# UNIVERSITÀ DEGLI STUDI DI TRIESTE

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# Memory and Confabulation in Autism Spectrum Disorders

Settore scientifico-disciplinare: M-PSI/08 PSICOLOGIA CLINICA


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# ABSTRACT

Hippocampus (HCP) is a very crucial neurofunctional hub: it plays a key role in spatio-temporal encoding, in identifying newness, classifying sameness (unicity and multiplicity) and in global and fine-grained representations. In general, it sustains the formation and retrieval of declarative memories. DeLong (1992) was the first to focus on hippocampal functioning in Autism Spectrum Disorders (ASD) and more recently other studies have offered evidence for an irregular functioning of declarative memory in ASD.

Our main goal is to further explore memory in children and adults with ASD; specifically, we hypothesize that disrupted upstream and downstream HCP-connectivity may lead to several types of confabulations (i.e. statements and actions incongruous to subject's background, current situation and future plans). We adapted the Confabulation Elicitation Questionnaire (Spitzer et al., 2017) to both typical and atypical developing participants, challenging their semantic and episodic retrieval. Moreover, we investigate the effects of a perceptual and imaginative enriched environment in a sample of children with ASDs, measuring their sensorimotor, cognitive and behavioral outcomes compared to the control group. This PhD project is rooted on the neurophenomenological framework and more specifically on the Memory, Consciousness and Temporality Theory (MCTT, Dalla Barba, 2002). MCTT postulates a direct bound within different patterns of neural modification and the subjective experience. Through our work we would like to highlight the importance of perceptual, imaginative, knowing and temporal consciousnesses during development, implementing new approaches towards ASD.

# 1 INTRODUCTION

Autism spectrum disorders (ASDs) are highly heterogeneous neurodevelopmental conditions characterized by: A) persistent difficulties to initiate and to preserve reciprocal social interaction and communication; B) restricted, repetitive, and inflexible patterns of behavior and activities that are atypical or excessive for the individual's age and sociocultural context (World Health Organization, ICD-11 International Classification of Diseases and Related Health Problems, 2019, American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed, DSM-5, 2013).

The prevalence of ASDs is estimated to be 1: 100 children worldwide (Figure 1) and goes from 1: 44 children in United States (CDC, Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years -Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018) to 1:89 in Europe (Autism Spectrum Disorders in the European Union, ASDEU programme summary report, 9/2018). In Italy the observed prevalence is 1:77 children (Osservatorio nazionale per il monitoraggio dei disturbi dello spettro autistico, Istituto Superiore di Sanità, 2019). Since the 90' prevalence has substantially increased and nowadays around 1% of the general population is estimated to be within ASDs (Haker H. et al.,2016). ASDs are predominantly idiopathic (i.e. of unknown causes) and only 4-20% of ASDs cases can be linked to a specific cause (M.F Casanova. et al. 2020). The 'autistic profile' emerges from different etiological components: genetic layer, pre and post-natal issues and neurocognitive dynamics that lead to different ASD phenotypes.

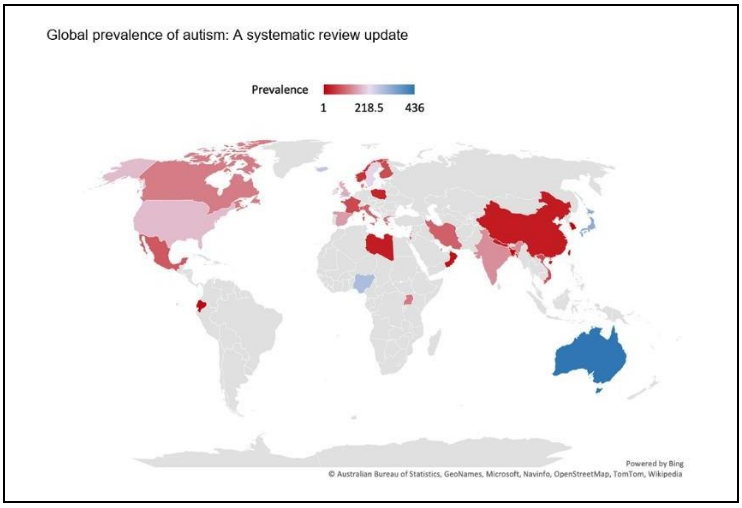


*Figure 1:Autism Prevalence Zeidan J et al. Autism Research (2022)*

These three groups of factors trigger events cascade that influence brain plasticity and, thus, determining various neurodevelopmental trajectories grouped under the word “spectrum”. Although ASDs are still mainly undetermined, research has made big progress during the last 15 years in the attempt to understand the pathogenesis and cognition of ASD population. Considering the three determinants above is fundamental, first, to understand the broad range of functioning contained by this neurodevelopmental cluster which range from severely compromised to highly gifted profiles and second to establish the premises for research and intervention needed by people with ASD and their families. The etiological factors are briefly described by the three points below.

1. Genetic layer. Over 200 genes are associated with ASDs, but individually they can account for 1% of cases, while the 10% of ASD population is considered a monogenic syndromic mutation. The remaining 90% are linked to “common polygenic risks”, such as de novo or inherited copy number variations and single nucleotide polymorphisms. Genetic layers encode proteins that regulate DNA and RNA-binding, protein-to-protein and neuronal cell-to-cell interactions. Thus, genetic determinants can disrupt several biological dynamics and affect, among others, the neuronal efficiency (Panisi, & Marini, 2022).
2. Pre and post-natal issues. During the prenatal period, epigenetic effectors modulate gene expression and transcription, allowing the expression of ontogenetic mechanisms in the nervous system (i.e. cell proliferation, differentiation, migration, maturation, synaptogenesis and pruning), but also preparing other tissues and organs for the extra-uterine environment. Given the implausibility of monogenetic mutations as explanation for ASDs cases increasing in just the last few decades, epigenetic factors are most likely implicated in such fast cases rising. The so-called ‘first 1000 days’ from conception to 2 years of age is the most critical period for child’s future developmental trajectory. Altered nutrition, stress, infections, drug assumption and chemical exposure can dramatically change homeostatic pregnancy’s mechanisms, and thus modify the optimal milieu for the fetus. Maternal immune activation can also change gene expression and the baby’s nervous system integrity in the womb, this influence continues postnatally (Panisi, & Marini, 2022). Neuroinflammation and neuroglial activation could be critical in triggering and maintaining central nervous system anomalies in Autism during growth (Carlos A., Pardo et al., 2005). The abnormal immune responses continue later in adulthood and could affect persons’ behaviors (Depino, A.M., 2013; Heuer et al., 2008). In addition, research suggests a link between the inflamed immune system (excessive activation of cytokines) and disrupted production of neural growth factors such as brain-derived neurotrophic factor (BDNF). Neurotrophins are proteins responsible for the synaptic formation, branching and connectivity during development and seem also involved in the pathogenesis of ASDs. BDNF deficiency has been found in people with ASD compared to controls and this shortage can hinder long-term potentiation and is critically involved in learning, memory, and higher-order thinking (Y.M.Y. Han et

al., 2022). Besides the immune system, both genetic and epigenetic factors can affect gastro-intestinal system (Molloy & Manning-Courtney, 2003) provoking gastrointestinal disturbances and gut microbiota dysbiosis in childhood and later in adulthood (Gonzales et al., 2021). Perinatal events, like placental abruption and birth asphyxia, can also affect the nervous system and constitute additional risk factors for ASD diagnosis among offspring (Getahun et al., 2017).

3. Neurocognitive dynamics. Even if risk factors and their reciprocal influences are becoming clearer, biological level alone cannot explain the variety of ASDs profiles, experts need to consider brain development and its impact in environmental adaptation. At the structural level, neural plasticity across ASDs shows a common factor: rapid brain rate growth despite the presence of normal brain at birth. This is mainly attributable to a greater proportion of white matter, possibly caused by axonal abnormalities and proliferation. Neuropathologic findings also support cortical overgrowth, particularly in the prefrontal cortex. Moreover, post-mortem data show an aberrant minicolumn structure in the neocortex. Cerebellar issues like a poor number of Purkinje cells and possibly cerebellothalamocortical circuit malfunctioning are also reported, but those findings are still inconsistent (Laidi et al., 2022).

   From the neurofunctional standpoint, some studies report greater and longer-lasting modulation of cortical reactivity to Transcranial Magnetic Stimulation (TMS), while another reported no modulation at all, these opposite data could reflect samples heterogeneity or paradigm differences (Oberman, Pascual-Leone, 2013). A recent study found that the atypical hemisphere's lateralization may constitute a neurophenotype for clinically meaningful stratification in autism, although any univocal right or left asymmetry at group level is observed (Floris et al., 2021). Overall, ASDs are associated with alterations in brain's connectivity, but both hypo- and hyper-connectivity are observed across studies and no specific pattern have been proved so far (Uddin et al., 2013). The identification of common factors and markers underlying various phenotypes continues to remain the main goal in autism research for increasing specificity in diagnosis and improving early detection.

Heterogeneity in ASDs is due to complex interaction between genetic, epigenetic, environmental and neuroplastic variables, this combination of factors lead to all the different trajectories and is conveyed into challenges for diagnosis and treatment. Accordingly, even if the onset of ASDs occurs in early childhood, symptoms may not become fully manifest until social demands exceed limited capacities (ICD-11, 2019).

Nowadays, it is around 18–24 months of age that children can be diagnosed with autism. In this period of life the infant show behavioral symptoms that can be distinguished from typical trajectory and from other delays or other developmental conditions. Atypical characteristics are observed in four main areas: language and communication, social skills and responses, playing, repetitive behaviors. Furthermore developmental screening is becoming very important to identify those children at higher risk of possible future diagnosis. The research realm in ASDs is undertaking two main challenges. On the one hand, is searching for common factors that characterize ASDs, such as biomarkers and neuropsychological specificities, which is paramount for reaching the right diagnosis as early as possible and starting early intervention. On the other hand, research is trying to identify the main clusters within the spectrum and their developmental-trajectory for implementing personalized intervention and facing specific needs of autism subtypes (Van Rentergem, Deserno, Geurts, 2021).

Autism field is complicated by data on co-occurring difficulties: people with autism are often affected by neurological problems like epilepsy, mental health problems, including anxiety and depression and psychotic disorders (Autism-Europe, 2019). These comorbidities can sometimes overshadow ASD identification at the first clinical observation (Haker et. al., 2016). Moreover, the level of intellectual functioning among autistic people varies from profoundly impaired to highly gifted. All these differences point to personalized intervention, and to integrate approaches for responding to the person needs.

The scope of this thesis is that of settle a comprehensive neurodevelopmental model for Autism, given recent findings and theoretical advances and to collecting more data in support of possible common feature in ASDs. Moreover, we show preliminary results from a new approach which can be highly suitable for personalized intervention towards children with ASDs.

Although, a long way has come for defining autism, behavioral symptoms are still the golden standard in everyday diagnostic settings, we agree with Frith (2012) when she writes: "*Many different causes can underlie the same behavior. On the other hand, behavior that looks different in different individuals may actually be due to one and the same cause. In this sea of uncertainty, cognitive explanations are like a sea-worthy ship to navigate between facts we know about the brain and facts we know about behavior*"). Frith also illustrate the interplay between biological, cognitive and behavioral levels which are constantly influenced by environment (Frith, 2012). This multilevel interaction is the present common ground for theory, research and treatment improvement.

## 1.1 Cognitive Theories of ASD

'Autistic' traits were first described by a young woman born in Kiev, doctor Grunya Efimovna Sukhareva. In her article published in Russian (1925) and in German in (1926), she collected six case reports based on her accurate observations while she was working in Moscow, at the therapeutic school for children with psychiatric problems. Two decades later, reports on similar cases were independently made by Leo Kanner (1943) and Hans Asperger in 1944 (Manouilenko, Bejerot, 2015). During 60's Lovaas made enormous effort to better define autistic traits, he developed applied behavior analysis (ABA) for autism conveying techniques from Skinner's conditioning to clinical practice (Larsson, and Wright, 2011).

Between the 1980s and 1990s, cognitive sciences influenced autism research by pointing to the 'primary cognitive deficit' as the common factor for symptoms of ASD, whereby autism was seen and defined as a unitary entity. Later, in 2000, autism was instead better defined as a dimensional construct, supported by evidence on the heritability of traits. Since then, autism has been viewed as one end of a continuum of traits and behavioral characteristics that may co-occur in some individuals and may be separate in others. The theoretical endeavor has changed accordingly, and investigation has become more oriented towards the specific phenomena underlying each trait. A theme that cuts across all viewpoints is that an early alteration in the way children interact with the social and physical environment can trigger a chain of cumulative difficulties that result in the cognitive and behavioral impairments observed in ASDs. It is assumed that various deficits are responsible for the dramatic developmental shift from typical pathways. It is also noteworthy that alterations in neural networks during growth can alter cognition in ASDs and they constitute neural basis for their observed features (Vivanti, Messinger, 2021). Today enormous data on ASDs have been accumulated, despite increased publication on the topic, the causes of this condition are still debated. Anyway, the future of theoretical explanation for ASDs is marked by innovative ideas that are overturning all neurocognitive fields. Still, past theories, clinical reports and papers compose a valuable legacy for young researchers.

Explanatory theories on autism could be classified into two classes, based on their period and background: 'first-generation theories' and 'second-generation theories'. We present the most important ones, in chronological order, in this section. However, it is necessary to keep in mind that "*paradigm shifts often obscured developments by changing the vocabulary used to address the topic and that many old findings become methods by which a new generation approach the topic*" (Posner, 2022). Therefore, some communalities can be hidden even among apparently opposite theories.

### 1.1.1 *First generation theories: primary deficit account and multiple deficits account*

First-generation theories are based on the fact that cognitive systems, such as computers, acquire information, process it and respond to the environment based on their own computation, through the input flow. Neurocognitive theories hypothesize one or more neurocognitive deficits rooted in atypical cognitive processes of autism. Three main theories have been proposed to circumscribe one core deficit : weak central coherence, deficit in the theory of mind and executive dysfunction.

Central Coherence (Frith, 1989) in 'neurotypical' persons is the tendency to gather information and process it according to contextual clues, deriving gist from the global pattern and neglecting meaningless details. When this cognitive tendency is somehow defective, as it is assumed to be in people with ASDs, they are more prone to fixate and remember details, sometimes irrelevant to deriving meaning, and struggle to integrate information into a coherent whole (Happé, 2021). The difficulty in people with autism in this domain-general process is called weak 'central coherence' (WCC).

Research in support of WCC derive from difficulties seen in people with autism compared to controls in perceptual tasks (Shah & Frith, 1983). One example of perceptual task is the small figures and shapes drawn within other larger figures that hinder the observer's search (Embedded Figure Test); people with autism have difficulties with it. The counterpart is that they perform better than controls in Block Design test, a task where salience for smaller constituent painted in red and white in each block help to build three-dimensional figures from two-dimensional ones (Shah and Frith, 1993). Moreover, common visual illusions can be enhanced in autism, because illusions rely on the neurotypical drive to make perceptual judgements based on global forms over its components (i.e. Ponzo illusion). Therefore WCC prevents people with ASD from being deceived. This prediction was proved by Happé (1996), while others (Ropar and Mitchell,1999, 2001) found the same illusion susceptibility for both samples with and without autism. For explaining contrasted results, it was argued that global processing in autism needs to be supported by attentional control or that higher-order processing is not automatic. Also, the demand phrasing can be crucial to trigger Central Coherence processes in participants with autism. For instance, when they are asked which of two targets "looks" longer/bigger their answer is congruent with the illusion, but when asked which one "is" longer/bigger they are not deceived (Brosnan, Scott, Fox, and Pye, 2004). Despite debate and mixed findings, WCC cannot be dismissed, and great research effort led to re-defining its role in autism. Every good theory is readjusted based on data, and Central Coherence switched from being considered as a global process, into being defining as superior local process (Rajendran, and Mitchell, 2007). Heppé (Booth & Happé, 2010) also reframed WCC as a cognitive style (more inflexible in autism, but still switchable) rather than a present/absent deficit. Today WCC theory is considered as a composite of superior processing and poor global encoding, that can account for different subgroups in autism. Reduced functional connectivity of the brain in the long-range and stronger local one could get along with WCC theory, but it is probably a phenotype subgroup in ASDs. Alternative accounts propose that global processing is spared in autism and local processing could be responsible for the autistic cognitive profiles ("hyper-systemizing theory and "enhanced perceptual functioning" theories) (Happé, from Encyclopedia of Autism Spectrum Disorders, 2013).

Theory of mind (ToM, Premack, Woodruff, 1987) is a compelling concept that refers to the ability to recognize and understand other's emotions, intentions and beliefs and to predict their behavior (Baron-Cohen, Leslie, Frith, 1985). Based on the fact that the 80% of children with autism failed in a second order false belief task (I think that he thinks) Simon Baron-Cohen (1990) formulated the idea that people with autism display difficulties in attributing mental state to others. He proposed a test in which participant with autism have to make judgement about the belief of a character (i.e. a doll in Sally Anne

Test) who is searching for an object that has been removed from the initial location. In this case the doll's belief to know where the object is a second order belief. This kind of judgement depends on the theory of mind that the participant formulates, a deficit in ToM might underlie the social and communicative interactions, that are main symptoms of autism. In a second order false belief-task (I think he thinks she thinks) none of children with autism passed the test, compared to 60% children with Down syndrome and 90% typically developing ones. It is debated whether or not ToM tasks only require the ability to understand other people's mind, or if a combination of many skills is necessary to be successful in the tasks (like language, executive functions). This theory could, however, explain some of the deficits in social cognition seen in ASDs, but not all aspects can be linked to ToM. Baron Cohen proposed that 'mind-blindness' should be considered delayed during development in autism. More recently, he created a series of tasks and questionnaires that evaluates basic components of ToM, clustering them in two cognitive tendencies, already formulated by Hans Asperger: "empathizing" and "systemizing". The Empathizing–Systemizing (E-S) theory of sex differences (Baron Cohen, 2009) suggests that neurotypical individuals may be classified on their performance in empathy-related or systemizing-related task or questionnaire. Empathizing includes attributing mental states to others (ToM), understanding goals, predicting behaviors and responding adequately to other's feelings. According to the author, this cognitive style is, on average, better developed in women, since healthy women tend to better perform at tests created for measuring empathetic skills ( like "Reading the mind in the Eyes Task", Baron Cohen S., 2001). Systemizing refers to rule's understanding and inferring physical laws and patterns to predict regularities from inanimate objects; in healthy subjects it is shown to be a greater ability, on average, in males. People within the autism spectrum show better performance in those tests that measure systemizing ability compared to empathizing, this difference seems to enhance the pattern of abilities found in the average man's performance. Healthy females on average perform better on short forms of the Empathy Quotient (EQ), and healthy males on average show higher scores on short forms of the Autism Spectrum Quotient (AQ) and Systemizing Quotient (SQ) (Greenberg et al., 2018). Simon Baron Cohen developed the Extreme Male Brain theory (EMB), suggesting that both males and females with autism show a superior ability in systemizing over empathizing compared to healthy men, and the difference is more pronounced in ASDs than in male population. Based on his study, Baron-Cohen also argued that prenatal intrauterine testosterone levels is higher when the newborn is diagnosed with ASDs, in womb, testosterone is usually higher boys than girls. He found that intrauterine testosterone is even higher than that measured in male's intrauterine environment, when the child is later diagnosed with ASD. Thus the testosterone influence neural morphology in a way similar to a male profile brain (Baron-Cohen at al., 2015).

Lawson claimed that this difference can be due to the fact that measure for empathizing and systemizing implies the use, respectively, of open and closed systems. Open systems are highly unpredictable, because they don't relay in fixed rules. For instance, one specific eye expression is an ambiguous input, as it can express different nuances of the same emotion or even different kinds of emotions. Closed systems are determined by fixed and universal rules and tends to be more predictable (Lawson , 2003, 2004). Kaland et al. (2008) noted that children and adolescent with autism made more mistakes and were slower in answering questions on both mental and physical states (measured by the Stories from Everyday Life and the Strange Stories), during a test that measured skill to make social and non-social conclusions from the story. Even non-social questions and reasoning is critical in ASD and mind-blindness theories cannot be the only solution.

ASDs symptoms like the need for sameness, difficulty in switching attention, perseveration, lack of inhibition and impulse control lead Ozonoff et al. (1991) to formulate a third neurocognitive theory, traced the link with Executive Functions (EF) as a potential candidate for better explaining autism profiles. Executive Functions are a group of abilities which allow human being to maintain an appropriate set of possible solutions for reaching future goals, and for problem-solving. In healthy subjects EF allow motor sequencing, planning, inhibition of habitual or automatic response, set maintenance or switching, organized search, flexibility of thought and action, decision making, self-judgement and self-perception. Autistic group perform poorly on executive function's task if compared to healthy subjects (Ozonoff, 1991; Pellicano et al., 2006), but similarly if compared to other neurodevelopmental conditions (like Attention and Hyperactivity Disorder or Obsessive Compulsive Disorder). Therefore it does not seem a specific disturbance of ASDs, but a more common feature. Ozonoff, however pointed out that flexibility is more compromised in autism compared to others disorders, and showed a more spared inhibition (Ozonoff and Jensen, 1999), even though he found that they do have difficulties in inhibition of prepotent responses (Russell, Mauthner, Sharpe, & Tidswell, 1991). In a review of studies, however, a specific deficit for one of the many executive functions (flexibility, inhibition, generativity, self-monitoring) seems remote (Hill, 2004a, 2004b). Distinction in EF between ASDs and others neurodevelopmental disorders could be possible, but it is difficult to find in studies based on group differences (Liss, 2001) because ASDs heterogeneity itself, can flatten different EF profiles in autism.

Overall the EF hypothesis helps to understand some features of autism, but so far they have not been proven to be specific to ASDs.

Instead of finding one main source responsible for the atypicalities in autism, multiple deficits accounts try to address the spectrum in a more comprehensive way, proposing a miscellaneous of cognitive disorders, without assuming any hierarchical association. ASDs could be an umbrella term for different subgroup with different combinations of ToM, WCC and Executive Dysfunctions deficits (Rajendran, Mitchell, 2007). Biological and neuroscientific innovations opened the door to iterative and bidirectional

models assuming multifactorial frameworks for atypical cognition displayed in ASDs in a dimensional perspective, meaning that autistic traits are distributed within the population.
More dimensional and biologically grounded conceptualization have thus been proposed, like the "broken mirrors theories" (Ramachandran and Oberman 2006; Williams et al. 2001) and the aforementioned Extreme Male theory. The "broken mirrors theory" points to the disruptions in the neurocognitive mechanisms that helps the observer to understand others' actions. Neurons fire in a similar pattern to the one triggered by the self-execution of that action.
Another account that points to social symptom is the Social motivation theory. It assumes that children with ASDs could experience poor pleasure from social engagement and activities compared to their peers and links the lack of motivation to the alteration in oxytocin activities (Dawson et al., 2012).
For achieving a good theorization of autism neurocognition it is necessary to address symptomatology as an extreme of typical traits-continuum and adopt developmental framework (Vivanti, Messinger, 2021). In this way it could be possible to shad a light upon neural heterogeneity and predict ASDs trajectories.

