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A Behavioral Study on the Adult Marmoset Interference Control in Spatial Working Memory

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Abstract

Interference control deficit in Working Memory (WM) is associated with neurodevelopmental disorders. The common marmoset (*Callithrix jacchus*) is an ideal non-human animal model for studying WM disorders. Previous studies of marmoset WM have used a touch-screen self-ordered sequencing task (SOST), which resembles an n-back paradigm and targets updating processes in internal interference control. However, the training time for the marmoset to reach proficiency on this paradigm is long given the short marmoset lifespan. In an attempt to accelerate marmoset learning of the task, we developed a new version of SOST that relied on foraging behaviour. The goal of this project was to validate an experimental design that resembles the naturalistic environment of the animal and speed up the learning phase of training. A below chance performance was observed. Two task-related issues were identified that could be the reason for poor performance. The training levels were modified to resolve the weaknesses of the task.

Keywords

Spatial working memory, internal interference control, n-back task, self-ordered sequencing task, the common marmoset, neurodevelopmental disorders.

Summary for Lay Audience

WM deficit is an identifying feature of neurodevelopmental disorders. Interference control is the ability to control unrelated information and plays a central role in WM functioning. Animal models play a critical role in advancing our understanding of human WM functioning and are essential for interventions in neurodevelopmental disorders. The common marmoset is a relatively new animal model suggested as an ideal model for neurodevelopmental studies. The first step to enhance our understanding of WM functioning in the marmoset and conducting preclinical studies is to validate tasks that target specific WM features and are suitable for developmental studies. The SOST is a task used to investigate WM in the marmoset. This task is based on the n-back paradigm, which is a well-established task used to study interference control in humans. However, a long training period is required, and marmosets have a relatively short lifespan and short developmental periods. Here, a novel task design for the SOST was developed that relied on foraging behaviour and represented the animal's natural behaviour. A naturalistic environment was used in order to accelerate the learning procedure, given the marmosets short lifespan.

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Chapter 1

1 Introduction

Working memory (WM) is a memory system that actively holds and manipulates information of short-duration in the service of planned action and decision making (Baddeley & Hitch, 1974). In the Baddeley and Hitch model (1974), WM is identified in three parts: A phonological loop that stores verbal data, a visuospatial sketchpad specific to visuospatial data, and a central executive system that assigns attention to WM content, protecting and controlling the flow of information. Identifying the processes that constrain or facilitate WM functioning can help to resolve related cognitive impairments in neurodevelopmental disorders. One of the identified factors in maintaining and manipulating information to achieve task-related goals is interference control. Interference control is a type of cognitive control and a function of the central executive system which facilitates active memory processing by controlling for irrelevant information in the content of WM. In other words, this system protects WM content from external stimuli or competing representations (Barch & Smith, 2008). For instance, in an experimental context, information related to stimuli in past trials (past memory) would be irrelevant to the representation of stimulus in the current trial. However, past stimuli compete with the related information in WM. The lack of attentional resources necessary to actively inhibit irrelevant information causes WM dysfunction (De Beni et al.,1998 as cited in Cornoldi et al., 2001; Engle, Cantor, & Carullo, 1992).

Neurodevelopmental disorders like Attention Deficit and Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are characterized by impairments of WM (Alloway & Gathercole, 2006). Studies show that children with ADHD perform poorly in WM tasks compared to typically developing children (Barkley, 1997; Mariani & Barkley, 1997 as cited in Cornoldi et al., 2001). Although there are conflicting reports of WM deficits in ASD (Ozonoff & Strayerm 2001), visuospatial, phonological (Habib et al., 2019), and spatial WM dysfunction in ASD are well-evidenced (Kercood et al., 2014; Steele et al., 2007; Wang et al., 2017). Interference control impairment is attributed to WM deficit in neurodevelopmental disorders. WM deficit in children with ADHD was significantly associated with greater accessibility for irrelevant information (Cornoldi et al., 2001; Palladino & Ferrari, 2013). Similarly, WM impairment in individuals with ASD is associated with difficulty in interference control (Geurts et al., 2014).

1.1 PFC and WM

The pre-frontal cortex (PFC) is an extended brain region that is roughly one-third of the brain. PFC goes through structural and connectivity changes throughout the lifespan. These changes have been reported to be associated with developmental changes and maturation of cognitive control across development (Diamond, 2002; Wilk & Morton, 2012). Cognitive control relies on PFC to guide behaviour. These processes involve filtering irrelevant information (interference control), inhibiting inappropriate responses (inhibitory control) and planning actions. Different regions of PFC regulate distinct aspects of cognitive function. In particular, dorsolateral PFC (dlPFC) is essential for WM functioning and attentional processing and is affected in neurodevelopmental disorders (Clark et al., 2007).

Human studies show that lesions to the PFC are associated with impulsivity, perseveration, inability to maintain information and control for interference. In addition, PFC volume and performance on executive functioning tasks are positively correlated (Yuan & Raz, 2014). Studies in individuals with PFC damage show these individuals have deficits in the maintenance of information (Braver et al., 1996). More specifically, PFC damage is associated with problems of interference control (Thompson-Schill et al., 2002).

Behavioural tasks that require active maintenance of information have been used to investigate the role of PFC in WM. The A not B task is a well-established measure of working memory in infants. In the classic version of the task, the infant is required to uncover a toy that is hidden in one of two locations. After several trials and as soon as the subject can reach the baited location (A), the toy will be hidden in the other location (B). Infants 9-12 months of age show perseverative responses on B trials. A near-infrared spectroscopy study on infants showed an association of PFC activity with performance on the A not B task (Baird et al., 2002).

The A not B task is similar in some respects to the delayed response task which is another measure of WM extensively used with non-human primates (NHP). Both tasks require the subject to hold information in mind for a short duration of time and guide responses based on previously presented information. dlPFC activity has been shown to be associated with performance on delayed response tasks. A higher number of errors on the delayed response task has been reported to be associated with stimulation of dlPFC (Pascual-Leone & Hallett,1994).

Lesion studies in NHP provided ground-breaking evidence for the role of dlPFC in the active maintenance of information. Jacobsen (1936) conducted a pioneering lesion study on the bilateral frontal cortex and investigated maintenance of information in Macaque monkeys. A delayed response task was used in which each trial started with the animal watching food covered under one of two similar objects. A mandatory delay was introduced. Access was then granted to the animal to approach one of the objects to find the reward. To perform correctly, the monkey had to maintain information during the delay. A chance level response was observed after the removal of dlPFC. In addition, the lesion of dlPFC in monkeys was associated with poor performance on Piaget's 'A not B' task. Results from Diamond & Goldman-Rakic (1989) suggested that improvement on 'A not B' task depends on the development of dlPFC. In another lesion study of PFC in monkeys, Mishkin and Manning (1978) showed the role of principal sulcus lesion for performance on the non-spatial delayed alternation task. Every trial of the object alternation task started with presenting two different objects, one being baited. In the subsequent trial, the previously baited object was empty. Therefore, in each trial, the monkey had to choose the object that had not been selected in the previous trial. This study showed that damage to the principal sulcus causes non-spatial memory deficit.

Single neuron recordings provide further evidence on the delay-related activity of dlPFC in tasks that require active maintenance (Goldman-rakic, 1987; Kubota & Niki, 1971). Kubota and Niki (1971) were one of the first to record the neural activity of the pre-frontal area during the delayed alternation task. Their results showed the activity of dlPFC neurons during the delay period of the task. The delay-related activity of dlPFC neurons suggests the involvement of this region in the active maintenance of information.

1.2 PFC and Neurodevelopmental Disorders

Disrupted PFC functioning has been shown in relation to neurodevelopmental disorders. Impaired performance of individuals with ADHD on psychological tests of cognitive control is associated with PFC dysfunction (Barkley, 1997). Various studies show decreased PFC activity in patients with ADHD on tasks of cognitive control (Arnsten et al., 1996; Depue et al., 2010). Further neuropsychological evidence shows the similarity of impaired performance in patients with ADHD to those observed in patients with PFC lesion (Clark et al., 2007; Itami & Uno, 2002; Levin et al., 1991). Additionally, structural imaging studies show a smaller size of PFC in patients with ADHD (Filipek et al., 1997; Giedd et al., 2001; Hill et al., 2003).

Functional neuroimaging studies report atypical PFC activity in patients with ASD (Just et al., 2007; Luna et al., 2002; Schmitz et al., 2006; Silk et al., 2006). Increased task-related brain activity in the left insula and left inferior and orbital frontal gyrus has been reported in individuals with ASD (Schmitz et al., 2006). Schmitz et al. (2006) used a spatial motor Stroop task in which subjects were required to touch the left or right side of the screen based on the direction of an arrow that appeared on the screen. The arrow could appear either on the left or right side of the screen. In incongruent trials, the direction of the arrow and its position on the screen were incongruent. Participants had to ignore the interfering information about the position of the arrow on the screen and respond based on the direction of the arrow. Increased task-related activity in PFC was observed in individuals with ASD compared to the control group.

More specifically, abnormalities in dlPFC have been reported in relation to performance on a spatial working memory task in individuals with ASD. Performance on an oculomotor delayed response task was observed. A stimulus appeared on the right or left side of the screen. After a short delay, the subject was required to make a saccadic eye movement to the location of previously presented stimuli. A decreased task-related activity in dlPFC in individuals with ASD compared to the control group was observed (Luna et al., 2002).

Understanding structure and functioning of PFC over the course of development is essential for having a better understanding of the underlying neural mechanism of neurodevelopmental disorders. Detecting alteration of the neural circuits in relation to behavioral traits of cognitive control deficits is an attempt to identify etiological mechanisms of neurodevelopmental disorders. Consequently, we would be able to better mediate or prevent these disorders.

1.3 Comparative Studies of WM

The use of human subjects to investigate the neural mechanisms of cognitive control in neurodevelopmental disorders is methodologically limited. Comparative neurodevelopmental studies, by contrast, offer more significant potential to understand the function of the normal and abnormal brain, human nervous system development, and the association of microstructural changes in the brain with cognitive functions (Philips et al., 2019). Animal models have the advantage of combining cognitive assessments with histological measures (Phillips et al., 2019) and conducting lesion studies and neurophysiology recordings. Additionally, clinical translation of drug studies for impairments of WM is possible through non-human animal preclinical studies.

Facilitating the connection between preclinical and clinical efforts requires that the predictive validity of findings be confirmed. Predictive validity represents the homology of results from comparative studies. In other words, predictive validity is about whether the animal model can predict the clinical efficacy of a potential drug. Predictive validity is demonstrated when a drug works in preclinical and clinical trials, or it does not work in both. Mismatch of results in human and animal studies represents a failure in such validity (Dudchenko et al., 2013).

The first step to increasing the predictive validity of WM tasks in comparative studies is to specify the relevant construct better. For example, identifying a specific WM deficit in ADHD helps modify and use tasks targeting that construct in human studies. However, the distinction of tasks in targeting specific WM constructs depends on whether these tasks are distinguishable by their pharmacological and neural profile. Therefore, targeting the relevant construct relies on a specific set of tasks that target specific WM processes and mechanisms.

The next step in enhancing the predictive validity of preclinical studies is to have homologous tasks for preclinical models and humans. It is essential to validate the human analogue of WM tasks for use with NHP. The use of homologous tasks for human and animal models that target specific constructs of WM, helps to translate the findings in comparative studies.

One challenge in using animal and human paradigms as counterparts to measure WM is the difference in the definition of WM between fields. In animal studies, WM refers to the cognitive system that holds information about a stimulus that is no longer present (Goldman-Rakic, 1994). Here, WM is identical to the definition of short-term memory. Short-term memory only requires the maintenance of information about the stimulus of interest. In contrast, in human studies, WM tasks demand application of general task rules, manipulation of information, and interference control to perform on each trial (Shettleworth, 1998, chap. 6 as cited in Basile & Hampton, 2013).

Non-human animal studies of WM usually refer to tasks that do not require information manipulation and interference control. To investigate questions about interference control, we need to use tasks that target interference control. This includes questions such as 1) Is WM performance in animals impaired when interfering information is present? 2) Do animal subjects use the same memory processes for interference control as human subjects? 3) Are WM processes in animals represented via the same neural substrates involved in human WM? Homologous behavioural tools that evaluate interference control in non-human animals and humans are needed to advance research on these questions (Basile & Hampton, 2013).

When choosing the methodology, comparative studies also require cautious attention to the task domain. In other words, comparative studies not only need to accurately choose the most suitable and compatible task to measure interference control and its specific processes, but they also need to consider the possible differences in neural functioning and cognitive performance given the required domain of the task.

The extent of the generalization of cognitive control from one task to another is a matter of debate. Some researchers reason that cognitive control processes are domain-general as they detect and manage conflict regardless of domain type (e.g., phonological, visual, semantic, syntactic, spatial; Miller & Cohen, 2001), while others argue that cognitive control is domain-specific, meaning that multiple systems perform independently within each domain (Egner et al., 2007).

