility to record all data from all outcome measures;
- Assessment time scale: required time for collecting all outcome measures (2 hours);
- Assessment procedures: failure to complete outcome measures assessment, measured as the numbers of subjects who completed the all the assessment procedures.

Session’s diaries were also collected to have the necessary data for the analysis of the nine criteria of feasibility.

Table 3: Feasibility checklist with nine feasibility criteria (Beani et al., 2020).

	Feasibility criteria	Definition	Feasibility question	Measurement
Feasibility of Virtual City assessment	*Acceptability*	Intelligibility of rules of the activity in terms of execution.	Do participants understand objective and rules of VC™, administered by psychologist?	Recording of clarification request to the psychologist
	VC™ compliance	Duration of the assessment with the VC™ device.	Do participants perform all the VC™ protocol in less than an hour and half?	Report from psychologist that administer the VC™ protocol.
	Technical smoothness	Functioning of VC™ (sensors and software), defined as the number of issues and malfunctioning experimented by the psychologist during the session.	Are there technical issues with VC™ (sensors, software, hardware)?	Number of participants that required stops during the VC™ assessment due to technical problems and missing data recorded from the sensors.

	Motivation	Motivation and reported effort in carrying out the VC™ assessment.	Are participant motivated to perform the VC™ tasks?	Number of participants that required stops due to subjects' loss of motivation and collaboration
Feasibility of study design and procedure	*Participation willingness*	Rate of acceptance of the participation in the study	What is the participation rate?	Number of eligible participants that agree to join the project
	Participation rates	Completion of the study	Do all eligible participant, who agree to join the project, complete all the study procedures (VC™ and neuropsychological)?	Numbers of dropouts
	Missing data from VC™ or Neuropsychological assessment	Possibility to record all data from all outcome measures	Can all data be collected without any problems?	Missing data from VC™ paradigm or neuropsychological assessment
	Assessment time scale	Required time for collecting all outcome measures (2 hours)	Can all data be collected within two hours and half?	Time spent for collecting all outcome measures.
	Assessment procedure	Failure to complete outcome measures assessment	Do all the participants who started the assessment procedure completed the study?	Numbers of subjects who completed the all the assessment procedures

2.3 Statistical analysis

Descriptive and inferential statistical analyses were conducted using Statistical Package for Social Science 2022, version 28.0.1.0 (SPSS, IBM Corporation, Armonk, NY, USA). Neuropsychological, feasibility and VC^{TM} data of ADHD children were therefore analyzed in order to describe the statistical distributions of such parameters in the clinical sample, also comparing different age range by means of a non-parametric U-Mann Whitney analysis. Relations among different neuropsychological functions, assessed with standardized test, were explored by means of Spearman correlation analyses. Non-parametric Friedman and Wilcoxon analyses were then conducted in order to analyze performance differences in different neuropsychological tests assessing the same neuropsychological processes. Correlations between each VC^{TM} parameters (span and time) and visuo-spatial short-term/working memory, verbal short-term/working memory and EFs were investigated through Spearman correlation analyses. Linear and multivariate regression analysis were therefore carried out in order to determined which neuropsychological processes were able to better explain the variance of the VC^{TM} parameters considered (span and time). Finally, VC^{TM} parameters and neuropsychological data of ADHD children were also compared with the ones of the control sample by means of non-parametric U-Mann Whitney analyses.

Results

3.1 Intelligence and neuropsychological functioning data

Data on intelligence (assessed with Wechsler Intelligence Scales, Third and Fourths Editions) of ADHD children are reported in Table 1. Results highlight better verbal and visual-perceptual reasoning skills (ICV, m=109,61; PRI, m=104,32), compared to working memory (WMI, m=88,90) and processing speed (PSI, m=88,48) abilities. The repeated measures Friedman test detected an overall effect on composite scores of the indices (χ^2_F=46,46, p = 0,000); Post-hoc pairwise comparison revealed statistically significant differences of WMI and PSI with PRI and VCI (Table 4).

	Test statistics	*Statistical significance*
WMI-PSI	-0,241	1,000
PRI-VCI	0,655	1,000
PSI-PRI	1,466*	0,004
WMI-PRI	1,707*	0,000
PSI-VCI	2,121*	0,000
WMI-VCI	2,362*	0,000

Table 4: Post-hoc pairwise comparison; * indicates a statistically significant difference of the indices means ($p < 0.05$). VCI: Verbal Comprehension Index; PRI: Perceptual Reasoning Index; WMI: Working Memory Index; PSI: Processing Speed Index

To test the goodness of the sample and ensure that there were no biases related to neuropsychiatric comorbidity, a U-Mann Whitney analysis has been employed between ADHD children with comorbid SLD (n= 13) and ADHD children without comorbid SLD (n=18). No statistically significant differences (Figure 8) were found in any of the cognitive indexes investigated (VCI, U= 97,50 p=0,448; PRI, U= 79,00 p=0,13; WMI U= 108,00 p= 0,93; PSI, U= 121,50 p=0,39; FSIQ, U= 108,00; p=0,73;).

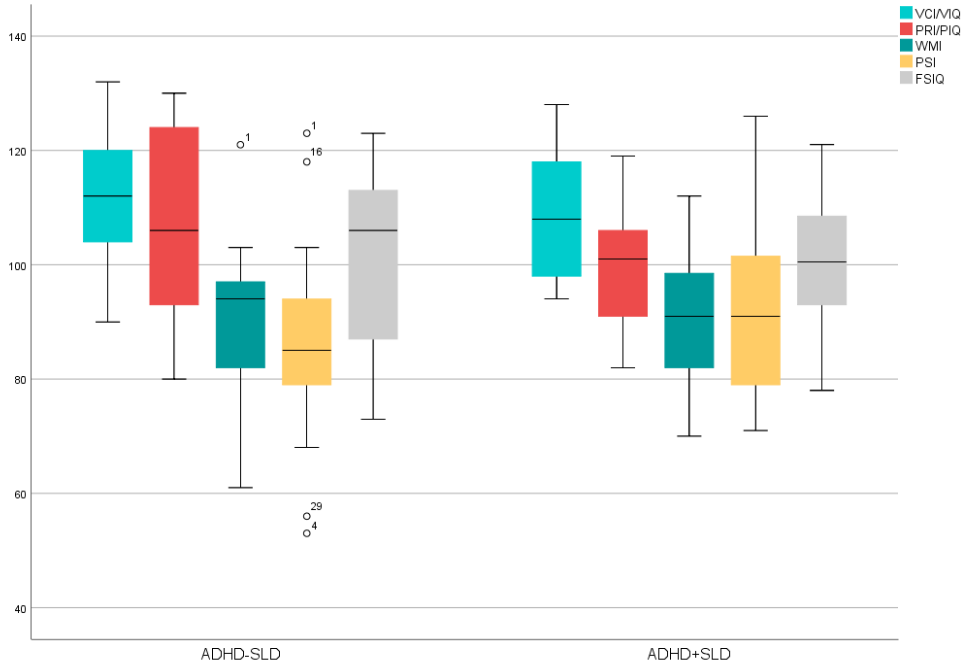

Figure 8: Box plot of intelligent scale mean indices according to diagnostic profile (ADHD with or without comorbid Specific Learning Disability-SLD-)

Neuropsychological data were available for thirty ADHD children. Concerning visuo-spatial memory in the reaching space assessed with the CBT, in the forward condition 32,3 % of subjects performed below the clinical cut-off. The span scores reported in Figure 9a are not normally distributed (W= 0,864; p<0,01), with span scores of 3 and 4 higher in frequency than the others (m=4,17 sd=1,02). In the backward condition, 35,5% of subjects performed below the clinical cut-off. The backward span scores reported in Figure 9b are again not normally distributed (W= ,849; p<0,01), with a span score of 3 higher in frequency than the others (m=3,59 sd=1,26). A statistically significant difference was found for span scores between ADHD children and control group matched for age, both in forward (U= 172,00; p<,05) and in backward conditions (U= 160,00; p<,05).

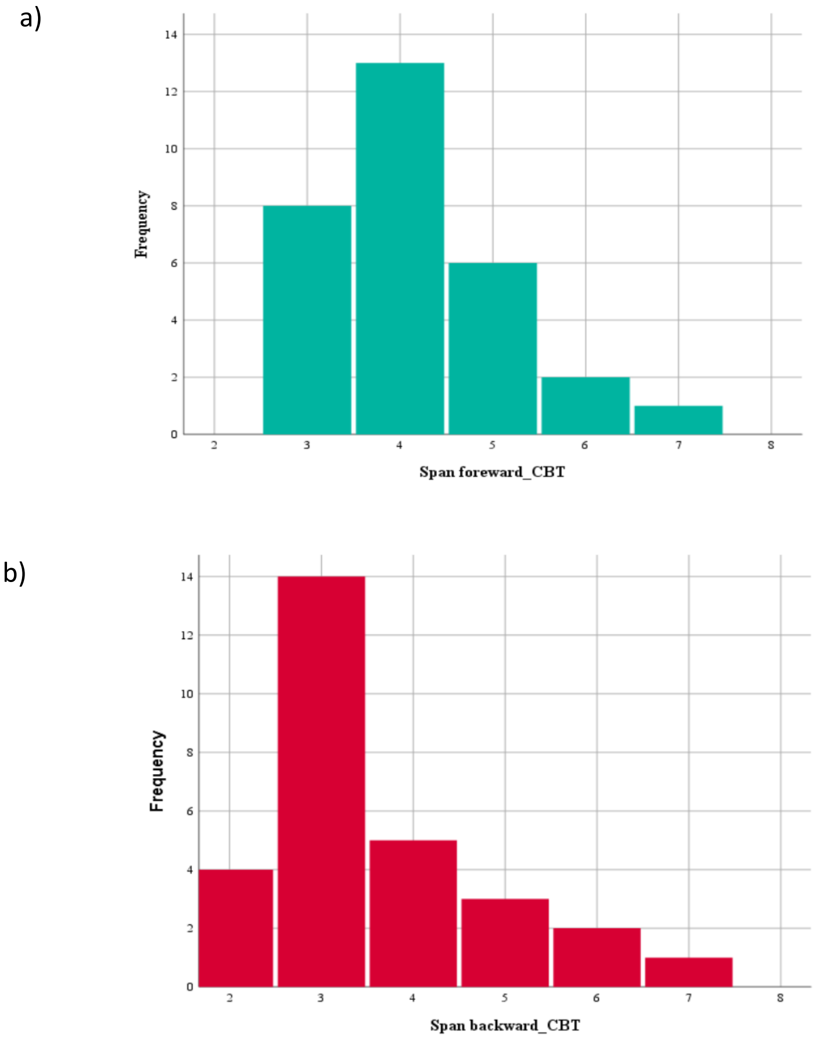

Figure 9: Corsi Block Tapping test **a)** Frequency of ADHD span forward scores. **b)** Frequency of ADHD span backward scores.

Comparing CBT forward and backward conditions by means of non-parametric Wilcoxon analysis, there was a statistically significant difference between span measures (Z =-2,53; p<0,05) (Figure 10), which were strongly positively correlated (rho=0,61; p<0,01).

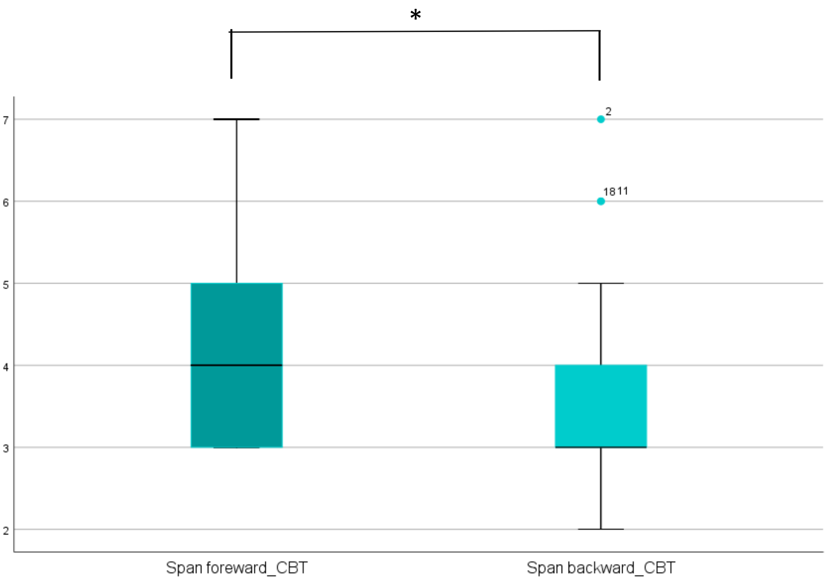

Figure 10: Corsi Block Tapping test**;** Box plot of ADHD span scores of forward and backward conditions; * statistical significance p< 0,05

Comparing the two age groups (7-9 years and 10-13 years), there were significant differences in the CBT span in the backward condition ($U_{(27)}$ =34,50, p < 0,01), with better scores for the 10-13 years group. The span measures strongly correlated with age both in forward (rho=0,51; p<0,01) and backward (rho=0,54; p<0,01) conditions.