### *1.1.2 Second generation theories*

First generation theories focused on peculiarities of autistic perception (WCC) social symptoms (mind-blindness or E-S theory), and more generally on higher cognition (Executive Dysfunction). No mechanism can alone ground a unifying account for all the entire range of symptoms in the 'spectrum'. In 2012 and 2015 some studies began to convey "Bayesian Theories" into the Autism realm, bringing new directions to the field (Pellicano and Burr, 2012; Van de Cruys S et al., 2014).
Bayesian interpretations of cognition state that everyone forms a first explanatory model of possible data and after the event those data update the model, therefore data observation transforms the prior belief into a posterior belief which represents the most likely reason for the observed data. Applied to perception, the Bayesian brain is no more a simple bottom-up encoder, but it is an inferring device which generates models for attending sensory inputs. According to the "free energy principle", human perception and action aim at minimizing prediction errors, the cognitive system can maintain its balance increasing the reliability of its own models and avoiding surprise and environmental uncertainty. For minimizing errors in prediction, a person can either engage with the environmental stimuli which adhere to the prediction, or can modify his own belief using learning processes. The model's modification depends on the ratio-based on the Bayesian formula-between prior belief and actual data, meaning between bottom-up sensory input and top-down predictions: higher ratios lead to more important updating of prior beliefs.
The 'Bayesian brain' definition is implicated in the so-called predictive coding theory, which is an appealing explanation for ASD difficulties (perceptual, motor, social and cognitive), because it reframes

the “autistic mind” as a poor predictor, implying that either their models are not accurate or that sensory incoming information override prior internal models. People with autism are highly sensitive to input from environment and are not able to ignore random noise (i.e. unimportant inputs). This theory is helpful and it gets along with a difficult in the abstraction of gist from perceptual stimuli (WCC), and the ability to deriving other’s intention (empathizing) and programming, inhibiting, switching (Executive Functions). As a whole, predictive coding can be seen as a core impairment in autism, that prevents the person from being flexible and tolerating a certain amount of errors (Van de Cruys et al. , 2014).

At least two kinds of expectations are involved in predictive account: anticipation on how a perceptual stimulus changes over time and expectations based on prior co-occurrence and stored memories. The former need a good coherence between the model and the physical world (in order to move and perceive accurately), while the latter is not inherently related to physical precision (in order to forecast the near novel stimulus). Predictive coding research has focused on perceptual expectations while stored expectations were poorly investigated. If perceptual models need feedback from the surrounding environment, memory models are formed by past experiences’ retrieval, and hippocampus seems to be a good candidate for using stored information to make future predictions (Hindy et al., 2016). The parahippocampal region can hold isolated items in memory shortly (several minutes) while the proper hippocampus supports the extraction of similarities across multiple contexts or items and so, enhances relational properties of the stimuli, comparing them to stored information, also novelty preferences are mediated by hippocampus (Nelson et al. 2015).

In Autism Spectrum Conditions there are difficulties in forming generalized abstract representations and they tend to rely on hyper precise representations from detailed environmental aspects. The failure in encoding and updating internal models suggests that predictable stimuli will be surprising even if repeated. The ASD model is dominated by sensory details and is difficult to generalize. The difficulties in forming and applying abstract models to guide actions can be even more challenging in a highly unpredictable (dynamic and ambiguous) environment, for instance social interactions and communications (Haker, et al., 2016). Concrete predictions can be drawn from the Bayesian Theory regarding optimal conditions for better learning. Haker et. al. (2016) affirm that “a well-known environment causes little surprise and offers new inputs with little noise (unexplainable variability) across many repetitions”. In the study two of the present text we describe an intervention which uses a predictable environment where new inputs are progressively delivered to challenge children expectations.

## 1.2 Goal and structure of the dissertation

The general goal of the present work is to propose a neurophenomenological framework for atypical development of individual with Autism Spectrum Disorders.

In the 1st Chapter we introduced the Autism Spectrum condition and describe how cognitive accounts, made progress in autism understanding while influencing each other. Explanations changed from a single deficit perspective to a more developmental view. According to more recent interpretation, ASDs seem linked to diminished ability to encode contextual information, and a difficulty in generating predictive models from their experiences. We argue that hippocampus is the most eligible structure for encoding contextual information and in creating models for future events.

In Chapter 2 we further discuss this statement, focusing on the role that the hippocampus has in memory, and examining what we know about memory functions in autism. Moreover, we formulate a possible developmental account based on the Memory Consciousness and Temporality Theory by Dalla Barba (2002). We believe that the modes of consciousness that are described in this theory, can offer useful insights on autism neurodevelopment. We also underline that previous theories about autism are pointing to general difficulty in integrating information in a coherent way, in flexible adaptation to the environment and in interpretation of ambiguous stimuli, like emotion. We think that investigating memory and learning, can make all these cognitive features clearer, and we believe that hippocampal complex sustains these processes very early in life. We also think that its circuitry alteration can lead to long-term difficulties in autism cognition and behavior.

In chapter 3 we illustrate an observational study conducted with participants between 8 and 25 years of age, comparing long term retrieval ability in children and adolescents with and without ASD diagnosis. The objective of this study is to investigate memory for semantic information (multiple information) compared with that for episodical events (unique experience). They are reciprocally supported by two distinct forms of consciousness: Knowing and Temporal consciousnesses, according to MCTT.

In chapter 4 we describe the implementation of an intervention based on a special context: the multisensory SHX[1] room. This setting is helpful for complexifying interactions with the child in a safe and predictable environment, adding constant and progressive novelty. The creation of different themes can help the child to integrate activities and stimuli by boosting hippocampal activity. The study describes preliminary results of a Randomized Controlled Trial without blinding. We discuss the potential implications for adaptive behaviors.

In the 5th Chapter we discuss the weaknesses and strengths of our work and the possible impact in therapeutic settings, but we also consider future challenges and new directions.

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[1] SHX is the software's name that allows all devices in the room to activates (https://www.easylabs.it/stanzemultisensoriali/view/category/virtuemart_category_id/68).

# 2 MEMORY, CONSCIOUSNESS AND AUTISM SPECTRUM CONDITIONS

Before framing possible developmental theories related to autism and the hippocampus, it is useful to analyze the condition in relation to memory. Boucher and Bowler in their book 'Memory in Autism' (Boucher, J, Bowler, D., 2008) gather much evidence on how this capacity is impaired in autism. Firstly, we need to define learning and memory: learning is the ability to acquire new information and memory is the ability that allows humans to retain and update this knowledge over time (Kandel et al., 2014). Both enable individuals to expand knowledge and improve our predictive abilities. Memory is an umbrella term that encompasses different cognitive processes and implies different kind of information and various lengths of time for storage (from milliseconds to years). The memory systems identified by Schacter and Tulving (1994) are many: perceptual representation, procedural memory, working memory, semantic memory and episodic memory. Based on the quality of information, memory can be defined as declarative and non-declarative: declarative memory contains events, general and personal facts and belongs to the temporal lobe; non-declarative memory is linked to other structures (basal ganglia, cerebellum, amygdala and neocortex) and is implicit, it cannot be referred verbally and it appears as a facilitation in the execution of tasks over several repetitions (i.e. riding a bike), without any explicit recall of previous events (Gazzaniga et al., 2013). For declaring what and how we learn we need a certain amount of consciousness, named autonoetic consciousness. It is the feeling of re-living the experience during recollection as if it were the original event. Noetic consciousness, on the contrary, is the mere feeling of familiarity during recognition of a previously known object or fact (Tulving, 1983; 1985).

For the purpose of the present work, we will focus on declarative, long-term memory. According to Tulving (1972) Declarative long-term memory is formed by Semantic memory (SM) and Episodic Memory (EM). The former (SM) is made by categorical knowledge about concepts, words and other verbal symbols, formulas and algorithms for manipulating symbols, concepts and relations. In semantic memory, schemas and scripts represent scenarios that contain generalized laws and information that are more informative than every specific concept stored in it. Episodic memory (EM) is the memory system for episodes or events temporally dated, pointing to temporo-spatial relations among them (E. Tulving, 1972). Importantly, neuroimaging research, along with progress in computational neuroscience, can better address cognitive-information-processing theories. It is central for memory research in humans to address experienced mental life, by phenomenological theories, which ask participants to report their awareness on the task and its content (Boucher and Bowler, 2008).

### 2.1 Hippocampus and Memory

Medial temporal lobe allows long-term declarative memory functioning, several authors (Mishkin et al, 1997, 1998; Aggleton and Brown, 1999; Brown and Aggleton, 2001) propose a hierarchical organization for medial temporal lobe: perirhinal and parahippocampal cortices receive input from different sensory modalities and send the information to Entorhinal Cortex (EC), which is connected with the hippocampus. This model implies that parahippocampal structures support familiarity-based recognition and semantic memory, whereas the hippocampus is necessary for episodic retrieval. Therefore, selective hippocampal damage can cause impaired episodic, leaving semantic memory spared (But see Squire et al., 1987, 1998, 2002).

Another framework called Complementary Learning Systems (CLS) identifies the role of Hippocampal Formation (HF) as being complementary to the neocortex (Kumaran et. al., 2016, McClelland et al., 1995, O'Reily et al., 2011). In the CLS model, the neocortex forms regularities across multiple observations contained in the long-term memory (LTM) and forms representations that overlap and interfere reciprocally. The HF learns unique observations, generating sparse representations and maintaining low or no interference among them, in HF the learning is fast but it goes into rapid forgetting, unless it sends information to neocortex for replaying them. Therefore, the hippocampus can store and retrieve unique patterns of information, which are specific in their contents and form separate events. Each event binds together pieces of information related to their spatiotemporal dimensions. An event is unique by definition and can be learned only once in a lifetime, the so-called "one-shot learning". Computational models are remarkably accurate example of this functioning and some even try to replicate the biologically grounded hippocampal functions, like the "Artificial Hippocampal Algorithm" (AHA!) for episodic machine learning (Kowadlo, Ahemed, Rawlinson, 2019, 2020).

Three main subfields constitute the hippocampus: the Dentate Gyrus (DG), and the *Cornu Ammonis* 1 and 3 (CA1, CA3). As we saw EC sends information to hippocampus, more precisely the superficial layer ($EC_{in}$) sends inputs to hippocampus via perforant path containing information from neocortex and subcortical structures, while a deeper layer receives outputs from Hippocampus ($EC_{out}$). The $EC_{in}$ projects information into DG which sends inputs into CA3 through mossy fibers. Each CA3 cells receives numerous input-fiber and the pyramid cells in CA3 project to CA1 through Schaeffer collateral synapses. EC has also bilateral connections to CA1. Thus, thin connectivity of dentate granular cells (but also direct connections with EC) projects towards few CA3 pyramidal cells (in mice around 40 synapses onto each CA3 unit). CA3 pyramid cells also receive inputs from their own collateral axons, named 'recurrent inputs' (Rolls, 2016). This many-to-few ratio is important to understand that during retrieval, the firing of few CA3 cells can trigger extensive activation in subsequent field and areas of projection.

As a matter of fact, memories are encoded (acquisition of information), stored (placing information into memory) and retrieved (recovering previous acquisitions). Even though the distinction between encoding and retrieval is the most fundamental construct in memory theory, the way human beings encode events is highly dependent on previous experiences. Simultaneously, memories recollection drives our perception and interpretation of newly events. In hippocampus the interactions between encoding and retrieval are well illustrated by subfield neurocircuitry. The CA1 is activated during the encoding together with EC neurons. Then, in memory recollection, CA3 patterns activate dense CA1 neurons activated during previous encoding and rehearsal, restoring $EC_{out}$ activities and thus, neocortex. During encoding, neurons from $EC_{in}$ fire, through the DG, to the CA3. In this phase, $EC_{in}$ inputs are strong and CA3 outputs are feeble. Whereas, at retrieval CA3 signals to $EC_{out}$ are stronger and those from $EC_{in}$ are weaker, but strong enough to triggers recollection. Recall is reached thanks to the right patterns of activity (cue) (Kowando et al. 2020; Rolls, 2016). Although hippocampus circuitry is still largely unknown in humans, its functional and neurobiological complexity suggests that its role is to set up useful categorization and to enable new connections between newly generated granular cells and new subsets of CA3 neurons (Rolls E.T., 2016). While the first goal helps human to address 'multiplicity' (thanks to categorization), this second goal in HF is maybe more important to address significant newness in the environment and subsequently to retrieve its 'uniqueness' (thanks to contextualization) (Serra, La Corte, et al.; 2014).

Therefore hippocampus activity and parahippocampal areas are paramount for memory formation and recollection. Chaddad et al. (2017) used radiomic analyses based on MRI texture features, finding that hippocampi (one for cerebral hemispheres) in autism differ from age-matched controls with regard to the texture features analyzed (MRI precise analysis of tissues in HF), the accuracy of their measures leads the authors to conclude that hippocampal anomalies in texture features could be used as a good biomarkers for ASD detection (Chaddad at. al., 2017). Overall, little is known about human hippocampus complex mechanisms and its impact on neurodevelopment.

### 2.2 Hippocampus, Memory and Autism

Understanding and remembering is important to take decisions and actions, hence, to move towards future goals. In Bayesian terms, to predict based on prior models. Explicit and conscious memories concern self-awareness and social interactions. In chapter 6 of the book "Memory in Autism" DeLong states that "only a hippocampally mediated representation can support the linkage and flexible expression of memories within a relational organization". This hippocampal fundamental characteristic has received general consensus in its role for declarative memory.

Studies on high functioning participants with ASDs show relative preservation of semantic memory and damaged episodic memory (Bowler et al., 2000, Salmond et al., 2005). However, a comparison between individuals with ASDs and two other groups (one with preterm children the other with children with developmental amnesia) show that children with autism's performances are comparable to those born preterm. But children with developmental amnesia have a more severe deficit in episodic retrieval supporting the idea that there is not a bilateral structural damage of HC cells in ASDs.

Conversely difficulties in communication and interaction are more prominent only in ASD compared to the two other groups, while no finding of social impairment in developmental amnesia group suggests that hippocampal compromission alone cannot bring to social deficits. Hence, neurobiological mechanism could be different in ASD compared to other conditions (such as developmental amnesia). For instance, a neuropathologic study by Wegiel et al. (2010) find dysplastic changes (different neural size and shapes) in 13 children with ASDs. Subcortical, periventricular, hippocampal and cerebellar heterotopias were observed among their sample. Hippocampus shows dysplastic tissues (in EC, DG and CA1 subfields) and could be one of the regions implicated in pre and perinatal alterations. The authors highlight that disrupted neurogenesis, migration and maturation could be compromised in autism from birth (Wegiel et al., 2010).

Bachevalier and colleagues (2001) studied extensive lesions in Medio Temporal Lobes structures (such as amygdala, hippocampal formation and near cortical areas) during the first weeks of monkeys' life. Globally they observe impaired performance on recognition of specific items, but spared procedural learning, even in the presence of stereotyped behaviors. Damage as early as one week in temporal lobes compromises emotionality and social interactions to a greater extent than a similar impairment in adult animals. MLT impairments might disrupt the maturation of the neural system which develops later on (like prefrontal cortex). Moreover, early damage limited to the hippocampus, entails impairment in processes of context-rich information (e.g. event) and increases anxious behaviors, however it causes little or no impairment in social interactions during early development. Neonatal temporal damage caused significant functional damages, suggesting that temporal lobes functions are difficult for the human cognitive system to compensate through neuroplastic processes. Authors concluded that amygdala, hippocampus and temporal cortices can be associated with specific symptoms observed in autism. Hence, multiple structure anomalies are likely to develop symptoms in Autism, but the role of temporal lobe's structure in early development remains important; as seen in the resistance that its premature lesions have to neuroplastic processes. For at least one ASD subtype, DeLong (1992) argues that ASD could be a developmental syndrome of the hippocampus. According to DeLong (Memory In Autism, 2008 pg. 103-116), hippocampus is a central cognitive processor that enables associations among different inputs, and also sustains language generation and its flexible use. He argues that two neurobiological factors target hippocampus in ASD: abnormalities in synaptogenesis that implies serotonin neurotransmission (with GABA and 5HT1 receptors) and genetic mutation (chromosome 15q11-13 expressed in hippocampus).

Other studies of memory functioning in over 100 children, adolescents and adults sustain a comprehensive memory impairment in 'high-functioning' autism (HFA) show different outputs according to demands of the memory tasks and the person's cognitive abilities. Nevertheless, difficulty with complex information acquisition, and processing is a broader problem of the autism conditions. The authors conclude from their studies that there is a patten within the memory functions in HFA. People with HF profiles, compared to typically developing controls (TD) manifest inefficient learning improving across trials; their memory performance decreases as the to-be-remembered material increases its complexity (more elements or more complex semantic or perceptual content). There is a strong reduction in delayed compared to immediate recall, at least in story recollection (Williams, Minshew, Goldstain, 2008). The authors highlight that encoding and retrieval processes are problematic in HFA, especially for complex information, and this difficulty results in neural connectivity. Hippocampus itself may not be structurally damaged in ASD, but its neurobiological functions may be globally altered.

In the clinical domain it is also very common to encounter outstanding memory abilities in ASD. The discrepancy with the conclusions above appears in contradiction. The nature of used tasks seems to be a elucidating element: impairment are more important when materials are semantically or contextually richer, this pattern is shown both in 'low' and 'high' functioning. Thus, it is difficult to formulate concepts based on multiple relationships in autism, even though they are very good at tasks where material needs to be remembered based on sensory and perceptual information, sometimes even better then neurotypical peers (Toichi et al. 2002). In general, perceptual enhancement of details reported in 'savant' individual could result in accurate memory representations, but this skill can compete and hinder higher-order knowledge and conceptualization (Pring, 2008).

Perhaps the most consistent finding in the field is the poor ability to remember personally experienced events which need autonoetic consciousness to be fully remembered according to Tulving. People with ASD show performance deflection in remembering what they have done, thus the autonoetic consciousness involvement in the tasks could lead to more straightforward conclusions on the nature of ASDs memory profiles in future studies. Recollection strategies are different from healthy subjects (Bennetto, Pennington & Rogers, 1996; Minshew & Goldstein 1993; Renner, Klinger & Klinger, 2000), but the way by which they differ is still unclear.

Overall, mixed results and inconsistencies in ASD memory profiles, suggest that more complex mechanisms are involved and that they originate early in development.

Banker and colleagues put forward a very simple argumentation regarding the link between hippocampus and ASD. Symptoms appear at 2 years of age, the clinician can observe in the child difficulties in eye contact, joint attention, orienting when called by name and delayed speech development. In parallel, the hippocampus undertakes important changes between 18 and 24 months: Dentate Gyrus and CA3 reach sufficient maturity and form connections to the cerebral cortex. Encoding and acquisition of spatio-temporal associations and use of spatial context to guide object search. All these functions depend on hippocampal healthy development Hippocampal immaturity

before 24-32 months is considered the reason for infantile amnesia (i.e. inability to recall personally experienced episodes before that age). Additionally, Hippocampus is directly and indirectly connected with subcortical areas, which are well-developed at birth (like amygdala), and cortical areas, that reach maturation later in life (like frontal lobes). Backer et al. also highlight the role of hippocampal activation in social interaction, memory and spatial reasoning, tolerance to changes: all affected domains in ASD.
It is plausible that the coincidence in timing between symptom onset in ASD and aberrant development of hippocampus can be determinant in understanding autism (Banker et al., 2021).

### 2.3 Neurophenomenological Perspective and ASD

The journey throughout memory and autism takes us to the importance of autonoetic consciousness for the clarification of memory profiles. This section wants to draw the path of consciousness development in human being and its implication for autism. The neuroscience of consciousness can be seen as if consciousness was a single system which can or cannot contain an information (Schachter,1989; Moscovitch,1989) or as if consciousness had different levels where information can be attributed to one or the other levels. The second view is exemplified with developmental perspective called levels of consciousness model (LOC), according to it, newborn experience minimal consciousness (minC) which is defined as a coherent sense of something, related to sensations, where intentionality arises (see Brentano,1973). This kind of consciousness drives babies in approaching or avoiding physical objects. It is present-oriented and unreflective (there is no concept of Self). In adults this minC remains linked to implicit processing of immediate environmental stimuli, again, without any self-thoughts and unavailable for future recollections. Approximately during the first year of life the minC is able to account for many acquisitions, later a new form of consciousness is required, called recursive consciousness (recC): it allows the child to connect the content of the minC to one moment with the same content of a second moment, combining two perceived objects into a unified singular meaning, in other words forming the identity of objects. The development of levels of consciousness results: in a reorganization of basic processes into more complex ones (progressively reflexive) and in changes from perseverative behaviors to flexible actions. With consciousness, also intentionality develops, going from stimulus-driven action to more consciously controlled acts (i.e. inhibition of automatic actions and postponement of reward). By the end of the second year of life, self-consciousness (selfC) is developed, it emerges when children begin to consciously assess the means available for goal-directed actions, and consequently begin to establish rules regarding ends. Three-year old child can switch between sets of rules that are no longer based on identity but by differences, these skills are supported, according to the LOC model, on a first form of reflective Consciousness (recC1), further a second form of consciousness allows children to link incompatible couples of rules into a coherent structure, expanding their range of metacognitive skills.

LOC model links increasing in reflective thoughts with rules understanding and their effective use; implementing LOCs means to modify and complexify rules thanks to the development of executive functions. The author concludes that reflective thought might be dependent on executive system (Zelazo P. D., 2004). Other theories tried to understand consciousness and its neural underpinnings. According to Integrate Information Theory (Tononi, 2004), consciousness integrates information, consequently only highly interconnected networks can produce a unified conscious experience, given by the long cortical connectivity of the brain (spatial inference). Global Network Workspace (GNW) theory (Dehaene and Changeux, 2011) is based on study of EEG patterns of brain activity and neuroimaging which associate the activation of primary sensory areas to stimulus presentation without subjective awareness, while conscious stimulus perception triggers at first the congruent sensory cortices and then sustains activation waves in prefrontal and associative areas arise (temporal inference). The delayed waves is believed to transmit significant information through the brain to have them available to other functional areas for different uses (verbalization, consolidation, decisions-making)

Overall theories on memory, even when experimentally supported, are not very effective in their predictions (Maillé, Lynn, 2020). For instance, conscious processes can be possible even at the level of primary associative areas via cortico-cortical loops, which are the supposed top-down processes for conscious perception (Cauller and Kulics, 1991 and Meyer, 2011). Neural correlate for consciousness considered in the study were: extensive networks, long-range neural feedback, local feedback loops. If there was a common mechanism for consciousness it should be applied to all sensory modalities, but signals from different sensory areas can interact even without conscious perception (Faivre, Arzi, Lunghi, Salomon, 2017).