Careful consideration of the task domain is a fundamental matter in neurobiological studies of interference. The domain generality of PFC neural activity is supported if the neural activity is similar for performance on task versions with different domains. However, domain generality will be contradicted if different neural activation patterns are present when comparing different domains. Conclusive inferences on domain generality of PFC in relation to interference control await further investigation.

In human studies, tasks have the advantage of using the phonological domain. Human tasks benefit from the language in two ways: 1) language conveys information about the task's general instructions, and 2) language allows for the use of verbal and written stimuli in the construction of tasks. While in animal studies, it is not possible to convey instructions by language or to use verbal and written stimuli to create tasks. Therefore, the visuospatial domain is the only bridge between human and animal studies.

Studies of WM primarily rely on computerized versions of the tasks. In human studies, several tablet-based instruments have been developed to assess aspects of executive functioning in human children and adults by using visuospatial stimuli. Since these tasks use visuospatial modules, they provide the possibility of application to NHP. Applying the same stimuli and optimizing touch-screen instruments to be applicable for use with NHP is one of the solutions to make findings between humans and NHP studies of WM translatable (Spinelli et al., 2004). However, training the NHP on the touch-screen tasks usually requires lengthy training, which causes difficulty for time-sensitive studies such as developmental studies.

1.4 Advantages of the Marmoset for Studying Neurodevelopmental Disorders

The contribution of genetic factors in neurodevelopmental disorders has been shown through genomic research (Folstein & Rutter, 1977; Galo & Posner, 2016). Biomedical and neuroscience research benefits from genetically modified animal models for understanding the biological and neural basis of behaviour and developing treatments. To provide insight into gene function and mechanisms underlying neurodevelopmental disorders, transgenic mice have been developed and prevalently used in preclinical studies.

Despite the prevalent use of mice, the predictive validity of mice models for neurodevelopmental disorders is limited; and direct translation of mice research into human research on neurodevelopmental disorders has proven difficult or impossible (Belzung et al., 2005; Leo & Gainetdinov, 2013). This difficulty arises, in part, on account of the more than 80 million years of evolutionary distance between humans and mice. The distance is evident in genomics, neural circuitry, brain anatomy, behaviour, and cognition. Thus, animal models that are phylogenetically closer to humans can advance our understanding of neurodevelopmental disorders and develop treatments by complementing rodent studies (Aida & Feng, 2020; Burkart & Finkenwirth, 2015).

Compared to rodents, NHPs have a closer phylogenetic connection to humans. NHPs have a remarkable resemblance to human physiology and anatomy. They share brain regions and cell types with humans associated with higher cognitive functions. More specifically, NHPs have a dramatically enlarged PFC similar to human’s PFC (Aida & Feng, 2020).

For a long time, genetic engineering technologies have been limited to research using rodents and fish. In 2009, Sasaki et al. (2009) developed genetically modified common marmoset monkeys as the first transgenic primate model. This breakthrough made use of the advantages of using marmosets over rodents and other NHPs as it syndicates accessibility of rodents in use of gene editing technologies with the suitability of NHPs in their phylogenetic relationship with humans (Burkart & Finkenwirth, 2015).

The marmoset has a well-developed PFC, and its cortical structure is very similar to humans (Okano & Mitra, 2015). Moreover, homologies of the marmoset and humans in PFC functioning have been shown (Roberts et al., 2007). Therefore, the use of the marmoset enables researchers to use genetic engineering techniques to study neurodevelopmental and neuropsychiatric disorders in a species evolutionarily closer to humans (Kishi et al., 2014).

Besides the advantage of using genetic engineering technologies with the marmoset, the marmoset has several additional advantages over other NHPs. Regarding the importance of animal welfare in the laboratory setting, marmosets are easy to handle. They have a smaller body size and lower body weight compared to macaques. Thus, they require less space, and their caging and feeding are convenient. In addition, compared to macaques, their breeding is faster. A female marmoset usually gives birth to twins or triplets, and since the gestation period is only 145-148 days, delivery can happen twice per year (Kishi et al., 2014).

The marmoset is especially advantageous for the study of neurodevelopmental disorders. The marmoset has a relatively short life span (10-15 years) and reaches adulthood by 1.5-2 years, making it possible to conduct neurodevelopmental studies in a reasonable time frame. It also has a relatively high reproductive rate compared to other primates that help to have an accelerated view of the developmental changes. In addition, the marmoset’s developmental trajectory of gray matter volume is similar to the macaque monkeys and humans. The volume of cortical gray matter is associated with cognitive functions. This shows the potentiality of the marmoset for studying cognitive functions (e.g., Sawiak et al., 2018).

Although the macaque monkey is a well-established NHP for studies of executive functions, with the abovementioned advantages of the marmoset over the macaque, the marmoset is suggested as an advantageous potential model for studying executive function in neurodevelopmental disorders.

1.5 Internal vs. External Interference

There are several interference control categories in WM literature. This section focuses on the distinction between internal and external interference control. Internal interference control is the ability to control unrelated internal information from former memories. For example, familiarity with previously encountered stimuli can create interference and require internal interference control. External interference control entails controlling for new information that is experienced during task processing (Bomyea et al., 2017). External interference control is attributed to situations where interference is inflicted through interruption (a secondary task that requires attention) or distraction (entirely irrelevant stimuli) (Clapp et al., 2009).

Interference control literature has commonly used two ways to inflict interference into a WM task: multitasking (e.g., dual-task) and familiarity (e.g., n-back task). In multitasking, two tasks are simultaneously presented and compete for attentional resources (interruption), or distracting stimuli are presented during the rehearsal period of the WM task and create interference (distraction). Familiarity interference is based on identifying the occurrence of stimulus and distinguishing related stimuli from unrelated stimuli. In other words, a familiar stimulus is presented. The participant is supposed to identify whether the familiar stimulus is related to the current trial or is one of the previously encountered stimuli unrelated to the current trial. It is essential to understand differences in interference control processes when determining whether interference has been created through familiarity with previously viewed stimuli or multitasking.

There are many unanswered questions regarding the interference control mechanisms in the brain. NHP single neuron recordings and human neuroimaging studies suggest that the activity of PFC is associated with WM performance (e.g., Cohen et al., 1997 as cited in Braver et al., 2007; Fuster et al., 1997). However, a group of studies suggests the role of PFC neurons in interference control rather than WM itself (Smith & Jonides, 1999 as cited in Braver et al., 2007). Considering the possibility of distinct neural mechanisms in relation to different types of interference control, a concise understanding of control mechanisms employed by PFC neurons is yet to be explored.

Understanding different types of interference control processes involved in the context of WM and their underlying neural substrates requires established behavioural paradigms. The use of distinguished paradigms that operationalize various research questions and animal models that enable the use of unapplicable tools for humans can shed a better light on such mechanisms. The following section is an overview of interference control tasks used in the human and non-human animal literature.

1.6 Tasks of Interference Control

Human WM research employs tasks that impose different cognitive demands and interference levels. Behavioural and fMRI studies of interference control have benefited from dual-task paradigms, recent-probe tasks, and n-back paradigms to understand neural mechanisms and disorders of WM in humans. These tasks require internal, external or both types of interference control and execute interference by multitasking or familiarity. Response accuracy and reaction time in these tasks are behavioural measures representing the relationship between interference and WM functioning.

Non-human animal research explored WM with a different approach. Since a large body of animal studies investigated WM with the definition of short-term memory, they applied tasks incompatible with those used in human research. Delayed match to sample (DMS) and delayed match to position (DMP) are two common tasks used in neuroimaging, lesion, and neurophysiology studies to investigate the neural circuitry of WM. In contrast, verbal/non-verbal and spatial/non-spatial versions of this task have been used in human studies to measure visuospatial short-term memory.

Classical versions of these tasks measure the ability of the animal to maintain the representation of a stimulus for a limited time. In other words, manipulation of information and interference control is not necessarily required for performance in these tasks. However, these tasks have been refined in animal studies to measure interference control and bring studies of interference control in human and animal models closer.

It will be beneficial to distinguish WM tasks based on their type of interference processes, domain, and level of difficulty (cognitive load). Researchers could benefit from this task dissociation to identify WM deficits in various disorders as there will be a clear understanding of the specialty of each task in targeting specific processes. In the following sections, the interference control tasks in human and non-human animal studies will be described and distinguished based on their differences in internal and external interference control and how they create interference.

1.6.1 Dual Task Paradigm

The majority of studies on interference control in the context of WM and neurobiological mechanisms underlying such processes applied the dual-task paradigm. The dual-task paradigm was used to study WM disorders (Garcia-Villamisar & Sala, 2002; Hilton et al., 2020; Sala et al., 1995) and attentional allocation development (Karatekin, 2004).

The dual-task paradigm simultaneously implements two tasks (multi-tasking) or presents one task and distracting stimuli. The use of multi-tasking is prevalent in human studies. The general rule is to perform two relatively complex tasks at once while each task has distinct rules and uses a distinct stimulus-response association. The purpose of the extra task is to force the representation of an additional set of information. Therefore, participants are forced to remember and apply appropriate information related to each task and control for competing information that is irrelevant to the current task.

The dual-task paradigm in human research is usually referred to as a complex span task. In a complex span task, participants are asked to remember stimuli (e.g., letters, words, numbers, pictures) while solving problems or doing an additional task (distinguishing the animal names). The behavioural measure on this task is the number of remembered stimuli which was originally taken as a metric of WM capacity. Numerous versions of complex span tasks have been adopted based on the combination of task module (e.g., visual, verbal) and task domain, the processes required to solve the problems in the tasks (e.g., reading, semantic judgment, math operations).

The reading/listening span task is one of the most well-known versions of the complex span task that applies to phonological stimuli. This experimental paradigm developed by Daneman and Carpenter (1980) has been used in several studies to show the dependability of working memory on active control of information. The task requires participants to identify the truth of statements (concurrent task) and remember the last word in each sentence (Cornoldi et al., 2001). Performance on this task requires a high level of interference control for the irrelevant information that is imposed by the concurrent task.

The WM span task with categorization has been used to investigate interference control in WM functioning of children with ADHD (Cornoldi et al., 2001), children at risk of ADHD, and children with Learning Disabilities (LD; Palladino and Ferrari, 2013). In this version of the WM span task, participants were asked to identify animal names from several word strings and remember each string's last word. The concurrent task (identifying animal names) induced interference by presenting irrelevant information to the task at hand. Therefore, performance on this task required inhibition of irrelevant information. The results showed that children with ADHD compared to normal developing children had significant difficulty in visuospatial memory related to lack of interference control. Compared to a control group, children at risk of ADHD and children with LD remembered significantly lower numbers of final words. The results from the dual-task paradigm suggest that ADHD/LD children are more prone to the accessibility of interfering items which is the reason for a significant number of errors in their performance.

Activation of the prefrontal cortex in relation to interference control for different sensory modalities and task modules has been investigated using the dual-task paradigm (Chein et al., 2011; D'Esposito et al., 1995; Klingberg, 1998). These studies aimed to investigate whether the neural substrates of interference control are distinct from those recruited for the general demands of the task. It is essential to differentiate a general task demand like WM load (which is a metric of difficulty), from interference control.

Klingberg et al. (1998) implemented auditory and visual WM tasks separately and in a dual-task condition to investigate the non-sensory specific activity of PFC. Positron emission tomography results showed no specific cortical activity in relation to the dual-task processing. Thus, essentially in the dual-task, no new brain region was activated that was not already activated during either the auditory or visual task. The authors concluded that these results support the hypothesis that interference of concurrent tasks is due to the necessity of the same brain region activity for performance on both tasks. In a similar study, Chein et al. (2011) evaluated the effect of modality on encoding and maintenance of information in a span task. Performance and neural activity on verbal and spatial complex span tasks were compared. Regardless of the task module, activation of prefrontal and parietal and anterior cingulate cortices was reported.

D'Esposito et al. (1995) used two non-WM tasks with different stimulus modules and task domains to investigate the selectivity of PFC activation. An auditory task (requiring semantic judgment: asking for the judgment on the truth of a statement), and a visual task (requiring an understanding of spatial rotation) were presented for participants in two conditions, simultaneously as a dual-task and separately. The dual-task condition required interference control, while the single task condition did not require any form of interference control. The activation of dlPFC was observed only in the dual-task condition, suggesting a relationship between activation of this region with interference control in WM.

Regarding types of control, the dual-task paradigm has been used to inflict external interference in WM. However, Bomyea et al. (2017) modified this paradigm to target internal interference control in addition to external control. Bomyea et al. (2017) showed which region is activated during controlling interference generated by prior trial learning (internal interference control) in the complex span task. Each trial of their task presented several letter or number stimuli that participants needed to put into serial order at the end of each block. Each stimulus in the block was followed by a sentence that required a participant's semantic judgement.

Interference was present from previous trials by matching the category of stimuli from the previous trial with the current trial. Their results are consistent with previous studies of complex span tasks (Bunge et al., 2000; Kondo et al., 2004), showing activation of the medial and inferior PFC and insula in relation to internal control of interference in working memory.