Statistically significant correlations were also found between CBT span forward and Digit span, both in forward (rho=0,42; p<0,05) and backward (rho=0,53; p<0,01) conditions. Furthermore, significant correlations were found between CBT span backward and Digit span backward (rho=0,44; p<0,05). Regardless of the type of information to be encoded, short-term and working memory are the core processes underlying these different tasks as shown by the correlational data.

Concerning visuo-spatial memory in the reaching space assessed with Spatial Span task (SSP) (CANTAB®), span scores of children with ADHD were normally distributed (W=0,93; p=0,094) (Figure 11), with span scores of 5 and 6 higher in frequency than the others (m=5,14 sd=±1,23).

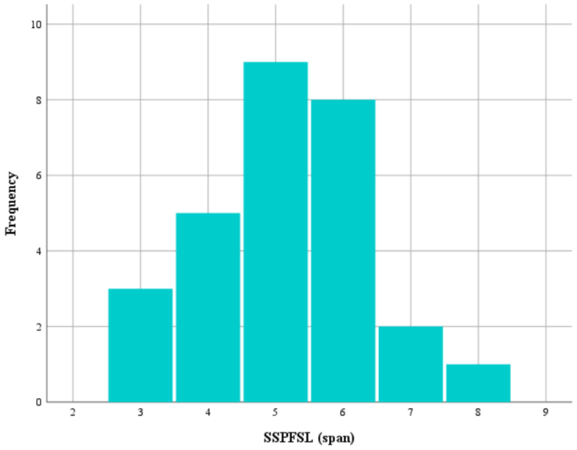

Figure 11: Cantab Spatial Span**;** Frequency of forward span length (SSPFSL) in ADHD children

A statistically significant difference was found for span scores between ADHD children and control group matched per age (U= 168,50; p<,05). Comparing the two age groups (7-9 years and 10-13 years), there were no significant differences in the SSP task outcomes (span and errors). The span measures strongly correlated with age expressed in months (rho=0,44; p<0,05).

Analysing ADHD performance in both tasks assessing short-term visuo-spatial memory in the reaching space, there were statistically significant differences between the two mean spans (Z =-3,38, p<0,01) (Figure 12), with better scores for the SSP CANTAB® task. The same result was also found analyzing the control group performance, with a statistically significant difference between the two mean spans (Z =-2.39, p<0,05).

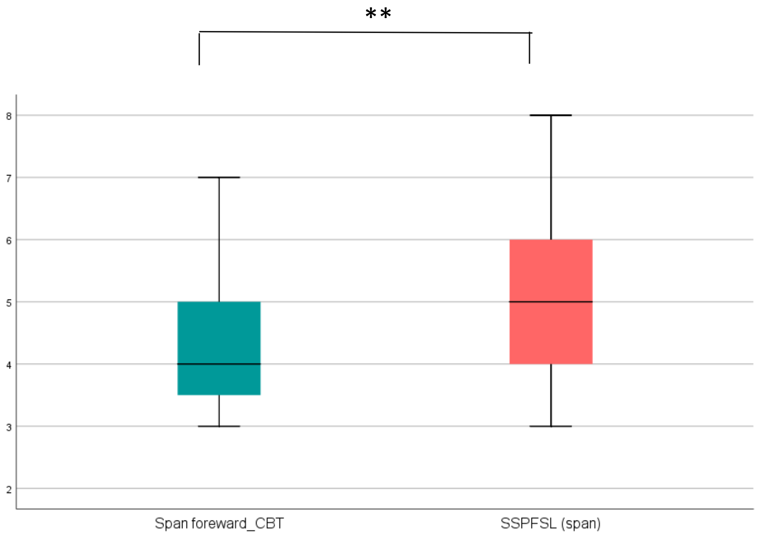

Figure 12: Box plot of ADHD span scores at CBT forward condition and of SSP CANTAB® task.

** statistical significance p=< 0,01

Statistically significant correlations were found between SSP span and CBT span, both in forward (rho=0,51; p<0,01) and backward (rho=0,54; p<0,01) conditions.

Considering data on attention and inhibition abilities assessed with the Stop Signal Task, computerized task (SST, CANTAB®), ADHD performed as following: Stop Signal Reaction Time (m=325,22; sd=67,4), Direction errors – Go trials (m=14,55; sd=16,91), Median reaction time – All go trial (m=601,41; sd=122,20), Missed trials (m=35,97; sd=35,13). Statistically significant difference was found between ADHD and matched controls in missed trials (U= 134,00; p<,01).

A statistically significant difference was found between the two age groups (7-9 years and 10-13 years) in missed trial outcome as a measure of sustained attention (with a total number of trials missed by the subject higher for the 7-9 years old age group) (U =48,00; p<0,05).

Statistically significant correlations were found between Stop Signal Task SSRT as a measure of inhibition and short-term memory, both verbal (rho=-0.41; p<0,05) and visuo-spatial (rho=-0,38; p<0,05). Furthermore, a significant correlation was found between Stop Signal Task missed trials as a measure of sustained attention and CBT backward span (rho=-0.41; p<0,05). Finally, a significant correlation was also found between Stop Signal Task direction errors and Digit forward span (rho=-0,37; p<0,05).

ADHD performance in a planning task (Tower of London) was lower than matched controls, considering as parameters decision time (m = 49,08; sd = 11,18), total time (m = 49,56; sd = 17,11), total score (m = 45,76; sd = 11,91) and number of rule violations (60% of children with ADHD performed above the clinical cut-off) (Figure 13).

A significant positive correlation was found between Tower of London decision time and visuo-spatial span (CANTAB®).

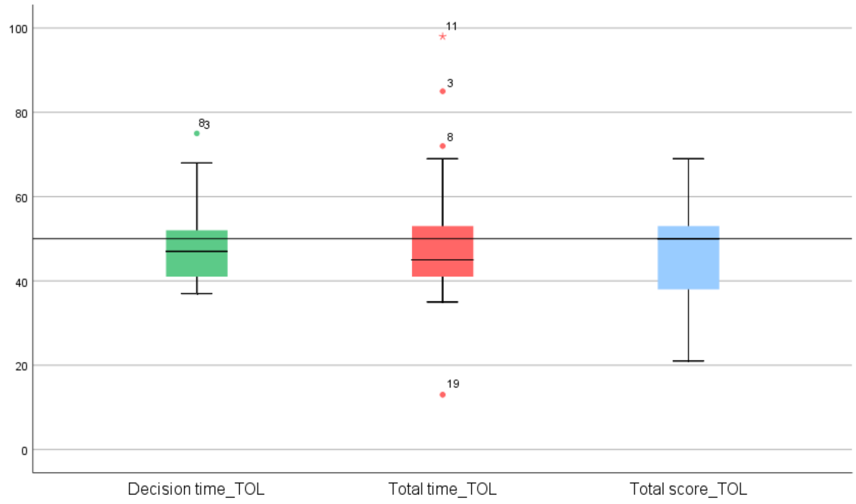

Figure 13: Box plot of ADHD children T scores on Tower of London test parameters.

Concerning executive functioning in daily life assessed indirectly with a parent report questionnaire, 50% of ADHD subjects obtained scores above the clinical cut-off (T score >65) in the Global Executive Composite score (m=64,83, sd=10,69). ADHD children's median T scores were higher for each index than control subjects (Figure 14).

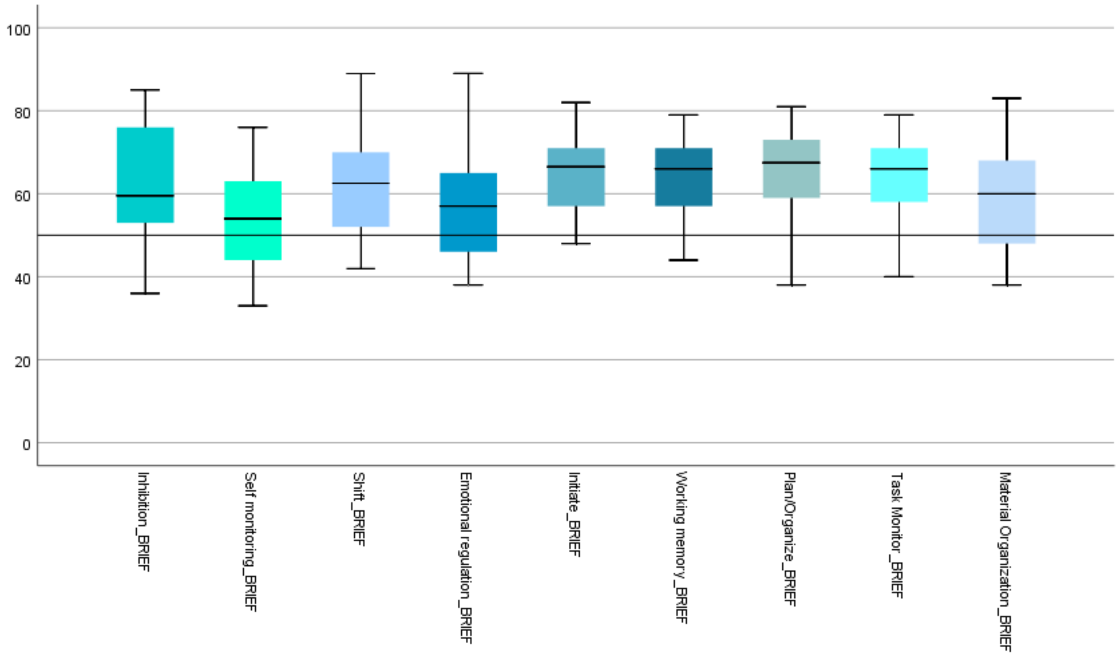

Figure 14: Box plot of ADHD children T scores of BRIEF-2 parent report questionnaire in the different scales.

Specifically, analysing scales assessing executive functions most challenged in the VC™ task, the result highlight that 43,3% ADHD children obtained scores above the clinical cut-off (T>65) in the inhibition scale (m=63,10; sd=13,14), 63,3% in the working memory scale (m=64,37; sd=8,87) and 60% in the plan/organize scale (m=64,43; sd=12,17).

Statistically significant differences were even found between ADHD children and matched controls, for all BRIEF-2 scales, indices and composite score (p<0,001).

In line with literature data, negligible correlations were found between BRIEF-2 scales and other EF measures assessed with direct standardized neuropsychological tests. Inhibition abilities assessed by CANTAB® Stop Signal task, positively correlated with the self-monitoring BRIEF-2 scale (rho=0,50; p<0,01).

All Spearman correlation analyses among different neuropsychological outcomes assessed with standardized tests have been included in Appendix 3.

3.2 Feasibility results

After such neuropsychological profile description of ADHD sample, the primary aim of the study was to evaluate the feasibility of the VC™ for assessing visual-spatial memory and EFs in a navigation task in children with ADHD. Feasibility questionnaire data and feasibility checklist measures were available for twenty-one subjects, recruited for the feasibility pilot study (Del Lucchese et al., 2021).

Concerning the checklist measures, feasibility criteria were met for all measures both for the VC™ assessment and for the entire study design and procedures (Table 5). In particular, for the outcome measures investigating the feasibility of the VC™ paradigm the results were as follows:

- Accessibility: all participants completely understood VC™ rules, aims and instructions administered by the psychologist. Only two children out of 31 requested further clarification than those set to carry out the activity. Furthermore, from a qualitative analysis, variables related to cognitive functioning, such as Verbal Comprehension Index (VCI) and Total Intelligence Quotient (QIT), did not impact the understanding of the VC™ assessment instructions.
- VC™ compliance: 20 participants completed the VC™ assessment procedure within an hour and a half, with a mean total duration of 34±7,49 minutes. The other two participants did not finish the whole paradigm, requiring frequent pauses and

interruptions during the assessment procedure. When considering time to complete the VC™ assessment, there were no statistically significant differences related to age group (7-9 yrs or 10-13 yrs), ADHD presentation (combined or inattentive) and order of administration (VC™ assessment performed as first or after the neuropsychological evaluation).

- Technical smoothness: the VC™ software and hardware equipment presented some technical issues in the use of the head and trunk sensors. In fact, seven out of 22 patients presented some missing data in the sensors recording of the subject's position in the array. Nevertheless, all these issues were fixed offline in a short time without remote assistance needed by a professional team of engineers, although the correction procedure was time consuming. Moreover, some data was recovered, asking the subjects to return to the hospital after few days to complete the VC™ assessment previously stopped because of technical issues.
- Motivation: all the participants except two completed the VC™ assessment. Two ADHD subjects were unable to complete the whole procedure, requiring a lot of stops and pauses, due to the loss of motivation and collaboration.