Consciousness seems theoretically wedged between perception and higher cognition (i.e. executive functioning seen above); the focus should be maintained on the core of human experience of consciousness. Neurophenomenological models may help, combining observed phenomena and conscious experience with neurocognitive correlates, and could clarify conditions such autism.

### 2.3.1 MCTT: towards a four-party theory of neurodevelopment

The Memory, Consciousness and Temporality Theory (MCTT; Dalla Barba, 1993; 2002) considers consciousness to be intentionally projected towards objects, either physical or abstract ones, in different ways. Given the same object like a pen "I can perceive it, if I close my eyes, I can imagine it (or imagine it were something else, like a magic wand), I can hate it or like it, I can know it, e.g., know that is it is a pen and not a sailing boat, I can remember it, e.g., remember where and when I bought it"(Dalla Barba; LaCorte, 2015). Every single relationship between objects and our own consciousness is considered original and irreducible, hence consciousnesses differ one another and they are not the product of an ontological effect chain, but rather they are considered as different ways to express only one consciousness. Four main forms of consciousness are identified in this model: Perceiving Consciousness (PI), Imaginative Consciousness (IC), Knowing Consciousness (KC) and Temporal Consciousness (TC). The emotional component (pleasantness or unpleasantness) attributed to the object could be considered a by-product of these consciousnesses, with different degrees of complexity from basic to complex emotions depending on which consciousness is involved. Consciousness is a set of distinct and original modes used to address an object. Memory, Consciousness and Temporality Theory (MCTT) encompass four consciousness: Perceiving, Knowing, Imaginative, Temporal, which are organized and irreducible form of consciousness and each mode of consciousness has two form: the reflexive (towards oneself) and the non-reflexive (towards objects). Each event produce modification within the organism and in the brain, patterns of neural changes do not contain any specificity per se, there is nothing at the biological level which can demonstrate that a group of neuron contains temporal or spatial information, or meanings or rules or algorithms, scientist can only correlate a certain activation with the phenomenological experience. For instance parahippocampal place area (PPA) activates more when the subject have to judge spatial information in landscape and places figures, or the fusiform face area (FFA) in the temporal lobe activates more when the subjects is processing faces but this cortical neurons are only increasing their electrophysiological responses and we can assume that they support a certain phenomenological state like "recognizing a countryside like an outer space" and "recognizing Einstein face" only knowing what the subject is experiencing, no neurotransmitter nor depolarization can confirm that Einstein is recognized instead of our own brother. Brain modifications are more or less stable and vulnerable depending on several factors such as attention at encoding, emotional connotation of the event, depth of encoding, rehearsal and repetition of the same event (Dalla Barba, 2002).

MCTT implies several considerations and previsions (Dalla Barba, 2002).

1) Importantly, in phylogeny and ontogeny, PC and KC precede IC and TC. The child begins with self-object identity, then proceeds with object categorization according to their quality, quantity and functions, and later the child begins to manipulate features, functions, and rules in imaginative play and only after 3-4 years of age the cognitive system can let TC flourish. With the progressive degradation of central nervous system, like in dementias, the opposite should verify: temporalization of current and future situations diminish, as well the memory for past events, then spontaneous imaginative abilities decrease and finally objects categorization, use and recognition can be the last to vanish.
2) Perceptive and Knowing Consciousness are the foundation for Imaginative (IC) and Temporal consciousness (TC). It is unlikely that deficit in knowing consciousness can be observed without deficits in IC or TC. Whereas, deficit in IC and/or in TC can be observed with the preservation of KC. Hence, neural networks of PC, KC, IC and TC may be partially overlapping. Different

patterns of activity in the brain may correspond to these modes of consciousness and therefore specific deficits can be observed for each.

3) Given that TC refers to the unicum of time in its components of past, present and future when TC is compromised the person who shows impaired retrieval in personally experienced events of the past, can also have deficits related to their current situation and the future plans, even though to different degrees.
4) KC knows objects' quality, quantity and function thanks to different relationships towards objects, therefore three separate deficits could appear regarding the three subdomains.

In MCTT theory representations proceed from Uniqueness to Multiplicity, that is, from instability to stability of traces in the nervous system. The theory of Temporal Consciousness assumes neural modifications that are consistent with consolidation theories: it predicts that a deficit in the hippocampus produces a degradation of memories contextualized in time (Temporal Consciousness), but not of memories detached from the spatio-temporal context, such as the capacity for recognition and free recall. Temporal Consciousness would thus be more vulnerable than Knowing Consciousness. We illustrate a developmental perspective and its link to several signs and symptoms seen in Autism during growth, to hopefully open a new comprehensive view in autism.

### 2.3.2 Perceptive Consciousness

PC appear as soon as first intentional motor action in the newborn, it could be defined as intention to give coherence to physical world it allows individual to act with perceived world in relation to one's own body, in order to have a conscious experience we need to flexibly change salient features of objects depending on our needs, goal and decisions in a particular context. Humans can learn relational laws between object's parts, and between that object and the self only by mean of interactions with it. Perceptual consciousness is experienced-based and the relation between subject and object is symmetrical and mutual. Initially, PC is mostly non-symbolic and it is based on sensory incoming inputs, but during the lifespan, as KC develops, PC could become symbolic (words, numbers, signals), too. Human being are equipped with a certain amount of 'perceptive consciousness', rooted in phylogenetic heritage and ontogenetic constraints, for instance 'core knowledge' (Spelke, 2000) help the child to represents outer word's animate and inanimate objects (and their basic physical, numerical and geometrical laws). During growth, toddlers increase and complexify their interaction with objects, so their intentionality and perception become more grounded on contextual information and top-down regulation. Bayesian theories are now revealing this interplay, but Gibson's ecological approach to perception identified affordances as being "*neither an objective property nor a subjective property, or both if you want*"(Gibson, 1979). Affordances can be seen as relationships that exist per se and are perceived differently depending on context (internal to the subject and external in the environment). In Gibson ecological theory, perception is an active process by which the baby-as the preceptor-can acquire information from a dynamic ensemble that surrounds him, and it starts even before birth. The scope of Perceptual Consciousness is that to form object's identity while they are forming their own physical identity (as an agent), therefore the aim is to-recognize-for-interacting. As early as 2 months babies show intentionality in maximizing the possibilities to perceive an object's qualities. They increase the sucking response to better visualize a fuzzy figures (Kalins, Bruner, 1973), they move the leg for obtaining the movement of the rotating object tied to it (Rovee-Collier, Fagan, 1981). Babies at 8 weeks of age learn to produce pleasant experiences in their environment pulling attached laces to their arms and become frustrated (pulling more strongly) when the laches are loosen. At 5 months children show a familiarity effect (i.e. attentional decreasing for familiar stimuli rather than the novel ones) for their own faces in videotapes compared to someone else's (Bahrick, 1996), and in an another study (Legerstee et al., 1998) they show the familiarity effect more when they are presented with their faces in movement rather than static (all the babies were exposed to the mirror at a daily-bases with their caregivers), therefore babies recognize theirs' faces better when they contain more experienced qualities (like visual and kinesthetic modalities). It could be argued that their perceptual consciousness is well-formed when they have experienced more interactions with that object or that they have better prior-model of their faces in movement rather than static. The development of Perceptive consciousness depends on the ability to do transmodal comparisons between different stimuli belonging to the same object, Meltzoff and Moore, (1977) named it Active Intermodal Mapping (AIM), the ability that allows infants to gather together two or more senses which is a-modal and helps to form symbolic relationship between their own movements and other's action. The maturation of this symbolic perception helps the child with imitation and language acquisition. AIM implies stimulus perception via one sense, its storage in a non-modal form, and its future recognition and use in other modalities. As explained previously, the hippocampus is responsible for recognizing identity. The Entorhinal and perirhinal cortices convey inputs from unimodal and polymodal sensory cortices to sparse neuronal units in CA3 for the future recognition of the "likeliness". This term refers to the ability in infants in finding equivalence across modalities (for instance in facial matching, oral-visual matching, and early speech perception), named intermodal coordination (Mezeltoff, 1991), which helps the child in at the beginning of the development to have a sense of "like" between two sensorial separate things. For instance, your movement that I see is like my movement that I experience (via proprioceptive signals) or "this thing that I see is like this other thing that I hear", the sense of "you are moving like me", is developed via imitation and encourages empathizing (Legerstee, 2005). This sense of commonalities between two separate things or the merging of two separate experienced features in the same object is the prerequisite for developing a good theory of mind.

In autism we believe that the symbolic perception is more compromised because both imitation and language acquisition are unusual; babies who receive diagnosis are those who show poor imitative behaviors, delayed or atypical language acquisition. The non-symbolic perception is instead linked to object recognition throughout different sensory modalities and its intentional use to interact with more than one modalities, infant with autism show restrictive and repetitive use of an object even at 1 or 2 years of age when their peers are experiencing a richer multimodal feedback from the same object's use, children with autism do not show intentionality for acquiring the greatest possible number of qualities from their environment (whether they are objects or agent). The more an object can be multimodally used, the less they seem to engage with it. The other person can be seen as a "multimodal object" that they need to deal with. Children with autism interact with few, restricted qualities, and have a decreased ability in objects categorization. Many studies have studied early innate knowledge in human and other species. As early as 3 months children expect some properties from certain categories like object or agents (inanimate or animate object of the environment). This expectation is called core knowledge and they have foundation within the preceptor itself: the child is indeed equipped with some rules on how the objects works. Core Knowledge helps to orient our intentionality (attention, motivation, seeking for something in a certain way) ant to build more complex laws for world understanding.

### 2.3.3 Knowing Consciousness

KC is the Semantic knowledge (Knowing Consciousness) and it refers to the ability to evaluate an object as known and familiar, but without memory of the context in which it was learned. This mode contains a synthesis of what the subject has known up to that moment: it concerns indeterminate and thus multiple categorical entities (multiplicity). KC is the mode for addressing the object to discover its quality, quantity and functions; it synthesizes past consciousness of objects, without the sense of time (a person can learn what a ball, a chair, a dog is, without any awareness of the time or space of the acquisitions).

Categorization and generalization of information pertain to KC. When the subjects learn which features belong to which category. The categorization may be considered supervised because it relies on associations between items and learned categories. Some other categories are the product of intuitive groupings of items, named unsupervised Categorization.

However, categorization performances vary largely in ASD, for some object's classification and categorization can be extremely difficult or very poor, in others this ability is sometimes enhanced even compared to controls (Froehlich et al., 2012). According to weak central coherence (WCC) theories, the greater over-selectivity in autism is responsible for their reduced ability to learn the category labels and category structures, which supported the learning deficits theories.

Categorizing might be the result of three different processes, all used by human brain to order the world: 1. forming one or more criteria; 2. create a prototype, which is the most typical example of the category (an apple for fruit, a sparrow for birds, 3, 7 or 9 for odd numbers etc.); 3. collecting numerous typical examples (for instance example of "games") or a combination of all these strategies (Vermeulen, 2012). In order to categorize, a person can choose different levels of category. It can be a specific and concrete aspect, named perceptual categorizing, or more abstract and general like conceptual categorizing. During development, children categorize at first based on perceptual features and gradually learn to categorize on more complex ideas, like object's functions. People with autism can categorize, but they are more focused on perceptual features which differentiate things and they need more examples to form the category. In autism, forming well definable concept (triangle, dog etc.) is easier than forming vague concepts with more atypical examples (joy, fear, anger etc.). Moreover, generalization is a common problem among people with autism. They express these difficulties through the resistance to change. Generalization is the abstraction of relevant information across multiple stimuli or situations and the subsequent transfer of this abstraction to similar stimuli or situations, it seems difficult across the entire spectrum (Edwards et al., 2012). In autism, generalization impairment is reported, particularly as the to-be-categorized object is less similar to the category's prototype, hence the categorization of novel stimuli can be particularly difficult in people with ASD (Frohelich, et al., 2012).

KC implies the abstraction from perceptual objects to their most frequent features, but also to the more relevant ones, which are the most shared with other objects in the same acquired category. The KC extracts the multiplicity in order to create more complex norms, laws and exceptions. KC thrives on connections and laws, human being can flexibly change levels of categorization depending on criteria and goals. At the beginning, it helps to create cause-effects links, but later in development it complexifies and it enriches the highest forms in language, algorithms and mathematical formulations. Hence, KC starts with object recognition via co-occurrences, but aims at abstraction and symbols manipulations. As previously written, children show core knowledge since the very beginning. This is paramount for understanding KC. Core knowledges are innate representations of laws that are linked to perception, but transcends the mere experience. They are already present when intentionality begins, and do not need any language. It is symbolic without any symbols. Both recognition and first laws are already there before labeling and naming. Language is the act of knowing the world in the atemporal relationship, perception and language assists KC to achieve knowledge and grows its scheme, knowing processes are partial and progressive.

### 2.3.4 Imaginative Consciousness

IC could be defined as the human tendency to create another reality which does not correspond to the actual experienced environment. According to Dalla Barba "the image which is present to consciousness is not a faded reproduction of a real object, but the reflection of an original relationship between consciousness and the object" (2002). It could start with one single attribute given to an object; for instance, using a cooking pot as if it were a musical instrument like a drum has low level of imagination because the pot has some quality closer to an instrument (it could make noise if beaten) or pretend to use a pillow as if it were a boat. This implies higher level of imagination because the pillow does not have any qualities in common with a boat. Moreover, imagination does not depend on the experienced world, a child can pretend to be on a boat even if he has never been there. IC appears later in development the first proof of imagination is play, and more specifically the transition from sensori-motor playing to pretending. At one year children can pretend only with objects similar to the one used in real actions (pretend to drink by a real or fake cup, but always a shape-like-cup), but they will hardly try to call someone with a shoe at that age. They also explore cause-effects functions of their games (i.e. press the button cause sounds). At this stage imagination can abstract an object's function but not transfer it to a completely different one (Creekpaum, 2019). Later in development children begins to use objects, actions, or ideas to represent some *other* objects, actions or ideas, thus they start to transfer perceptual properties and function laws that are not present and inherent to the objects itself, for instance they can "animate" "inanimate objects"(dolls, pets, but also socks, spoon etc.).The subject imagination can be more or less creative but it always place individuals in a mental state that it is not representative of one's actual reality, meaning that the brain's activity does not correspond to the perceptive world (Thibodeau-Nielsen, 2020). They also explore their own body potentialities, changing usual rules to achieve their goals. Early in autism, children do not show much interest in engaging in play with others and they do often not initiate symbolic play. Play when pleasant, challenging and motivating for the children, it is also "the highest form of learning" (Bruce, 2012), when delayed or restricted as in ASDs it makes also learning more difficult.

Ideation, flexibility, delayed goal, are all behaviors corresponding to a certain amount of imagination. Why? Because the child starts to think of qualities that are not immediate to perception and neither they are a simple real object in another room, nor real object in an imminent future. The ideation of a movement, the creation of totally new uses of one's own body (i.e. dancing) or the ideation of a new goal, are all first signs of imagination. Imaginative skills expand in play and later, whit fine-motors achievements, in drawing. Imagination function like "a weak version of afferent perception" (Pearson, 2019), but it allows a multitude of environmental interactions with the world that are way broader than the mere perception. IC is the way that a child enjoys interacting with the social and no social environment, but it is profoundly intentional and an early sign of a healthy developmental trajectory.

Children with autism do not show high levels of imagination, they tend to show rote play and restrictive behaviors. They seem glued into perceptual play and when they do show creativity in their play this is based on the mechanisms of objects, named on their logical and inferred properties not fictitious ones (for instance they can built very complex structures with blocks and lego, but very rarely they can make a butterfly with play-doo).

Thibodeau-Nielsen et al. (2020) in a study with 44 subjects around 4 years of age measured the sympathetic nervous system response (skin conductance levels) with an imaginative task of 'storytelling' prompted by fantastic pictures (for instance a magic castle). They found an increase in sympathetic response during the storytelling compared to the control task (verbally identifying objects in a pictures collage). The authors conclude that imagination during highly fantastic and novel scenarios increases arousal and support the hypothesis that imagination gives children the chance to practice emotion regulation through immersive imaginary situations. This argument needs to be further explored, but it seems very plausible that better mood regulation abilities are seen in those children who test themselves in highly imaginative scenarios because they have more chances to train and modulate emotions. In adulthood we maintain the drive for highly immersive scenarios even without any practical aim, such as going to the cinema or at the theater, to imagine other lives and situations, ultimately to simulate unexperienced feelings while we are sitting in the stalls. In an fMRI study, researchers (Benedek et al., 2017) found that, compared to recollection of common ideas on an object's use, the generation of new or old original ideas has basically the same pattern of activation. It involves hippocampus bilaterally and the medial Prefrontal Cortex. Also, with a new object use ideation involves higher activation in left supramarginal gyrus. The authors conclude that retrieving unique episodes and figuring out new ideas share common neural processes, involving the hippocampus. Hassabis et al. (2006) conduct a fMRI study asking subjects to imagine fictitious experiences to activate the hippocampus, parahippocampal gyrus, and retrosplenial cortex, demonstrating the hippocampal involvement in rich scene construction.

Responses in anterior medial prefrontal cortex, posterior cingulate cortex and precuneus may instead support self-schema and familiarity processes and are implicated in distinguishing imaginary from real memories (Hassabis et al, 2006).

Imaginative consciousness is even more powerful than perceptive consciousness in terms of learning: when the child starts to imagine a non-present world, they improve cognition, agency and metacognition.

Imaginative consciousness is likely essential to make symbols and laws among them, but it is per se-rich and delightful for the child. A lack of imagination in their activities is seen in autism across various behaviors such as imaginative playing (DSM-5, 2013), drawings (Low , 2010), Theory of Mind tasks and praxis ideation (Serrada-Tejeda et al., 2021). Vyshedskiy (2021) highlights that the pervasive problems in autism imagination may be based on the voluntary imagination network that involves long frontoposterior connections between the lateral prefrontal cortex and the temporal-parietal-occipital area. This voluntary difficulty differs from the involuntary imagination. The activation of involuntary imagination is based on more posterior activation and causes phenomena like dreams. Again, Imaginative Consciousness implies instead the intentionality to imagine something in its entirety, therefore conscious volition changes the neuroactivity and not the opposite. Importantly IC does not aim to know, it is a-finalistic per se. Rather, it degrades the knowledge, but it depends on knowing, we cannot imagine something, its contrary, something with other's attributes etc. without knowing. Interestingly younger children need more prompts to create stories than more older children, imagination increases as knowledge increases and not the opposite.

### 2.3.5 Temporal Consciousness

TC denotes an unique form of awareness that "*allows individuals to locate objects and events according to the subjective temporality* "(Dalla Barba, 2002). In other words, this capacity allows us to go beyond the mere notion of the object ("what?") and place it in the temporal dimension ("when?"); the person has phenomenological experience of remembering her personal past, of being oriented in her present world and of predicting her personal future (Dalla Barba, La Corte,.2013). Temporal Consciousness concerns specific, determined and therefore unique entities (e.g. personal episodes, objects belonging to episodic memory). Only the relationship of temporality between consciousness and the object can lead to the object to be seen as temporal; temporality means to have consciousness of time and thus, the temporality of an object appears in the world in a certain temporal perspective (Dalla Barba, 2002).
Recent neuroscientific research also divides the process of familiarity from that of actual retrieval by attributing them to two different neuro-functional patterns (Aggleton, Brown, 1999). In the first case, the identity of a stimulus is recognized via the perirhinal cortex, located outside the hippocampus. In the second case, contextual associations are created and encoded to allow the object's identity to be related to its spatiotemporal source in which it was experienced through the posterior parahippocampal cortex and hippocampus (Ranganath et al., 2003; Montaldi et al., 2006).
During development the child at first recognizes objects as past and later recognizes himself as being the actor who made an action in the past. Therefore, temporalization is at first directed to the object and lately reflects to oneself in a temporal mode, called "temporal thematization of consciousness" (Dalla Barba, pag. 143). TC expresses personal temporality like the event of "your wedding", while KC expresses impersonal temporality like what age were when you got married, in which city you were etc. Episodic memories and their uniqueness are addressed by TC. The memory profile in autism shows in general poor episodic recollection and thus, but a globally spared semantic memory. Some studies also investigated their inner time experience and speculated that the spatio-temporal aspects of neural processing may be impaired in ASD (Voegel et al., 2019).
Different clues by everyday practice and mixed results from the research field, reveal that something is wrong in the ability to learn and remember in autism. Vivanti et al. (2021) bring another clue to the table: they find that the risk for ASD under the age of 65 to be diagnosed with Alzheimer dementia and other

forms of dementia were approximately 2.6 times more likely compared to the general population. The hypothesis of a partial overlap between Alzheimer Dementia and autism has already been suggested by DeLong in 1992, who identify in hippocampus malfunctioning the possible shared neurobiological common point. Today, Dalla Barba MCTT can formulate an even more detailed hypothesis, conveying neuropsychological data in adults with dementia and other acquired pathologies, to the ASD population. The MCTT main point is that in amnesic patients the absence of recollection of their personal past (present and future) depends on the impairment of the hippocampi which support Temporal Consciousness, therefore amnesia emerges when TC vanishes. When hippocampus is, at least partially preserved, TC is still present but malfunctioning: the patient can remember but he often tricks himself with "honest lying", a clinical symptom called confabulation. People with ASDs can remember, but they do not remember like healthy peers, Boucher and Bowler extensively argue the imbalance between Semantic material and its recollection and poor or unusual Episodical retrieval. Spitzer and Burgess in 2017 for the first time tried to experimentally observe whether ASD children confabulate and find that two of the four confabulating participants produced an abnormal number of confabulations during a confabulation elicitation questionnaire. They conclude that in some cases autism can show confabulation assumed to be a symptom of poor executive functions or source monitoring. Instead, MCTT points to an active role of the hippocampus to explain distorted episodic memories. Accordingly, the main hypothesis of the thesis is that the atypical profile seen in memory of people with autism could be linked to anomalies in the hippocampal dependent network, within its subfields.

As a whole, MCTT provides not only a good account for explaining the anomalous profile seen in Autism and its possible link with TC, but it could also be useful for combining described phenomena observed during the growth of children with autism with a more precise neurocognitive model. The link between ASD symptoms and hippocampal neurodevelopment needs to be investigated at least at the same degree of the actual neurocognitive accounts. The strength of this neurophenomenological model consists in including the main theoretical view in a developmental and dimensional trajectory where HCP is crucial for balancing previous subcortical alterations and to prevent broader cortical disfunctions.

### 2.3.6 Beyond the episodic-semantic dichotomy: Uniqueness and Multiplicity, implications for ASD

Within the phenomenological framework consciousness is always consciousness of an object. Objects can represent the synthesis of the past in an indefinite, repeated experiences of that object, named Multiplicity. Or it can be what the object is for the actual consciousness, thus the subject can address object Unicity. To address uniqueness TC relies on a less stable and more vulnerable pattern of modifications, while the interaction between KC and multiplicity needs more stable and less vulnerable brain changes (Dalla Barba, 2009 pag 38).