Based on these studies, the limitation in the application of external interference control is shown to be associated with poor performance in the dual-task paradigm in children with ADHD and LD. In addition, no specific difference is shown in neural mechanisms involved in dual-task paradigms with different domains. However, further studies are needed to distinguish the neural substrates of interference control from general task demands (e.g., difficulty level, task domain). Replicating studies and investigating interference control in other modules such as spatial vs. visuospatial dual-task paradigms can help better understand potential differences in neural mechanisms in relation to different domains and modules. The human literature also shows that the neural mechanisms involved in the dual-task paradigm differ depending on the involvement of internal interference control. However, a clear conclusion requires further investigation.

1.6.1.1 NHP Studies of the Dual Task Paradigm

Although human studies using the dual-task paradigm have an advanced scientific understanding of human cognitive architecture and WM disorders, amenable dual-task paradigms are needed for use with animal subjects. As it was discussed, animal studies provide the opportunity to further answer questions regarding neural mechanisms of interference control that cannot be reached with human studies. Therefore, they allow for a better understanding of the precise functional role of brain regions associated with interference control processes (Watanabe & Funahashi, 2015).

Data on NHP working memory in cognitively demanding tasks are scarce, and there is limited understanding of the processes involved in monkey WM impairment (Basile & Hampton, 2013). Few studies that have implemented the dual-task paradigm (e.g., Watanabe & Funahashi, 2015) usually have used the Delayed Match to Sample (DMS) task and introduced distracting stimuli instead of multitasking during the delay period.

The DMS task consists of three phases. The first phase (sample presentation) is the presentation of a stimulus in which the object’s identity or location is essential to encode. The next phase is the rehearsal period (delay), in which the stimulus is no longer present, and the subject needs to retain the information about the stimulus. The final phase is the test phase (test presentation), in which two stimuli are presented—one matching the sample stimulus and one that differs from the sample stimulus in identity or location. The rewarding answer is to choose the matching stimulus.

A study by Moise (1970) was one of the first attempts to understand the effect of an interfering activity on performance in the delayed match to sample (DMS) task in the Macaca speciosa. This study introduced a distractor during the delay period, which demanded a motor activity. The distractor motor activity was assumed to present an interfering effect on memory rehearsal and subsequently adversely affect performance on the task during test presentation. A significant decrease of correct responses was correlated with the amount of distractor introduced during the delay interval of the DMS task. An increased reaction time for incorrect responses compared to correct responses was reported.

Similarly, Prendergast et al. (1998) modified the DMS task in a way that their design included interference. They used a DMS task with additional interrupting stimuli introduced during the delay. In the DMS task, subjects were supposed to identify the test stimulus that matched the colour of a sample stimulus. Every trial started with a sample stimulus (luminated coloured disks). The sample would stay lit until the animal pushed the stimulus disk. Three disk flashing lights appeared during a 3 s delay on three separate locations. The distractors were flashing in alternating colours. One of the distractors was the disk at the location of the sample stimulus, and the other two matched the location of the following test stimuli. After the delay period, the distractors went off, and two locations of the test stimuli were lit in two different colours. The monkey had to identify the test stimuli that matched the colour of the sample stimulus (Prendergast et al., 1998).

Basile and Hampton (2013) were one of the first studies that applied multitasking to create interference. Their study also differed from previous studies in that they devised a dual-task with different cognitive demands and different domains. They introduced a concurrent task with different levels of cognitive demand during a delay period of the visuospatial DMS task to investigate active maintenance in the macaque. The concurrent task was designed in three levels inducing different levels of cognitive processing. The interference task required subjects 1) to touch a square or 2) to touch a picture or 3) to classify the central picture into one of the categories on the screen. The third level was also different, requiring a response from a different cognitive domain (categorization). It was hypothesized that if active cognitive control is required, then the accuracy of responses should be affected the most with the concurrent task that requires most cognitive processing (categorization). Their result showed that the response time was significantly higher for the image categorization condition compared to the other two conditions. Based on these results, the authors concluded that the most cognitively demanding concurrent task (categorization) competes for limited cognitive resources available for memory performance. However, since image classification differed from the other two conditions (touching picture and touching a square) in the task domain, a clear conclusion depends on a further investigation with controlling for task domain.

One more difference of Basile and Hampton's (2013) study with previous ones was their investigation of internal interference control by using familiar image sets vs novel image sets as the test stimuli in DMS task. Familiar images were reused stimuli from previous trials. This approach assumed that familiarity of test stimuli in the DMS task imposes higher interference than novel images. To perform correctly on the task, internal interference control is required to control the interfering effect of familiar but unrelated images. The results show that concurrent cognitive demand only affected the accuracy of performance for the familiar images. Performance was impaired for familiar images in the DMS task showing that macaques use internal cognitive control in memory.

The dual-task paradigm has been used in macaque studies that do not directly target interference control (Smith et al., 2013; Washburn & Auster, 1998). However, their design is valuable to guide research on macaque interference control. Washburn and Auster (1998) did a comparative study of rehearsal between the macaque and humans. They investigated whether rehearsal is an obligatory process in the macaque WM as it is in humans. They used a motor activity as a distractor during the delay period of DMS task. During delay intervals in the DMS task, two numbers were presented. Participants were required to move a cursor or joystick to touch one of the two numbers on the screen to move to the test phase. The response time for the motor response was hypothesized to increase in the case of active maintenance/active cognitive control. Meaning, the concurrent task performance was measured to investigate the absence or presence of rehearsal rather than interference of a secondary task in the DMS task. Although their research question did not directly target cognitive control processes, the task design inflicted interference by presenting interrupting stimuli and requiring motor movement during the delay period.

Smith et al. (2013) used a DMS dual-task paradigm only to investigate the cognitive basis of uncertain responses. The DMS task was concurrently implemented with a discrimination task providing the opportunity to explore the macaque's response in uncertain situations. The stimuli in the discrimination task were on a continuum of sparsely-densely filled boxes all in white. The macaque was supposed to touch 'S' icon on the screen identifying the presented stimulus as sparsely filled and 'D' icon to categorize it as a densely filled stimulus. Subjects also had the option to decline items by choosing an uncertainty response by choosing the '?' icon. Subjects were presented with the sample stimulus from the DMS task and during the delay period, the sparse-dense task was presented. Then, the test stimuli were presented to the animal to identify the matching stimulus. The information about the sample stimuli needed to be retained while performing on the sparse-dense task. Although their research question was not interested in interference control, their design created interference through multitasking. This task can be a potential candidate to study external control by inflicting interference throughout multitasking.

The dual-task has the advantage over other paradigms as it is a candidate to study external control. However, based on the literature, we can identify two general task demands that might influence the behavioural and neural results and need to be distinguished from interference control processes. The first factor is the task difficulty level. The dual-task paradigm requires mental effort (D'Espasito, 1995), depending on the mental processes required to perform on the concurrent task. Interaction of difficulty level of both tasks creates different levels of mental effort. In addition, depending on whether the interference is created through multitasking or interruption, the task might have different levels of cognitive demand. WM functioning is affected by task difficulty, which might contribute to the inconsistent results that prevent a unified understanding of the interference processes in WM.

The second factor is the task domain. It is still an open question whether different domains require different levels of interference control or involve distinct brain regions in the interference control processes. Task domain is essential in any paradigm. However, it is especially important in the dual-task paradigm as the mismatch of the domain in concurrent tasks across comparative studies might make a difference in mental processes. The type of processes might then contribute to the rehearsal and potential use of encoding strategies that can be varied in humans and animals (Padilla, 2019).

In order to have homologous comparative studies using the dual-task paradigm, we need to give careful attention to control variables in task design. So far, diverse literature in human dual-task makes it challenging to have a concise understanding of cognitive mechanisms and neural processes involved in different versions of this task. Therefore, using this paradigm for NHP models is especially difficult due to the diversity of general task demands in different versions of this paradigm.

1.6.2 The Recent-probe Task

Another task that measures interference control in human studies of neurodevelopmental disorders is the recent-probe task (Sternberg, 1966). The recent-probe task has a similar organization to the DMS task consisting of 3 phases: sample presentation, delay, and test. However, it is different in the number of sample and test stimuli which enables the introduction of interference. Interference is caused by presenting test stimuli that are familiar (past memory) but unrelated to the current trial. Familiar test stimuli, therefore, demand internal control.

In the resent-probe task, a trial consists of several sample stimuli. After presenting sample stimuli, a short delay is introduced, followed by a test stimulus. The participant is asked to identify whether the test stimulus matches (positive probe) or does not match (negative probe) any of the sample stimuli. A percentage of negative probes are stimuli from previous trials (recent). Negative recent probes create a sense of familiarity. Since control of unrelated but familiar responses is taxing, negative recent probes inflict an interfering effect on memory processing. Increased response time and higher error on recent compared to non-recent negative probes represent difficulty in interference control (Badre & Wagner, 2005; D'Esposito et al., 1999; Loosli et al., 2014).

The recent-probe task has been used to investigate the neural mechanisms of interference control in the WM context. PFC neural activity is shown to be higher for the test phase of trials with negative recent probes compared to negative non-recent probes. D'Esposito et al. (1999) investigated neural correlates of the sample, delay, and test stimuli presentation in a verbal probe task using event-related functional MRI (fMRI). A more significant fMRI signal within the inferior frontal gyrus (IFG) was observed for negative recent probes only in test stimuli presentations. Studies of left IFG damage also present evidence for the role of this region in inhibitory control of interfering information (Burgess & Braver, 2010; Hamilton & Martin, 2005; Thompson-Schill et al., 2002). In addition, negative recent probes have been associated with increased activation of the left mid-ventrolateral PFC and bilateral frontopolar cortex (Badre & Wagner, 2005).

The activity of brain regions in relation to types of interference control was studied by Burgess & Braver (2010) using a recent-probe task. They studied a specific classification of the interference control, involving proactive vs. reactive interference control. Proactive control occurs as a preventive tool when the presence of unrelated stimuli is predicted, and prevents any interference so that the attentional system maintains the goal-related representations active in WM. On the opposite, reactive interference control refers to the cognitive control processes that become involved after the onset of interfering information. This occurs when the interfering information is less predicted, and cognitive control mechanisms get involved after detection of interference (Braver et al., 2007).

In this study, proactive and reactive interference control both relied on internal control. Their task relied on the expectation of interference as a determinant of the type of interference control (proactive vs. reactive). Reactive interference was assumed to be activated when unrelated information is infrequent. Thus, a low expectancy (LE) condition containing 20% negative recent probes was designed as the reactive interference condition. While high expectancy (HE) blocks with 80% of negative recent probes were designed as a proactive interference condition. During the HE condition versus LE condition, greater activity was found in dlPFC, IFG, right lateral parietal regions, and pre-supplementary motor area (pre-SMA). An overlapping analysis to investigate regions that show activity for both expectancy conditions showed a region in the right medial frontal gyrus (pre-SMA)) as the region activated for both forms of interference control. However, no such overlapping activity was observed in IFG.

The recent-probe task has been used to test the domain generality hypothesis for PFC activity. Badre and Wagner (2005) investigated the neural activity of PFC neurons in a visuospatial (pattern) and verbal version of the recent-probe task. However, no conclusion could be drawn due to the low accuracy of their results in the visuospatial task.

Neurobiological investigation of interference control using the resent-probe task showed activity of IFG as well as bilateral PFC neurons in internal control. While the activity of PFC neurons has been reported in dual-task studies, IFG activity is reported explicitly in studies using the recent-probe task. Further investigation is needed to understand the role of IFG activity in interference control distinct from task demands.

The overlap of neural activities involved in internal proactive and internal reactive interference control is also a research question that needs further investigation. Proactive interference control is referred to as internal control. The use of familiarity to introduce interference is a common way to investigate both internal and proactive interference control. Drawing a clear distinction between proactive interference control and internal control depends on further investigations. Generally, a recent probe task is a candidate to study internal interference control separate from external interference control. Compared to the dual-task paradigm, recent-probe task versions are less diverse regarding task domain and task difficulty due to the absence of secondary tasks.

1.6.3 The N-back Paradigm

The n-back task is a well-established WM task frequently used in neuroimaging research. Human research has benefited from the n-back paradigm to measure inference control (Dudchenko et al., 2013; Schleepen & Jonkman, 2009). This task was applied to investigate WM in ADHD (Marx et al., 2011) and ASD (Barendse et al., 2018; Braden et al., 2017; Yuk et al., 2020). The n-back task has also been used to train individuals with ADHD to address cognitive and inhibitory issues associated with ADHD (Dotare et al., 2020; Jones et al., 2020).

In a classical n-back task, participants are required to remember a certain number of most recent stimuli presented in a serial order. Participants are instructed to identify whether the presented stimulus matches the stimulus presented ‘n’ trials previously- with ‘n’ representing the number. Performance on the n-back task relies on updating the content of WM. With the presentation of every new item, constant modification of WM content (n) becomes necessary. Updating causes interference because of the constant modification of content, making it difficult to bind information in working memory.

Like the recent-probe task, the n-back paradigm involves internal control. In other words, these tasks represent the conflict between recollection and familiarity, two processes elaborate in recognition memory. Familiarity is an automatic response that relies on the identity of stimuli. However, recollection is a deliberate and effortful process slower than familiarity, related to positional information about a stimulus presented previously (Szmalec et al., 2011). The competition between familiarity and recollection creates internal interference during updating of WM information (Oberauer, 2005). This conflict needs resolution by prioritizing recollection over familiarity. Successful performance relies on recognizing whether the familiar item is in the ‘n’ position or has been encountered in a different position (Szmalec et al., 2011).