Concerning the feasibility of study design and procedures:

- Participation willingness: only one eligible child was not recruited as the parents did not give the consent in participating to the project.
- Participation rates: only one eligible participant, who agreed to join the project, did not complete all the study procedures, as parents refused the neuropsychological assessment to be carried out in a different day than the VC™.
- Missing data from VC™ paradigm or from the neuropsychological assessment: some missing data were present both for the VC™ assessment (sensors technical issues) and for the neuropsychological assessment (Digit Span, Tower of London).
- Assessment time scale: the outcome measures of all participants except three were collected within 2 hours and half, with a mean total duration of 78,66±10,46. Two participants did not complete the whole VC™ paradigm, requiring frequent pauses and interruptions during the assessment procedure with the experimental device. Furthermore, one participant did not complete all the study procedures, as parents refused the neuropsychological assessment to be carried out in a different day than the VC™ one. When considering the executed amount of the whole assessment (VC™ and neuropsychological), there were no statistically significant differences

related to age group (7-9 yrs or 10-13 yrs), ADHD presentation (combined or inattentive) and order of administration (VC™ assessment performed as first or after the neuropsychological evaluation).

- Assessment procedures: all the participants who started the assessment procedures except three completed the study. Two participants did not complete the whole VC™ paradigm, requiring frequent pauses and interruptions during the assessment procedure with the experimental device. Furthermore, one participant did not complete all the study procedures, as parents refused the neuropsychological assessment to be carried out in a different day than the VC™ one.

Table 5: Feasibility criteria for success and outcome measures for each feasibility criterion

	Feasibility criteria	**Measurement**	**Feasibility criterion for success**	**Outcome measures**
Feasibility of VC™ assessment	*Accessibility*	Recording of clarification request to the psychologist	At least 80% of participants	90,4%
	VC™ compliance	Report from psychologist that administer the VC™ protocol.	At least 80% of participants	90,4%
	Technical smoothness	Number of participants that required stops during the VC™ assessment due to technical problems and missing data recorded from the sensors.	Less than 50% of participants	28,6%
	Motivation	Number of participants that required stops due to subjects' loss of motivation and collaboration	Less than 20% of participants	14,2%
Feasibility of study design and procedure	*Partecipation willingness*	Number of eligible participants that agree to join the project	More than 80% of eligible subjects	95,5%
	Participation rates	Number of dropouts	Less than 20% of participants who gave consensus	4,7%
	Missing data from VC™ or Neuropsychological assessment	Missing data from VC™ paradigm or neuropsychological assessment	Less than 20% of participants	VC™ 9,5% Neuropsychological 14,26%
	Assessment time scale	Time spent for collecting all outcome measures.	More than 80% of participants	90,5%
	Assessment procedure	Numbers of subjects who completed the all assessment procedures	More than 80% of participants	90,5%

The feasibility questionnaire was filled out by the two experimenters immediately after the VC™ assessment procedure for 22 participants. The results for usability and acceptability revealed a prevalence of positive responses, indicating a satisfactory feasibility of the VC™ paradigm. For usability (6 questions), there were 74/126 responses graded as 5 and 29/126 as 4. For acceptability (8 questions), there 73/168 graded as 5 and 44/168 as 4. By averaging the responses of each subject within the two different domains, the results indicated satisfactory usability (m=4,37; sd=0,51) and acceptability (m=3,88; sd=0,59) (Figure 15).

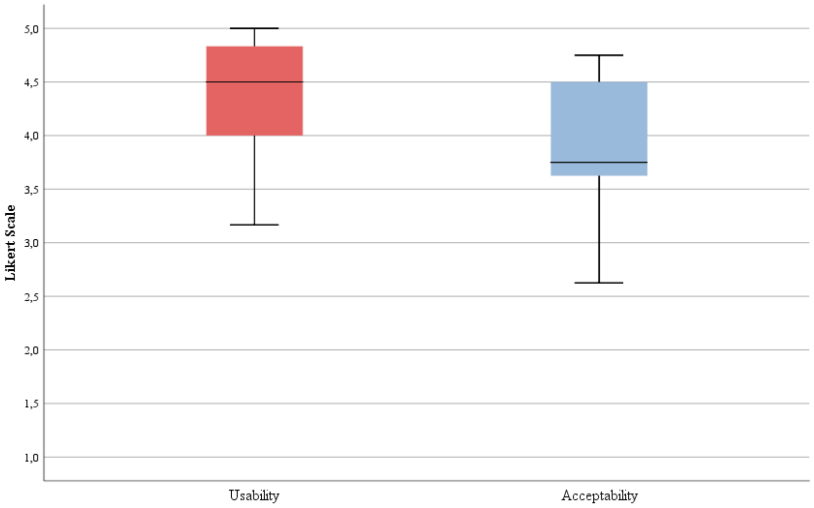

Figure 15. Box plot of the mean of each subject's answers on usability and acceptability domains at the feasibility questionnaire

The two measures were strongly correlated (rho=0,94; p<0,05).

A significant effect both on usability (U=21,00; p<0,05) and acceptability (U=15,50; p<0,01) was found between the two age groups (7-9 yrs; 10-13 yrs) (Figure 16a,16b).

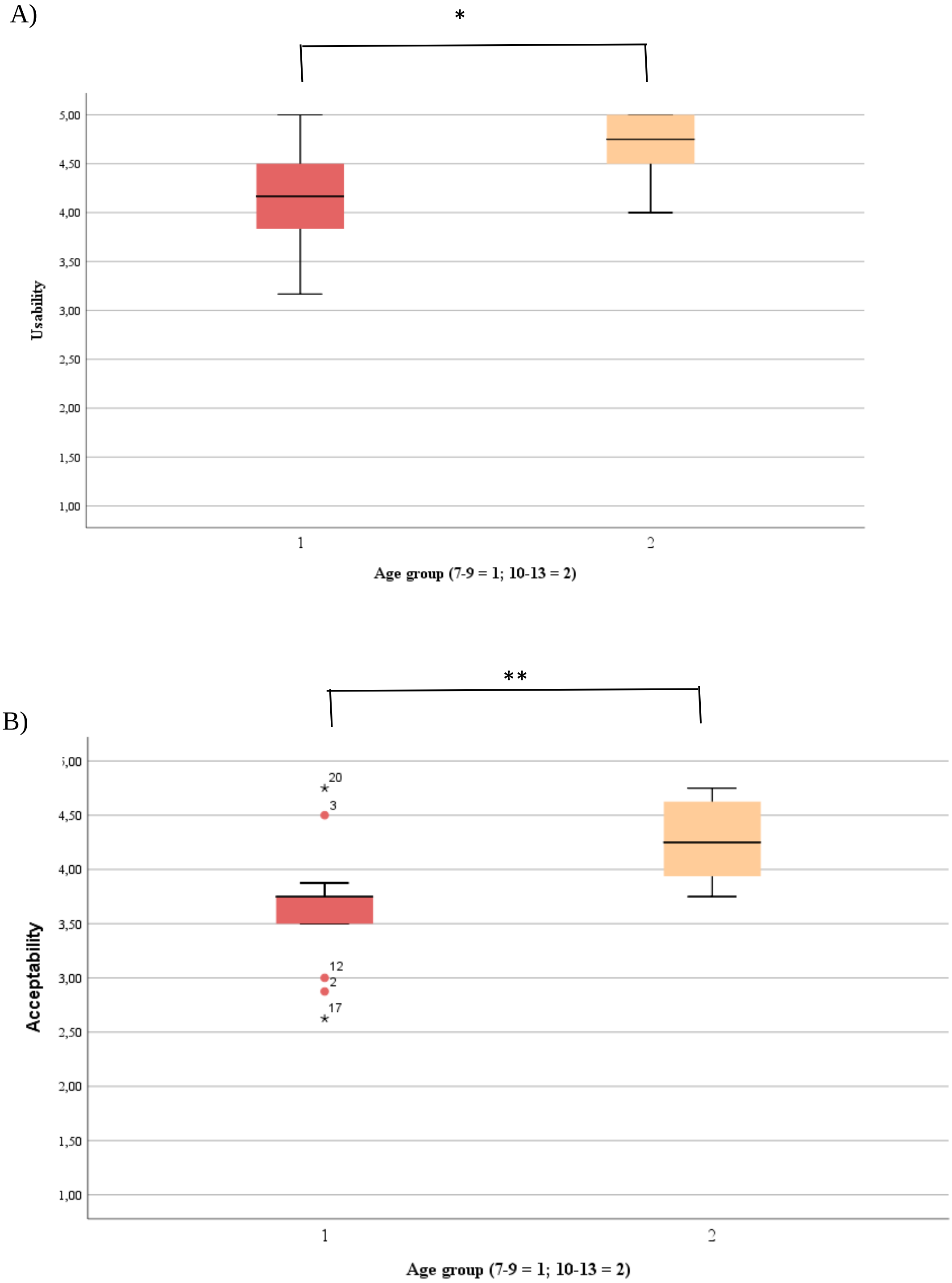

Figure 16. (A) Box plot of mean answers on the usability domain divided per age range groups in the ADHD sample. (B) Box plot of mean answers on the acceptability domain divided per age range groups. * p < 0,05; **p < 0,01

There were no statistically significant differences both in usability and acceptability outcome measures for ADHD presentation (combined or inattentive) and order of administration (VC™ assessment performed as first or after the neuropsychological evaluation).

3.3 Virtual City quantitative data analysis

3.3.1 Span following condition

VC™ following condition data were available for 28 subjects out of 31 recruited. One participant did not complete the whole VC™ paradigm, requiring frequent pauses and interruptions during the assessment procedure with the experimental device. Furthermore, another participant did not complete all the study procedures, as parents refused the neuropsychological assessment to be carried out in a different day than the VC™ one. For some technical issues, the VC™ was not completed by another ADHD subject.

The VC™ span (the highest level passed in the following condition) as a measure of visuo-spatial memory assessed in a locomotor task was not normally distributed in ADHD children (W=0,86; p<0,01), with a span score of three more frequent than the others (m=4,17 ds=±1,02) (Figure 17).

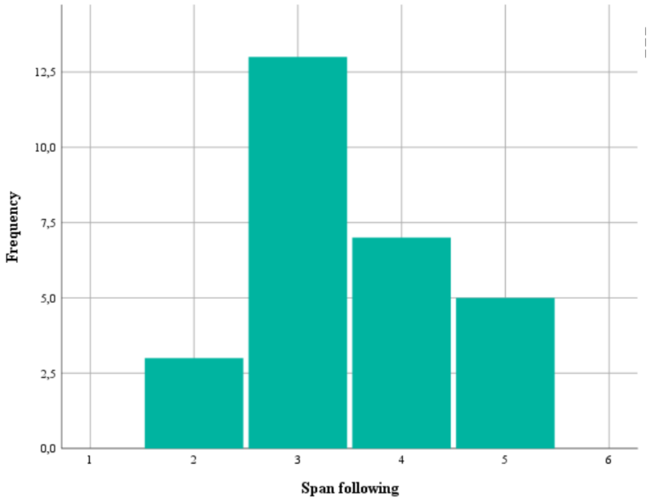

Figure 17: Frequency of ADHD span scores at the VC ™

A statistically significant differences was found between ADHD and control group, with a greater span for typically developing children (U= 174,50; p<,05) (Figure 18).

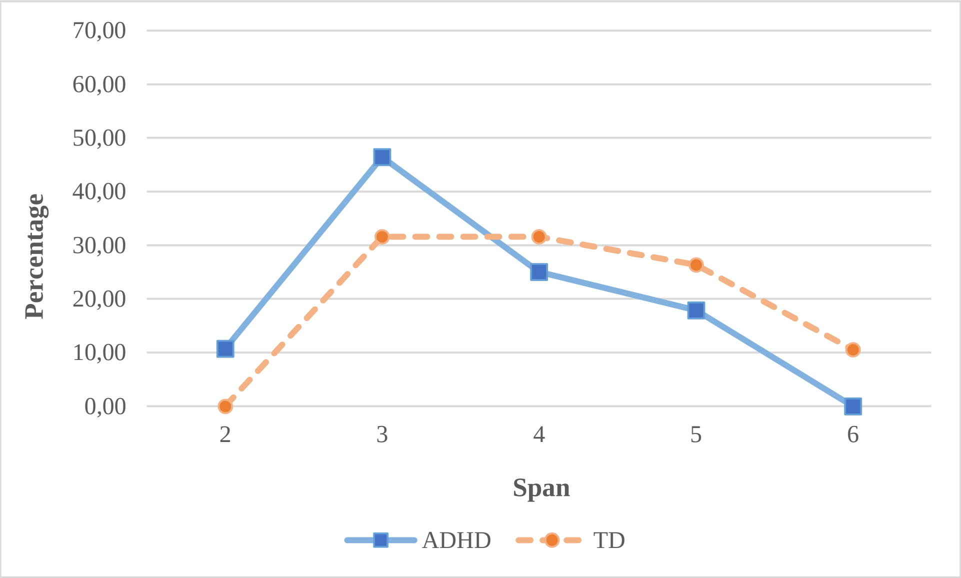

Figure 18: Line graph of the percentage frequency of the span in the VC ^{TM} following condition, both for typically (TD) and ADHD groups.