When the number of repeated past experiences of the objects is low, and the subject address object unicity TC and IC are at stake (for instance "the first kiss" or "the first house that I am going to build"). When there is a high degree of previous experiences, we call upon KC ("books that I read"). Since multiplicity and unicity of the object of consciousness are functions of both the modes of consciousness and the degree of repeated experience, TC may see multiplicity as unicity and KC may see unicity as multiplicity.

To better understand, we can illustrate the relationship between Multiplicity and Uniqueness, taking into account well known episodic and semantic content. Tulving (1972,1983) proposes a distinction between two systems that contain the synthesis of knowledge held by the society, i.e. meaning and rules that bind these meanings. Episodic memory implies the conscious recollection of personally experienced events and their spatio-temporal features. As suggested in MCTT the unicity of the memory and its multiplicity can be alternatively addressed respectively by CT and KC. The relationship between Episodic and Semantic memory has been debated among theorists: according to Tulving (1972), learning new episodes is hindered by semantic information, for instance paired association learning is affected by the degree of association between the two words. In accordance with Tulving, the SPI model suggests that information are encoded by perceptual system, then by the semantic and finally by episodic system (Serial encoding), information is successively stored in parallel and can be independently retrieved in Episodic or Semantic form. Contrarily, Baddley (1988) takes a different perspective and considers the Semantic memory the product of acquired episodes that have passed a process of abstraction and de-contextualization from their spatiotemporal and detailed contingencies. The most plausible explanation is "a variable" interdependence between Semantic and Episodic information: different types of semantic recollection imply a different contributions of episodic content and the integrity of the knowledge system supports the acquisition of new experiences. In the neuropsychological field reports of amnesic patients with extensive damage to medio temporal lobe (MTL) describe that they can learn new information, but with poor integration into semantic store, often characterized by hyper-specific details, and with major effort during encoding processes. Semantic learning seems still possible for these patients, but it relies on neocortical learning system, rather than more efficient structures -such as hippocampus- that supports consolidation underlying episodic retrieval. Therefore, encoding of newness could be scaffolded by preserved and rich semantic knowledge. At retrieval, the opposite seems to verify: The episodic system facilitates new semantic retrieval via an efficient access to information, amnesic patient has difficulties in retrieving autobiographical type of information that strongly rely on self-experienced events (like listing "things given as a birthday presents" compared to "things that are usually the color red").

Longitudinal studies also show a decrease in autobiographical memory as the semantic information weakens. Indeed, degradation of new semantic memories is associated with impoverished and over general episodic memory. Autobiographical memories are nourished by richness of content stored in semantic memory. Overall, important interdependencies are possible between general information and unique and precise memories at different stages from encoding to retrieval (Reader et. Al., 2009; Greenberg D. and Verfaellie M., 2010).

It is essential to address the episodic-semantic dichotomy, to return to hippocampal neurofunctions. Posterior hippocampus (pHPC) elaborates local and fine-grained information, Dentate Gyrus occupies a large portion of pHPC and it is the area where neurogenesis of granular cells take place continuing even in adult human brains. Poppenk and colleagues (2013) speculate that DG properties explain the observed increase of pHPC associated with spatial learning and suggest that environmental changes may require production of new cells in pHPC. Anterior hippocampus is instead implicated in global and more coarse representations (La Corte V., Dalla Barba G., 2015) and its cells could more easily match environmental changes. Furthermore, Rolls (2013, 2016) in his theory of hippocampal functioning identifies two properties of hippocampus subfields: the first is "pattern separation" which enables hippocampus to store different memories of events and to distinguish even high degree of similarities among events; the second is "pattern completion" which implies an autoassociative network (CA3 and its recurrent collaterals synapses) especially involved in rapid, one-trial object-place recall, and also when it is required to fully retrieve the spatio-temporal context from one element or even from partial cue.

Dalla Barba hypothesizes that pattern separation and completion are possibly implicated in the phenomenological experience of recalling the uniqueness of an episode (functions of TC). Thus, when disrupted, to replace the precise full-retrieving, multiplicity (addressed by KC) may come into play.

Hippocampal anomalies are very broad within ASDs: smaller or larger HPC volume, shape alterations, atypical texture features and anomalies in white matter fibers between HPC and the fusiform gyrus have so far been reported. Functional data also support anomalies in hippocampus-based networks. Performance in the relational learning of associations between stimuli that have not been explicated, namely transitive inference tasks, declines as ASD symptoms worsen. During episodic retrieval, a reduction in functional connectivity of the hippocampus is observed. Instead, the connectivity between HPC and Default Mode Network is stronger during rest. Hippocampus also shows an enhanced activity during executive function tasks within ASD.

It may be possible that the variety of hippocampal discrepancies play a role in the definition of ASD phenotypes, however a clear account can be given only by overcoming the dichotomy between episodic and semantic content for a finer definitions of memory contents, as expressed by Dalla Barba with Uniqueness and Multiplicity (Dalla Barba, 2002). However, it is difficult to grasp the exact difference between neurotypical people because the ability to retrieve de-contextualized objects (multiple) and contextualized ones (unique) depends on highly complex circuits from the core of the hippocampus that need further investigation.

#### 2.3.6.1 The Context blindness theory

Peter Vermeulen in his book "autism as a context blindness" (2012) provides a supplementary account for advancing in the theoretical and practical fields of autism. According to the author context could be immediate and broad; internal (environment) and external (inner body feelings and thoughts); significant (critical stimuli for understanding object's meaning) and incidental (co-occurring irrelevant stimuli). Given this three-faced nature of context he defines it as "what is going on inside or outside our brain, that influences our way of giving meanings to things." (Vermeulen P., 2012). The ability to select meaningful and useful elements in the context is what he calls "context sensitivity" and suggests that while neurotypical brains are sensitive to context, atypical minds in ASDs struggle with it. He also highlights that context processes in the brain are fast and subconscious and do not depend on one unique area, but are related to the well-known top-down control and broad connectivity. Context sensitivity allows humans to not only process stimuli in absolute terms (association apple means food) but relatively (it could also be a simple for a computer brand, a cheek in Arcimboldi's painting or a synonym for New York city). Therefore, context is particularly important when stimulus is inherently ambiguous, in that case we use context in a more conscious way to solve the ambiguity. In autism there is a tendency to form uncontextualized meanings. Vermeulen considers his theoretical formulation as specification to one aspect implicated in the first version of Weak Central Coherence theory in which Frith (1989) explicitly states that the central cohesion is revealed by the tendency to organize information in progressively larger context and that "drive for coherence" is equal to context use (Frith, 2005).

Vermeulen also points out that people with autism can use context to some extent, but present research methodologies are not always able to provide them with a realistic context. One of the most ambiguous fields is social interaction and communication. Individuals indeed use context for disambiguating facial expressions and body language. Symptoms in the social domain could be seen as consequences of context blindness. For instance, children with autism have also problems with nonsocial questions about stories, like question about physical aspects of the story (i.e. "what does Jan's room look like?") (Kaland et al., 2004). Context in general helps concepts to be formed and apply flexibly. When people with autism deal with fixed properties of concepts they perform well, besides, performances are poor when concepts need to be adjusted.

Looking closer to Vermeulen's definition of context, a richness of relationships emerges between the world within the observer (mainly stored memories) and in the spatial and temporal outer environment. A reduced context sensitivity is considered a failure to use context and not its complete absence. Therefore, practical strategies to address the context difficulties are proposed, for example starting from concrete tasks and guiding the person to take account of important elements of the context and propose variations while teaching new skills and not using only unambiguous associations. Importantly processing context is more demanding for people with autism and should be trained when the person is willing and emotionally regulated to do so.

Overall context blindness could be considered the common ground for different trajectories seen in ASD. Vermeulen extensively argues that perceptual, conceptual, episodic processing are difficult in ASDs, especially when rich and flexible contextual information need to be considered. Again, Dalla Barba's Uniqueness and Multiplicity concepts can be useful keys to analyze ASD performances and everyday behaviors. This diminished sensibility for context, in other terms the inability to address uniqueness and the tendency to address multiplicity, is pervasive and encompasses all aspects of cognition, even if it seems to improve with age, it could be the common ground for practical intervention.

The present thesis traces back to a common theoretical patten from Frith to Vermeulen but adds an important intuition made by DeLong (1992) in attributing to hippocampus a decisive role as a "central processor" and in fast and flexible contextual encoding of subjective experiences in the environment. The argument does not deny the importance of other discoveries (empathizing deficits, executive dysfunction), but these may be consequences which appear later in development. We believe that the hippocampus is not fully damaged, but instead malfunctioning and anomalies could be observed at different levels of complexity (neurobiological, electrophysiological, structural) affecting all the micro and macro HPC-dependent circuitry. Moreover, predictive coding impairment matches with the ability of Temporal Consciousness to address time not only in the past, but also in the current and future situations. Furthermore, some researchers are making a link between pattern completion (necessary for TC) in hippocampus and mnemonic expectations (Hindy N. C., et al., 2016).

In line with the need to highlight the context urged by Vermeulen, our effort is to understand how contextualized events are recalled (first study) and to strengthen the ability to perceive and encode the context in autism (second study).

# 3 FIRST STUDY: Confabulation Elicitation Questionnaire for children and adolescents with ASDs

## 3.1 Introduction: Remembering during growth

During human development, episodic and semantic memory have a different onset: children at 2 years of age would be able to recall things they had witnessed at 13 months (Bauer & Wewerka, 1995), this kind of recalling is accompanied by what Tulving called noetic awareness and is linked to semantic content. Whereas the onset of the ability to include oneself as part of the memory grows with self-awareness and would allow for a more complex organization of memory, children at about 3 years can recall one event happened six months previously, although an equal number of information are reported for what happened three or less month in the past (Fromhoff, 1987).

Neither the amount of experience gathered, nor the language acquisition alone cannot explain how report exhaustiveness increases with age, Fivush et al. (1992) observed that children exposed to the same novel event reported increasing information as they were older. It is between 4 and 6 years of age that children identify the source of their knowledge and experience a subjective sense of re-experience past events (subjective time travel). The sense of re-living past experience which accompanies autobiographical recall is named autonoetic consciousness (Bauer P., Fivush 2014). At 3 years of age children memories include mostly routine and everyday life, they tend to report actions in the sequential order most frequently experienced and well-known, they report became more accurate but minimal content is expressed When children are 6-8 years old, they can describe more facts and details of an event, their reports contain more optional ("sometimes") and conditional activities ("if") (Nelson K. and Gruendel, 1986).

In the preschool period and later, children become more and more accurate: they begin to acknowledge the source of their information, the spatial location where they experienced something and the time flow (which event happened before and which after). Consequently, they become more adept at using the community's shared rules about time (days of the week, seasons, calendar).

When children understand that their own thoughts and memory are unique to them and that other people also have this private mind, they start to have a personal perspective on events and to learn to shared experiences and to ask for them, fostering empathizing ability (Bauer, Fivush, 2014)

Changes in autobiographical memory is related to hippocampus maturation which is especially fast during the first 2 years of life observed by volume increasing; before that the HCP is too immature to retain consistent memories and infantile amnesia verifies (infantile amnesia is the impossibility to autonoetically recall memory before 2-3 years of age). Between 2 and 6 years of age autobiographical memory is still immature (childhood amnesia) and the anterior hippocampus loses volume while the posterior gets larger, possibly due to subfield specialization fostering the ability to relate various information (relational memory). HCP growth finally stabilizes by 10-12 (Gogtay et al., 2006) and so does relational memory and autobiographical ability. Hippocampi development in humans is difficult to investigate because longitudinal design is costly and complicated to pursue, but medio temporal lobe as a whole is assumed to be globally mature at 10 years. Other areas, such as the prefrontal cortex, have longer maturation and are highly interconnected with HCP. Therefore, reciprocal connectivity affects maturing processes within the hippocampus and other structures.

Theories concerning autobiographical memory assume that there are different levels of representation of experiences: from highly detailed episodes (graduation day, first day at work, etc.), to more general ones covering longer periods of life (school life, working life, etc.). There is an intermediate level concerning a type of generic memories that seem to reflect the synthesis of many similar experiences into 'scripts' (Schank and Abelson, 1977) of experiences categorically represented (e.g. seaside holidays in childhood). Conway (Haque and Conway, 2001; Conway & Pleydell-Pearce, 2000), elaborates an autobiographical model hypothesizing an organization into memories based on knowledge of different periods of one's life, so many episodes are merged into one categorical unit and contribute to organize the concept of the self. Such mixed autobiographical-categorical awareness would be crucial for the achievement of personal and collective goals (J. M. Gardiner, 2008).

Humans mainly use narratives for sharing experiences: adults usually express what, where, when something happened and who was involved, they often add information about how things went and detail the report with elements like persons' belief back then and in the current situation, updating information relative to the most recent period. All the reported elements are coherent and understandable by the listener. In younger children this is not the case, the listener tries to understand with more questions and to infer key passages. Similarly, in people with autism, the narrative is poor and key information are difficult to understand by the listener (who, where, when), they sometimes even believe that a listener can remember their own personal experience.

The subjectively sense of time is most involved in autobiographical recollection and allows individuals to perceive a continued existence in time, named chronoesthesia (Tulving, 2002 Dalla Barba, 2002).

In a study by Vogel and others (2018) they investigate the experience of time in 27 adults with ASD (Asperger syndrome) using a Time Questionnaire based on the distinction in past present and future. They observe that the structured directness of time is not disrupted, but the experience of time flow is interrupted and perceived as discrete and non-continuous ("passage of time is vaguely felt", "present consist in one distinct activity", "the past is a repetition of facts and the future in uncertain and frightened"), concluding that a general alteration in time-experience in ASD, even when verbal IQ is matched to controls. Thus, according to MCTT, people with autism have TC and can experience time subjectively but in a fragmented and more objective way, based on KC.

MCTT is in line with the above contents and some assumptions can be made:

1. Long term retrieval improves with age, both for unique events and semantic knowledge, because temporal lobe structures and fronto-temporal connections have long-lasting development, hence memory gets stronger, more stable and more interconnected.
2. As temporal lobe mature so does TC; the ability to mentally travel back in the past and forth in the future increases with age, the younger the child, the less is able to access memories that are far from his current situation.
3. Knowledge also increases with time and with long-axis maturation, thus the ability to connect information is richer in adolescents compared to children, KC also improves with age.

It is not known, however, whether the same improvements can be observed in populations with atypical development such as the population with Autism, given the neural divergence and differences in plasticity during growth; the hypothesis is that they do not show the same increased memory. Autobiographical memory function is lower even in ASD without intellectual disability (Coutelle et al., 2020).

In the "neurotypical" population it is more difficult to develop the autonoetic consciousness for events compared to noetic consciousness for facts and knowledge and this unbalanced advantage seems to be due mainly to hippocampal maturation. In Autism autonoetic consciousness and free recall and report of contextualized events is lacking or odd. Trajectory could differ between episodic and semantic recall given that the first needs a healthy hippocampus to be achieved, while semantic memory depends upon more distributed connections.

Undoubtedly, it is more difficult to develop the ability of remembering unique event with precise relational features and time and place location than to know facts about personal life (i.e. school attended, date of birthday etc.), the world (i.e. the actual president of United States of America), and the others (i.e. where relatives live). Hans Asperger in a case report describes a child who "told fantastic stories"(Frith, 1991) without any reasons for lying. This is one of the first example of a particular memory symptom called confabulation. Only recently Spitzer, White and colleagues (2017) bring new examples of confabulation made by their participants like the following answers to their question, like the following:

"*When did you last travel by train?" Participant: "One month ago, to London."*

*The subject's mother reported that she had not travelled by train for eight months.*

(From Spitzer, White et al., 2017)

The present study aims at analyzing whether confabulation is more common within the ASD sample compared to control.

### 3.2 Confabulation in ASDs

Confabulations are here defined in accordance with Dalla Barba (1993, 1997, 2015) like "statements or actions that are unintentionally incongruous to subject history, background, present and future situations". Elsewhere named "honest lying" (Gilboa, Moschovitch 2002) to highlight that the subject is not aware of the partial or total falseness and inconsistency of his statements and action. Plausibility often characterizes confabulation content, thus a naïve listener could be deceived by the patient, unless he verifies with a person who knows the patient's life.

In the neuropsychological field, confabulation is commonly observed in adult patients with acquired brain damage and neurodegenerative disorders (Alzheimer Dementia, Korsakoff's syndrome). More than 20 anterior and posterior brain sites have been linked to confabulation (Dalla Barba and Boissé, 2010), but all confabulators have a relatively preserved hippocampus. When the hippocampal damage is extended bilaterally the patient is amnesic and does not confabulate.

According to MCTT, the hippocampus is the neural correlate for Temporal Consciousness (TC) and when lesions occur along the hippocampal-pathways (in areas for and from HCP), or partial dysfunctions are verified within the HCP circuitry, confabulation may arise. In confabulators TC is malfunctioning and all the individual's temporality is affected: past memories, current situations and future events become difficult to address (La Corte, Dalla Barba, 2015).

According to MCTT, the ontogenetic development of memory proceeds from the initial storage of decontextualized information to a gradually more contextualized storage of information, and it is in line with developmental findings. Hence, during development, Knowing Consciousness and noetic awareness would form before Temporal Consciousness and autonoetic awareness (Dalla Barba, 2002).

The cognitive mechanism which underlies confabulation is still under investigation, and few main theories are currently proposed to explain this symptom: strategic retrieval (Moscovitch and Melo, 1997; Gilboa et al. 2006), temporal context confusion (Schnider et al., 2000), motivational factors (Fotopoulou et al.,2007) are all hypothesized mechanism for confabulation. In the present work we rely on the temporality theory of confabulation elaborated by Dalla Barba (2002) who affirms that confabulating patients confabulate not only about their past, but also about the current reality and in personal planning for future. Dalla Barba et al. (2020) focus on the fact that confabulation involves the entire personal temporality (past, present and future) whereas the objective temporality, is sustained by KC (Dalla Barba et. al., 2020).

Usually, confabulations are treated during the course of a broader neurorehabilitation plan that focus on improving awareness and metacognitive ability. Treatment goal is improving compensatory strategy for faulty memories (William Hirstein, 2009), since patients are usually unaware of confabulation (anosognosia). Confabulation have been reported in several neurologic conditions (Alzheimer Disease, Korsakoff syndrome), psychiatric disorder (Schizofrenia). Importantly, even healthy brains confabulate, but usually "to create a coherent and predictable world" (Wheatley T., 2009), in healthy brains confabulation content appear true and is adaptive and based on shared facts. To the contrary, in patients, confabulation is mostly maladaptive, odd and uncommon.

Studies carried out in children and adolescents with ASDs show a fragility in remembering contextualized information (Hermelin & O'Connor, 1967), poor autobiographical memory (Bruck, London, Landa & Goodman, 2007), poor source-monitoring skills (Russell & Jarrold, 1999; Hala, Rasmussen, Henderson, 2005), impaired executive functions (Frith, 2003; Towgood, Meuwese, Gilbert, Turner, Burgess, 2009; Luna et al, 2002; Hill, 2004a; Gilbert et al., 2008; Happé et al., 2006) and difficulties in emotional regulation (Mazefsky et al., 2013). All these difficulties are similar to the ones implicated in confabulatory phenomena.

A further similarity between confabulating patients and people with autism consists in the neuroanatomical data. The heterogeneity of the damage to the nervous system of neurological confabulating patients (from frontal lobe areas to temporal lobe sites) is compatible with the variety of the neuro-functional impairments seen in autism. Both pictures emphasize scattered abnormalities in the brain parenchyma, but also an underestimated active role of hippocampal circuitry in autism conditions, which begin to be clarified (Banker et. al., 2021).

Finally, DeLong (1992) compares autism with Alzheimer Disease by hypothesizing a hippocampal disconnection theory. This would be in line with evidence of confabulations produced by patients with lesions in the pathways to and from an at least partially preserved hippocampus, whereas patients with bilateral hippocampal damage are severely amnesic, but do not confabulate (Dalla Barba, La Corte 2011). When this structure is malfunctioning, learning tends to be inflexible, hyper-specific, detailed and repetitive (DeLong, 2008).

### 3.3 Confabulation: taxonomy and Confabulation Elicitation Questionnaire

Many classifications about confabulation have been proposed, such as momentary vs. fantastic (Berlyne, 1972), spontaneous vs. provoked (Kopelman, 1987), but a more extensive classification is proposed by Dalla Barba and colleagues (Dalla Barba e Boissé, 2010; La Corte, Serra, Boissé e Dalla Barba, 2010). They identify 6 forms of confabulation based on their content:

1. *Habits confabulation*: personal routine considered by the patient as specific personal episodes.
2. *Misplacements*: consisting of true episodes and facts misplaced in time and place.
3. *Memory Fabrications*: semantic or episodic plausible memories, where no link with personal or public events is identifiable.
4. *Memory Confusions*: exchanging other personal or public events for the target memory (usually they are associated) or the confusion between family members.
5. *Autoreferential Contaminations*: answering about public or historical events in a personal context.
6. *Semantically Anomalous*: confabulations with an extremely bizarre or semantically incongruent content.

Dalla Barba and coworkers (Dalla Barba, 1993; Dalla Barba & Decaix, 2009) elaborate further with the Confabulation Battery (CB) consisting of 165 questions (15 for each domain). Each question is formulated considering the temporal context (Past, present, future). The question's object (general knowledge, self, others) and the memory system most involved (Episodic and Semantic). The 11 domains identified in CB were used by Spitzer D. and colleagues (2017) for investigating confabulation in children and adolescents, with some variations from the original battery. The Tab 1 shows the domain comparison.

| **Confabulation Battery (Dalla Barba et al.)-for adult** | **Confabulation Elicitation Questionnaire (Spitzer et al.)-for children and adolescent** |
|---|---|
| Personal Semantic Memory (age, date of birth, current address, number of children, etc.). | CURRENT PERSONAL SEMANTIC (do you have any cousins? what are their names?) |
| none | REMOTE PERSONAL SEMANTIC (Who was your first teacher at school?) |
| Episodic Memory. Episodic, autobiographical questions | Current personal episodic (Tell me about your most recent holiday). |
| **none** | REMOTE PERSONAL EPISODIC (Tell me about a trip to the zoo you have been on) |
| Orientation in Time and Place | NONE |
| Linguistic Semantic Memory. Items 16 To 30 Of The WAIS Vocabulary Subtest Were Selected For A Word Definition Task | None |
| Recent General Semantic Memory. Knowledge of facts and people, which have been repeatedly reported in the news during the last ten years. For example, "Who is Ben Laden?" | CURRENT GENERAL SEMANTIC (who is the current prime minister?) |
| none | REMOTE OTHER SEMANTIC (did your mum go to university?) |
| Contemporary General Semantic Memory. Knowledge of famous facts and famous people from 1940 to 1990. For example, "What happened in Paris in May 1968?" | None |
| Historical General Semantic Memory. Knowledge of famous facts and famous people before 1900. For example, "What happened in 1789?" | REMOTE GENERAL SEMANTIC (Who was Princess Diana?) |
| Semantic Plans. Knowledge of issues and events likely to happen in the next ten years. For example, "Can you tell me what you think will be the most important medical breakthrough likely to take place in the next 10 years?" | None |
| Episodic Plans. Personal events likely to happen in the future. For example, "What are you going to do tomorrow?" | FUTURE PERSONAL EPISODIC (Where are you going to eat lunch tomorrow?) |
| "I don't know" Semantic. These were questions tapping semantic knowledge and constructed so as to receive the response "I don't know" from normal subjects. For example, "What did Marilyn Monroe's father do?" | DON'T KNOW SEMANTIC (Which country did the longest skateboard journey finish in?) |
| "I don't know" Episodic. These questions tapped episodic memory and were constructed so as to receive the response "I don't know" by normal subjects. For example, "Do you remember what you did on March 13, 1985?" | DON'T KNOW EPISODIC (WHAT WAS NUMBER ONE IN THE CHARTS ON YOUR FIFTH BIRTHDAY?) |

*Table 1 Domain comparison between Confabulation Battery and Confabulation Elicitation Questionnaire.*

The present study aims at identifying whether or not children and adolescents with autism confabulate in a sample with ASD compared to healthy peers (without any clinical diagnosis). In order to do so we used an adapted version of Confabulation Elicitation Questionnaire, from the study of Spitzer D. and others (2017) and adapted it to an Italian sample thanks to Dalla Barba and colleagues.