A meta-analysis of 24 studies of the n-back paradigm shows robust activity of dorsolateral and ventrolateral PFC, medial and lateral posterior parietal cortex, and dorsal cingulate cortex in relation to performance in the n-back paradigm. The variability of the n-back versions is in the module of the task (e.g., phonological, visual, spatial). However, the broad activation of frontal and parietal cortical regions is shown regardless of the task module (Owen et al., 2005).

One advantage of the n-back task as a measure of internal interference control compared to the recent-probe task is the rich literature showing the same neural substrates involved in the n-back task performance regardless of the task module. The use of the n-back task is also advantageous compared to the dual-task paradigm as it is cognitively less demanding. Regarding difficulty level and task module as variables that require attention in choosing the task, the n-back task is a candidate for comparative studies of internal interference control.

1.6.3.1 NHP Studies of the N-back Paradigm

Most NHP interference control studies use a modified version of the DMS task to measure interference control. Besides a considerable body of literature that used the DMS task in the context of the dual-task paradigm, the DMS has also been used in the context of the n-back paradigm to investigate interference control (Miler et al., 1996).

Miller et al. (1996) used a DMS task for studying PFC cells in the macaque. Each trial started with a sample stimulus, followed by a delay period. After the delay, a set of 1-5 test stimuli was presented as intervening stimuli. The stimuli differed from the sample stimulus except one that matched the sample. The subject was supposed to release a lever held throughout the trial as soon as the matching stimulus was presented. Based on Prefrontal (PF) cell activity during the test phase of the DMS task, their results show that PF cells convey information on whether a stimulus matches the sample stimuli.

Although Miler and colleagues (1996) referred to the task as a DMS, the design of the task is similar in structure to the n-back paradigm necessitating interference control. The animal needs to update WM content after the presentation of every new test stimuli. In this case, it is essential to control for the interference of any familiar but unrelated stimuli that were presented between the sample stimulus and the target test stimulus or any stimuli presented in previous trials.

Besides the DMS task developed in the context of the n-back paradigm, one of the tasks that resembled the n-back paradigm is the Hamilton search task. It was developed to study spatial learning and memory in monkeys and other non-human animals (Hamilton, 1911). It resembles an n-back task in that it requires updating. The task requires the subject to find the reward by choosing among a group of options. To do that, the animal needs to remember previously searched options. Therefore, upon each search, it needs to refresh the content of WM to keep track of previous searches.

1.6.3.2 Rodent Studies of the N-back Paradigm

Despite scarcity of the n-back studies with NHP, interference control tasks that have been developed for use with rodents are based on the n-back paradigm. The general structure of the tasks is that the subjects are presented with a sequence of stimuli and asked to identify when the current stimulus has been previously encountered (Dudchenko et al., 2012). These tasks are designed to require monitoring and updating of information and rely on familiarity to impose interference.

An operant version of the n-back paradigm was developed by Ko and Evenden (2009). This task was a translation of the n-back task used to measure WM impairment in schizophrenic patients. It required 1-back and 2-back memory. Every trial consisted of 2 parts. A sequence part and a recall part. A trial started with presenting a sequence of 5 levers individually. The rats were required to press the lever and to poke their nose for the next lever to be presented. In the recall part of each trial, all levers were presented simultaneously. In the 1-back group, rats were required to identify the lever that was last pressed in the sequence phase. While in 2-back group, rats needed to identify the 4th pressed lever in the sequence phase in order to receive the reward. In this task the 4 samples that are not in the target temporal position, cause interference because of familiarity. Therefore, the animal needs to apply recollection memory and to overwrite familiarity interference with deliberate effort of remembering the temporal order of stimuli.

The continuous temporal relational memory test is another task relying on object recognition developed for rodents (Dudchenko et al., 2012; Jackson-Smith et al., 1993;

Kesner et al., 2001;). A specific sequence of several mazes/objects are presented. The subject receives the reward by picking the object or reaching the end of the maze. Some of the objects/mazes are presented more than once within a sequence; however, object/maze can only be rewarding once. The number of stimuli between the first presentation of a stimulus and its repetition is called lag. The number of lags represent n in the n-back task. The latency for checking the novel rewarding maze/object versus repeated ones is the measure of WM in this design. Studies show that the response time for repeated mazes/objects are higher for shorter lags rather than longer lags (Dudchenko et al, 2012). WM updating in the continuous temporal relational memory test profoundly resembles updating processes in the n-back task due to continuity of item presentation. This task relies on the interfering effect of familiarity. The animal performs correctly only if recollection wins over familiarity of presented mazes or objects that have been repeated before but are not in the temporal position of item n.

Another task used to measure interference control in rodents is the discrete temporal relational memory test. This task assesses temporal discriminability of presented stimuli (Chiba et al., 1997; DeVito & Eichenbaum., 2011; Dudchenko, 2012). The reward is presented in different locations/mazes in a specific sequence. Then, at the test stage, two of previously presented locations/mazes are shown simultaneously, and the animal is reinforced for choosing the stimulus that was first presented in the sequence. The percentage of correct trials represent the degree to which the rodent can remember and control the interfering effect of unrelated visits between two of the test locations or those presented in previous trials. Their results show that unlike the continuous test, objects that were separated by more interfering objects/mazes were more recognizable than those which were presented temporally closer to each other.

The difference of results in the discrete and continuous temporal relational tests show that these tasks potentially engage separate memory and the interference control processes. In this case temporal discriminability versus within trial object recognition involve different memory processes (Dudchenko, 2012).

Generally, various types of interference control based on the n-back paradigm for use with rodents suggest that the n-back has a difficulty level suitable for use with these species. Therefore, the n-back task is an interference control task requiring a low cognitive load due to general task demands. Relevant to this project, we have limited understanding of the marmoset's ability to perform in tasks with different cognitive demands. Starting from the low level of cognitive load, the rodent literature suggests the n-back task as a suitable candidate.

1.7 Interference Control in the Common Marmoset

There is a relatively rich body of research using different paradigms to measure spatial and visuospatial WM in apes, monkeys, rodents, and human infants and adults. However, the literature on marmoset WM is comparatively small because the marmoset is a relatively new model for studying WM. Therefore, only a few WM paradigms have been adapted for use with the marmoset. Given that marmosets rely on their spatial WM for foraging, most studies have focused on studying spatial working memory in this species (MacDonald et al., 1994; Spinelli et al., 2004).

A group of WM studies in the marmoset usually approach it with the usual definition in non-human animal studies and benefit from the DMS task and Delayed Match to Position (DMP) task, a spatial version of the DMS. There is evidence on the ability of the marmoset to perform the DMP (Sadoun et al., 2018; Yamazaki et al., 2016). However, conflicting findings on the ability of the marmoset to perform on the classic version of the DMS task (Nakamura et al., 2018; Ridley & Murray, 1988) suggest the necessity of further investigation of marmoset visuospatial short-term memory.

One of the studies of working memory in marmosets was a validation study using the NHP CANTAB test of WM. Spinelli et al. (2004) tried a concurrent DMS (CDMS) task to study marmoset WM performance. Their task consisted of two sample stimuli that were different in shape and colour. For each sample, two test stimuli were presented that were alike with the sample in shape and colour, but one of the stimuli differed in location. One sample was presented on one corner of the screen in each trial, followed by a .1s delay. Then, the second sample was presented on another corner of the screen, followed by a longer delay of .5s. Afterwards, the two sets of test stimuli for the first or second sample were presented on the screen. The order of test stimuli was randomly selected for every trial. The correct response for each pair of test stimuli was the one that matched the location of the sample stimulus. Their results showed that marmosets could perform significantly above the chance level in the CDMS task.

One could argue that concurrent stimuli in the DMS impose an interference control resemblance of multitasking in the dual-task paradigm with one difference: in the CDMS task the primary stimuli and the secondary task share the same domain. Results from Spinelli et al. (2004) suggest the ability of the marmoset to perform on a task that requires cognitive control.

Another task used to study WM in the marmoset is the self-ordered sequencing task (SOST)\. The classical version of the SOST presents several identical stimuli on different locations on the screen and requires the subject to select each stimulus only once. Depending on the number of stimuli, this task engages varying degrees of WM, interference control, response inhibition, and response planning (Collins et al., 1998).

Collins et al. (1998) developed spatial SOST for the marmoset. Their training started with the simple task version that consisted of one stimulus in each trial based on an eight-location grid. The task requirement was to touch the stimulus on the screen. After proficiency on this version, the number of stimuli on the screen was gradually increased. In each training trial with more than one stimulus, the subject was required to touch each stimulus once in a self-determined order to receive the reward. Any correct response was associated with a sound and change of colour for that stimulus. However, the reward was delivered only after successfully completing a sequence. Any mistake resulted in the immature termination of a block. Upon performance improvement, the difficulty level was gradually increased by adding the number of stimuli. The baseline performance of the subjects showed the ability to perform up to five stimuli in this task and become proficient within 12 months. However, it was observed that performance on the task decreased by increasing the difficulty level.

Walker et al. (2009) adapted the same experimental design as Collins et al. (1998). First, they started training by presenting one stimulus in each trial. Once the monkey could respond to the stimulus on all eight locations on the screen, trials with two stimuli were presented. In each sequence, as soon as the monkey selected any of the presented stimuli, that stimulus changed colour, a tone associated with the correct response was played, and both stimuli vanished from the screen for 0.5s. After the vanish time, both stimuli reappeared on the screen. If the subject chose the previous stimuli, the sequence terminated prematurely, the house light went off, the screen went blank, and a sound was played associated with the incorrect response. If the monkey selected the other stimulus, the colour of both stimuli changed, and the tone was played associated with the correct response. Simultaneously, the reward was delivered. When performance improved, trials with three stimuli were introduced. Unlike Collin et al. (1998) that trained the monkeys until they got proficient at performing on the five-stimuli version, this experiment stopped training after proficiency of the subjects in trials with three-stimuli.

Axelsson et al. (2021) used a modified version of the task used by Collins et al. (1998) and Walkers et al. (2009). They removed the possibility of selecting one stimulus twice consecutively (perseverative errors). After each selection, only the selected stimulus vanished for a set amount of time. During vanish time, subjects could continue selecting the other stimuli. The vanish time decreased, and the number of stimuli increased as the animal proficiently performed on the task. However, this experiment stopped training once subjects reached proficiency in trials with three-stimuli.

Studies using SOST provide evidence on the ability of the marmoset to perform on a task that requires internal interference control. SOST resembles the n-back paradigm and the Hamilton search task in its requirement for updating. All three tasks require continuous updating of WM content. In the n-back task, the subject needs to change the content of WM after the presentation of any new stimulus. The subject needs to overwrite the interference caused by the familiarity of stimuli from previous and current trials that are not the target anymore (do not match the nth serial position). Similarly, the Hamilton task and SOST require the subject to update the content of WM after each response. That is to keep track of selected stimuli to prevent visiting them twice.

The abovementioned studies using the SOST and CDMS task show the ability of the marmoset to prevent interference during updating processes. However, using these tasks in developmental WM studies requires specific consideration. The duration of the training must match the time window for the developmental stages of the marmoset. For instance, a task that requires one year of training is not applicable for use in developmental studies of WM as the training time exceeds the developmental stages of the marmoset.

1.8 Current Study

The marmoset is a promising model for neurodevelopmental studies of WM disorders. The translation of findings in comparative studies in WM investigation requires compatible tools. Optimizing human tasks of WM to be applicable for use with the marmoset is a solution to make findings between human and neurodevelopmental studies of WM in the marmoset translatable. To pursue this goal, we need to have tasks of WM suitable for the marmoset and its developmental trajectory that are also compatible with those used in human research.

Interference control plays an essential role in WM functioning. Interference control has been studied in humans and NHP using various paradigms (Schleepen & Jonkman, 2009; Villemonteix et al., 2017). The dual-task, recent-probe task, and n-back paradigms are common tools to measure interference control in humans. Non-human animal studies of WM have applied one of these paradigms that best matches their research question regarding specific aspects of WM and the level of cognitive ability for the target species.

Our understanding of the marmoset interference control is limited, and few studies have utilized WM paradigms with the marmoset. However, the ability of the marmoset to perform on tasks that require interference control has been shown in studies using SOST, which requires updating and resembles the n-back paradigm. Although SOST is an effective tool to study internal interference control in the context of WM, the training period for the touch-screen version of this task has been reported to take about 12 months (Collins et al., 1998) which exceeds the time limits for conducting developmental studies with the marmoset.

Adolescence is a critical developmental period associated with extensive changes in all areas, including cognitive control. It is flagged by puberty, characterized as the time of sexual development and maturity. The adolescent period for the marmoset monkey is only 14-15 months (mean age for onset of puberty: 6-7 months, the mean age for sexual maturity: 21 months; Abbot et al., 2003). Due to short developmental stages in the marmoset, developmental studies using the marmoset are limited to a short training period.