Comparing the two age groups (7-9 years and 10-13 years), there were no significant differences in the VC™ span following condition (U =53,00, p = 0,80). The span measures strongly correlated with age expressed in months (rho=0,59; p<0,01).

Statistically significant differences were found between VC™ span (following condition) and visuo-spatial span assessed in the reaching space, both with CBT test (U = -3,78; p<0,01) (Figure 19) and CANTAB® Spatial Span task (U=-4,16; p<0,01).

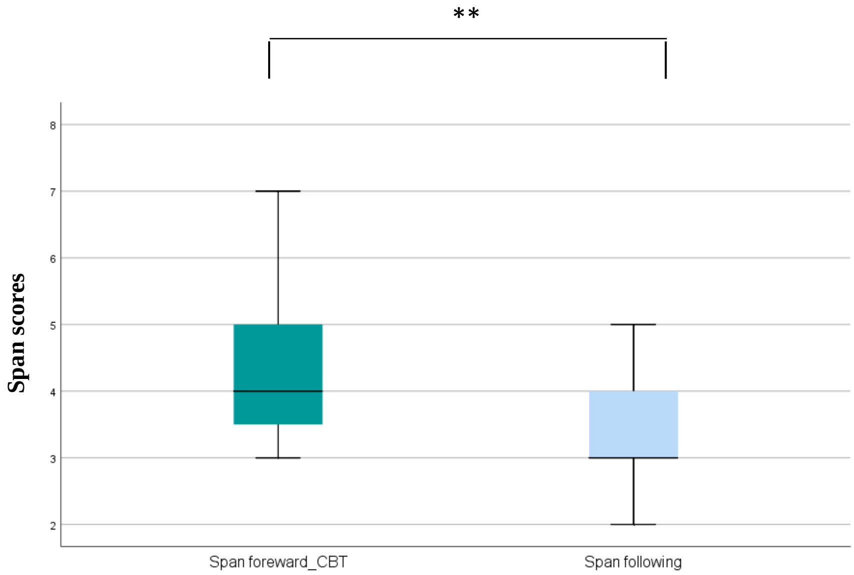

Figure 19: Box plot of ADHD children span scores at VC™ paradigm (following condition) and at CBT test. ** statistical significance p=< 0,01

Statistically significant correlations were found between VC™ span and span outcome measures assessed by other neuropsychological tests. In particular, results highlighted a significant correlation between VC™ span and visuo-spatial span assessed in the reaching space (CBT), both in forward (rho=0,61; p<0,01) and backward conditions (rho=0,42; p<0,05). Significant correlations were found also between VC™ span and verbal working memory (rho=0,49; p = 0,01). Significant correlations were also found between VC™ assessment and intelligence, both for the Full-scale index (rho=0,39; p<0,05) and the Verbal comprehension index (rho= 0,44; p<0,05). No statistically significant correlations were found with any of the executive function outcome measures.

In order to investigate which neuropsychological function better predicted VC™ span, linear regression analyses were carried out, after checking for skewness and kurtosis of each variable included in the models (Appendix 4). Results were therefore further analysed by means of multiple regression analyses, revealing that the VC™ span in ADHD children was better predicted by a model including the following factors: CANTAB © spatial span, verbal working memory (Digit backward) and self-monitoring scale of BRIEF 2 questionnaire (R^2 = 0,66; F= 13,65; p<0,01) (Figure 20).

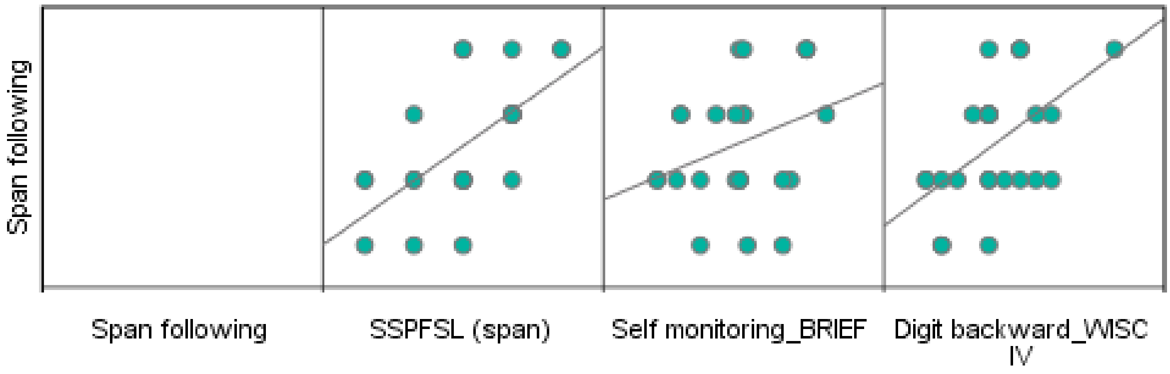

Figure 20: Scatter plots of Span at the VC^{TM} following condition as explained respectively by SSPFSL span (CANTAB), Self.monitoring (BRIEF-2), digit backward (WISC IV)

3.3.2 Mean total execution time (Following condition)

As a measure of the efficiency of neuropsychological processes involved in the VC™ (following condition) such as visual-spatial memory, path planning and impulsivity, the average execution time at the first three items of level two in the following condition was considered. Data were available for 28 clinical subjects, were normally distributed ($W_{(28)}$=0,96; p=0,41). Children with ADHD showed mean total execution times of

22675,69 ms (± 4584,10), that did not correlate with VC™ following span. Mean execution time at level two was significantly lower in ADHD children than in control group (U= 160,00; p<,05) (Figure 21). No statically significant differences were found comparing the two age groups (7-9 years and 10-13 years) and no significant correlation was obtained with age expressed in months.

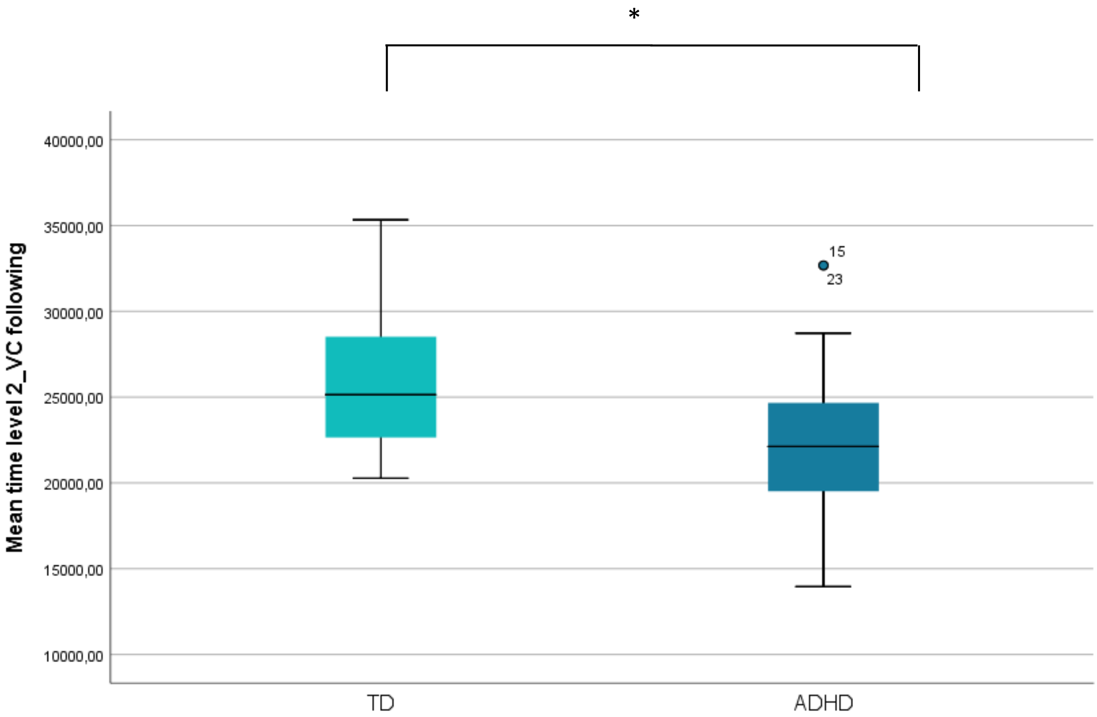

Figure 21: Box plot of mean execution time (ms) at the first three items of level 2 (VC™, following condition) in ADHD children and control group. * Statistical significance p< 0,05

Considering the cognitive and neuropsychological functioning outcome measures, mean total execution time correlated significantly with working memory (rho=-0,39; p<0,05), planning (rho=-0,45; p<0,05) and material organization (rho=-0,51; p<0,01) scales of the BRIEF-2 questionnaire. The greater the time spent in the VC™ trials, the better the abilities of working memory, planning and material organization as reported by parents.

In order to investigate which neuropsychological function better predicted VC™ mean total execution time (following condition), linear regression analyses were carried out, after checking for skewness and kurtosis of each variable included in the models (Appendix 4). Results were therefore further analysed by means of multivariate regression analyses, revealing that the VC™ mean total execution time (following condition) in ADHD children was better predicted by a model including the following factors: material organization and self monitoring scales of BRIEF-2 parent-report questionnaire ($R^2 = 0,35$; F= 6,94; p<0,05) (Figure 22).

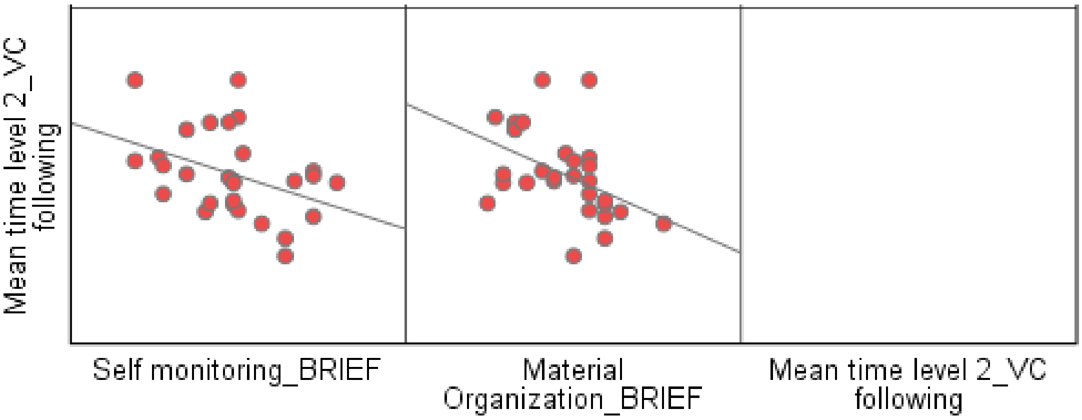

Figure 22: Scatter plots of mean execution time (ms) at the VC™ following condition level 2 as explained respectively by Self-monitoring and Material Organization (BRIEF-2)

3.3.3 Error analysis (Following condition)

Starting from the error classification by Belmonti and collegues (2014) previously described, four basic point errors were identified:

- omission: a location present in the stimulus is absent in the response, and the number of locations in the response is lower;
- substitution: a location present in the stimulus is replaced by a different one in the response;
- insertion: a location present in the response is absent in the stimulus, and the number of locations in response is higher;
- permutation: two locations present in the stimulus are present in the response in inverted order.

In addition to these types of errors, if more than half of the sequence was not correctly reproduced, the response was classified as random.

Videos of the child's behaviour during locomotion and the trajectories of 18 ADHD children during the 10 trials of the last level reached in VC™ Following condition were analysed to identify the different types of errors. The number of rule violations committed at the same level was also reported for each subject. The results revealed a higher frequency of substitution errors (Figure 23), differently from Belmonti et al., 2014, where permutation errors were more common.

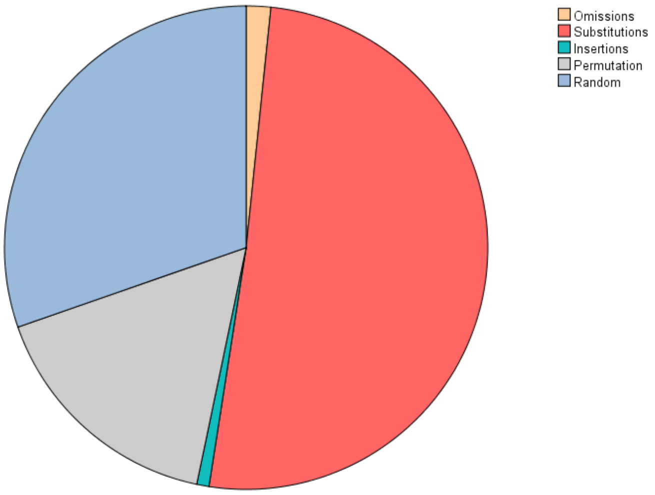

Figure 23: Frequency distribution of error types in the ADHD group

Substitution errors could be further diversified into regional (a house is replaced with a neighboring house) and semantic (a house is replaced with one of the same color), identifying different strategies for solving the task. The mean proportion of regional substitution errors on the total substitution errors was significantly higher than the semantic one (Z = -3,530; p < 0,001)

Comparing the two age groups (7-9 years and 10-13 years), there was a statistically significant difference only for rule violations, higher in the 7-9 years group than in the 10-13 years group (U=18,50; p<0,05) (Figure 24).