### 3.4 Objective

In this observational study, the main objective is to understand whether the confabulatory phenomenon is present to a greater extent in individuals with autism compared to controls and to understand if this difference reflects a qualitative (type of confabulation) or quantitative (number of confabulation) difference in confabulations expressed by participants with ASDs, or whether it implies both. In order to do so we analyze the total number of confabulations, as well as their rate (number of confabulations on total answered questions). For the confabulating answer we also measure whether the probability to do so is higher in the ASD group compared to controls.

We also analyze semantic versus episodic overall ability in recollection comparing not only confabulation, but also omissions and errors. We create an overall score for Semantic mistakes and Episodic mistakes. These two computed variables are calculated from the addiction of omitted answers, committed errors, committed confabulations.

Furthermore, we observed whether correlations between age and other variables indicate improvement in memory looking at confabulation overall number and in the semantic and episodical recall, but also omissions and errors are analyzed.

### 3.5 Method and procedures

<u>Confabulation Elicitation Questionnaire</u>

The study was approved by the University of Trieste Ethical Committee (approval n° 99 on September 23rd, 2019) and all parents signed a written informed consent, children and adolescents were also asked if they were willing to participate and an additional oral presentation was given, and slides provided for both groups.

Confabulations were examined by means of the number of confabulations expressed through the Confabulations Elicitation Questionnaire, an instrument taken from the version used by David Spitzer and colleagues (2016) and modified for the Italian sample. The Questionnaire consists of 56 questions presented in random order and was created specifically to assess the quantity and quality of confabulations in 11 different domains. In the original version, the Confabulations Battery (Dalla Barba 1993; Dalla Barba and Decaix, 2009) is structured into 165 questions 15 per each domain; the version submitted to the participants was created by modifying the version proposed by Spitzer and al. (2017) for the Italian sample. The modifications were taken from a confabulation battery created for Italian primary school children, available to Dalla Barba and his colleagues. The eleven domains relate to three different dimensions that can be identified:

1. Semantic information or episodic memories.
2. Memories referring to oneself, to others or general information about the world.
3. Remote, recent or current memories and future plans.

These also included two groups of questions, semantic and episodic, whose expected response from healthy participants is 'I don't know', these questions point to the possible tendency to respond just to fill the gap of omissions.

No domain for Semantic plan was created, because the ability to predict what is going to happen at a general scale it is usually linked to the knowledge of the current news (i.e. "is Russia going to provide gas to Europe next year?"), and it was considered too difficult to be analyzed in children, given the poor knowledge of current general events and their ability to have such perspective.

To score the correct answer, the caregiver was also involved, after signing written consent, the mother or the father assessed the reliability of personal memories and participant's background.

Due to the pandemic, control group was interviewed in part remotely, and later by a trained master student.

All participants in the ASD group were interviewed in person after at least one meeting with the interviewer so as to directly ask children and adolescents whether or not they were willing to answer questions about general knowledge, their family and about their own memories. All participants were willing to participate and no one dropped out of the interview. Two participants started the interview, but they couldn't complete it due to health issues and to changes in their attendance.

The CEQ includes 20 questions to measure orientation in space and time (i.e. "where are we now?", "what year are we in?") to measure the ability to orient in space and time and process current context. Inter rater reliability for confabulation classification was also obtained by 2 raters, reaching the 98% of agreement.

*Self-Rating Scale of Memory-Functions*

Before the CEQ a, Self-Rating Scale of Memory Function (SRSMF, Dalla Barba 1993) was proposed to measure the metacognitive ability of children regarding their own memory.

SRSMF is a short 12-question questionnaire that investigate the level of awareness of one own memory recollection ability for specific item (i.e. "how bad or good is your memory for names and faces?"), each answer is scored from 0 (very bad) to 4(very good), children and adults with ASD were helped with visual cues during the questions. These brief questions aim at having a measure of awareness for memory skills, scores below 24 indicate that the subject believe to have a bad memory, while above 24 indicate a positive opinion about one's owns abilities. Confabulators usually do not have awareness for their deficits, regardless of their IQ.

Due to the pandemic, the TD group questionnaires were initially administered remotely via video call with expert examiner 1 (E 1), while untrained examiner (E 2) was alongside the child/adolescent in person.

Sessions were recorded for transcript, under a signed consent. After the training, E2 conducted questionnaire with the E 1 supervision, and eventually alone with the participant. Interviews were conducted in the office or in a quiet room at the participant's house, children and adolescents already knew the examiner 2, thus they were comfortable and familiar with her.

The questionnaire for the ASD group was administered in person by examiner (E 1), all children and adults spent some time with the examiner during their daily activities to get acquainted before the

interview. Moreover, except for a few cases agreed with the child, participants were always alongside with a familiar figure (psychologist or educator).
Importantly, at the beginning of the interview participants were instructed not to try to answer when they don't remember, because "forgetting is a very common and normal experience and no note is given to your ability to recall, and I (the examiner) don't want you to guess the answer"(translated from introductory initial instructions). It was also explained to the participant that they have the right to say "I'd rather not talk about this question" or to interrupt or get a break from the interview when they were tired. In addition, before the interview, parents were asked whether any of the questions' topic could be stressful or painful for the participant and alternative questions were formulated in those cases (for instance if asking about the natural father was stressful, we agreed with the caregiver an alternative well-known person like the actual mother's husband).
Three questions tested whether instructions were clearly understood by the child and otherwise they were re-explained until answers were corrected.
For both groups, the caregiver was then asked to review their children/adolescents/adult memories for questions about personal event and personal or family facts. Therefore, no embarrassing or very private topic were asked to participant (i.e. intimate relationships). Appendix 1 shows the Italian version of Confabulation Elicitation Questionnaire.

### 3.6 Participants

Seventeen children and adolescent with Autism Spectrum Disorders (ASD group) were recruited from Progettoautismofvg Onlus foundation, a private educational and therapeutic center in Udine (Italy), while thirty-one typically developing youth (TD group) were recruited from a sportive club in Monfalcone (Gorizia). The inclusion criteria were: the age between 8 and 25 years and good verbal comprehension skill tested by introductory questions and for the TD group no diagnosis of neurodevelopmental disorder or intellectual development disorder.
Participants in the control group (TD) were 17 Females and 14 Males (Mean age=12,2 ±2,8); minimal chronological age was 8 and maximal was 18. The participants of ASD group were 5 Females and 12 Males (Mean age=15,7 ±5,60), with minimal chronological age of 9 and maximal 25, three adults scored below 60 in IQ measured by Raven matrix. Descriptive data are presented in table 2. IQs were initially measured (by non-verbal intelligence test, 1998-TINV), after the pandemic, procedures length were reduced in time and IQs were retrieved from the most recent record (Wechsler Intelligence Scale for children, 2003 WISC-IV and Raven matrix), IQ was missing only for 3 ASD participants (IQ mean=95, DS=25).

| Group | Mean age (SD) | Gender(F:M) |
|---|---|---|
| ASD (17) | 15.7 (5.6) | 5:12 |
| TAU (31) | 12.2 (2.9) | 17:14 |
| Average IQs for the ASD group = 95* | | |

*Table 2 Participant characteristic. *IQ have been assessed by several measures (Raven, TINV, WISCIV)*

### 3.7 Results and analysis

For the analysis of CEQ non parametric Independent Mann-Whitney T-test was performed including all participants, regardless their age, under the hypothesis that ASD group commits more confabulation compared to TD group ($H_1$= ASD conf>TD conf). Raw confabulation number was significantly higher in ASD compared to controls (p=0.04, effect size=0.3). It was also analyzed whether this is maintained on the total number of confabulation rate (total confabulation on answered question) this data can be more useful for comparison with other questionnaires that can have a different number of questions. The hypothesis was confirmed (p=0.03, effect size=0.3).

We also tested the hypothesis whether confabulations in episodic domain and semantic domain were higher compared to controls. We found that the total number of confabulations in the episodic domain does not differ between groups (p=0.05) while they differ for semantic confabulation (p=0.03, effect size=0.3).

According to confabulation categorization, only fabrication number was significantly higher in the ASD group compared to the TD (p=0.007, effect size=0.4), but the content of fabrication in some cases had a routine component (clothes most used, food most eaten) this is also due to the rigid habits they have. However mean age between group did differ (p=0.02) and further analysis was conducted for an age matched subsample selecting only individual under 18 years old, the balanced subsample (mean age TD=11.8 mean age ASD=12.2 with p=0.3) of 11 ASD participants vs 29 controls showed again significant number of Semantic confabulation but equal number of episodical ones.

Total omissions and errors were also equal between groups.

| Variable | Mann-Whitney-U | p | Effect size (Rank biserial correlation) |
|---|---|---|---|
| TOT_n. confabulation | 182 | **0.04*** | 0.31 |
| %confabulation | 179 | **0.03*** | 0.32 |
| Semantic_conf_KC | 185 | **0.03*** | 0.30 |
| Episodic_conf_TC | 192 | 0.05 | 0.27 |
| n. Fabrication | 155 | **0.01*** | 0.41 |
| n. Habits | 253 | 0.69 | 0.04 |
| n. Misplacement | 249 | 0.65 | 0.06 |
| n. Memory confusion | 227 | 0.10 | 0.01 |
| % omissioni | 214 | 0.14 | 0.19 |

**Indipendent T test for H1: ASD > TD**

*Table 3 non parametric independent Mann-Whitney t-test under the hypothesis that ASD group>TD group.*

Correlation matrix was also performed. The general hypothesis is that, in healthy subjects, with growth and progressive temporal lobe maturation and long-axis network maturations with other areas, omissions, errors and confabulation decrease. According to MCTT, the more specific claim, is that in healthy subjects the number of confabulation decreases with age, particularly in the Episodic domain, while in the semantic domain it is stable. In fact, TC and free-recall of contextual episodes is more immature in younger children compared to older ones, to test this hypothesis we perform several correlations (one tailed negative correlation) for the TD group.

We found the following results:

1. Confirming the general hypothesis, omissions (rate and total number), Errors (rate and total number), Confabulations (rate and total number) significantly decrease with age (Spearman's rho with $p<0.01$).
2. Interestingly, only Episodical total confabulation decreased with age while Semantic total confabulation did not. Meaning that Semantic confabulations, when present, are stable for Semantic domain in neurotypical children and adolescents.

| Variable | Correlation | age |
|---|---|---|
| n. omissions | Spearman's-rho | **-0.78*** |
| | p-value | **<0.001** |
| Errors | Spearman's-rho | **-0.35*** |
| | p-value | **0.028** |
| % confabulation | Spearman's-rho | **-0.62*** |
| | p-value | **<0.001** |
| Tot_n_confabulation | Spearman's-rho | **-0.59*** |
| | p-value | **<0.001** |
| Semantic_conf-KC | Spearman's-rho | -0.27 |
| | p-value | 0.07 |
| Episodic_conf-TC | Spearman's-rho | **-0.62*** |
| | p-value | **<0.001** |

**Negative correlation matrix TD group**

*Table 4 Negative correlations for the control group (TD group). Omissions number, number of errors, rate of confabulation on given answers, total number of confabulations, number of confabulations committed in the semantic domain, number of confabulations committed in the episodic domain.*

We also found that as the total number of confabulations in the episodic domain increases, also the number of omissions committed by participants increases, suggesting that the confabulations are more likely to appear when the ability to remember is faulty. Interestingly, the positive correlations were found for episodic confabulation in TD. This means that more omissions in both domains can be expected when confabulations appear for episodic memories within this group.

| Variable | Correlation | omissions | errors |
|---|---|---|---|
| % confabulation | Spearman's-rho | **0.51*** | **0.51*** |
| | p-value | **0.002** | **0.002** |
| Tot_n_confabulation | Spearman's-rho | **0.48*** | **0.51*** |
| | p-value | **0.003** | **0.002** |
| Semantic_conf-KC | Spearman's-rho | 0.17 | **0.57*** |
| | p-value | 0.18 | **<0.001** |
| Episodic_conf-TC | Spearman's-rho | **0.53*** | 0.27 |
| | p-value | **0.001** | 0.07 |

**Positive correlation matrix TD group**

*Table 5Positive correlations for the control group (TD group).*

The non-parametric correlations in healthy subjects, suggest that confabulations increase as error and omissions increase in the "neurotypicals", regardless of their semantic or episodic belonging, indicating that long term memory recall increases with age. Moreover confabulation (number and rate) correlate positively with omission and errors, meaning that participants who show faults or mistakes in reported memories or knowledge also express more confabulation.

For the ASD group we did not observe any negative correlation, except for semantic confabulation number which decreases with age akin to controls (Spearman's rho=-0.5 p=0.04). These result shows that episodic confabulation, omissions and errors do not decrease with age in ASD.

Again, we found positive correlation between Episodic confabulation number and omissions but, only for the episodic domain's omissions.

Total semantic errors were not correlated to age meaning that omissions and errors in Semantic questions do not improve with age. Episodic retrieval does not have the same advantage observed in TD group, indicating that memories for long term autobiographical recollection does not increase with age in ASD and a different trajectory in memory can be drawn. We found no correlations between spatial temporal orientation and confabulation, neither between SRSMF and confabulation number or other variables. Moreover SRSMF, does not differ between groups.

| Variable | Correlation | omissions |
|---|---|---|
| Episodic_conf-TC | Spearman's-rho<br>p-value | **0.49***<br>**0.022** |

**Positive correlation ASD group**

*Table 6 positive correlations for the ASD group. Number of confabulations within the episodic domain*

Even if ASD participants confabulate more than the control group, can they be considered confabulators? Which is the frequency of confabulators in the ASD group compared to TD? To answer those questions we referred to case-controls comparisons by Crawford et al. (2010) which tests the individual's score with a control sample (Crawford, Garthwaite, & Porter, 2010). We tested under the Bayesian hypothesis test for single case, the probability that a member of the control population would obtain a lower score than the case, and we found that ASD015 and ASD017 total confabulations number=5 has one-tailed probability = 0,014 to be obtained in the control group (with effect size for difference between case and controls= 2,355), in our sample only a subject TD013 obtains 5 confabulation. Moreover, we found that the production of 6 confabulations has one-tailed probability=0,003 (with effect size=3,01) to be obtained in the control group. In our sample only TD06 has 6 confabulatory responses. Globally, the results suggest that average number of confabulations is higher in ASD group, and that 3 subjects out of 17 (17%) can be considered confabulators, in the TD 2 subjects out of 31 can be considers also confabulators (6%). Interestingly all confabulators (both in ASD and in TD group) scored above 24 in the SRSMS, indicating that they believe to have good memory skill.

### 3.8 Discussion

The strength of this study consists in its effort to give a clearer image of long-term memory in both neurotypical and atypical developing sample, while the weakness is that the equivalence between the groups was not fully controlled, and only cautious inferences can be drawn from these results.

Some MCTT previsions were confirmed. First, we observed that in healthy participants (TD group), episodic confabulation, which express a faulty TC, decreases with age, while semantic confabulations, which depend upon KC, are stable from 8 to 18 years of age. This pattern suggests that TC develops throughout years even after 8 years old, while KC stabilizes earlier and is more stable during growth.

Second, the ASD group confabulate significantly more than the TD group and their confabulations do not decrease with age. This pattern is possibly due to the lack of typical maturation for the hippocampal-dependent networks and its long-range connectivity. An alternative explanation might be that, given that IQs in 3 adults were lower than 60, intellectual ability could be one possible influencing variable.

However, the 3 subjects were not labeled as confabulators, their tendency was not to confabulate more than the controls, but rather to omit more answers. This hypothesis is still ambiguous considering that episodic confabulation number does not differ between groups, while surprisingly, only semantic confabulation numbers differ from controls. The immediate explanation could be that TC is spared in ASD, and KC is instead malfunctioning. To interpret this finding qualitative data should be given.

As an example, we illustrate the answers regarding a unique event proposed by the examiner.

**E: "Tell me about a trip that you have done with your parents some years ago."**

TD018:"*We went to [City], two years ago, we decided to go to[Island] after having been in [City] and we left. It was the [Day/month], we stopped in an hotel, halfway, it was rainy, I was upset for the departure, we took the ferry boat, we had a celebration on [Day] but it was postponed to the day after. My dad was unhappy about the holiday house because it wasn't what he had planned, we arrived very early for the ferry boat, we apologize to my mother because we complained and at the arrival the place was actually very nice.*"

ASD10: "*We were on the mountain in 2019* [he tries to recall the name of the country, but he fails] *and we went to ice cream museum, the bed was huge and very comfortable."*

*ASD06:"I don't remember"*
*E: You do not remember any trip, neither on the mountain nor on the beach?*
*ASD06: "On the beach! We were at [City]"*
*E: Anything else about it?*
*ASD06: "no, I don't remember, it's been a while since I went there"*

*ASD04:I remember a concert*, in [City], by [Famous singer name].
*E: how long ago? Where you alone with your parents?*
*ASD04: one year ago, there also was a friend of mine with her mother.*

These are answers confirmed as correct by the caregivers, participants are (TD018) 18, (ASD10) 19, (AD06) 25, (AD04) 15 years old. As attended, given ASD characteristics, the number of details and the content is poorer in the ASD participants, also emotional content and social dynamics are often omitted. However, the example ASD participants, is given to illustrate that the listener has very poor understanding whether the respondent has a full memory or only partial information. Compared to the TD group, it seems a list of facts, rather than an integrated memory with rich contextual details. The time of the context is very recent, the place is recalled only at generic level (mountain), and the actions made are very poorly described ('went'), no information are given for the time flow and the detail of the bed it is not informative for the listener to understand the unicity of this memory. ASD06 response is classified as "omission", because the participant does not recall, however when a cue is given (mountain or beach), he could retrieve at least the place (City). The caregiver confirmed that they have been to that city a couple of times in 2019, but the participant does not express any specific memories from such recent and repeated experience. ASD04 reports very little about the event she had been to, and her main answer would stop at the singer's name and where the concert took place, without spontaneous expression of other elements. The caregiver confirmed the event and told that they all were wearing the raincoats because it rained a lot and she was surprised that the participant didn't mentioned it. Even if people with ASD do not confabulate in the Episodic domain, it seems that their episodical memory is expressed in a more schematic way, less attached to precise time and space coordinates, and facilitated by cueing.

Contrary to what expected, in our ASD sample confabulation appears more in the Semantic domain. Episodic domain was equally affected between groups, again it could be argued that if the number of confabulations are equal between groups, Temporal consciousness, which supports recollection of unique events is spared in ASD, while KC is not. We observed that very poor contextual reference is given in episodical answers, and many answers seem narrated as a pure fact. Autonoetic elements in ASD answers are often linked to details (i.e. "very comfortable bed") instead of the activities done.

**E: what did you have for lunch on a Monday a fortnight ago?**

ASD05: *pasta with Bolognese sauce*

Caregiver: *he always eats at the center and I've got the menu. It is incorrect, he refers to last week.*

ASD06: *pasta with tuna*

Caregiver: *incorrect, it is probably another meal.*

ASD10: *hamburger and the other day.. baked fish.*

Caregiver: *incorrect, these are meal from last week.*

The above examples of confabulations are classified as misplacement because they answer with real memory for the target one, but they confound days or weeks.

ASD11: *we ate at the* [fast food's name].

Caregiver: *correct, we use to go there on Mondays.*

The above answer is scored as correct, but it is a weekly routine for the family to go to fast food on Monday, the participant relies on multiple trace to answer that question, rather than on a unique experience. This question is formulated because the majority of people tend to answer "I don't know".

Given that the confabulation questionnaire is made ex novo for the Italian sample we compared the frequency of committing response to these questions (correct or confabulatory), in order to assess if the probability of committing response it was higher than 30% in TD (we settle a restrictive rule meaning that if at least 9 participants on 31 committed responses, the item needed to be changed).

We found that the frequency of committing response to those questions goes within the TD group was from 0 to 16% (5 subjects on 31 committed responses), while in the ASD group it went from 0 to 59% (10 subjects on 17 committed responses). We found significant difference between groups for the frequency of committing response (independent t test for the hypothesis ASD>TD, $p=0.007$, effect size=0.5). Moreover, in the ASD group, the average frequency rate for semantic don't know questions is 9%, but for episodic don't know questions rises up to 31%. On the other hand, the TD group tendency to respond to don't know questions goes from 2% in the semantic domain, up to 6% in the episodic domain, this difference is not significant for TD. In both groups the tendency to respond is higher in episodical domain, although non significantly (independent t test for semantic rate<episodic, $p\geq0.05$), anyway for the ASD group it is almost 4 times higher compared to control. This data indicates the tendency to respond for both groups, in ASD 45% of the IDK questions are answered. In healthy subjects the majority answered correctly "I don't know" as expected.

Qualitatively, the most frequent confabulation in the ASD group was fabrication (mean= 1.7, SD =1,49, median=2), and it is the only confabulation that is expressed more compared to the controls. Other confabulation presented in the ASD are: habits (mean=0,6,SD=0,2), misplacement (mean=0,6, SD=0,8) and memory confusion (mean=0,2, SD=0,4), and semantically anomalous. These other categories, however, don't differ between groups. In TD group the most frequent confabulation is fabrication (mean=0.6, SD=0,8) and misplacement (mean=0,5, SD=0,8).

It is helpful to illustrate example for each confabulation.