This project was to provide a solution to limit the training period of SOST for the marmoset monkey. The goal was to make training procedures faster and easier to administer for younger marmosets. And one step in that direction was to develop a version of the SOST that is close to the type of problems that the marmoset was evolved to solve. Foraging is one of the contexts in which learning and memory have been adapted. Optimal foraging theories portray the environment as rich in information that the forager needs to make decisions. Therefore, how marmosets learn from the environment to guide their behaviour developed in the context of foraging. Investigating goal-directed behaviour and memory in the context of foraging gives information on the way species learn and perform (Kamil & Yoerg, 1982). In addition, training the animals on a task in an environment close to the natural environment may accelerate training on WM tasks.

In summary, this project developed a SOST for the marmoset that resembled the n-back paradigm. It allowed for insight from research on WM in neurodevelopmental disorders to be more readily translated from the marmoset to the human. Consequently, translational studies in the marmoset may complement studies using rodentds. To accelerate training procedure, the SOST task was devised to enable us to exploit natural foraging behaviour in the marmoset monkey.

1.8.1 The Foraging SOST design

The SOST task developed as part of this thesis involved four different locations. Locations were located on two levels of a panel. The task was developed into blocks that required a sequence of responses. Every block was a unique random grouping of three rewarding locations and one unrewarding location. The task required visiting only rewarding locations, and each rewarding location could be harvested only once. All responses were self-paced. The subject chose the serial order of visits in every block. Updating the memory of visits in each block was crucial for performance. After each visit, the animal had to update the content of WM to distinguish visited locations from those left to visit.

The grouping of three rewarding locations randomly without replacement out of four possible locations allowed having unique groups of rewarding locations in each block that was different from previous ones. Therefore, it forced the marmoset to keep information in WM to plan its behaviour accordingly. The subject could not rely on long-term memory because grouping three locations prevented response planning based on the information recall from long-term memory.

This task required interference control as the subject had to control the interfering effect of previously visited locations to guide its action throughout the block. The correct performance throughout the block indicated the use of interference control. It showed that the marmoset remembers the previously harvested locations and guides its action by controlling the interfering effect of familiar but irrelevant information.

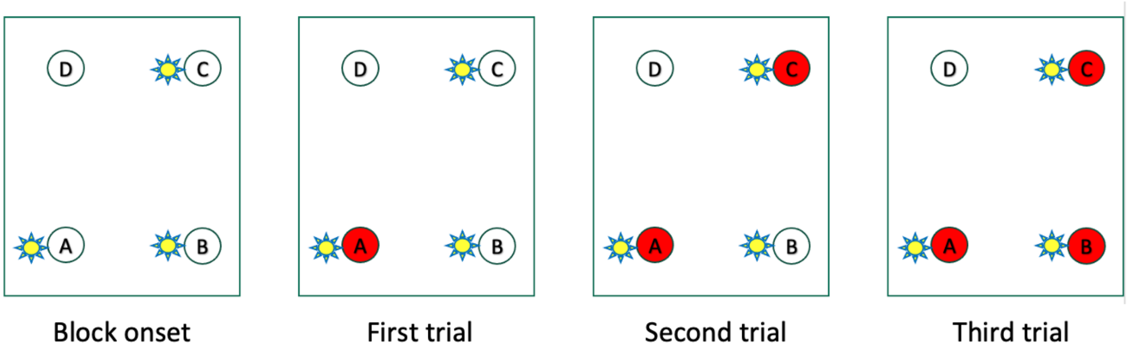

Figure 1. Schematic diagram of correct performance on a block of foraging SOST. By block onset, three locations started blinking. Blinking locations were rewarding only once, but they kept blinking until the end of the block. In the first trial, the animal had three rewarding options. Assuming the animal visited location A, the reward was delivered, and this location remained unrewarding for the rest of the block. In the second trial, two rewarding locations were left: B and C. The subject had to remember the previous location and avoid it. If the animal chose one of the

unvisited locations, the animal received the reward. In the Third trial, only one out of three blinking locations was left rewarding. Therefore, the animal had to remember two previously visited locations and visit the unvisited location. In this figure, B is the only rewarding location left in the third trial.

Chapter 2

2 Methods

2.1 Subject

One adult female marmoset aged six years were used in this experiment. The subject's body weight was 350 grams and was maintained throughout the training period. The marmoset was reared in the marmoset colony room in West Valley Animal Care Facility at Western University. Marmosets were kept in large family groups housed in cages measuring 204 cm x 73 cm x 94 cm. The relative humidity of the colony room was 30%-70%, and temperatures approximately 24 C°, +/-3 were maintained. The behavioural testing was conducted in a separate experimental room. The marmoset had no visual, olfactory, or auditory contact with other marmosets during the experiment. This experiment was approved by the Western University Animal Care and Use Committee (protocol number: 2016-055).

Marmosets were provided with environmental enrichments daily except for the weekend. A regular diurnal lightning cycle was provided. The room was cleaned by hosing down with lukewarm water and removing debris daily. Water was available at the libitum. Water quality was routinely monitored to ensure that it was free of chemical or infectious contaminants. Other food items were available during the day. Nutritional mixtures (e.g., boiled egg, shredded chicken, fruits, cereals, and nuts) were provided according to a weekly menu twice daily. Additionally, enrichments (e.g., apple gum and saps) were provided for the marmosets daily during weekdays. Food leftovers were removed daily.

For a previous project, the marmoset had been implanted with 32ch microwire arrays in the hippocampus to record single-unit neural activity. In the previous experiment, the subject was trained on the foraging task (discussed in the training section) to associate the reward with blinking lights. Subsequently, the subject received training on a spatial memory task. In the spatial memory task, the animal has been trained to receive the reward from specific locations signified by visual cues. After a few trials, the visual cue was removed, and the animal was required to visit rewarding locations in the absence of visual cue sequentially. The rewarding locations changed every session. By the start of this project, two months have passed from the end of the previous project.

2.2 Procedure

The experiment was conducted four days per week, usually between 9:00–11:00 a.m. in the experiment room. Data collection was conducted in one session per day. Every session of data collection lasted approximately 90 minutes. For each data collection session, the marmoset was transferred with a plexiglass box from the colony to the experiment room. The experiment room was divided into two sections: entrance and main experiment room. The entrance had a bench for placing the primate chair. Upon transferring the subject to the experiment room, the subject was chair restrained to place the cap with reflective markers on her head. Then, the marmoset was transferred from the chair to the apparatus by hand. The apparatus was placed inside the main experiment room. As soon as the subject entered the apparatus, the task started. The main experiment room had a dim light and relative humidity of 30%-70%. The marmoset was kept for up to 60 minutes per session in the experiment room.

The current experiment started around 9:00 a.m. Based on the morning schedule, all animals in the colony were fed at 7:30 a.m. with high on protein palatable food. Following the feeding schedule meant the animal could have access to food for 1.5 hours before the experiment. Therefore, if the animal received food at 7:30 a.m., there was a high chance that the subject would express no interest in receiving the reward and engaging in the tasks. To eliminate the chance of disengagement in the task, the animal was deprived of palatable morning food prior to the session. The food was available to the marmoset after the experiment session. To ensure the subject’s balance in diet and to prevent sugar saturation, one study session could only continue until a maximum of 170 times delivery of the reward. Despite the possible interest of the subject to continue, after delivery of the reward 180 times during one session of data collection, the session terminated.

2.3 Apparatus

A plexiglass 3D maze with three vertical levels (60 cm x 120 cm x 120 cm) was used as the experimental environment (Figure 2). The apparatus was in the main experiment room. All sides of the room were covered by black curtains that blocked visual contact with the experimenter.

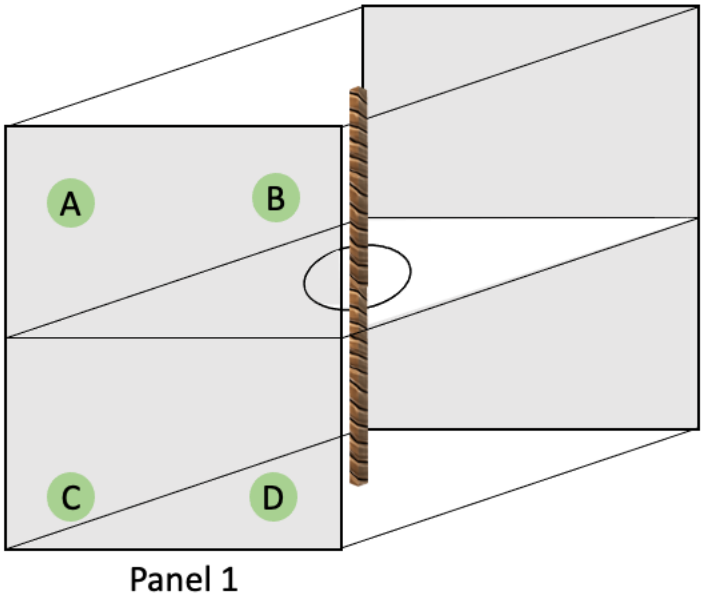

Figure 2. A schematic diagram of the apparatus. The apparatus had two levels connected via a hole at the center of the second floor. A rope passed through the hole and connected the top and bottom of the apparatus. The subject could climb the rope and move between the levels. Two rewarding locations were positioned on each level. Green circles show possible reward locations.

Reflective markers on top of skull PEEK implants allowed for six degrees of freedom camera tracking at 60 Hz. A total of 13 motion capture cameras were installed at different places in the room to cover every angle of the apparatus. Motion capture cameras allowed marker-based 3D tracking of the animal's body position and head orientation. The data was streamed from cameras to monkey logic. The animal learned to approach reward fields cued via LED lights to earn a liquid reward (mixture of 70% condensed milk and

30% apple gum fluid). As soon as the marmoset got close to a rewarding location, monkey logic received the data about the subject's location from motion capture cameras; and signalled the solenoid at the target location to release the reward. The reward was delivered through a sipper tube placed on reward locations.

2.4 Pre-Task Training

2.4.1 The Foraging Task

A Foraging task was the first step in the training procedure. Foraging training aimed to establish the association of the visual cue and reward. The subject was trained on a foraging task in a previous experiment. However, two months of delay have been introduced between the previous experiment and this experiment. Therefore, it was necessary to retrain the animal and observe performance to ensure the establishment of reward and visual cue association.

In the foraging task, the reward was presented equally and randomly at one of four possible locations on one panel of the apparatus. In each block, one location was blinking. The blinking light represented the presence of reward at that location. If the marmoset approached any other location, a load noise would be played associated with an incorrect response. The rewarding location kept blinking until the marmoset harvested the reward. Correct responses elicited a pleasant sound. Upon visiting the blinking location, the reward was delivered for .15s. Simultaneous to delivery of the reward, the light for that location went off, and the next trial started immediately. Every new trial was signified with a new blinking location. The blinking location in each trial was randomly selected without replacement. A latency of two minutes in response in any given trial resulted in the termination of the trial and a new one started. Two consecutive blocks with no response resulted in the termination of that data collection session. Blocks that were terminated without any response were deleted from the analysis.

Accuracy. The accuracy of response in each trial was the behavioural measure in the foraging task. Performance on a trial could be correct or incorrect. The mean average of performance accuracy was then calculated for each trial with a window of 15 trials. The mean average was to investigate the below or above-average performance and possible learning trends across training. The chance of correct performance over each trial was calculated. Since one location out of four was blinking, the chance of correct performance in each trial was .25.

2.4.2 The Subtask

After training on the foraging task, the subject was trained on the subtask. This level of training was devised based on the common shaping method (Skinner,1938). The Shaping method involves decomposing a complex task into subtasks to ease the learning procedure. The subtask was designed to ease the learning of the foraging SOST. It was a variant of foraging SOST with lower difficulty. Every block in the subtask contained two blinking locations, while the foraging SOST consisted of three blinking locations in each block.

Having blocks with two blinking locations imposed less difficulty in working memory, inhibitory control, and organized planning. Every block of the subtask started with both locations blinking. Locations kept blinking until the end of the block. Every blinking location was rewarding once. The first reward in each block was delivered for .15 s, while the second reward was delivered for .2 s. The larger reward size for the second response was to increase motivation to engage in the task (Minamimoto et al., 2008). Completion of a block required two correct trials. The block would only end if both rewarding locations were harvested. The animal could make any number of mistakes by visiting the unblinking locations and/or revisiting blinking locations over a block. Mistakes were accompanied by a loud noise. After completing a block, a 5s interval was introduced, followed by a new block. The combination of blinking locations in each block was randomly selected without replacement. A data collection session was terminated if the subject did not engage in two consecutive blocks. Any two-minute delay in response during data collection ended the block prematurely.

Accuracy. Correct performance over a block was the measure of accuracy. The performance in each block was categorized as correct or incorrect. A correct performance required visiting each of the blinking locations and making no mistake (either revisiting blinking locations or visiting unblinking locations). The chance of the first correct response in each block was .5 since there were two rewarding locations out of four locations. The chance of a second correct response was .25 because only 1one location out of four was rewarding. The chance level for correct performance in each trial was multiplied to calculate the chance level for performance on a block of the subtask, which was .125.