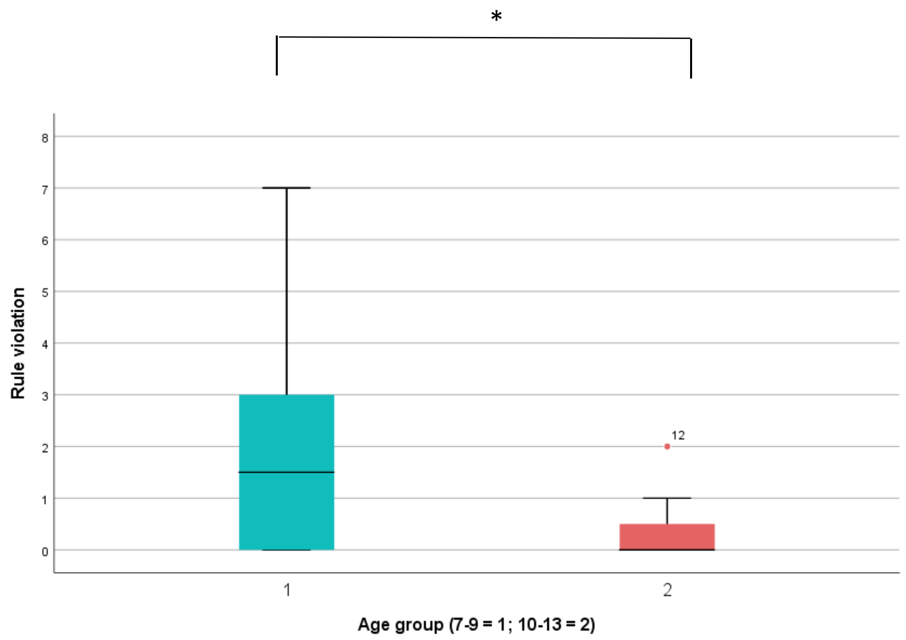

Figure 24: Box plot of ADHD rule violations in the last level reached in the VC™ Following condition, considering two different age groups. * p <0,05

Considering cognitive data, a statistically significant negative correlation was found between rule violations ad perceptual reasoning index (rho= -0,53; p<0,05). A statistically significant negative correlation was also found between rule violations and visuo-spatial short-term memory span in the reaching space, assessed with CBT (rho=-0,48; p<0,05) and with SSP (CANTAB®; rho=-0,57; p<0,05). The number of rule violations negatively correlated also with executive functions direct measures, in particular with Tower of London test total score (rho=-0,49; p=0,50). As regards indirect outcome measures of executive function, rule violations positively correlated with BRIEF-2 scales (T-Scores) for Self Monitoring Scale (rho=0,49; p<0,05) and Behavioral Regulation Index (rho=0,51; p<0,05). Substitution errors positively correlated with the Working Memory Scale (BRIEF-2) (rho=0,55; p<0,05).

Considering the other VC™ outcome measures, rule violation negatively correlated with mean total execution time at the first three items of level two in the following condition (rho=-0,52; p<0,05). No other statistically significant correlations were found with VC™ span.

The error analysis in the VC™ Following condition through the videos was also conducted for 18 matched control children. The results revealed an error distribution similar to the ADHD one (Figure 25), with a higher frequency of substitution errors. Further classifying the substitution errors into regional and semantic, also in the control subjects the mean proportion of regional substitution errors on the total substitution errors was significantly higher than the semantic one (U = -2,78; p <0,01). Comparing ADHD and control groups, no statistically significant differences were found, neither in the number of errors nor in the number of rule violations.

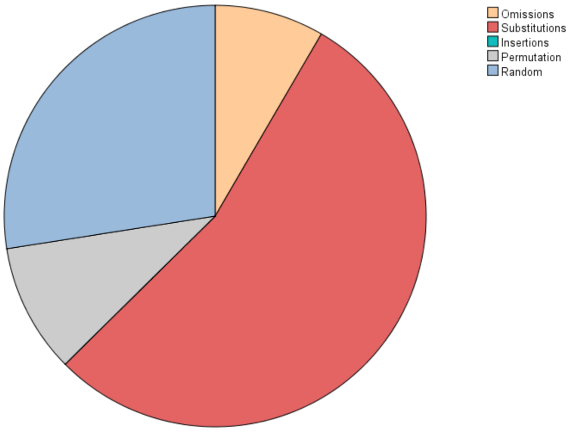

Figure 25: Frequency distribution of error types in the control group at the Following condition, represented through a pie chart

3.3.4 Mean total execution time (Planning condition)

As a measure of the efficiency of neuropsychological processes involved in the VC™ (planning condition) as path planning, inhibition and impulsivity, the average execution time at all items of level three, performed by the majority of subjects (n=22) was considered for analysis. Children with ADHD showed mean total execution times of 30029,75 ms (±6215,39), normally distributed ($W_{(22)}$=0,96; p=0,52).

No statically significant differences were found comparing the two age groups (7-9 years and 10-13 years) and no significant correlation was obtained with age expressed in months.

Considering intelligence measures, mean total execution time at level 3 correlated significantly with the Perceptual reasoning index (rho=0,58; p<0,01) of the WISC-IV. A statistically significant correlation was found with short-term memory assessed with a computerized CBT task (rho=0,54; p<0,05). Concerning executive functions outcome measures, total execution time at level 3 correlated significantly with the Tower of London decision time (rho=0,57; p<0,05) and with some of BRIEF-2 questionnaire scales. In particular, statically significant correlations were found with working memory (rho=-0,55;

p<0,01), plan/organize (rho=-0,54; p<0,05), task monitor (rho=-0,51; p<0,05) and material organization (rho=-0,48; p<0,05) scales. The greater the time spent in the VC™ planning trials, the better the abilities of working memory, planning and material organization as reported by parents.

In order to investigate which neuropsychological function better predicted VC™ mean total execution time (level 3, planning condition), linear regression analyses were carried out, after checking for skewness and kurtosis of each variable included in the models (Appendix 4). Results were therefore further analysed by means of multivariate regression analyses, revealing that the VC™ mean total execution time (level 3, planning condition) in ADHD children was better predicted by a model including the following factors: material organization scale of BRIEF-2 parent-report questionnaire and PRI/PIQ index of WISC IV ($R^2 = 0,62$; F= 15,69; p<0,01) (Figure 26).

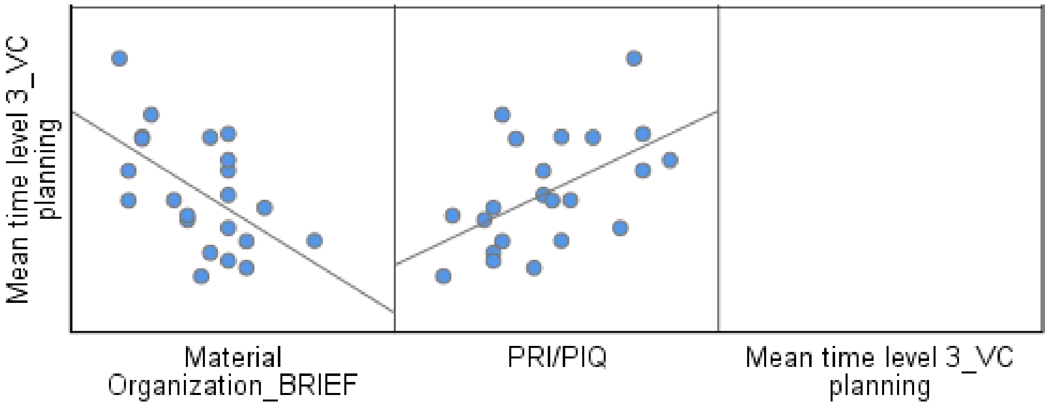

Figure 26: Scatter plots of mean execution time (ms) at the VC^{TM} planning condition level 3 as explained respectively Material Organization (BRIEF-2) and PRI/PIQ (WISC IV/WIPPSI III)

The mean execution time for all the items performed by each subject in the planning condition was also calculated. Considering that each subject performed different levels according to the Following condition span, the number of houses was weighted through the following algorithm:

$$\text{Total mean execution time} = \frac{\frac{\mu(\Delta t^{l-1})}{n+1} + \frac{\mu(\Delta t^{l})}{n+1}}{2}$$

μ= mean; Δt=execution time for each trial performed at the same level; l=level; n=number of houses that flickered at the level considered.

Children with ADHD showed mean total execution times of 22790,71 ms (±4630,06), normally distributed ($W_{(27)}$=0,94; p=0,15). No statically significant differences were found comparing the two age groups (7-9 years and 10-13 years) and no significant correlation was obtained with age expressed in months.

Considering intelligence measures, mean total execution time correlated significantly with the Perceptual reasoning index (rho=0,50; p<0,01). For executive functions assessed with the parent report questionnaire, the total execution time correlated significantly with task monitor (rho=-0,39; p<0,05) and material organization (rho=-0,39; p<0,05) scales. The greater the time spent in the VC™ planning trials, the better the abilities of task monitoring and material organization as reported by parents.

In order to investigate which neuropsychological function better predicted VC™ mean total execution time (planning condition), linear regression analyses were carried out, after checking for skewness and kurtosis of each variable included in the models (Appendix 4). Results were therefore further analysed by means of multivariate regression analyses, revealing that the VC™ mean total execution time (planning condition) in ADHD children was better predicted by a model including the following factors: material organization scale of BRIEF-2 parent-report questionnaire and PRI/PIQ index of WISC IV (R^2 = 0,48; F= 11,42; p<0,01) (Figure 27).

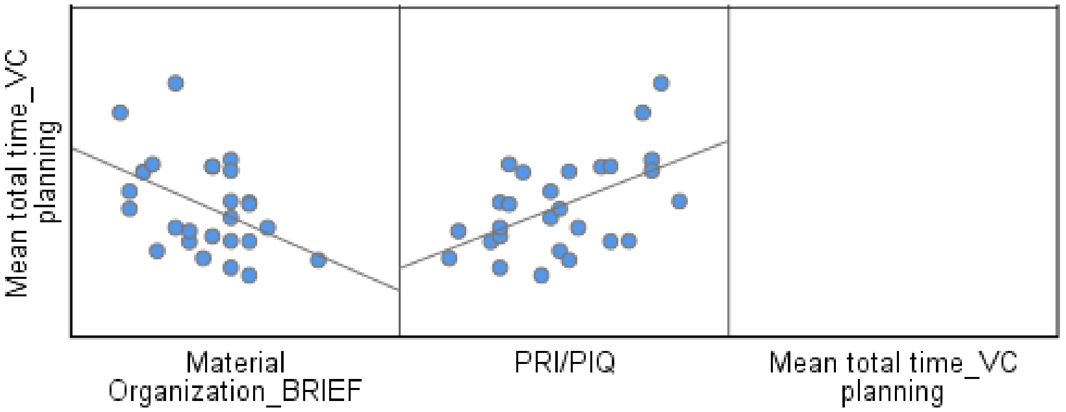

Figure 27: Scatter plots of mean total execution time (ms) at the VC^{TM} planning condition as explained respectively Material Organization (BRIEF-2) and PRI/PIQ (WISC IV/WIPPSI III)

Comparing the ADHD group and typically developing children, a statistically significant difference was found, with greater level 3 total execution time for the control group (U= 67,00; p<0,05) (Figure 28).