**E1: What is the sugar glinder [Petauro in italian]?**

ASD02: *It's a sort of* [Petardo: object which sounds similar to the animal's name], *it is highly likely that it is a thing like that, I've never studied it at school.*

**E1 repeat the question.**

ASD02: *Ah! It is a mythological creature… well no that is a minotaur, it is a mythological creature, but I can't recall which one.*

In this answer the participant is linking the world to other known words and concept, but she keeps trying even if she does not have this knowledge (after the question E1 explains what kind of animal it is and only at that point she admits that she doesn't know). This answer is an example of fabrication.

**E1: Who's the actual President of Italian Republic?**

ASD015: Is the school headteacher.

This answer shows again that participant is answering linking the target topic "President" to another phonetically linked item [in Italian the words "*presidente*" is similar to "*preside*" meaning the school headteacher school]. It is classified as fabrication.

**E1: "Do you remember what you have done during the last New Years'Eve?"**

ASD10: "*This year my cousins,* [Name1] *and* [Name2*], came from* [City] to[ City] *and they ate a cheesecake with berries and chocolate that I bought at* [bakery's Name]".

Caregiver: *"He didn't understand, the cousins came last Sunday, not for New years'eve, we have been at home that day."*

This confabulation is classified as misplacement, because he addresses another event that happened in different time-context (one week ago) and place it instead of the target one (one year ago).

**E1: Tell me about a trip that you have done when you were little.**

AD006: *I have been in* [City 1] *to the doctor.*

Caregiver: I went there, he didn't. He went to [City 2], but we did not see the doctor, I did in [City 1].

We consider this answer as memory confusion, because he mistakes an event that the caregiver experienced for his own.

**E1: Tell me about one time that you have been in a foreign country.**

ASD08: "*I have been in [Country], the region is that of [Capital]. Back then I was 5 and I used to hide under the wardrobe* [of the classroom], *because classmates scared me, I'd rather be alone. Once I went alone in a pub for meeting dad. I remember people staring at me, I was about 1 year old.*"

Caregiver: He was 4, the classroom's fear is true, but he never, categorically, went alone in [Country].

This answer is classified as semantically anomalous, because of its semantically incongruent content. Globally, the Confabulation Elicitation Questionnaire shows that children and adolescents with autism spectrum disorder, are not amnesic (because omissions were equal between groups), they express more confabulation compared to their peers and confabulation are more likely to appear in the semantic domain. However, the answers within the episodic domain are often poor in details, and in contextual (space and time) references. It was also observed that ASD tendency in answering "don't know" to question is higher than the controls, this tendency is more frequent for episodic don't know questions, although it isn't significantly different from controls. Semantic and Episodic distinction is controversial, and it can be helpful to address the content of the answers with more detailed analysis on contextual versus a-contextualized content. For instance, terms referred to specific place and specific time versus generical details. It could be important to apply computational tools for assessing questions (like Natural Language Processing-NLP) to better understand which kind of memory is used in some clinical condition, such as ASD. Importantly, we highlight that the responses in the episodic domain seem expressed as facts with poor contextual connotation in autism. Thus, we suggest that confabulation in the semantic domain is more likely to happen compared to controls simply because Knowing Consciousness is preponderant in ASD.

# 4 SECOND STUDY: Multisensory SHX room intervention for children with ASDs

## 4.1 Introduction: "enriching" intervention for children with Autism Spectrum Disorder

Enriched Environments are so-called because they are settings embellished with stimuli which foster exploration, actions and social interaction. Such apparatus have been extensively studied in animal models and are associated with neuroplastic changes in cortical thickness, in dendritic and synaptic complexity and in neuro- and gliogenesis (Clemenson et al., 2018; Lu et. Al, 2003). In animals, complex environments influence many regions of the brain, especially the hippocampus. Expanding sensory and motor experience, cognitive challenges and positive social interactions can produce positive outcomes in animal's cognition, but which kind of environmental changings can produce comparable benefits in human is more difficult to understand because most people normally live in a very enriched environment. However, in some cases we could experience sensory, motor and social deprivation. For instance, with Covid-19 pandemic and consequent lockdown a massive-scale environmental deprivation has been experienced by people, and new studies are now evaluating the consequences.

Studies with adults demonstrate that motor exercise (like cardiovascular fitness) is associated with increased hippocampal volume and greater volumes in several cortical areas (Erickson et al., 2009, 2010). Spatial exploration of novel environment can also have effects on humans' hippocampi (Freund et al, 2013) even when exploration is performed in a 3D virtual environment. Positive social interaction and stress reduction also has neuroplastic effect on the amygdala, prefrontal cortex and hippocampus (Davidson, 2012; Hölzel, 2010).

Identifying which features and activities can lead to neural plasticity and to better cognition is especially important in the field of neurodevelopmental disorders. In ASD, children's perception, cognition and behavior prevent them from having the same experiences that their peers have. Therapeutic intervention is extremely challenging as its main goal is to restore the delay in important acquisitions or to compensate impoverished experiences with more adaptive strategies.

Many approaches are now available and most of them focus on the "enrichment" of the experiences that children can learn, based on their developmental stage. Most of the approaches point to infancy and childhood, when the cognitive system is more prone to neuroplasticity and learning can be maximized.

In the report "Interventions for children in the autism spectrum" Whithouse A. and colleagues (2020) synthesize the state of art regarding evidence-based practices and highlight that while some interventions have good empirical bases, other intervention categories are based on less robust underpinnings.

Interventions vary by setting, format, agent and mode and usually target specific age-ranges, in particular the authors identify in their report nine categories of intervention illustrated in Tab 5.

| **INTERVENTION CATEGORIES** (from Whithouse et al. 2020) | |
|---|---|
| 1. | Behavioral<br>The most known intervention is Applied Behavioral Analysis (ABA), which brings behaviorists techniques into clinical practice. The intervention's goal is to modify measurable behaviors and improve social abilities. The modification is based on functional relationship between intervention, persons responses and positive effects that they get from targeted behaviors (antecented-behavior-consequence).<br>Each strategy is linked to the theory and procedures that can be easily replicated.<br>The goal is to foster clinical and social change in behaviors allowing generalization in other contexts and long-term maintenance.<br>The setting can be either therapist with the child at the table (Discrete Trial Training) or a more natural situation like home, school or recreational spaces (Naturalistic Environment Training), but always targeting specific observed behaviors. |
| 2. | Developmental<br>Based on a hierarchy of developmental milestones and stages, the intervention aim is to provide or compensate delayed or lacking skills that are critical for healthy trajectory (i.e. join attention, imitation, communication). An example is the Developmental Individual Difference Relationship- Based Floortime (DIR-Floortime).<br>The intervention involve both the caregiver and the children, moreover considers parents as an active figure in the intervention, promoting their own skills, too.<br>The setting goes from the therapist's study, to school and at home. |
| 3. | Naturalistic developmental and Behavioral (NDBIs)<br>Grounded on developmental expected acquisitions, the intervention aim is to teach new skills in different domains (e.g.communication, play, social and motor skills). During intrinsically motivating routines the therapist progressively increases complexity over time in activity and play in order to obtain more adaptive and complex responses and to diminish the gap with expected acquisition by means of behavioral strategies. The context of intervention must encourage social interactions with parents, peers and other figures. Generalization is also promoted by changing the intervention setting (home, school, community). Intervention included in this category are Early Start Denver Model (Rogers et al., 2010), Pivotal Response Treatment (Koegel, Koegel, Harrower, & Carter, 1999), and Joint Attention, Symbolic Play, Engagement, and Regulation (Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015). |
| 4. | Treatment and Education of Autistic and related Communication-handicapped Children (TEACCH) This intervention supports children independence and learning by adapting tasks and structuring teaching.<br>It is used in the classroom, at home and in community settings. |
| 5. | Cognitive Behavior Therapy<br>CBT encompasses various components, but the intervention aims at modifying thoughts, behaviors and emotion in a more adaptive way. It helps people to face distressing situation and thoughts in a more beneficial way. It is particularly helpful with autism, because CBT can equip the person with coping strategies that can be very useful considering the great distress they feel in everyday situations. The therapeutic context is usually psychology's study. |
| 6. | Technology-based<br>Several techniques to improve cognitive skills are based on technologies. They go from application for personal computer and tablets, to virtual and augmented reality and sensor-based application, or even robot-mediated interactions.<br>One example is Timocco, a motion-based application which use the person's movements to simulate it in a projected game where an avatar can reproduce the movements in order to achieve specific goals. |
| 7. | Sensory based<br>The goal is to organize and integrate sensory experiences and generate positive effects on skill acquisition, attention and self-regulation.<br>The most used by occupational therapists is Ayres Sensory Integration Therapy (ASI) which use a gym-like-setting enriched with various tools to encourage active exploration in children (e.g. pillows, ball pools, swings etc.).<br>Other sensory-based techniques often use stimuli for one or few modalities.<br>Another a-specific sensory-based approach is the so-called Snoezelen that use specific settings with several tools (like music, vibroacustic pillow, bubble tube, ball pool, colored lights, projected images etc.) to promote relaxation, wellbeing, communication and emotion regulation not only for the patient but also for his caretaker. Given that the stimuli can be controlled, adapted and modulated it is suitable for several disabilities. Sensory-based intervention are not specific for ASD, but the room has been used for ASD as a complementary support to therapies.<br>Many kind of multisensory room are now available and the use of technologies is also influencing the ways they can be used. |
| 8. | Animal-assisted-intervention<br>This approach encourages the interaction between children and animals to support emotion regulation, wellbeing and social abilities. An example is PET Therapy. |
| 9. | Others intervention |

*Table 7 Category of interventions for children in the autism spectrum according to Withouse (2020).*

Interventions are mainly guided by the biopsychosocial model which implies to consider both the child and his own environment to influence their learning, inclusion, participation and ultimately their health (World Health Organization, 2001). Even though neurodiversity model avoids the normalization of ASD profiles and focuses on unicity of each person within the spectrum, it is important to note a series of important challenges and difficulties that are faced daily by people with ASD and their families across many (but not all) situations and contexts (Mole, 2017) and only offering effective and valid tools and opportunities within the community can give them support. The aim of our study is not to create a new therapy, but rather to measure how a special environment can help usual therapies. However, the ontological development of hippocampus and its possible role in autism, as well as is role in neural plasticity throughout life, made this structure the principal target of an environmental based intervention. Considering that hippocampus can grasp highly complex relational association with spatio-temporal connotation and the fact that it is one of the structures that benefits from enriched activities and exploration in humans; it is plausible to think that the right use of an enriched environment could compensate a difficulty in such processing and maybe have an impact on learning.

### 4.2 An Enriched Context: multisensory room for ASD

Multisensory rooms (MS) now available are several, but the use of such space for disabilities is attributed to Jan Huslegge and Ad Verheul who in the 70' developed "Snoezelen" approach, from "*snuffelen*", explore, and "*doezelen*", relax (Huslegge and Verheul, 1987). They created the first room in 1984 and gave birth to a specific philosophy where the only aim is person wellbeing. Nowadays, however, MS are used with more structured objectives, and many do not fit the "Snoezelen" original approach. Social care, occupational therapy, education, nursing, psychology, psychiatry and palliative care are only few of the fields where these rooms are applied, addressing children, adults and elderly people. In his book, "The multisensory handbook" (2012) Paul Pagliano explains how to design different MS configurations that could support programs for children or adults with compromised perception and cognition.

Few studies, however, measured the effect that such special context can have on autism. Recently, Novakovic and colleagues (Novakovic et al, 2019) find that in a sample of 20 ASD who participated for three months in Snoezelen room sessions (30 minutes each), the severity of repetitive and stereotyped behaviors was reduced compared to controls as measured by Childhood Autism Rating Scale (CARS). Another study reports that Snoezelen room decreased "the frequencies of aggressive and stereotyped behaviors" in nine adults with autism compared to individuals without autism, but with intellectual disability (Fava and Strauss, 2010).

Both studies suggest that only frequent sessions and continuous attendance in a multisensory environment should improve adaptive functioning in everyday activities.

Basadonne and coworkers (Basadonne, 2021) find improvements in sustained attention, selective attention, association, single inhibition, receptive communication, verbalization and turn taking in a group of 13 ASD children and 8 adolescent and adults who attended 5 times 30 minutes-sessions inside a MultisensoryInteractiveRoom (MIR).

Investigation of generalization "out room" (i.e. outside that particular environment) is still poor, Kaplan et al. (2006) conducted a single subject design and observed the carryout of beneficial behavior the 5 minutes after each 30 minutes session inside the Snoezelen time with the Occupational Therapist. Overall, studies on ASD benefits from multisensory rooms point to general behaviors measures, increased skill mastering during activities inside the room, and carryover of benefit for target behaviors. As far as we know, no study tried to measure gains in cognitive, motor and behavioral profile with standardized measures, meaning that it is not known whether improvements obtained inside the MS can be beneficial at clinical and educational level and whether they are last-longing. Moreover, no protocol is available for using multisensory environment with ASD, this could be due to the variety of possible multisensory settings and tools, but it is necessary to put more effort in structuring a program that can be highly adaptable to any room, in a personalized fashion for the person with ASD, regardless their functioning.

### 4.3 The multisensory SHX room

The multisensory room set up in ProgettoAutismo-fvg ONLUS foundation offers stimulation through the use of technological means (SHX system installed on computer and tablet) in order to allow all resources and tools in the room to act in a coordinated manner for creating an immersive environmental stimulation. Stimuli are controlled and adjustable via the SHX software which integrates various technological devices and their activation or deactivation in a customized manner.

For better explanation, stimuli can be classified according to 3 categories: static stimuli, dynamic stimuli and interactive stimuli (see figure 2 for illustration).

1. Static stimuli are those always present like rigid pillow, elements for motor activities.
2. Dynamic stimuli are those that can be switched on and off in several modes: the *bubble tube* can change the frequency of activation, and the color (it contains little fake fishes inside, which become visible with bubble activation); the *ball pool* can also change color (but it is normally explored in off modality);the *fan;* the *scents diffuser*; and the *soap bubbles*, the soundbar for different sound effects and music; the *vibroacoustic pillow* that can be activated with music to vibrate accordingly to bass sounds; *optical fiber* enlightened in different color, a *white wall* that can be used to projected a variety of stimuli,.
3. Interactive tools are the *tablet* (the stimulation can be selected by touching the screen), controllers (six buttons to press with hand and an interactive carpet that can be used by hand or with feet),

interactive *cards* (for activating one stimulus or a combination of them via a sensor inside the room) and *microphone* to change rooms color by sounds or words production.

*Figure 2 Multisensory SHX room in foundation ProgettoAutismoFvg-ONLUS*

To decide how to deliver the intervention the clinical staff shared ideas and main issues with children, it was also asked to therapists whether they prefer to maintain the control of SHX application via tablet or to have a second person with the complete software management. A feasibility session was also conducted with four volunteer healthy children (two female and two males from 3 to 8 years old) to understand the amount of divided attention that could be afforded for controlling stimulation and paying attention to children. It has been decided to maximize each session with the therapist's full attention toward child in one-to-one session inside the room, while the SHX system were simultaneously controlled via computer and tablet in a nearby room by another figure. The "activities' director" is so called because from the directory room can deliver stimuli, using computer and tablet and prepare the setting and the activities in advance, after proper training on how to use the devices.

For each session it was essential to plan the stages that can better fit the child needs. In order to do so, we studied and examined the current use of multisensory room for person with special needs. Nowadays the most used MS room is Snoezelen that aim to fully personalize environment for the person wellbeing and assess user's preferences (or dislikes) by initial questionnaire to the person or her caregiver. Some stimuli activation can be produced by the tablet, although the majority of stimulation are manually turned on/switched off, many objects are present in the room (e.g. music instruments, white board etc.), stimulation is delivered by a trained practitioner to mainly foster relaxation, emotion regulation and social interaction. For the full- relaxation of the person, more specific approaches can be used in positive, uplifting and non-demanding, like Gentle Teaching (McGee, Menolascino, 2013).

Another sensory-based intervention is the Ayres Sensory Integration approach which is provided by Occupational Therapists in rooms and gyms with many motor stimuli for increasing activation, exploration and goal directed actions and for progressively organizing perception and behavior (Ayres, 2012).

In our study when we program the child session, we rely on the current sensory-based approach, integrating the sensory stimulation with cognitive and motor activities that can be individualized based on the child's preference, but also according to the therapeutic plan. Sensory-based approaches are not specific for ASD, but the ways they communicate with the children via stimulation-for-relaxation and via stimulation-for-organized activation can be integrated in each session.

Three stages were planned:

- **Exploration phase** to let the therapist observe participant spontaneous exploration for 5 to 10 minutes and gradually propose and model ways to interact. The room is enlightened in white (simulating the external enlightening from where the child came). During this phase the child is free to explore the room in a stable environment and to interact with novelties (room rearrangements with pillow and elements for motricity). The therapist is non-directive in this moment and encourages child spontaneous exploration; after a few minutes some changes start to happen in the environment and the therapist guides the child's attention and verbalizes what is happening.
- **Activation phase** (a combination of cognitive and motor activities) for about 15 minutes many dynamic changes in the room guide the child to engage with the therapist across several activities, activities can be partially (few selected stimuli activation) or fully immersive (coherent stimuli activation). The room can change colors, sounds or both several times, stimuli are proposed to the child and the therapist joint their actions and attention for pursue each goal. The therapist knows the activity plan before the session, and practical tips are given at the beginning to operationalize the activities. Therefore, in this phase the therapist is more demanding and directive.
- **Relaxation phase** to gradually accompany the child to find calm in a non-demanding relationship with the therapist for 5-10 minutes. The music is calming and regular and the room enlightenment is soft, almost dark, with only few enlightened elements. The child is free to choose his position and the stimuli for reducing the activation, however the therapist is invited to propose variation and new ways to obtain relaxation.

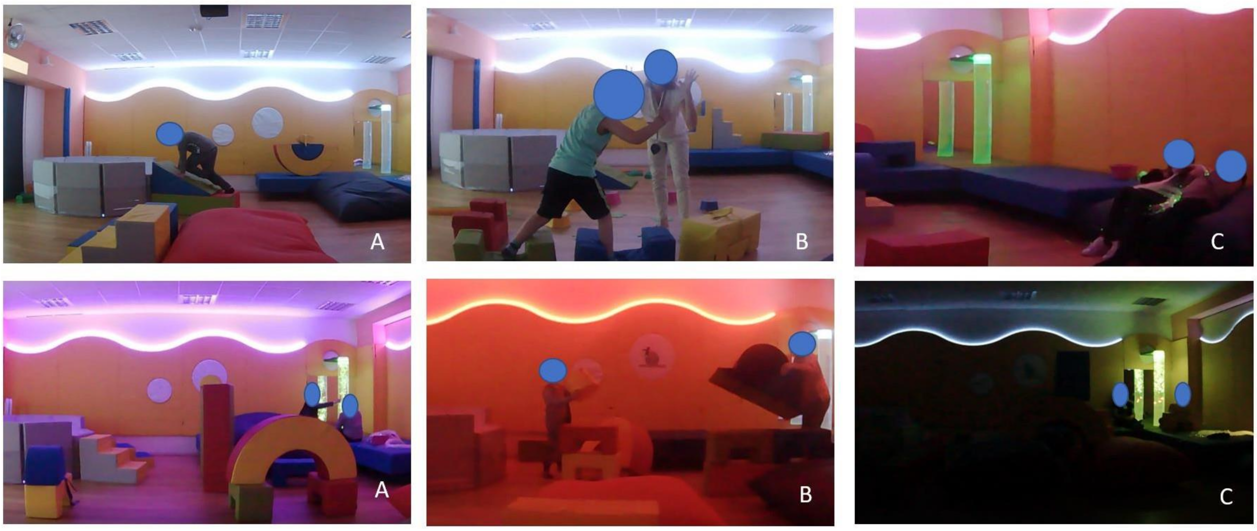



*Figure 3 A) exploration phase. B) Activity phase. C) Relaxation phase*

This activity plan is fixed, but flexible according to the child needs, for instance if at the beginning the child is tired, some pauses and relaxing moments can be given at the beginning: if physical efforts is too challenging for the child some calming moments can be added within the session. On the contrary if the child is very active, some additional motor activities can be suggested by the therapist at the beginning.

Throughout the session, the therapist mediates the interaction between the child and the stimuli in the room, while the activity director modulates the environment for guiding the couple into all three phases, the director can see and hear the couple from her position and can help if necessary.

The phase change is announced by fixed sound stimuli and lighting changes known by the therapist, but not by the child who is invited to learn the meaning of the changing signals from consecutive experiences.

Each session is settled in a thematic context (ex. Jungle, Sea, Emotions, Buildings and Shops, Family, the House, Princess, Body parts, Sports etc.), infinite themes can be created personalizing the session, the child does not know about them, he discovers each new thematic context session by session. The number of different themes is variable as it depends on child abilities and motivation. Each theme contains associated concepts, stimuli and related activities. For instance, if the theme is "means of transport" the child and therapist can build a plane with pillows and activate wind, and sky videos by pushing controllers. Theme changes and expands gradually from session to session, to let the children maintain a constant expectation and learn many contextual cues throughout sessions. Therapists were briefly trained on the type of stimulation to be used and the scheme of activities and the clinical cases of each therapist were discussed in order to decide main themes and identify the child's initial preferences. The 'activities director' prepares stimuli, sessions setting and plans activities paying attention to balancing novelties with sameness: too much newness and variability in the environment can scare the child or cause anxiety, on the other hand too much sameness and repetition can be poorly motivating or

lead to unwanted behaviors (i.e. repetitive and restrictive behaviors, interactions with irrelevant stimuli or elements that do not match the ongoing activity etc.).
Session by session the therapist is invited to propose variations, to progressively complexify activities and challenges and to foster autonomy and child's initiative when they are coherent with the activity and adapted to the moment. This project aims to use a safe and rich environment that can support usual therapeutic practices and help children with autism in better understanding and adapt to the external world. As extensively explained in the chapter 1, processing contextual stimuli and contextualized experiences is difficult in ASD and depends upon hippocampal functioning. HPC is also one of the most plastic areas of the human brain which benefits from an enriched environment and one of its subfields, Dentate Gyrus, neurogenesis can continue throughout life.