2.5 The Foraging SOST

After training on the subtask, the foraging SOST was administered in which each trial consisted of three blinking locations. A combination of blinking locations was randomly selected without replacement. Blinking locations kept blinking until the end of the block. Blinking locations were rewarding only once. Completion of a block required visiting all blinking locations. Any first visit to any blinking locations was accompanied by a reward associated with a sound. The first reward in each block was delivered for .15 s, the second for .2 s and delivery of the third one lasted for .25 s. Any visit to an unblinking location or revisiting blinking ones was an incorrect response accompanied by different noise. If any trial in the block lasted longer than two minutes and the animal did not engage with the task during that time, the block ended, and another one started. A 5s delay was introduced between blocks, followed by a new block. Any two consecutive blocks with more than two minutes delay in response terminated a data collection session.

Accuracy. Correct performance over a block was the measure of accuracy. A correct block had only three correct trials without any mistake. The chance of the first correct response was .75 because three locations out of four were rewarding. Only two rewarding options were left for the second correct response, and the chance of correct response was .5. The chance of the third correct response was .25 since only one rewarding option was left out of four possible locations. The chance level of performance for a block in the foraging SOST was .093, resulting from multiplying the chance level of performance on each trial in one block.

Rule acquisition. Poor performance over the foraging SOST could result from difficulty in understanding the task rules. It was necessary to investigate the success of training in establishing the task rules. One of the first rules for this task was that the unblinking location is never rewarding. The number of visits to the unblinking locations was calculated as a measure of rule acquisition. A significant decrease in the number of visits to the unblinking location was a measure of success in training the animal to understand the first rule of the task.

2.6 Post-Task Training

2.6.1 Modifications of the Task and Apparatus

By observing task performance, the downfalls of the task design came to light. Below chance performance on the foraging SOST (Figure 7) motivated adaptation of training procedure to establish the prerequisites for performance on the foraging SOST. Poor performance accuracy could be related to two factors: first, difficulty in understanding the first rule of the task that unblinking locations are always unrewarding. Application of light and reward association was one of the prerequisites for correct performance on the task. Difficulty in understanding this association could be a reason for poor performance. Second, poor performance accuracy could be due to the inability to plan responses in each block. To perform on each block correctly, the marmoset needed to understand the distinction of blocks and plan its action according to the specific grouping of three rewarding locations. The animal could then visit blinking locations while keeping track of the harvested ones. It was observed that the subject did not wait for the delay time to pass and kept checking locations during the delay period. This behaviour could be because of the unclear distinction of blocks.

The abovementioned possibilities for poor performance that were unrelated to the subject’s WM ability proposed the necessity of further training. The extra training was to address two goals:

1. To establish the association of reward and light within the task.
2. To establish the distinction of blocks from each other.

By considering the structure and characteristics of the apparatus, we needed to tackle these goals for which the following solutions were implemented.

1. Applying visual cues representing the presence of reward. Performance On the foraging task and the subtask showed that the association of light and reward was followed. However, the subject did not apply this association during the foraging SOST. It was necessary to train the animal on the association of light and reward in the foraging SOST. Applying visual cues was a solution. Turning off the

blinking light as soon as the reward was delivered was a visual cue to establish the association of light and reward within the task. We devised two levels of training based on the shaping method to train the subject on the association of light and reward in blocks with two and three blinking locations.

2. Use of two panels of locations. Previously, the task was implemented on one panel of the apparatus, and there were four locations. Since all blocks were running on one panel, it was possible that the subject could not differentiate the offset of one block from the start of the next one. The difficulty in differentiating blocks could lead to difficulty planning appropriate responses for each block. The use of a second panel was a solution to signify the onset of new blocks. Introducing the second panel of four locations enabled us to alternate blocks between two panels. After each block, the subject needed to move to the far side of the apparatus to perform on the new block. A schematic figure of the apparatus with two panels is shown (Figure 3).

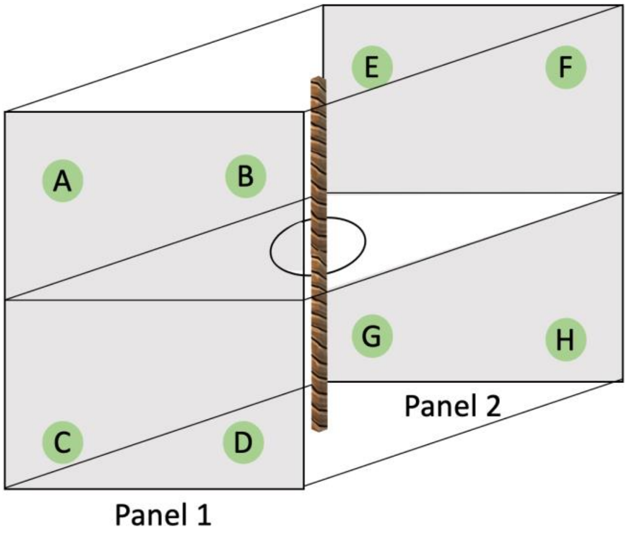

Figure 3. A schematic diagram of the apparatus after modifications. A second panel was adapted facing the first panel. A total of eight locations, four on each panel, are identified with green circles. Blocks of the task were alternated between two panels so that no consecutive blocks were administered on the same panel.

2.6.2 First Level of Training

The first level of training was a combination of two blinking locations in each block. Every block started with two locations blinking on one panel. Any blinking location went off as soon as it was visited. The completion of a block took two correct responses, visitations of the two blinking locations. Any visit to unblinking locations was an incorrect response. Any two minutes delay in response resulted in the termination of the block. The session ended if the subject did not engage in the task for two consecutive blocks. No two consecutive blocks were implemented on one panel. Blocks were alternated between two panels. The new one started on the opposite panel as soon as one block ended.

Accuracy. Correct performance over a block was the measure of accuracy following the association of light and reward. Any block with one or more incorrect trials was considered an incorrect block. A correct block consisted of only two correct trials. The mean average for performance accuracy over each block was calculated (window of 15 blocks). In the first trial of each block, two locations out of eight locations were rewarding. After the first correct visit, only one of eight locations was rewarding. The multiplying chance level for each trial in a block was .031, the chance level for correct completion of a block in the first level of training.

Panel perseveration. To investigate whether the animal has difficulty to differentiate blocks, the number of visits to locations on inactive panel (panel mistakes) during each block was calculated. Panel mistakes were the behavioural measure to understand whether the subject improved to understand the distinction of blocks throughout training.

2.6.3 Second Level of Training

In the second level of training, blocks started with three blinking locations. As soon as the subject harvested any of the blinking locations, the light for that location went off. Therefore, after the first correct trial in each block, only two locations were blinking. Consequently, after the second correct trial, only one unvisited rewarding location was left, which was the only blinking location. Correct completion of a block in this level of training would take three correct responses without any mistakes. The subject could make any number of mistakes by visiting the unblinking locations. Blocks alternated between panels. The next block was played on the opposite panel when one block was implemented on one panel. The onset of a new block was immediately after the offset of the previous block. Any delay longer than two minutes terminated the block, and a new block started on the opposite panel. Disengagement of the subject in the task for two consecutive blocks terminated the session.

Accuracy. Block-level accuracy was calculated as the measure of the establishment of light and reward association. The mean average of accuracy for each block was then calculated with a window of 15 blocks. The subject failed a block upon visiting unblinking locations. Three out of eight locations were possible correct responses for the first trial. Thus, the chance of correct response was .375. After the first visit, there were only two rewarding options left. The chance for the second visit was .25. The chance of correct response for the last visit was .125 because only one rewarding option was left. The chance of correct performance over a block for the second level of training was .011, resulting from multiplying the chance of correct performance on each trial of the block.

Panel perseveration. We needed to investigate the subject's ability to differentiate blocks from each other. The number of panel mistakes over each block during the second level of training was calculated to investigate the learning of the block entity.

Chapter 3

3 Preliminary Results

3.1 Foraging Task

All data were analyzed using custom code in MATLAB (version R2019b). Three sessions of data on the foraging task were recorded. The chance level for this task was .25 as, in each trial, one location out of four was the correct response. The marmoset was considered to have completed foraging task training if it achieved an arbitrary response rate of 100% for 50 consecutive trials.

Figure 4 represents the learning curve for the foraging task. The graph illustrates the moving average from 15 trials. Moving average as the measure of response accuracy was above chance level for 98.8% of trials. The marmoset showed above threshold performance during the second session of training. A pattern of decrease in performance was observed towards the end of each session; decreased performance at the end of each session can be explained by the low motivation to receive the reward. As the animal received cumulative reward during the session, its motivation to receive more reward could decrease (Minamimoto et al., 2008).

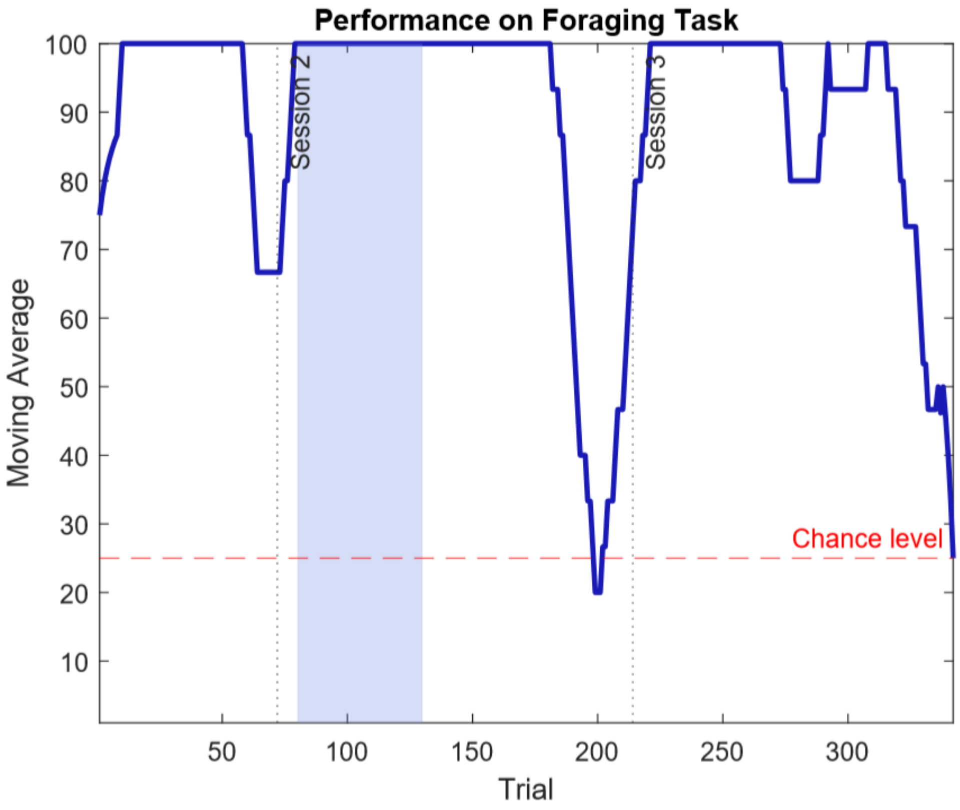

Figure 4. Moving average of performance in the foraging task (moving window of 15 trials); red dashed line represents chance level; gray dotted lines indicate the start of training sessions; highlighted section identifies the above threshold performance; above chance performance for 98.8% of trials was observed.

3.2 The Subtask

Above threshold performance in the foraging task was sufficient to move to the subtask training. Two data sessions were collected, and performance on the subtask was evaluated across 105 blocks (300 trials). Each correct block had two correct trials, while any incorrect block had at least one incorrect trial. The subtask was considered complete if the subject achieved 100% correct performance in five consecutive blocks.

Figure 5 represents the moving average of performance from 15 blocks for the subtask training. The figure shows that the above-chance performance is consistent after 20 blocks of training. The five consecutive correct blocks pattern was repeated three times throughout the training. The first set of five consecutive correct blocks on the continuum of training blocks is shown as the highlighted section in Figure 5. Figure 6 shows the above-chance performance for each training session.

The consistency in the above-chance accuracy of performance confirms that the animal understood the need to: 1) only approach blinking locations; and 2) only approach the unharvested blinking location after the first harvest to receive the reward. The results indicate the success of training to establish task rules in the subtask, which motivated increasing task difficulty and moving to the foraging SOST.