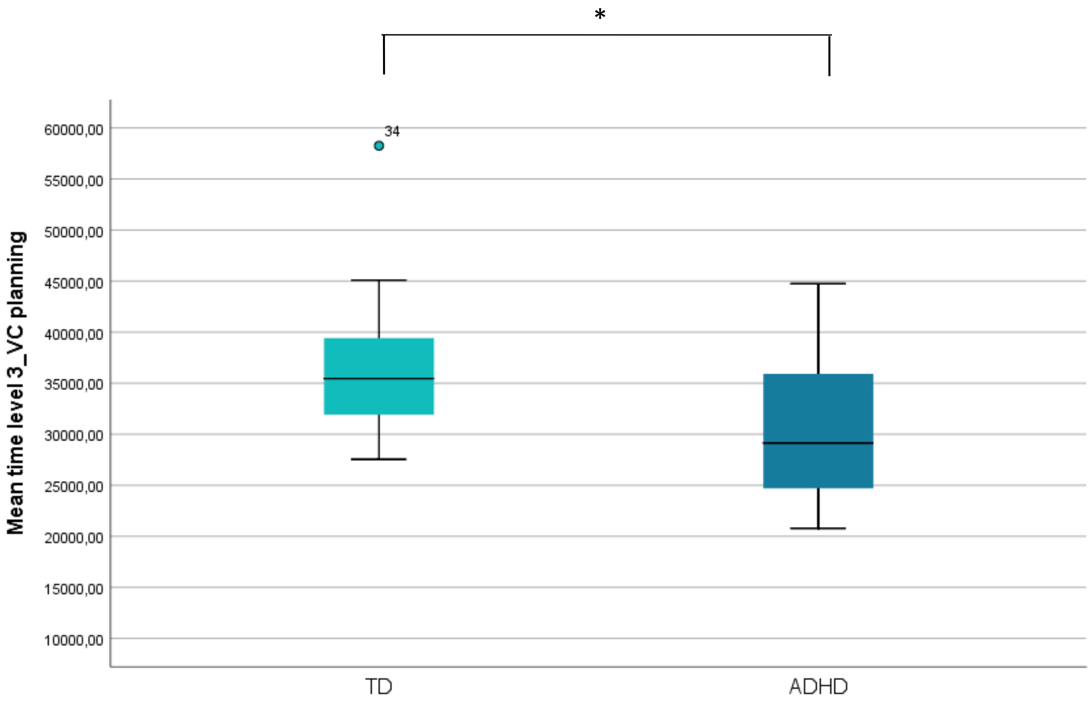

Figure 28: Box plot of mean level 3 total execution time (ms) at the VC™ Planning condition in the ADHD children and control group. * p<0,05

3.3.5 Incorrect trials and number of errors (Planning condition)

The analysis of videos and trajectories of 18 ADHD children in VC™ Planning condition made it possible to identify the number of incorrect trials (from a minimum of 0 to a maximum of 10) and the number of errors (omissions, substitutions, insertions and permutations) within the span level of the navigation task. Children with ADHD showed mean total errors of 4,05 (±3,03), with an average of 3,16 (±1,88) of incorrect trials. No statistically significant differences were found between ADHD and typically developing children for any of the two error parameters. Furthermore, no statically significant correlations were found with the other VC™ paradigm, such as Following condition span and total execution time both in ADHD and typically developing children.

Comparing the two age groups (7-9 years and 10-13 years), there was no statistically significant difference, nor correlations between age express in month and the accuracy VC™ Planning outcome measures. According to the assessment presentation order, statistically significant differences were found, with greater total errors ($t_{(16)}$=-1,72; p< ,05) for children who carried out the neuropsychological evaluation first.

Considering intelligence and neuropsychological data, a statistically significant negative correlation was found only with material organization BRIEF – 2 scale, as an ecological indirect measure of daily life executive functions (wrong trials: rho=-0,53; p < 0,05; total errors: rho=0,64; p<0,01).

3.4 Virtual City preliminary data on trajectories

Based on trajectories analyses, a qualitative description of the behaviour during VC^{TM} performance is presented for two children with ADHD and the control subject. Figure 29 compares the trajectories of the same sequence (span level 3, trial 3) in the City Following condition, where the child was asked to reach three houses flickering in an easy sequence. In Figure 29A, the child with Combined ADHD performed the trial correctly by reaching the 3 target houses in the right order. However, he reached the first and second target houses, then stopped, not remembering the exact position of the third target house. He therefore returned to the starting position, looked around (as indicated by the red arrows), then he presumably remembered the position of the third target house and headed toward it. The head movements while the child was standing in the starting position were greater in number than those of the control subject, although correctly directed towards the flickering target houses. The total execution time was significantly lower than those of the matched control subject and of the child with Inattentive ADHD. In Figure 29B, the child with Inattentive ADHD failed the sequence. The child started from the initial position and correctly reached the first and second houses. He then reached a wrong house, then stopped, looked around, understood that he had failed and thus proceeded to reaching another (incorrect) house. From Figure 29B, this child’s head movements, shown by red arrows, indicate a high distractibility of the subject, given his frequent deviation from the trajectory and they do not predict the following direction of the movement. Also in the starting position the head movements were greater in number than those observed in the control subject, as well as of greater amplitude also with respect to the child with Combined ADHD. Figure 29C shows that the control child reached the target houses in the right order with a linear locomotion trajectory. The head movements did not deviate from the path when linear, while they were anticipatory when body rotations were necessary, predicting the following movement directions. While standing in the starting position the head movements were reduced and directed toward the target houses, presumably to support the encoding phase of the task. Neuropsychological assessment data of the two children with ADHD and the control subject revealed some important qualitative differences. Both visuo-spatial memory (Corsi span forward and backward) and EFs performance were markedly lower in the two children with ADHD. At the parent report questionnaire BRIEF-2, cognitive regulation abilities (Cognitive Regulation Index) were much poorer in the children with ADHD than in the control, with T scores in the clinical/borderline range. Tower of London performance indicated significant difficulties only in the child with Inattentive presentation.

Thus, crucial skills for carrying out the VC™ task may include planning, working memory and self-monitoring.

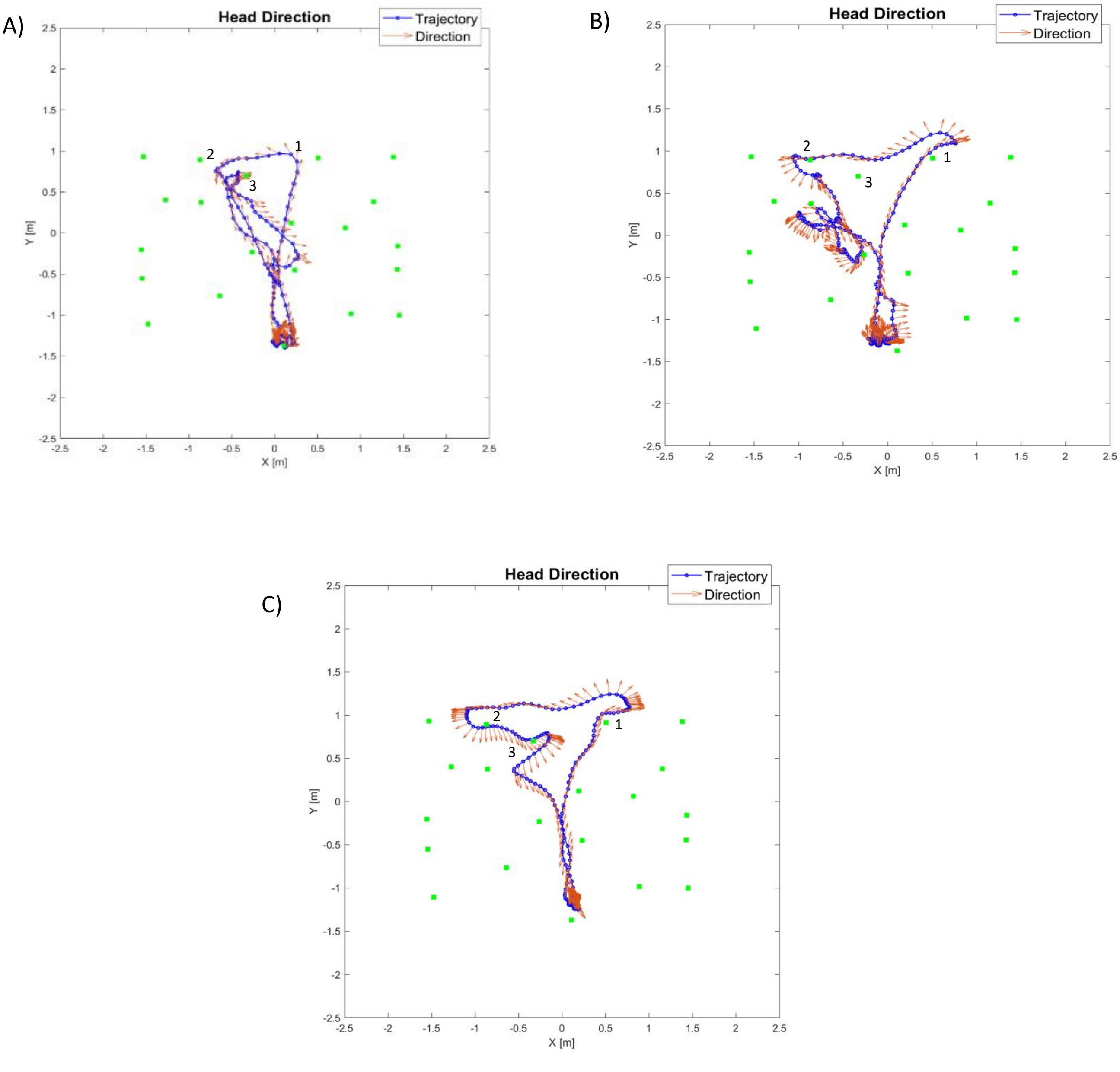

Figure 29: Trajectories at the VC^{TM} paradigm following condition (Level 3 trial 3) of two children with ADHD and one control child. Blue lines and circles: motion trajectories; Red arrows: head direction with respect to the trajectory; Green squares: house position with sequence number on top. X and Y axes indicate the sensors' position in the

navigational array (meters). (A) trajectory of a combined type ADHD child, male, aged 10;7 years; (B) trajectory of an inattentive type ADHD child, male, aged 10;3 years; (C) trajectory of a control subject, male, aged 10;4 years

Discussion

The aim of the study was to create a new motivating task, simulating real life situations in a gaming format, to assess real locomotor navigation in a controlled laboratory space and under specific experimental conditions, tapping degree of task difficulty and cognitive processes believed to underlie this task, namely executive functions and visuo-spatial memory. Traditionally, spatial navigation has been assessed by means of paper mazes, in the reaching space, not requiring locomotion. However, recent evidence indicates that different processing of spatial data is required during navigation, compared to the peri-personal space. Whereas during a reaching space task, the object position is processed according to an egocentric strategy that leads to the creation of body-centered representations, based on subject-to-object relation, during a navigational task more options are available: updating egocentric locations or switching to an allocentric reference frame. The latter one leads to a representation independent from the subject's point of view, based on object-to-object relation and acquired later in life, requiring the maturation of specific neuronal networks.

The VC^{TM} paradigm, which evolved from the Magic Carpet tasks, was created to allow assessing cognitive strategies in navigation, simulating skills needed in real-life scenarios which include complex neuropsychological functions beyond spatial memory as executive functions, frequently impaired in children diagnosed with neurodevelopmental disorders, such as ADHD.

The paradigm proved to be easily understandable by school-aged children with ADHD, who approached the task with a good level of motivation. In fact, a feasibility analysis and data from acceptability and usability revealed a good compliance, as the great majority of the subjects completed the entire task and within the designated time frame. The children were also very motivated and reported a limited effort in carrying out the task. All the participants completely understood task instructions and rules, administered by the psychologist, with only two requiring further clarifications. Concerning the feasibility of the entire study design and procedures, the participation rate was extremely high, as none of the participants except one dropped out of the study and all the subjects except three completed the entire study protocol within the maximum total time (2 hours and half). The feasibility questionnaire highlighted a good usability, as the device could be used efficiently with no need for external technical support, with intuitive hardware and software instructions, the sensors being non-invasive and the entire device not posing any danger to the child. Concerning acceptability, the VC™ proved to be a motivating and playful task for children, potentially informing clinical practice, recruiting different cognitive strategies than the ones underlying tests presented in peri-personal space and simulating skills needed in real-life scenarios. The VC™ appeared to be a more informative assessment, investigating skills required in daily life as recruited together in a navigation task, potentially useful also as an intervention paradigm. However, some technical issues with the motion sensors limited correct data acquisition. This could be due to the high level of hyperactivity combined with the sensors' high sensitivity, both interfering with the position acquisition by the cameras. In a future perspective, the use of smaller and smarter sensors could further increase the compliance of participating children, reducing data loss and the inconvenience occasionally reported in wearing a helmet and belt.