### 4.4 Objective

The study stems from the idea that a protected, personalized and motivating environment could be beneficial to children with autism at different levels from perception to cognition and behavior. The multisensory SHX room might trigger, support and enhance cognitive development in children with Autism Spectrum Conditions and maybe foster neural plasticity. Our hypothesis consequently is that cognitive, sensorimotor and behavioral gains could be observed in the group that had experienced multisensory-based intervention during their normal therapies, moreover we suppose that improvements could be equal to or even enhanced compared to an age-matched control group with ASD receiving only cognitive/behavioral interventions (mainly Applied Behavioral Analysis techniques) in the usual environment (room with table and chairs only and playroom). Some of children recruited also participate in speech therapies, motor therapies, social group training or a combination of those in addition to the usual behavioral interventions. Random participants allocation into two groups tried also to balance these uncontrolled variables.
The first aim is to analyze whether sensorimotor skills, cognitive skills, and adaptive behavior can benefit from a continuous intervention in the room. In the light of existing research, it was hypothesized a general gain in adaptive behavior. As for the cognitive profile, no specific hypothesis was made since no robust data were found on the topic for ASD, however we expect to observe some improvements, at least in sensorimotor domain. As a matter of fact, other population show increased attention, memory and social abilities after intervention in multisensory environment (Ashby, 1995).
The second objective was to evaluate the pleasantness of the intervention by means of a brief qualitative questionnaire for parents and therapists. The purpose was to understand: the child wellbeing and motivation during the three month- intervention; parents remarks; therapists opinion on the methodology and on possible improvements. The point of view of all actors is important to assess to assess feasibility and for ongoing improvements.

### 4.5 Method and procedures

A Randomized-Controlled Trial design has been arranged, with pre (T0) post (T1) assessment without blinding and a follow up (FU). Approval was obtained by the Ethical Committee (University of Trieste, approval n° 107, on September 21st, 2020) and informant consents were signed by families. Three main assessments were proposed to participants at the baseline: motor assessment ABC 2 movement battery (ABC2 m), cognitive assessment Developmental NEuroPSYchological Assessment (NEPSY-II). While caregivers were interviewed by the examiner. Vineland Adaptive Behavioral scales (VABS-II).

*Movement assessment battery for children-second edition ABC-2 m (Biancotto., Borean, Bravar, Pelamatti., Zoia, 2013)*

The movement assessment battery for children-second edition (ABC 2 m, by Henderson, Sugden, Barnett adapted by Biancotto, Borean, Bravar, Pelamatti, Zoia, 2013) implies fine and grosso-motor functions tasks adapted to three age range (3-6, 7-10, 11-16). This test implies several tasks in different motor skills: manual dexterity, aiming and catching an object and balance. The total score can be interpreted based on absence of motor difficulties (green zone if score>15%ile),

- Manual Dexterity 1 in this task the child has to accomplish as quickly as possible a fine motor activity (for instance posting coins), in task 2, Threading Beads, the child has to use both hands and grasp the thread correctly for achieving the goal, 3 Drawing trial is a graphomotor task, performed with a pencil.
- Aiming and catching object: Catching a beanbag from a certain distance and throwing it aiming at red circle on the floor.
- Balance: the child is asked to balance on one leg only and time is measured, another task consists in tip toe walking along a line on the floor and jumping on mats.

The motor assessment was conducted in one-hour session by trained examiner. Assessment was conducted before and after the intervention for the MS group, and after a comparable period of usual treatment for the control group (TAU group).

*Developmental NEuroPSYchological Assessment (NEPSY-II) (Urgesi, Campanella, Fabbro, 2011)*

This battery in the Italian version is composed of 33 tests for children and adolescents between 3 and 16 years of age. It assesses basic and complex aspects of cognitive skills, it measures attention and executive functioning, language, memory and learning, sensorimotor functions, social perception, visuospatial processing. These skills are important for the child not only at school, but across multiple areas of life. The choice of tasks was matched with the age range (from 3-11) and considered the low verbal demand required to the child. The assessment was therefore suitable for wide range of functioning. Cognitive assessments consist of 9 chosen tests:

1. Visual Attention: the child has 3 minutes to search all the target presented on the paper, the target is one rabbit for children under 5 years of age, and two faces for older children.
2. Instructions Comprehension: several objects (colored rabbits or colored geometric shapes) are shown to the child, who is asked to point at the ones that are indicated by verbal instructions. Instructions are initially simple (show me the yellow cross), then thy got more and more complex (show me the third shape on the second row).
3. Memory for Designs (immediate) the child should recall a pattern of cards that progressively grow in number, after a quick look at the page.
4. Memory for Designs (delayed): 15-20 minutes after the immediate memory task, the examiner asks to recall the learned series of figures and to position them in the right way on a grid.
5. Imitating Hand Positions: the child is asked to imitate hands posture first with the dominant hand and then with the other.
6. Manual Motor Sequences, the child is asked to learn brief sequencing of movement (like clapping and banging fists on the table) that the child should replicate correctly for 5 times.
7. Affect recognition, the child is asked to point at children's pictures that are feeling the same emotion of a target picture.
8. Copy of designs. The child is asked to copy geometric shapes with a pencil, their difficulty increase progressively (this test has 2 separate scores for general and specific designs features).
9. Block construction. In block construction the child is asked to reproduce 3D images the fast as possible from 2D images.

The cognitive assessment was conducted in one and a half session by a trained examiner, however in some cases the assessment was conducted in two consecutive sessions. Assessment was conducted before and after the intervention for the MS group, and after a comparable period of usual treatment for the control group (TAU group).

*Vineland Adaptive Behavioral scales (VABS-II) (Balboni, Belacchi, Bonichini; Coscarelli,2016)*

Vineland-II Survey Interview Form (are composed by 4 scales and 11 subscales measuring adaptive behaviors from birth to the age of 90. VABS-II offer the possibility to assess adaptive behaviors, defined as "the collection of conceptual, social, and practical skills that all people learn in order to function in their daily lives" (Shalock et al., 2010). The American Association on Intellectual and Developmental Disabilities apply Shalock's definition to several behavioral manifestation:

- Conceptual skills are displayed by literacy; self-direction; and concepts of number, money, and time.

- Social skills imply interpersonal ability, social responsibility, self-esteem, gullibility, naïveté, social problem solving, following rules, obeying laws, and avoiding being victimized.
- Practical skills are those activities for personal care, occupational skills, use of money, safety, health care, travelling and use of transportation, observing schedules and routines, and use of the telephone.

Behavioral interview with caregivers illustrates usual behaviors observed in the child, according to 4 scales: communication (receptive, expressive, written), daily living skills (personal, housing, community), socialization (personal relationships, play and leisure time) and motor skills (gross motor and fine motor). Each scale results in one score, and together they are computed in the overall IQ (mean =100, DS=15).

VABS-II are particularly important because they give a complete picture of the child functioning and can provide scores for children that cannot be assessed directly (with Abc-2 m or NePsy-II).

Interviews were initially conducted in person with the caregiver, and lately in remote, (videocall) by a trained examiner. The interviews were repeated after at least 3 months from the end sessions for the MS group, and after at least 3 months from the last cognitive assessment for the control group.

The assessments phase at the baseline provides sensorimotor, cognitive and behavioral data to calibrate the intervention and provide pleasant and unpleasant contents to create stimulation. After the intervention period both controls and MS participants are tested on cognitive and motor skills (pre-post assessment), whereas the VABS-II are proposed after at least 6 months.

The intervention for each child consists in a total of 24 sessions, 30 minutes each, twice a week for around 3 months. Each session is accomplished by the child and his/her therapist. Therapists are trained to the room's functioning and using before to start the intervention. The environment and the activities are arranged and planned by the activities director along with therapists after case discussion and standardized assessment (T0). Preliminary results on a small group are here presented and discussed.

### 4.6 Participants

To assess our hypothesis, we enrolled a total of 26 participants aged 3 to 11 from ProgettoAutismo FVG onlus foundation (Udine, Italy). Additional oral presentations were given to families in order to answer all questions and to qualify family motivation. Pros and cons of both the MS and TAU conditions were exposed to caregivers, and assessments were completely free for families and offered from the foundation.

Inclusion characteristics were: meeting criteria for ASD certificated by public health assessments; attendance frequency to the therapeutic center (at least twice a week).

The therapeutic staff categorized each child based on the general "level of functioning" with five labels: 'low'(1), 'half-low'(2), 'mixed'(3), 'half-high'(4), 'high'(5). The computerized randomization process (shown in Figure 2), allocated participants to two conditions: the multisensory group (MS group) and the treated as usual group (TAU group), mean age does not differ between groups (MS=6.8; TAU=6.4) and neither their "level of functioning" (mean functioning= 'mixed' for both groups).

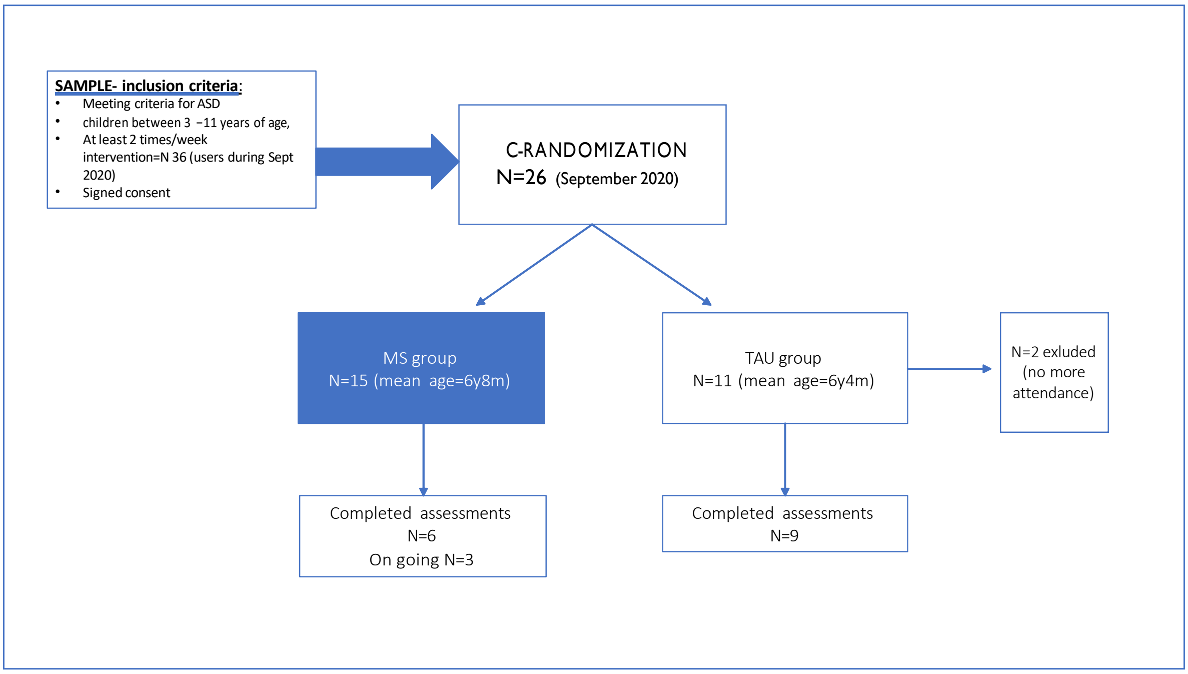



*Figure 4 Participants' allocation to conditions MS and TAU*

In this dissertation are illustrated preliminary results pertaining to the period between October 2020 and June 2022 are illustrated.

We started collecting data in October 2020 and by June 2022 seven subjects from the experimental group and nine from the control group completed all the evaluations, however 2 participants in the control group were not able to undergo neither cognitive tests nor the motor one thus, and only 7 were included in the analysis Sample description is presented in table 8: MS group mean age was 8.05 ±1.28 (min=6, MAX=10) and M: F rate was 5:2; mean age for the control group was =7.03±1.42 (min=5; MAX=9) with 6 Males and 1 Female.

| Group (N) | Mean age (SD) | Gender(F:M) |
|---|---|---|
| MS room (7) | 8.05 (1.28) | 2:5 |
| TAU (7) | 7.03 (1.42) | 1:6 |

*Table 8 descriptive for the Multisensory room condition (MS group) and the Treated as usual condition (TAU group)*

### 4.7 Results and analysis

Motor assessment (Abc2 m). Total scores do not differ in pre-intervention (T0) assessment between the two groups ($t_6$=6.00 p=0.7). Unfortunately, the administration rules in Abc-2m assessments implies that scores are computed only under certain conditions of task's execution, and 3 participants nor at the pre or at post assessment do not perform the test under the given conditions. Therefore, 4 children have not received a total score (3 in the MS group and 1 in the TAU group). Only four participants in the MS group completed the assessments and were compared to the 6 of the control group. No differences between three subjects and the 7 in the control group were found (Mann-Whitney U $t_6$=6.00, p=0.7, rank biserial correlation=0.25). Interestingly, however, we describe common difficulties in motor ability in the overall group.

| Score differences (T1-T0) | Mann-Whitney-U | p | Effect size (Rank biserial correlation) |
|---|---|---|---|
| ABC2 m TOT | 8.50 | 0.689 | 0.150 |
| Manual Dexterity | 8.50 | 0.689 | 0.150 |
| Aiming and catching object | 7.00 | 0.266 | 0.300 |
| Balance | 6.50 | 0.837 | 0.350 |

**Indipendent t test for MS group>TAU group**

*Table 9 score differences between pre and post (T1-T0) assessment on ABC 2 m test*

Cognitive assessments (NePsy-II). Scalar scores at the pre intervention (T0) do not differ between the two groups at subtest (all p>0.05) except for motor sequencing that was better in the TAU group at the baseline (MS group<TAU group: t=8.50, p=0.02, effect size=0.7). For assess the differences in pre-post intervention between the seven participants we perform non-parametric Mann-Whitney U t-test for the score's differences.

No difference was found between two groups after 24 sessions in the cognitive measures where differences in the scalar scores were analyzed (see Tab. 10).

| Score differences (T1-T0) | Mann-Whitney-U | p |
|---|---|---|
| Visual Attention | 19.5 | 0.762 |
| Instructions Comprehension | 17.5 | 0.193 |
| Memory for Designs i | 18.5 | 0.670 |
| Memory for Designs d | 19.0 | 0.640 |
| Imitating Hand Positions | 22.5 | 0.423 |
| Manual Motor Sequences | 21.0 | 0.700 |
| affect Recognition | 17.0 | 0.857 |
| Design Copying gen | 15.0 | 0.903 |
| Design Copying spe | 16.5 | 0.864 |
| Block Construction | 20.0 | 0.741 |

**Indipendent t test for MS group>TAU group**

*Table 10 score differences between pre and post (T1-T0) assessment on NePsy-II tests*

**Vineland Adaptive Behavioral Scales-VABSII**

To date the Vineland II were completed by 6 parents for the MS group and 7 for the control group. Tot deviation IQ score does not differ at the baseline in a comparison MS group (IQ mean=86, SD=16) vs control one (IQ mean=72, SD=22), and neither of the scale scores differs at the baseline. Overall, from baseline to the follow up (at least 3 months after the end of intervention), only motor skills significantly improved (paired Wilcoxon t-test p=0.04).

The parents of the participants in the MS group reported major improvements in overall adaptive functioning (measured by total IQ), in communication and in motor skills compared to the control group.

The caregivers were the same at the baseline and in the follow up, but the methodologies changed from frontal and in person interview to online videocall interview due to the pandemic. This switch involved both the control and the MS parents. Parents were instructed to report both possible change and that they could have observed as diminished behavior or skill lost.

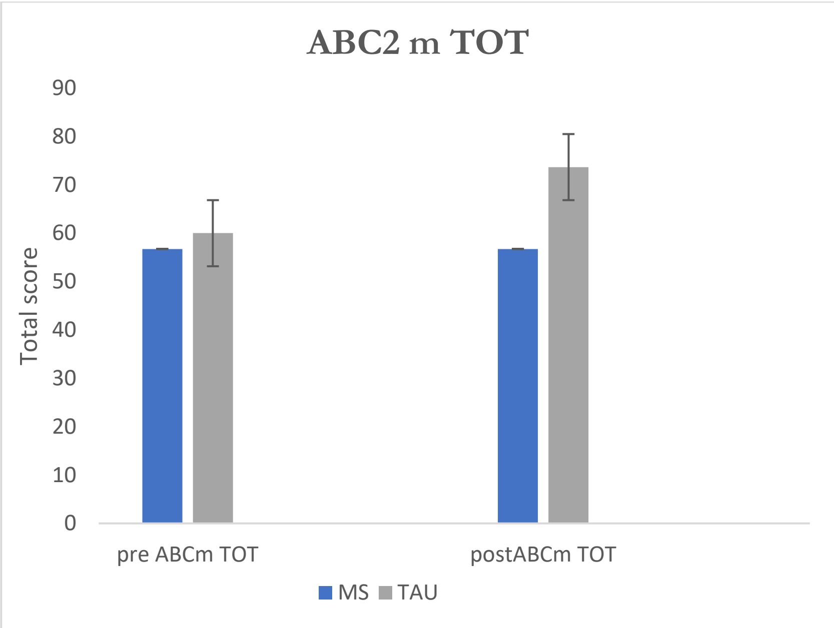
| Score differences (FU-T0) | Mann-Whitney-U | p | Effect size (Rank biserial correlation) |
|---|---|---|---|
| IQ | 3.00 | 0.010* | 0.833 |
| communication | 4.50 | 0.018* | 0.750 |
| daily living skills | 9.50 | 0.100 | 0.472 |
| socialization | 16.00 | 0.405 | 0.111 |
| motor skills | 6.50 | 0.038* | 0.639 |

**Indipendent t test for MS group>TAU group**

*Table 11 score differences between pre and post (FU-T0) assessment for VABSII.*

Considering the importance of gathering data regarding autism population, we illustrate the data that were found in our sample across the three measures (motor, cognitive and behavioral) comparing MS group and TAU and commenting qualitative data.

In graph 1 total score in Abc-2 m assessment is presented between MS group (N=4) and TAU group (N=6). It should be noted that 2 children within the control group participated in motor skills training during their therapies during the period of assessments. The average score for MS group (for both pre and post assessments) is 56, according to the manual, this score points to important difficulties on movement skills (5 percentile). For the TAU group, the total score goes from 60 (mean pre, SD=19) to 73 (mean post), indicating that their motor profile changed from risk of movement difficulties to absence of movement difficulties. It should be pointed out that coordination, fine motor skills and balance (which are all assessed by Abc-2 m) are not trained at the level of performance during the MS room intervention. Children are exposed to gross motor activities, but they do not have to perform within a certain time or with movement precision, moreover fine motor activities (writing, fingers movement) are not trained during MS sessions. The motor activities inside the multisensory environment aim to expose the children to movement with purpose, and to match motor activity with the meaning of the contextual stimuli, moreover the aim is to expand the repertoire of actions made with the same objects assigning them different meanings. Therefore we believe that Abc-2 m can be useful to measure possible gains in the gross motor functions after the training. Unfortunately, few data were suitable for the comparison and other variables could have influenced the results (motor activities practiced by control participants, different level of motor demand in the MS room by MS room participants).




*Graph 1 total average score at in pre and post ABC2 m assessment for MS group (blue) and TAU group (gray)*

Importantly, at group levels fine and gross motor difficulties are common in the 10 participants analyzed here, we stress out that motor activities in autism should be more integrated with cognitive and social interventions, at the very least for improving the ability to move in the environment and to be more aware of bodily sensations and environmental feedbacks after action execution.

The cognitive average profile for the MS group (N=7) and the TAU group (N=7) is presented in graph 2, the 9 tests (two scores for copy design) are named from the Italian version of the battery[2]. The average score in the healthy population is 10 (SD=3 scalar score). The most compromised group is the MS group, especially for Instruction Comprehension (mean=3,2), and Motor Sequencing (mean 2,4). They also performed poorly in Hands Posture imitation (mean=4,8) and Affect recognition (mean=4,5). Visuospatial skills are, instead, the stronger area (Design Copy gen mean=10,7 Design Copy spec mean=12,4 Block Construction mean=8,85). In the TAU group those same areas are weaker (Instruction Comprehension=6,4, Hands Posture imitation=5,7, Motor Sequencing=6, Affect recognition=6,42). In both groups Memory tests are between 6 and 8, within 1,5 standard deviation from the normal score, however sometimes they perform these tests under their rules or randomly, the score for this test is calculated independently to this variable and sometimes it can overestimate memory performance.

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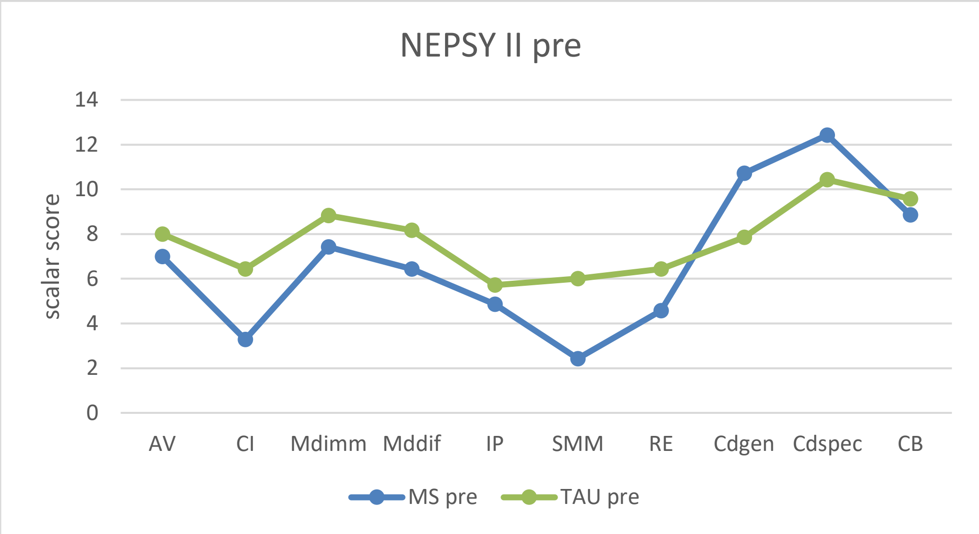
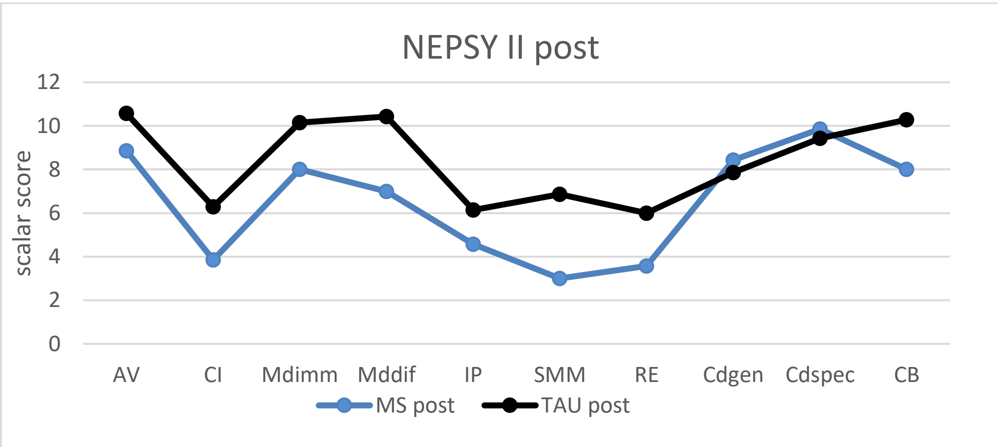
[2] AV:Attenzione Visiva, CI=Comprensione di Istruzioni, Mdimm=Memoria di Disegni immediate, Mddiff= Memoria di Disegni Differita, IP=Imitazione di Posture Manuali, SMM=Sequenziamento Motorio Manuale, RE=Riconoscimento di Emozioni, Cdgen=Copia di Disegni generale, Cdspec= Copia di Disegni Specifica, CB=Costruzione di Blocchi.