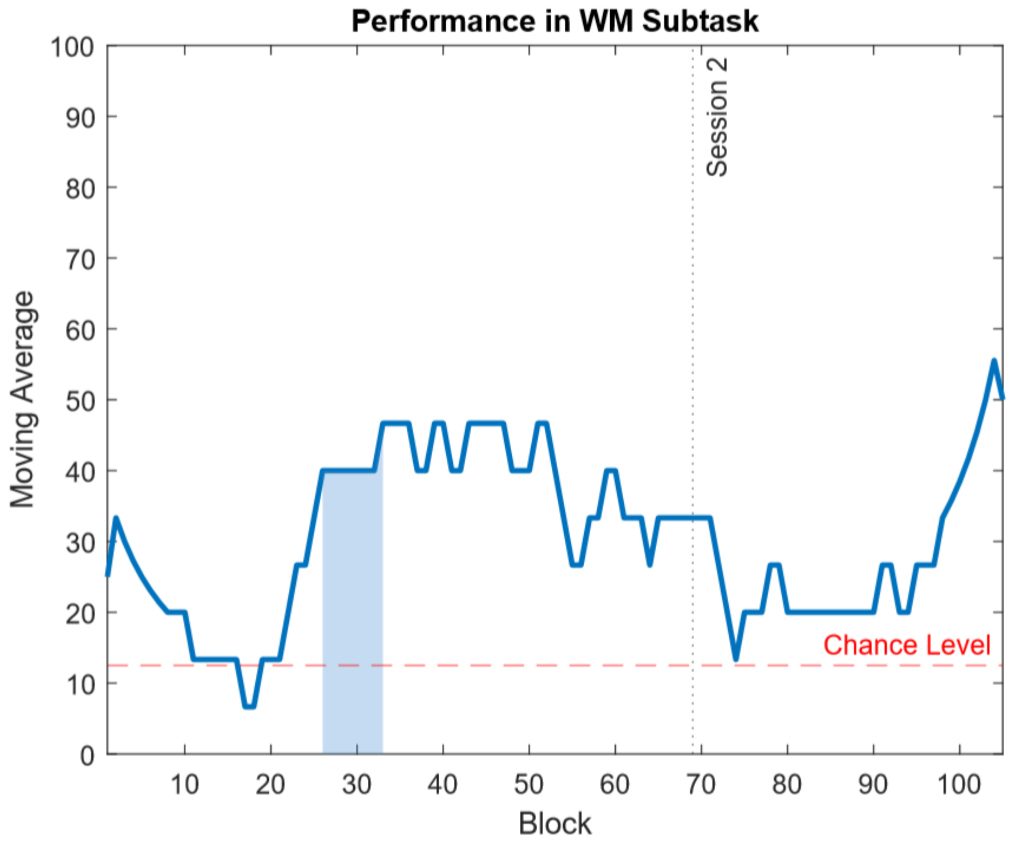

Figure 5. Moving average of block-level performance accuracy (moving window of 15 Blocks) in the subtask; consistent above chance block-level accuracy was observed after 20 blocks of training; red dashed line represents chance level (.125); highlighted area marks a series of five consecutive correct blocks representing the point in time when the performance threshold was first met.

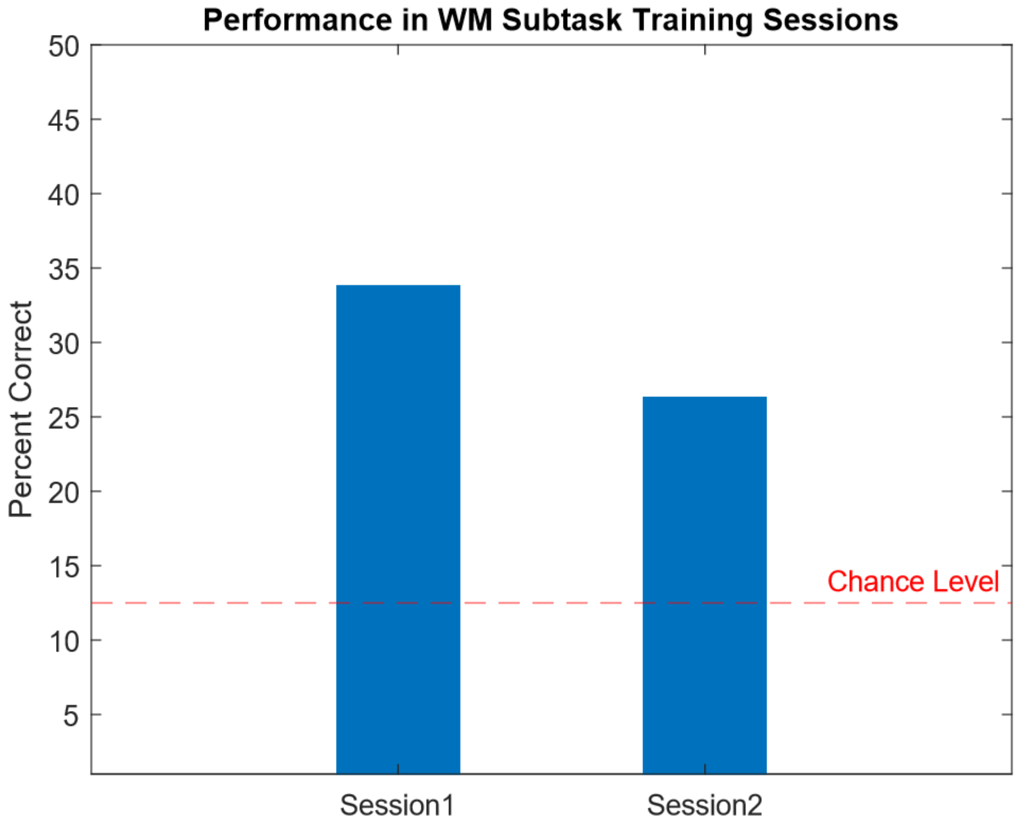

Figure 6. Percentage of correct response for training sessions of the subtask; above chance performance for both sessions was observed.

3.3 The Foraging SOST

The subject’s performance on the foraging SOST was observed across 41 blocks (206 trials) during two training sessions. Figure 7 represents the moving average of performance in every block. A correct response was a block that consisted of three correct trials. Correct performance in five consecutive blocks was considered the learning threshold.

The moving average of performance (Figure 7) and the percentage of correct performance for each session (Figure 8) show a decrease in block-level performance accuracy throughout training. The subject did not achieve the learning threshold during two sessions of training.

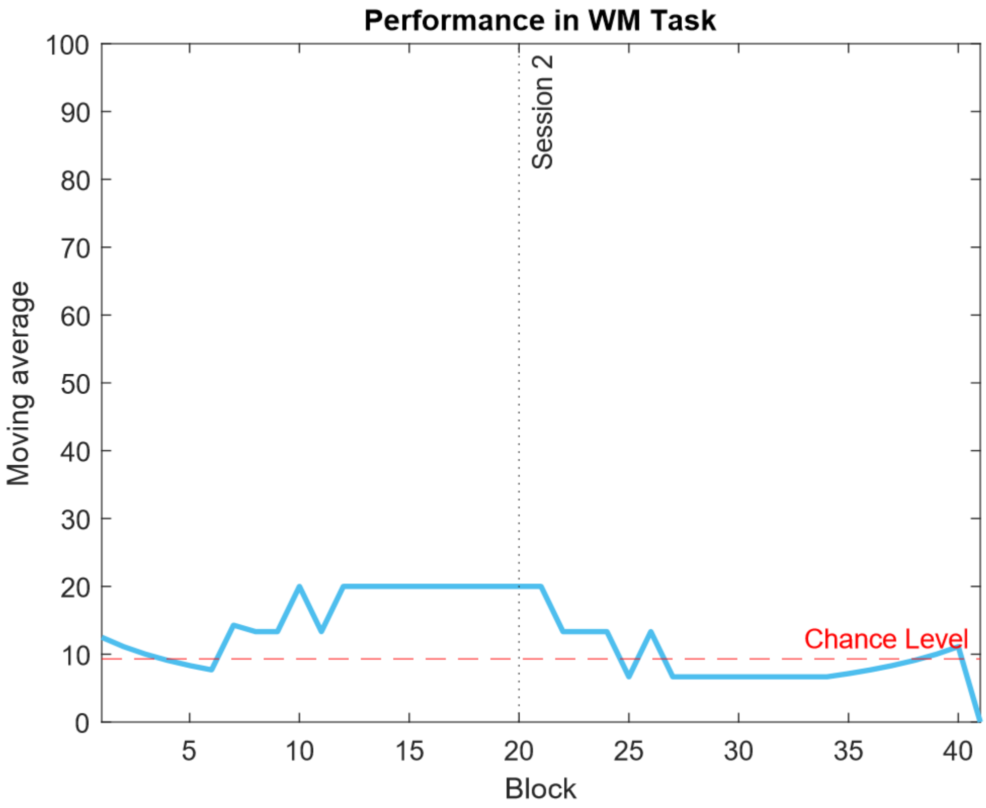

Figure 7. The moving average of block-level performance accuracy (moving window of 15 trials) on foraging SOST on one panel; red dashed line represents the chance level of correct performance (.93); A decrease in performance accuracy throughout training is shown.

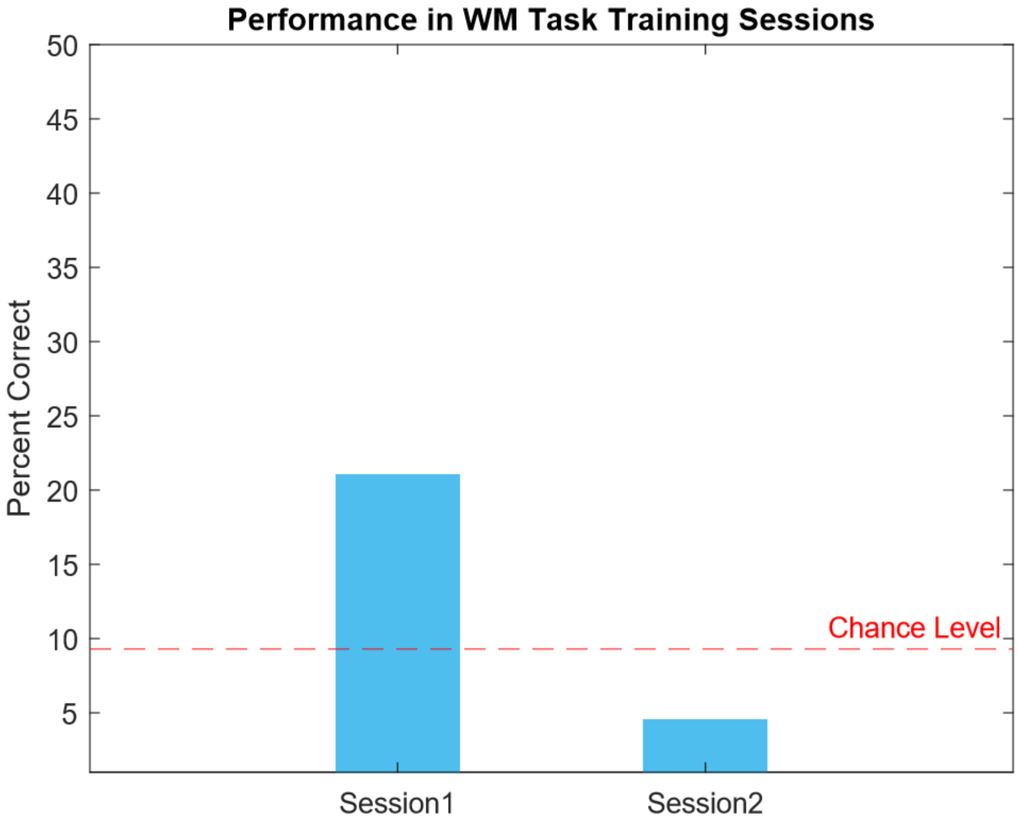

Figure 8. Moving average of performance for each session of the foraging SOST on one panel; correct performance decreased to below chance level in the second session of training.

Besides poor performance, it was observed that the subject frequently visited unblinking locations (unblinking mistakes) and therefore did not follow the first rule of the task (unblinking locations are unrewarding). To statistically test this observation, the number of unblinking mistakes was calculated. Figure 9 represents a polynomial fitted curve to the data. A simple linear regression was used to model the number of unblinking mistakes as a function of training time. The fitted model explains 34% of variance in data (R2= .34) and the regression coefficient was found to be significant, (*b* = .186, 95%, C.I. (.023,.349), *T* = 2.49, *p* < .02). Training time was measured as clusters of 5 mistakes made across training.

The increased proportion of visits to unblinking locations confirms the observation that the subject randomly visited all locations and did not apply the association of light and reward. Therefore, performance on the foraging SOST was not accurately reflecting WM performance.