Neuropsychological and intelligence assessment confirmed that those abilities supposed to be recruited for successful performance in the VC™ paradigm as selective attention, visuo-spatial memory, inhibiting a prepotent response, updating visuo-spatial information in working memory, are specifically challenging for children with ADHD. The 31 children with ADHD in this study showed an intellectual and neuropsychological functioning in line with evidence from the literature. The Wechsler data revealed significantly lower performance on tasks involving memory and processing speed rather than on tasks that call into question semantic knowledge and verbal reasoning, thus underlining weakness in attention, processing speed, verbal short-term and working memory functions, when compared to verbal and perceptual reasoning skills. These weaknesses were also confirmed on specific visuo-spatial short-term / working memory tests (as the traditional Corsi block tapping task and the computerized version of the same task - CBT and CANTAB®) and by direct and indirect (parent-report questionnaire) measures of EFs. In line with Miyake and co-workers (2001), the strong correlation observed between EFs and visuo-spatial memory, both in the forward and in backward condition, supports the idea that processing-and-storage working memory tasks and storage-oriented short-term memory tasks in the visuo-spatial domain equally implicate executive functioning. When investigating the specific correlation between visuo-spatial memory and inhibitory control, the literature suggests the role of inhibition in managing interference, thus reducing the memory accessibility of non-target and irrelevant information (Passolunghi, 2001). Some authors also suggest the role of attention as a common factor underlying both visuo-spatial memory and inhibition, therefore sustaining their strong correlation (Cowan, 1988; Criaud et al., 2012). Such results highlight also the so called “impurity problem” (Miyake et al., 2000), when discussing EFs assessment results. In fact, considering that EFs refer to a set of different but interrelated abilities and operate on other cognitive processes, any executive task will involve both different EFs and other neuropsychological processes, reducing the accuracy in measuring “pure” executive functioning (Burgess, 1997). Correlations and multivariate regression analyses between VC™ quantitative parameters (span and execution time) and neuropsychological measures of EFs and visuo-spatial memory (assessed with standardized tests) allowed to identify focused attention, memory, planning and inhibition as neuropsychological processes involved in the navigation task. The positive strong correlations among standardized neuropsychological tests such as Corsi block tapping test (CBT), its computerized version (Spatial Span -CANTAB®-) and the VC™ span were indicative VC™ strongly calls into question visuo-spatial short term memory. However, considering correlations with visuo-spatial and verbal backward condition scores, results suggested in addition the involvement of working memory as the task requires not only to retrieve the sequence as encoded, but also to actively manipulate information and to update the spatial maps during the navigation relating to the body position. This was also confirmed by multivariate regression analyses, which highlighted the role of other executive functions in determining the performance, thus confirming the recruitment of different neuropsychological functions and cognitive strategies for accurately performing a visuo-spatial memory task in the navigational space. Therefore, it was not surprising to find that the VC™ span was on average significantly lower than span assessed in the reaching space (BVS Corsi and CANTAB®) having also a significant correlation with age, confirming the studies of Belmonti and co-workers (2015). Considering the involvement in such a navigation task of neuropsychological functions recruited together, as short-term memory, working memory, executive functions (self-monitoring), particularly challenging for children with ADHD, the clinical group showed significantly lower performances than the controls. Results obtained by analyzing VC™ execution times in the planning condition (where the executive component of planning is most stressed), but also in the Following condition, further confirm the involvement of EFs, both evaluated through direct (Tower of London) and indirect (BRIEF-2 questionnaire) outcome measures. In particular, inhibition, working memory, planning, material organization and task monitoring skills seem to be particularly challenged by the VC™ task, with significantly lower execution times in ADHD children than control subjects, confirming impulsivity as a main feature of this neurodevelopmental disorder. This was also confirmed by number of rule violations analysis showing a correlation with EF measures and also with the total execution time, as the greater the rule violations, the worse EFs scores and shorter the execution time. Obtaining the VC™ decision time as quantitative data would allow a better interpretation of the described results, allowing to distinguish the response latency from the total execution time, providing better insight into planning abilities and impulsivity. The stronger correlation between VC™ scores and indirect EF outcome measures (parent-report questionnaire) highlight how the navigational paradigm is a more ecological task, able to simulate real-life situations better than traditional neuropsychological assessment. The significant correlations between VC™ data and traditional standardized neuropsychological results suggest that the construct validity of the VC™ is acceptable.

The paradigm, given the possibility of directly quantifying the child's behaviour while moving in the virtual space to reach the houses, allowed to hypothesize the processes recruited while planning and executing the task. Preliminary data about errors performed during VC™ paradigm on a portion of ADHD and control subjects showed a higher frequency of substitution errors than permutation ones, differently from what expected from the literature (Belmonti et al., 2015). This could be explained as the VC™ task is much more complex and has a higher number of targets than the Magic Carpet (20 tiles). Furthermore, compared to the Magic Carpet, the presence of roads in the VC™ promote a "locomotor" coding, with a greater need for a navigation strategy than the Magic Carpet which was better assimilated to a CBT task in the reaching space. Further analyses allowed to distinguish semantic (a house is replaced with one of the same color) and regional (a house is replaced with neighbouring ones) substitution errors, highlighting that although the VC™ task can initially be approached through a colour coding strategy, the number of regional substitution errors is however higher as this coding strategy reveals to be more effective during the navigation task execution. Rule violations were also investigated, showing a statistically significant difference between age groups and a strong correlation with standardized visuo-spatial memory and EF measure, proving to be a good performance marker.

The comparison with a small matched-for-age control group provided preliminary results about performance differences in a complex navigation task and about specific patterns of behaviour characterizing the clinical population, also providing insights into cognitive strategies and neuropsychological processes involved in the control population when facing the VC™ paradigm.

Finally, the trajectories obtained through motion sensors and the errors made during the two experimental conditions were analysed on two ADHD children (inattentive and combined) and a typically developing child matched per age, allowing preliminary data on cognitive strategies necessary for successfully completing this locomotor navigation tasks, such as egocentric and allocentric strategies.

Although the child with combined ADHD performed the sequence correctly, the locomotor pathway was non-linear. In fact, this child went back to the starting point possibly to rehearse the trajectory previously encoded. This suggests that he recruited an egocentric storing strategy less functional than an allocentric one. This return-to-start behaviour has been described in adults (Iglòi et al. 2009) in a "virtual star-maze" task and accounted for as "a mixed strategy." During navigation, sensory stimuli can be encoded in spatial reference frames centered on the sensory organs (egocentric) or in an allocentric reference frame, with allocentric spatial encoding strategy introducing a substantial computational simplification, acquired later in childhood and probably subsumed by EFs. Since executive dysfunction is one of the core deficits of ADHD, these children may have difficulties in activating an allocentric strategy to store the targets. Head movements while standing in the starting position and total execution time, confirmed high impulsivity and poor planning abilities, both interfering with the encoding phase and the activation of cognitive strategies useful for performance. The child with inattentive ADHD showed the worst performance, being highly distractible, failing the sequence, following a linear path (he did not return to the starting point), with head and trunk not moving in the same directions. Head movements while standing in the starting position confirmed high distractibility interfering with the encoding and the recalling phase.

To conclude, preliminary data suggest that the VC™ paradigm (a visuo-spatial navigational task) is a playful and feasible tool, simulating real-life situations and allowing a quantitative measurement of the performance in a motivation contest, assessing different neuropsychological processes and cognitive strategies than paper and pencil or computerized tests, as recruited in a navigational space. Such neuropsychological functions as visuo-spatial memory and executive functions were found to be particularly challenge and impaired in a group of school-aged children with ADHD, as assessed during this PhD study with standardized tests, thus confirming existing literature data. As these skills were proved to be involved in the VC^{TM}, ADHD performance was not only quantitatively but also qualitatively different than that of typically developing children, thus suggesting the recruitment of immature cognitive strategies.

Since spatial navigation is the process of traveling to distant destinations, from target localization, trough route planning or retrieval, to physical displacement, it is clear how much such ability is involved in many daily life activities. Suboptimal navigational skills, as shown in ADHD children, may impair one's ability to find things, reach targets, avoid obstacles, and return home, therefore significantly reducing quality of life, also leading to a complete dependence on caregivers. Investigating and enhancing neuropsychological functions involved in a navigation task within a locomotor space, thus sustaining spatial navigational skills, is therefore important to be considered when a rehabilitation program is outlined. Considering the VC^{TM} paradigm as a motivating and playful activity, adaptable to new tasks and scenarios, results obtained from this study pave the way for the improvement of such a paradigm also for rehabilitative interventions aiming to enhance, within a navigational task, the neuropsychological processes involved. Simulating real-life situations, a greater generalization of the achieved competences and far transfer effect on daily life functioning and clinical symptoms are also expected according to literature data (Bombonato et al. 2023). In this framework, therefore, orienteering educational activities are also useful in order to improve such navigational skills and the cognitive functions involved, as reported in the existing literature on typically developing children (Macquet et al. 2012; Notarnicola et al. 2010). Despite the promising results, in order to use this paradigm in clinical practice as a diagnostic and a potentially rehabilitation tool, some limitations of the study must be considered. In particular, the Covid 19 emergency limited access to health and education facilities and thus undermined the recruitment of the control sample, resulting in a reduction of the number of participating children compared to the initial project. Considering that the analyses carried out on the control group matched for age and sex, do show the same correlational trends observed in ADHD children, without however reaching significance, a greater number of subjects would allow to better investigate also in the control sample the neuropsychological processes involved in the navigation task and to highlight differences in performance with respect to children with neurodevelopmental disorders. Furthermore, other investigations will be necessary, taking into account quantitative parameters from the trajectories calculated with Matlab software, such as head and trunk deviation from trajectory, head deviation from trunk position and decision time, to name the most relevant that have been studied in other navigational tasks. This could provide further insights into specific behaviors characterizing control and ADHD populations and strategies recruited when facing a navigational task, allowing to better typify neuropsychological profiles for a more personalized therapeutic approach. Considering some technical issues with the motion sensors that limited correct data acquisition, probably due to the high level of children's hyperactivity combined with the sensors' high sensitivity, the use of smaller and smarter sensors could improve data acquisition and increase the compliance of participating children.

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Appendix 1. Santa Barbara Sense of Direction Scale-Parent and Child Version: p-SBSOD and c-SBSOD adapted by Murias et al. (Murias et al. 2017)

CHILD MODIFIED SBSOD

1. I am very good at giving directions to help people find places or things
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

2. I am good at guessing how far away things are
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

3. I can imagine directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

4. I like to use north, west, east, south when I find places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

5. I get lost easily
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

6. I like to read maps
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

7. It is hard for me to follow directions to new places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

8. I am good at reading maps
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

9. I don’t usually remember how to get to places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

10. I don’t like giving people directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

11. I like it when to know where I am and where I’m going
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

12. I can remember how to get somewhere after going there once
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

13. I can imagine where things are in my environment
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

14. I am good at knowing when I’ve been to a place before
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

15. I can tell the difference between left and right
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

16. When I am lost, I cannot find my way back
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

17. I like visiting new places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

18. I visit new places often
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

SBSOD – PARENT VERSION

After reading each statement carefully, circle the number that indicates how well each statement applies to your child. If you are unsure or have not observed these behaviours in your child, circle unsure.

1. My child is very good at giving spatial directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

2. My child has poor memory for where he/she left things
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

3. My child is very good at judging distances
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

4. My child's "sense of direction" is very good
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

5. My child tend to think of environment in terms of cardinal directions (N, E, S, W)
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

6. My child gets lost very easily in a new city
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

7. My child enjoys reading maps
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

8. My child has trouble understanding spatial directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

9. My child is very good at reading maps
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

10. My child doesn't remember routes very well while traveling in a car
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

11. My child doesn't enjoy giving directions
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

12. It is not important to my child to know where he or she is
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

13. My child can usually remember new route after he or she has traveled it only once
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

14. My child doesn’t have a very good “mental map” of his or her environment
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

15. My child is good at recognizing familiar places
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

16. My child is good at discriminating between left and right
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

17. My child gets lost easily in familiar environments that he or she visits at least once a month
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

18. When my child gets lost, it is difficult for him or her to find the way back
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

19. My child likes to explore new environments
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

20. My child frequently visits new or unfamiliar environments (e.g., a park that he or she has never been to before)
Strongly agree 1 2 3 4 5 6 7 Strongly disagree Unsure

Appendix 2. Virtual City feasibility questionnaire

FSM_FEASIBLITY QUESTIONNAIRE

(Virtual City Paradigm)

Please complete with examiner, participant and testing information

1. Name and title of examiner

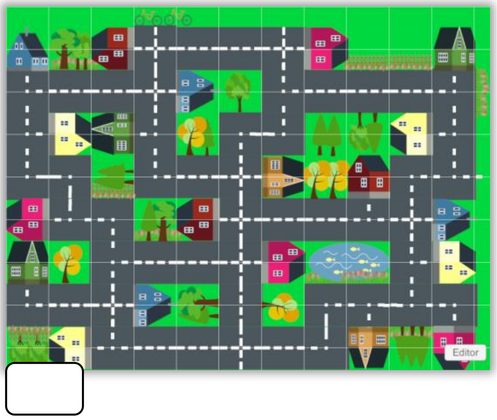
2. Participant’s ID code and age

3. Date of testing

4. Indicate order of testing (1 or 2)

Virtual City Paradigm

Neuropsychological testing



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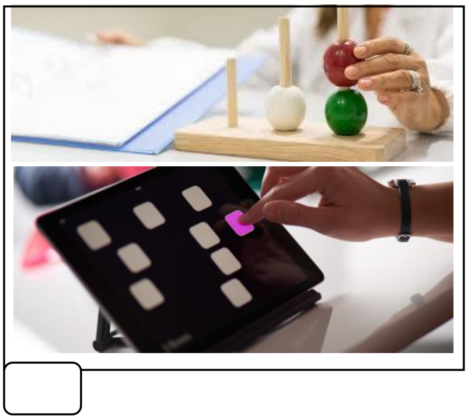

☐

5. Length of time needed to complete the Virtual City Paradigm:

  - ○ 10-30 minutes
  - ○ 30-45 minutes
  - ○ 45 minutes- 1 hour
  - ○ Greater than 1 hour

6. Total time needed for testing (Virtual City + Neuropsychological testing)
   - ○ 30-45 minutes
   - ○ 45 minutes- 1 hour
   - ○ 1 hour – 90 minutes
   - ○ 90 minutes – 2 hours
   - ○ Greater than 2 hours

Please answer the following questions on a scale from 1 to 5: 1 not at all - 5 very much (satisfied, how often); 1 never - 5 all the time (how often)

Please be aware that for some items the scale is reversed

Usability

7. In general, relative to this specific participant, how satisfied are you with the Virtual City Paradigm (in terms of software, hardware and sensors- taken as a whole-)?