*Graph 2 total average score in 10 tests for NePsyII at pre assessment. Acronyms are derived from the Italian version.*

Graph 3 illustrates what happened at post assessment. For the MS group average scores in Instruction Comprehension (mean=3,8), Motor sequencing (mean=3) show little increase, and performance on Hands posture imitation (mean=4,5) remains stable. Affect recognition shows little decrease (mean=3,6). Attention (mean=8,8) and Memory (immediate mean=8, delayed mean=7) show little improvements.

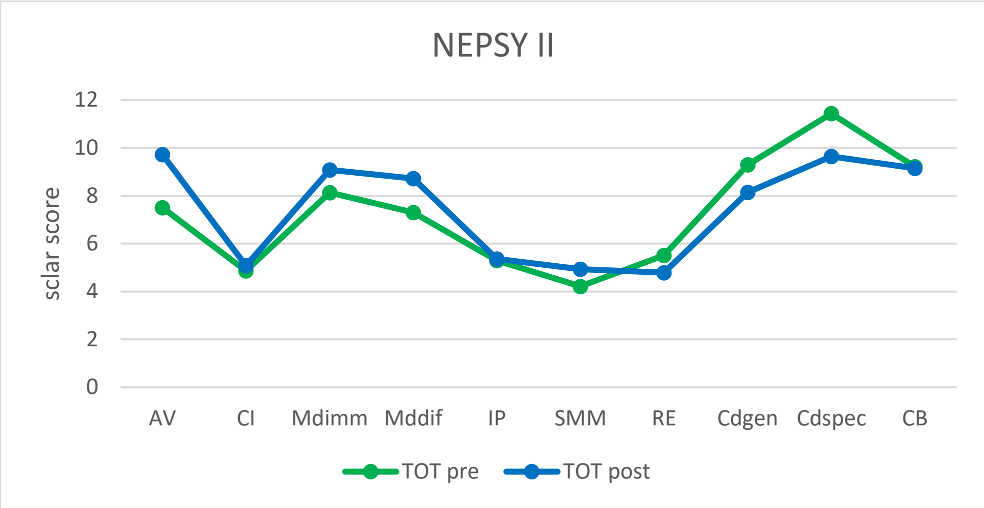
In the TAU group Visual Attention (mean=10), Memory of Designs (mean=10) and Block Construction (Mean=10) increases, Hands posture imitation shows little improvement (mean=6), other scores remain stable or with little decrease.




*Graph 3 total average score in 10 tests for NePsyII at post assessment. Acronyms are derived from the Italian version.*

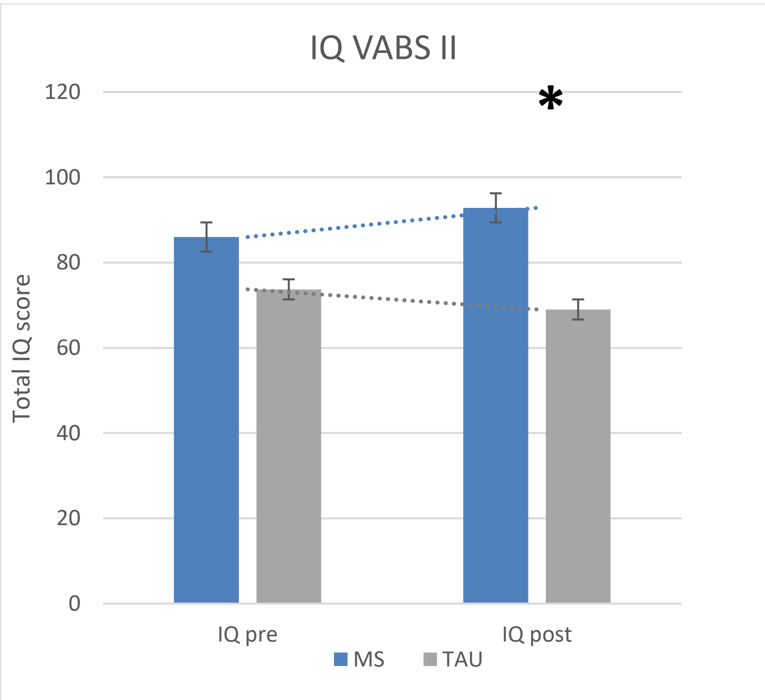
Overall, no significant change is observed between groups from pre (T0) to post (T1) assessments. We conducted a paired-t test for pre and post measures of all participants (N=14, only for Memory tests one participant has no score) and we found that visual attention (paired t14 Wilcoxon W=5.50, p=0,014, effect size=-0.8) and immediate memory (paired t13 Wilcoxon W=12, p=0,040, effect size=-0.6) for design significantly increased at group level from T0 to T1.

Graph 4 illustrates the overall evolution from pre to post assessment, in line with the core feature of ASD language and communication, and social perception are the most compromised, importantly, sensorimotor functions are poor in our sample, again emphasizing the importance of including motor activities and training into clinical practice with ASD.




*Graph 4 total group score on NePsyII tests at pre (blue) and post (green) assessment.*

Graph 5 illustrates total IQ scores between groups from T0 to the follow-up. Overall, adaptive behavior seems to benefit from the MS intervention in the long term. Parents reported a general change in the child's autonomies, in his attempt to do actions more autonomously and in more flexible playing. Parents also report more tolerance to changes in plans or to new environmental changes.




*Graph 5 average IQ total scores on VABS-II, pre assessments and follow up are shown for MS group (blue) and TAU group(gray).*

### 4.8 Discussion

This is the first study using standardized tools for cognitive and motor assessment for a multisensory room intervention. Although no difference was found between groups in pre and post assessment so far, we emphasize the importance of assessing the effects of multisensory environments with commonly used tests, in order to provide comparable outcomes among clinician and therapists that use different multisensory rooms for children with ASDs. Some limitations depended on external factors.

We draw attention to the fact that the intervention in multisensory room should be frequent and continuous, however, the first 6 participants attendance were intermittent and prolonged closure of the center, due to Covid-19 pandemic, frequent illness interrupted up to three weeks children attendance in the room and prolonged the assessment process, on average during the 24 sessions period the first group was absent for 17 sessions (from a minimum of two consecutive absence up to 9 consecutive absence). We argue that the frequency rate of the MS group influenced the score of NePsy-II and ABC-2m after three months, and more data should be collected with higher frequency rates. In some cases, even if performance's score remains the same, we observed that the child changed some qualitative characteristics.However, we believe that the effort to overcome limitations and begin the study was very important, moreover several parents reported that the multisensory room was helpful for children especially during this period of decreased school attendance. To date, two subjects are finishing their sessions in the multisensory room, and they maintained a good attendance rate, hopefully in 2022 new participants will maintain the same rate completing the 24 sessions within 3-4 months. In the future it is important to analyze how the participants score are influenced by the frequency rate in the room, however we need to collect more data in order to do so.

Another study limit was that therapists underwent a non-specific training, meaning that they were trained for stimuli use and for the attitude towards the child that they should maintain during the three-phases of the sessions (exploration/non-directive, activities/directive, relaxation/non-directive) and also in how to put activities into practice and modify the environment according to the purpose. The 7 therapists that participated in the room sessions were mainly educators (Bachelor degree N=4) and psychologists (Master degree, N=3). Activity director was, however, trained in several approaches (Applied behavioral analysis, Ayres Sensory Integration, Early Start Denver Model, Snoezelen room) and has a master's degree in psychology.

VABSII has the advantage to be useful for all levels of functioning, because it offers a complete image of child's usual behaviors across multiple contexts (home, school, hobbies) as observed by the main caregiver. One limitation of this tool is that the interview is given by parents and caregivers interviewed are motivated from the multisensory room intervention, their answers could be biased. However, it should be noted that controls children also participated in many activities and therapies (motor skills trainings, speech therapies, social skills training groups), thus, their parents are equally motivated to observe positive changes in their children. Moreover, participants that were assessed during the lockdown and restrictions were also negatively biased, because they expected some regressions due to the lack of outer experiences, and to the intermittent attendance to therapies and at school.

Considering that VABS-II are proposed to the parents at the baseline and after at least 6 months (three months after the intervention end). The improvement in overall scores in adaptive behavior can be interpreted in several ways.

- The multisensory room intervention directly facilitates the therapeutic sessions with therapist in the following three months, and indirectly benefit behavior across context.
- The multisensory room intervention directly boosts the child's agency and autonomy, increasing the overall drive to exploration of new activities and improving behaviors.
- The multisensory room increases flexibility, learning, and exploration, that are fundamental environmental adaptation.
- The multisensory room has no effect on adaptive behavior and other influencing variables affect child's adaptive behaviors.

Activities inside the multisensory room span from highly imaginative (like space travels, princess and castle adventure, pirates adventure), to more concrete and familiar themes (going to the supermarket, going to bed, driving car, going to a birthday party), depending on the child. Thus, the main trained ability is adaptation to several environmental change and new rules and ability to execute the right behavior, pursuing activities' goals with the therapist. Hence, conceptual, social and practical skills are demanded to the child. If these data will be confirmed in the near future, the multisensory room intervention can be used as a safe and protected environment that helps generalization of behavior. The advantage of the room compared to other therapeutic settings is the fact that stimuli can be delivered in several manner (video, audio, image etc) and that the child should perform complex actions based on stimuli received, besides the cognitive demand. As a whole, It is unlikely that usual treatment alone may give rise to this effects considering the stable context, the few changes in sessions materials and activities, we argue that the multisensory room, used in a flexible manner with both cognitive and motor activities is more suitable for this outcome.

Importantly, we conducted a qualitative questionnaire to check feasibility and satisfaction of family and children. We also analyzed therapists' point of view on the room's benefits.

*Parents questionnaire.*

We asked parents if any, which kind of changes they observed in their child.

Seven children have been attending to the center for more than a year, while only one child attained from less than six months. Six children out of eight follow other therapeutic interventions (like speech therapy). Seven caregivers gave answered to “If any, what changes did you observe in the child during the 3 months of intervention?” (6 parents answered to the question and one parent did not).

- Nothing in the short term.
- The child overcame his fear of the dark.
- There has been an improvement in the child's attitude with new learning.
- I have seen the child more serene, and he/she uses her/his imagination a lot more.
- My daughter/son has started to propose new games of his/her own at home, which he/she used to do with great difficulty.
- Attention has improved and the autonomy too, [Name] is more serene and happy.

We asked to parents to rate the experience in 5-point scale (from highly negative to highly positive) from their child’s perspective: according to parents, 5 children consider the experience as highly positive, while 3 a positive experience.

*Therapists’ questionnaire*.

We also asked to the seven therapists “which benefit did you find in the MS room compared to the usual treatment (in small rooms called boxes)?” They can freely choose from some answers or propose other benefits. Here below we report their answers

- the user pays more attention to instructions given (1)
- greater user involvement during activities **(6)**
- better frustration management (2)
- less unwanted behaviors (1)
- more desired behaviors (3)
- emergence of new appropriate/desired behaviors **(5)**
- better understanding of the user's requests by the therapist (3)
- improved participation in box activities due to the PREVIOUS activities in the MS room (3)
- improved participation in box activities due to the SUBSEQUENT MS room activities (4)
- more help in sessions management thanks to an external observer (activity director) **(5)**

Six therapist observed greater involvement in activities, 5 observed the emergence of new appropriate behaviors, and experienced more aid from the external observer during sessions.

Therapists rated the MS room intervention from a scale with 5 possible answers (from very negative to very positive) as positive (5 therapists) or highly positive (3 therapists). They were asked which judgement their users would give to the experience and the rating was highly positive (for 4 users) and positive (for 3 users). Overall, Study two leads to preliminary results that support the continuation of research and expansion of the sample, with the goal of reaching more robust conclusions to help the therapeutic field.

# 5 GENERAL DISCUSSION AND OPEN QUESTIONS

This thesis stems from the need to integrate more research into clinical field, with all the practical obstacles that this implies. Families, clinicians and people with autism need more direct communication from the academic community and also experimental procedures sometimes renounce to environmental validity to preserve methodology rigor that is very rarely applicable to every-day practice with people within the 'spectrum'. The main argument of this dissertation is that hippocampal development plays an important role in autism and the complexity of its circuitry and the way it connects to long distant areas overshadows its role in the genesis of first hallmarks of ASD and the subsequent symptoms emergence. In the first observational study we investigate long term memory in children and adolescents with ASD, in order to clarify the role of hippocampal-mediated remembering. We find that confabulators are more frequent in the ASD group and overall they confabulate more than controls. However, the distinction between episodic and semantic recollection does not show the expected advantage in semantic retrieval, on the contrary confabulation appear more in the semantic domain. We argue that the ASD responses were qualitatively poor compared to controls and their memories appear as facts to the listener, with more attention to unimportant detail and less contextual information. Thus, it appears that episodic answers are "*semantisized*" and the listener has few clues on how autonoetic consciousness is involved in memory recollection. This conclusion is however just a speculation and more precise techniques should be adopted to obtain a more detailed answer. In the future, the application of natural language processing (NLP) computation may be fruitful to classify the semantic and episodic response in a more dimensional way (from highly decontextualized to highly contextualized memories); following Dalla Barba MCTT theory, we suggest that multiplicity and unicity could be two important constructs for a better understanding of human memory and how could be affected also in neurodevelopmental clinical conditions, such Autism. Finally, the role of consciousness on "Semantic" and "Episodic" recall should be more carefully considered in future research, here we propose that Knowing consciousness is implied in semantic content, while Temporal Consciousness is implied in episodic contents. The questionnaire could be a good tool for assessment of memory, however, ecologically validated methodology should be implemented to control semantic and, especially, episodic stored content as well as future plans.

In the second study we planned and implemented a multisensory SHX room intervention for children with autism, to investigate the effects that this intervention can have on the motor, cognitive and behavioral profiles. Although the study illustrates only preliminary results, some conclusions can be drawn. First of all the first 7 MS room participants do not show improvements on motor and cognitive profiles compared to controls, however parents and therapists reported positive effects on the use of the MS room for this sample. According to other studies (Novakovic, 219; Fava and Strauss, 2010) we believe that the frequency and continuity of MS sessions is fundamental to see some results in the short term. After three months from the end of intervention, parents answered questions regarding how their children do daily activities, communicate, socialize and move in their daily lives. We observe a gain in the total IQ score compared to controls, meaning that the multisensory intervention can foster learning in other contexts and have some long term effects (after three months from the end of intervention). More data should be collected to confirm this aspect, but some speculation could be formulated.

First of all, the room's program alternates activity and relaxation. Voluntary action and active learning promote theta oscillation in hippocampus, these EEG waves seem to facilitate retrieval of item specific information coordinating the pattern of activation in the brain (Estefan et al., 2020), we believe that motivating the children to perform voluntary actions and expose them to imaginative exploration of space and objects can foster hippocampal activity and, thus learning. During relaxation children usually listen to calming, pleasant music with the therapist, they choose a place in the room and can manipulate stimuli for the purpose of calming down and breaking from activities, the therapist is trained to share the space with the child and propose ways to use stimulation for the relax. Sarkamo and Soto (2012) review emotional and cognitive effects of music listening and conclude that listening to pleasant music can improve memory (auditory and verbal), attention, and mood. According to them, three mechanisms can induce neurocognitive changes: modulation of dopaminergic system, stress reduction (decreasing cortisol levels) and enhancement of glutamatergic transmission. Glutamate is critical to learning and memory, thus music listening could be beneficial at different levels, at the very least for emotion regulation. One "high functioning" child who was part of the MS room group, reported that once he experienced a stressful situation at school and he imagined to be in the multisensory room, during relaxation, to modulate his negative mood state. Independently of the rate of changes in the context, each child experienced various contextual themes for their activities. The asset of MS room is its potential to provide multiple contexts in one single environment. It offers to the child a predictable and safe environment where physical and imaginative changes are progressively displaced. As Vermeulen writes in his book, it is the context that can disambiguate stimulation and behaviors. The just right amount of newness and the changing rate might help to develop flexibility and ideation, and thus, adaptation. The effectiveness of Multisensory room intervention on cognition and motor performances is not demonstrated so far, it is possible that neurocognitive changes can occur in the long term and therefore cognitive follow up should be maintained. Qualitative observations made by therapists, parents and by children themselves (often they asked to go back in the MS room) motivate to improve methodology and practical intervention. Overall, our studies join those that consider autism as a "decontextualized mind" (Vermeulen, 2012; Morsanyi et al., 2010), to produce more effort in autism understanding and in the formulation of new approaches. It is however necessary to collect further data to implement our preliminary results. Possibly, the ability to "track contextual continuity and discontinuity" is related to hippocampus activity (Maurer and Nadel, 2021) and can be crucial in child development.

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**APPENDIX 1-Draft Confabulation Elicitation Questionnaire -Italian version**

***Parte Semantica (info recenti, remote, aspetti generali, domande per valutare la tendenza a rispondere).***

| |
|---|
| Che classe frequenti, in quale scuola? |
| Che cos'è un petauro? (marsupiale/mammifero/australiano/coda) |
| In quale città si trova la scuola materna/asilo che hai frequentato? |
| In quale città è nata tua mamma /o/Tuo papà? |
| Sai il nome della regina di Inghilterra? |
| Tua mamma/o/papà ha fratelli o sorelle?(nomi) |
| Come si chiamava il padre di Cenerentola? |
| Chi ha causato la seconda guerra mondiale? (Hitler, Germania) |
| In quale città (quali se sono diverse) è cresciuta tua mamma/o/papà? |
| Chi è l'attuale Presidente della Repubblica Italiana?/Chi è l'attuale Presidente della Russia? (personaggio noto attuale). |
| Di che colore sono i tuoi occhi? |
| Come si chiamava il cacciatore nella favola "Cappuccetto Rosso"? |
| Tua mamma o papà lavora? Se sì che lavoro fa? |
| Quant'è la profondità massima della fossa delle Marianne ? |
| Perché si sente spesso parlare dell'ISIS al telegiornale? |
| Quanto sei alto? /se non conosce le misure chiedere altezza relativa a due oggetti (armadio/sedia) |
| Come si chiamava la madre di Simba ne "il re leone"? |
| Ti ricordi il nome della tua prima maestra della scuola materna/asilo?/o in alternativa compagno di ASILO /o/ in alternativa elementare |
| Tua mamma/o/ papà ha fatto l'Università /o/in alternativa quale scuola superiore? |
| Mi diresti il nome di un tuo attuale compagno di classe//amico con cui giochi? |
| Quanti anni ha tua mamma?/tuo papà? |
| Ti ricordi chi ha vinto il Nobel per la Pace nel 1993? |
| Quanti anni aveva tua mamma quando ha conosciuto tuo papà? |
| In che città sei nato? |
| Nonni sono viventi? Dove abitano i tuoi nonni /zii (materni/e/o/paterni?) |
| Chi era (Personaggio famoso remoto) Marilyn Monroe/o/Freddy Mercury?/o/Michael Jackson?/ |
| Tua mamma da bambina ha abitato in una casa o in un appartamento? |
| Chi è Harry Potter? |
| Chi è l'attuale presidente degli stati uniti d'America? |
| Qual è il tuo indirizzo di casa? |
| Sai dirmi a quale evento importante è legata la data dell'11 settembre? |
| In quale degli stati europei /o americani si trova Disneyland?( Francia, California) |
| Come si chiama l'attuale Papa? |
| Chi è Greta Thunberg? |
| Chi è (personaggio famoso recente) Lady Gaga? |
| Tua mamma/papà ha la macchina? Se si di che colore? |
| Quale titolo di studio hai fino ad ora ottenuto?/qual è l'ultima scuola che hai completato? |

***Parte Episodica (dettagli di base dove, con chi, quando/quanto tempo fa, eventuali informazioni di distinzione da altri ricordi non specifici*).**

| |
|---|
| Hai qualche vacanza/viaggio in programma? |
| Che cosa è successo di importante il 5 giugno del 2014? |
| Che cosa farai domani pomeriggio? |
| Quando hai fatto l'ultimo viaggio in treno?//alternativa aereo (giorno, mese, anno e destinazione, intervallo temporale). |
| Ti ricordi/mi racconti una vacanza/viaggio che hai fatto quando eri molto piccolo?(luogo, mese, anno// circa la propria età al momento del viaggio, o quanti anni fa) |
| Ti ricordi che cosa hai fatto a Capodanno di un anno fa? |
| Ti ricordi chi ha vinto il concorso di Miss mondo/Miss Italia, quando tu avevi 5 anni? |
| Sai andare in bicicletta/monopattino? Ti ricordi Quanti anni avevi quando hai imparato ad andare in bicicletta/monopattino? (dove con chi). |
| Farai qualche attività (come giocare, guardare un film, passeggiare, incontrare qualcuno..) che ti piace moltissimo nei prossimi giorni? |
| Raccontami di un viaggio (di un giorno, un paio di giorni) che hai fatto con i tuoi genitori qualche anno fa. (Destinazione/luoghi visitati/attività) |
| Che cosa hai fatto questa mattina/pomeriggio?(a seconda del momento dell'intervista) |
| Raccontami un episodio in cui sei dovuto andare in ospedale o dal dottore perché non stavi molto bene/ti eri fatto male? |
| Raccontami di una volta in cui sei stato in un paese diverso dall'Italia/in una regione diversa dal Friuli. |
| Ti ricordi dov'eri quando è stato creato WhatsApp (2009)/o in alternativa Facebook(2005)? |
| Che cosa hai fatto ieri sera? |
| Che lavoro vorresti fare quando finirai la scuola? |
| Dove pranzerai domani? |
| Raccontami di una volta in cui sei andato in piscina da piccolo?//in alternativa al parco divertimenti? |
| Mi racconti la prima volta che sei stato in un supermercato? |
| Mi racconti la prima volta che hai preso un bel o brutto voto a scuola? |
| Cosa hai fatto durante queste ultime vacanze da scuola? (luogo /attività/con chi) |
| Sei mai stato in qualche stato/nazione/Paese oltre all'Italia? Se Si elencamene alcuni//in alternativa raccontami la prima volta che sei stato su una nave/aereo/treno. |
| Di che colore/di che razza era il primo cane che hai visto nella tua vita? |
| Qual è il primo frutto che hai mangiato nella tua vita? |
| Dove sei stato nell'ultima gita scolastica che hai fatto? |
| Cosa hai mangiato a pranzo di lunedì di 2 settimane fa? |
| Di quale colore erano i tuoi pantaloni/calzini (indumento) l'ultima volta che sei stato in una gelateria?(segnare quanto tempo fa) |

## APPENDIX 2-MULTISENSORY SHX ROOM-DEVICES