Not at all	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	Very much

8. Your current knowledge of the system's functioning (software, hardware and sensors -taken as a whole-) is sufficient for use with this specific participant?

Not at all	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	Very much

9. Do you believe that the system is suitable for this pecific participant (in terms of carpet's size, sensors' size and wearability)?

Not at all	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	Very much

If not at all , please suggest modifications to the system:

____

10. Were you able to achieve the goals you set for this specific participant?

Not at all 1 2 3 4 5 Very much

11. How dangerous is it to use this system with this specific participant?

Very much 1 2 3 4 5 Not at all

12. How easy was it to set the hardware for this specific participant?

Not at all 1 2 3 4 5 Very much

Acceptability

13. How easy was it to use this system with this specific participant?

Not at all 1 2 3 4 5 Very much

14. Did the Virtual City Paradigm allow you analyze the skills that you intended to measure for this specific participant?

Not at all 1 2 3 4 5 Very much

15. How often did you have to interrupt the paradigm and provide a greater number of rests than established with this specific participant due to reduction in motivation or eccessive mental or physical fatigue on the part of the participant?

Never 1 2 3 4 5 All the time

16. How often did you need to interrupt the paradigm with this specific participant due to technical issues arising during the system's utilization?

All the time	1	2	3	4	5	Never

17. Do you believe the system needs to be modified to address this specific participant's needs?

Very much	1	2	3	4	5	Not at all

18. If so, what needs to be modified and why?

____

____

____

____

____

19. Do you believe that the system's data report is useful in clinical terms?

Not at all	1	2	3	4	5	Very much

20. Please illustrate why or why not

____

____

____

____

21. Would you use this system as an intervention paradigm for this specific participant?

Not at all	1	2	3	4	5	Very much

22. Has the Virtual City data stimulated your thinking on aspects of behavior that had not emerged from clinical evaluation?

Not at all	1	2	3	4	5	Very much

Appendix 3: Table of Spearman correlation analysis among neuropsychological outcome measures assessed with standardized test.

Spearman Correlation Analysis

	Span foreward_BVS	Span backward_BVS	Digit forward_ WISC IV	Digit backward_ WISC IV	SSPFSL	SSTSSRT	SSTDEG	SSTMRTG	SSTMT	Decision time_TOL	total time_ TOL	total score_ TOL	Inhibition_ BRIEF	Self monitoring _BRIEF	Shift_ BRIEF	Emotional regulation_ BRIEF	Initiate_ BRIEF	Working memory_ BRIEF	Plan/Organize_ BRIEF	Task Monitor_ BRIEF	Material Organization_ BRIEF
Span foreward_BVS	1,000																				
Span backward_BVS	,542**	1,000																			
Digit forward_ WISC IV	,426*	0,073	1,000																		
Digit backward_ WISC IV	,539**	,449*	,403*	1,000																	
SSPFSL (span)	,519**	,544**	0,148	0,242	1,000																
SSPFTE (permutation errors)	0,282	0,327	-0,017	0,051	,823**																
SSPFTUE (insertion errors)	0,135	-0,057	-0,273	-,417*	0,255																
SSTSSRT	-,385*	-0,070	-,418*	-0,186	-0,251	1,000															
SSTDEG	-0,356	-0,238	-,379*	-0,340	-,376*	,393*	1,000														
SSTMRTG	-0,064	-0,222	-0,070	-0,148	0,012	-,372*	-,410*	1,000													
SSTMT	-0,247	-,410*	-0,158	-0,360	-0,243	-0,208	0,084	,738**	1,000												
Decision time_TOL	0,143	0,349	0,101	0,327	,407*	-0,070	-0,195	-0,062	-0,173	1,000											
total time_TOL	-0,135	0,184	0,205	0,189	0,117	-0,097	-0,131	-0,217	-0,201	,645**	1,000										
total score_TOL	0,319	0,233	-0,024	0,128	0,283	0,214	0,202	-0,285	-0,332	0,283	-0,030	1,000									
Inhibition_ BRIEF	-0,280	-0,010	-0,131	0,157	-0,173	0,225	0,221	0,071	0,186	0,139	0,178	-0,172	1,000								
Self monitoring_ BRIEF	-0,226	0,009	-0,139	0,141	-0,114	,505**	0,220	-0,107	0,067	0,219	0,176	0,102	,740**	1,000							
Shift_BRIEF	-0,223	0,008	-0,025	0,017	0,077	0,069	-0,069	0,222	0,198	0,170	0,015	0,390	,412*	,511**	1,000						
Emotional regulation_ BRIEF	-0,256	0,061	0,025	0,116	-0,055	0,141	0,083	-0,021	0,014	0,208	0,260	0,133	,695**	,557**	,665**	1,000					
Initiate_BRIEF	-0,150	0,061	0,091	0,056	0,025	0,279	0,026	-0,106	0,014	0,095	-0,165	0,376	,370*	,390*	,621**	,684**	1,000				
Working memory_BRIEF	-0,131	0,171	0,112	0,024	0,127	0,298	-0,146	-0,020	-0,050	0,071	0,044	-0,002	,448*	,461*	,390*	,528**	,673**	1,000			
Plan/Organize_ BRIEF	-0,068	0,203	0,012	0,087	0,027	0,365	0,148	-0,331	-0,207	0,043	-0,157	0,210	0,346	0,272	0,175	0,324	,678**	,749**	1,000		
Task Monitor_BRIEF	-0,163	0,069	-0,050	0,043	-0,216	0,194	0,218	-0,139	0,004	-0,084	-0,325	0,034	0,224	0,012	0,052	0,156	,489**	,517**	,785**	1,000	
Material Organization_ BRIEF	-0,094	-0,089	0,112	-0,078	-0,224	0,214	0,201	-0,208	-0,077	-0,271	-0,343	-0,003	0,305	0,030	0,014	0,358	,587**	,506**	,736**	,688**	1,000

BVS: Corsi Block tapping test from Italian battery on visuo-spatial memory; WISC IV: Wechsler Intelligence Scale for Children IV edition; SSPFSL: Spatial Span Forward Span Length; SSTSSRT: Stop Signal Task Reaction Time; SSTDEG: Stop Signal Task Direction Errors - Go Trials; SSTMRTG Stop Signal Task Median RT - All Go Trial;

SSTMT Stop Signal Task Missed Trials; TOL: Tower of London; BRIEF: Behaviour Rating Inventory of Executive Functions.

Appendix 4: Table of neuropsychological and VC^{TM} data descriptive analyses.

		Statistics	Stand. error
VCI/VIQ	Mean	111,57	2,22
	Stand. dev	10,63	
	Skewness	0,11	0,48
	Kurtosis	-0,78	0,93
PRI/PIQ	Mean	107,70	2,94
	Stand. dev	14,11	
	Skewness	-0,08	0,48
	Kurtosis	-1,17	0,93
WMI	Mean	90,35	2,62
	Stand. dev	12,56	
	Skewness	-0,54	0,48
	Kurtosis	0,22	0,93
PSI	Mean	90,87	3,25
	Stand. dev	15,58	
	Skewness	1,03	0,48
	Kurtosis	0,26	0,93
Digit forward_WISC IV	Mean	7,39	0,39
	Stand. dev	1,88	
	Skewness	-0,22	0,48
	Kurtosis	-0,13	0,93
Digit backward_WISC IV	Mean	9,74	0,57
	Stand. dev	2,72	
	Skewness	0,50	0,48
	Kurtosis	1,26	0,93
Decision time_TOL	Mean	48,43	2,33
	Stand. dev	11,16	
	Skewness	1,38	0,48
	Kurtosis	1,26	0,93
total time_TOL	Mean	51,30	3,34
	Stand. dev	16,04	
	Skewness	1,65	0,48
	Kurtosis	2,49	0,93
total score_TOL	Mean	45,17	2,56
	Stand. dev	12,25	
	Skewness	-0,46	0,48
	Kurtosis	0,06	0,93
Span foreward_BVS	Mean	4,35	0,22
	Stand. dev	1,07	
	Skewness	0,68	0,48
	Kurtosis	0,28	0,93
Span backward_BVS	Mean	3,74	0,28
	Stand. dev	1,36	

	Skewness	0,88	0,48
	Kurtosis	0,14	0,93
Inhibition_BRIEF	Mean	63,30	2,79
	Stand. dev	13,38	
	Skewness	0,10	0,48
	Kurtosis	-0,90	0,93
Self monitoring_BRIEF	Mean	53,96	2,67
	Stand. dev	12,80	
	Skewness	-0,04	0,48
	Kurtosis	-0,97	0,93
Shift_BRIEF	Mean	60,35	2,63
	Stand. dev	12,63	
	Skewness	0,74	0,48
	Kurtosis	-0,06	0,93
Emotional regulation_BRIEF	Mean	57,61	3,09
	Stand. dev	14,83	
	Skewness	0,54	0,48
	Kurtosis	-0,60	0,93
Initiate_BRIEF	Mean	63,57	1,75
	Stand. dev	8,38	
	Skewness	-0,55	0,48
	Kurtosis	-0,73	0,93
Working memory_BRIEF	Mean	65,57	1,60
	Stand. dev	7,66	
	Skewness	-0,46	0,48
	Kurtosis	-0,04	0,93
Plan/Organize_BRIEF	Mean	66,43	2,10
	Stand. dev	10,09	
	Skewness	-1,05	0,48
	Kurtosis	0,96	0,93
Task Monitor_BRIEF	Mean	64,13	1,97
	Stand. dev	9,46	
	Skewness	-0,89	0,48
	Kurtosis	0,34	0,93
Material Organization_BRIEF	Mean	60,04	2,21
	Stand. dev	10,61	
	Skewness	-0,23	0,48
	Kurtosis	0,02	0,93
BRIEF 2 BRI	Mean	61,00	2,89
	Stand. dev	13,85	
	Skewness	-0,05	0,48
	Kurtosis	-0,96	0,93
BRIEF 2 ERI	Mean	59,96	2,95
	Stand. dev	14,14	
	Skewness	0,64	0,48
	Kurtosis	-0,70	0,93
BRIEF 2 CRI	Mean	66,35	1,91
	Stand. dev	9,17	
	Skewness	-0,75	0,48
	Kurtosis	-0,32	0,93
BRIEF 2 GEC	Mean	65,35	2,14

	Stand. dev	10,25	
	Skewness	-0,08	0,48
	Kurtosis	-0,65	0,93

		Statistics	Stand. error
Span_ VC following	Mean	3,27	0,21
	Stand. dev	0,80	
	Skewness	0,42	0,58
	Kurtosis	0,38	1,12
n wrong trials_VC planning	Mean	3,33	0,46
	Stand. dev	1,80	
	Skewness	0,61	0,58
	Kurtosis	-0,42	1,12
Total errors_VC planning	Mean	4,27	0,80
	Stand. dev	3,10	
	Skewness	1,17	0,58
	Kurtosis	0,44	1,12
Mean time level 2_VC following	Mean	22575,49	1197,46
	Stand. dev	4637,74	
	Skewness	0,36	0,58
	Kurtosis	0,65	1,12
Mean time level 3_VC planning	Mean	29123,43	1361,19
	Stand. dev	5271,87	
	Skewness	0,24	0,58
	Kurtosis	-0,72	1,12
Mean total time_VC planning	Mean	7496,97	324,98
	Stand. dev	1258,63	
	Skewness	0,28	0,58
	Kurtosis	-1,23	1,12

VCI: Verbal Comprehension Index; VIQ: Verbal Intelligence Quotient; PRI: Perceptual Reasoning Index; PIQ: Performance Intelligence Quotient; WMI: Working Memory Index; PSI: Processing Speed Index; BVS: Corsi Block tapping test from Italian battery on visuo-spatial memory; WISC IV: Wechsler Intelligence Scale for Children IV edition; SSPFSL: Spatial Span Forward Span Length; SSTSSRT: Stop Signal Task Reaction Time; SSTDEG: Stop Signal Task Direction Errors - Go Trials; SSTMRTG Stop Signal Task Median RT - All Go Trial; SSTMT Stop Signal Task Missed Trials; TOL: Tower of London; BRIEF: Behaviour Rating Inventory of Executive Functions; VC: Virtual City.

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