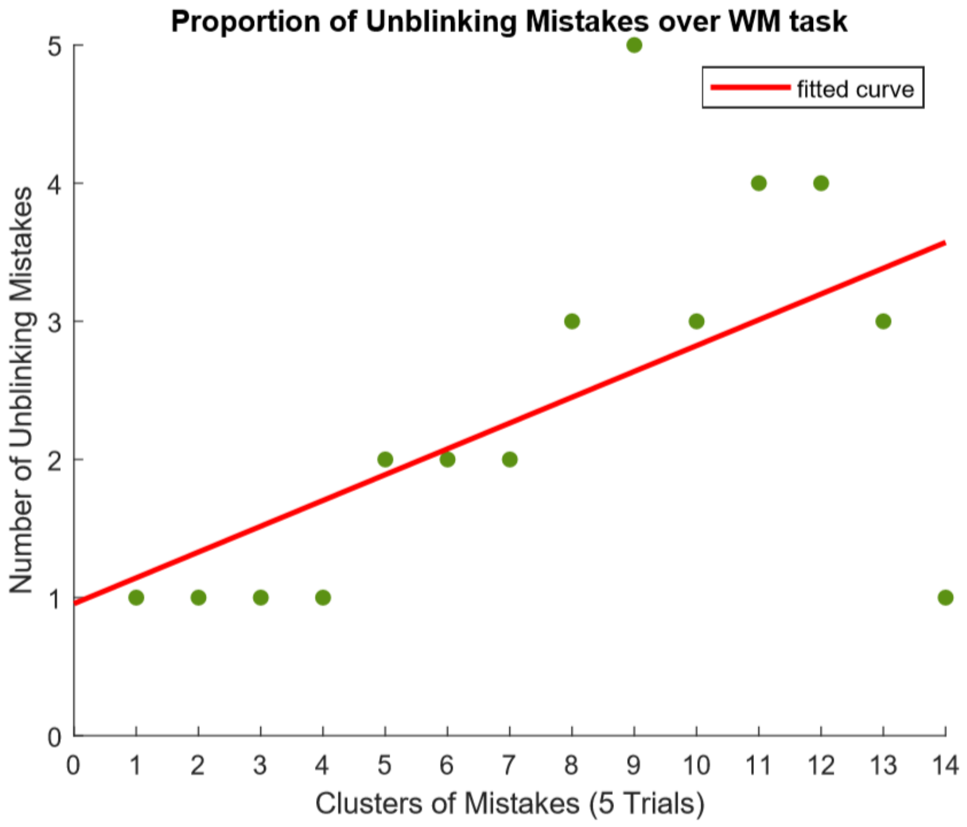

Figure 9. A simple linear regression model for the number of panel mistakes throughout training in the foraging SOST on one panel; the number of panel mistakes has a regression over training procedure (R^2 = 0.34).

3.4 First Level of Training

To establish the distinction of blocks from one another, two opposite panels of the apparatus were used. The distinction of blocks was necessary for correct performance in each block. The correct response in training levels was defined as a correct block. A correct block in the first level only had two correct trials.

A total of 4 sessions of training were conducted. Data on 153 blocks (417 trials) were collected. In this level of training, the goal was to see the establishment of light and reward association. Figure 10 shows the moving average of performance from 15 blocks for the duration of training. The moving average of performance for all blocks was above chance level. Above chance level performance for all blocks indicates the consistent use of light and reward association.

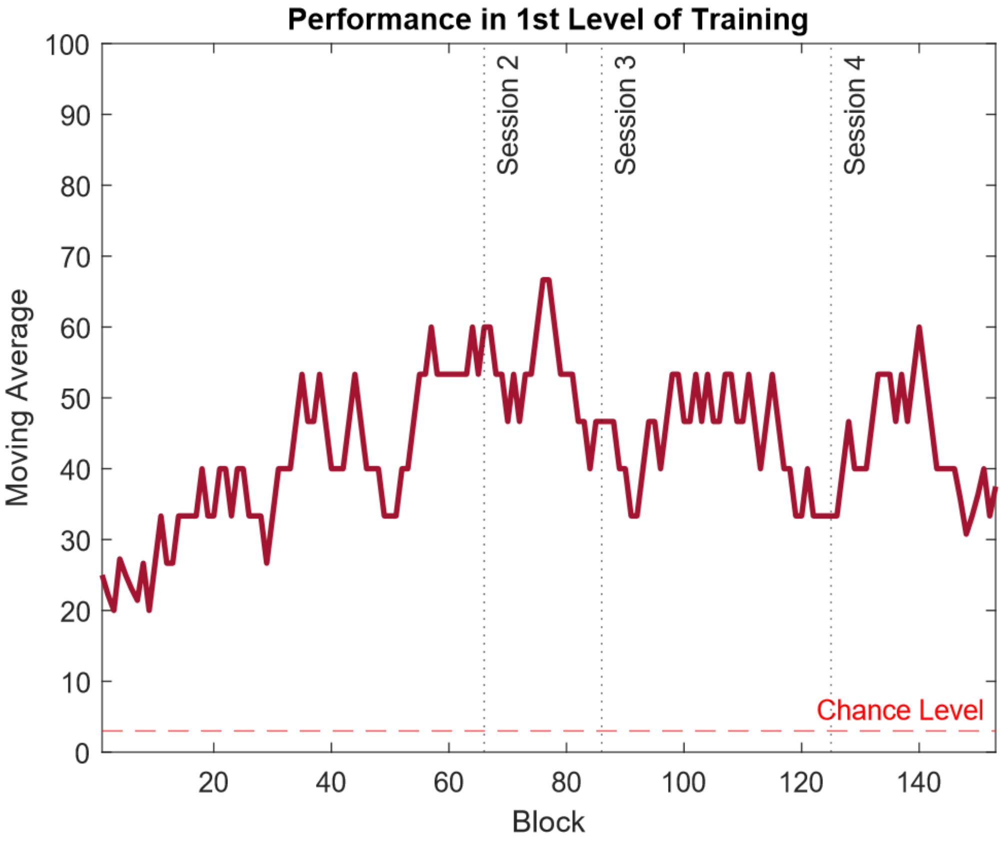

Figure 10. The moving average of block-level accuracy of performance in the first level of training; red dashed line represents the chance of correct performance; above chance performance for all blocks indicates the establishment of training goals.

3.4.1 Panel Mistakes

The number of panel mistakes in each block was calculated. Figure 11 shows the number of panel mistakes on the y-axis as a function of block clusters (training time) on the x-axis. A simple linear regression was used to predict the number of panel mistakes based on the training procedure. The fitted model explained 30% of variance in the data (R2 =

.3) and the regression coefficient was found to be significant (*b* = -.077, 95%, C.I. (-.121, -.033), *T* = -3.5, *p* < .001). Training time was operationalized through clusters of five blocks.

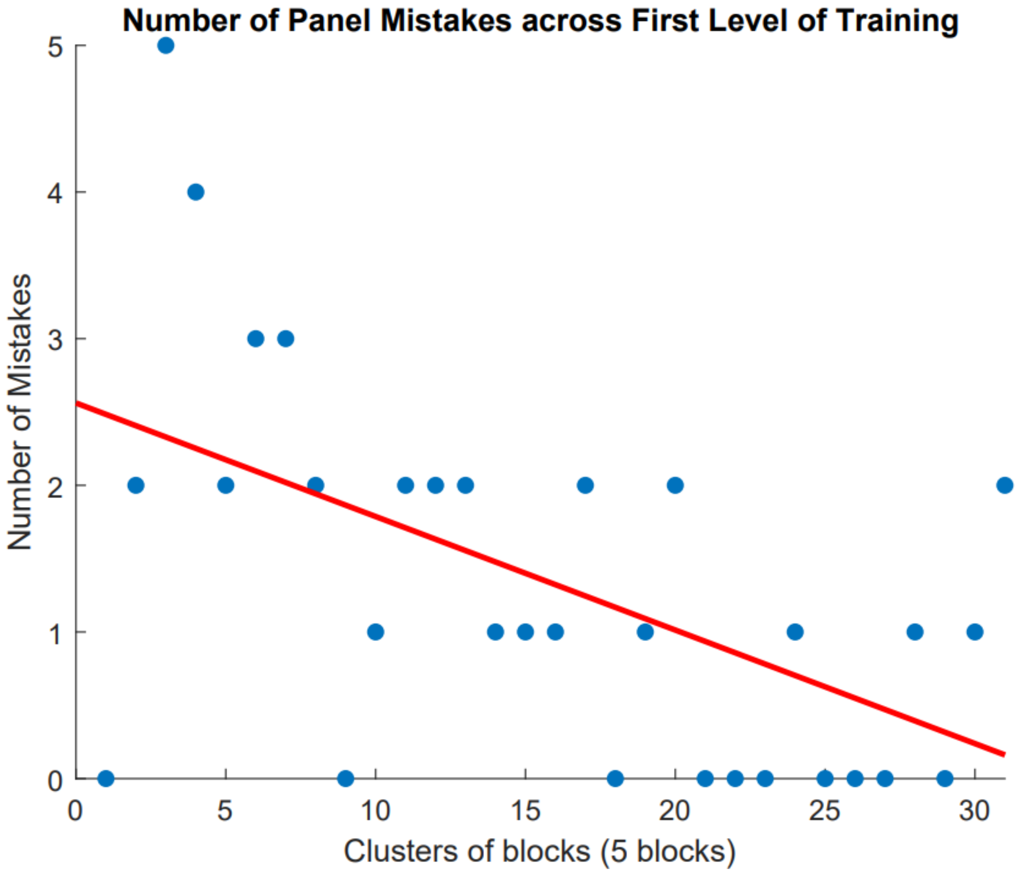

Figure 11. A simple linear regression model for the number of panel mistakes in clusters of 5 blocks in the first level of training; a significant negative regression for the number of panel mistakes based on training procedure was observed (R^2 = .3).

Two types of panel mistakes were distinguished to identify further whether panel mistakes were at the beginning or during the block. Type I panel mistakes were defined as those that occur at the beginning of each block. Type II panel mistakes were defined as any panel mistakes between the first and second correct trials within a block.

A decrease in the number of type I panel mistakes across training was considered an identification that the animal could distinguish blocks. Type I panel mistakes occur at the beginning of blocks before making any correct response in the new block. If the subject understands that as one block finishes, the next block starts on the other panel, there is a low chance of visiting the non-active panel right at the beginning of the block.

Two simple linear regressions were fitted to the data to predict the number of type I and type II mistakes during the training procedure. For panel mistakes type I the fitted model explains 15% of variance in data (R2 = .15) and the regression coefficient was found to be significant (b = -.035, 95%, C.I. (-.066, -.004), T = -2.31, p < .02; Figure 12). The training procedure was operationalized through clusters of 5 blocks.

Based on the above-chance performance for all the trials in the first level of training, and since a significant decrease in the number of panel mistakes I was observed, the second level of training was implemented. The second level of training added more difficulty to the task and was used to establish the panel alteration and new block association.

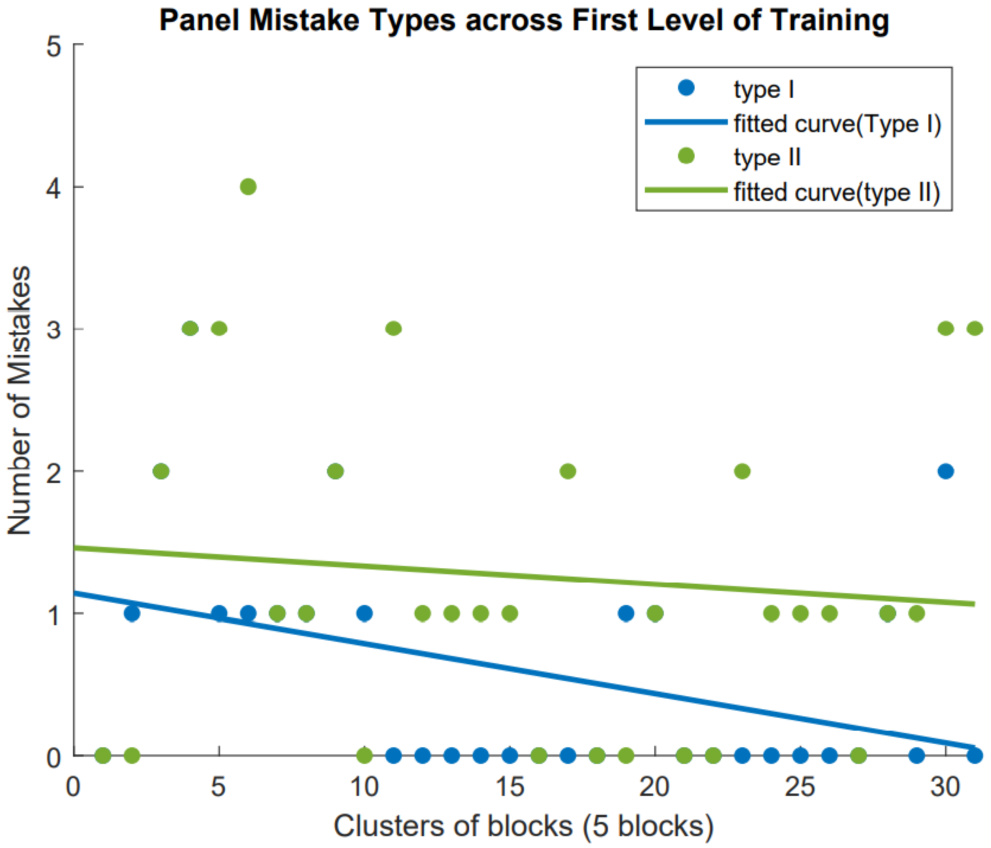

Figure 12. A simple linear regression model for the number of two types of panel mistakes in the first level of training; a significant negative regression for panel mistake type I based on the training procedure was observed (R^2= .15).

3.5 Second Level of Training

The block-level accuracy in the second level of training was calculated for 65 blocks (246 trials). The moving average of performance over blocks is presented in figure 13. Above chance level accuracy was observed for the duration of training. The animal was trained over four sessions. However, the data from session four is not included as the animal was injured before the training session, and the performance could not be reliable.

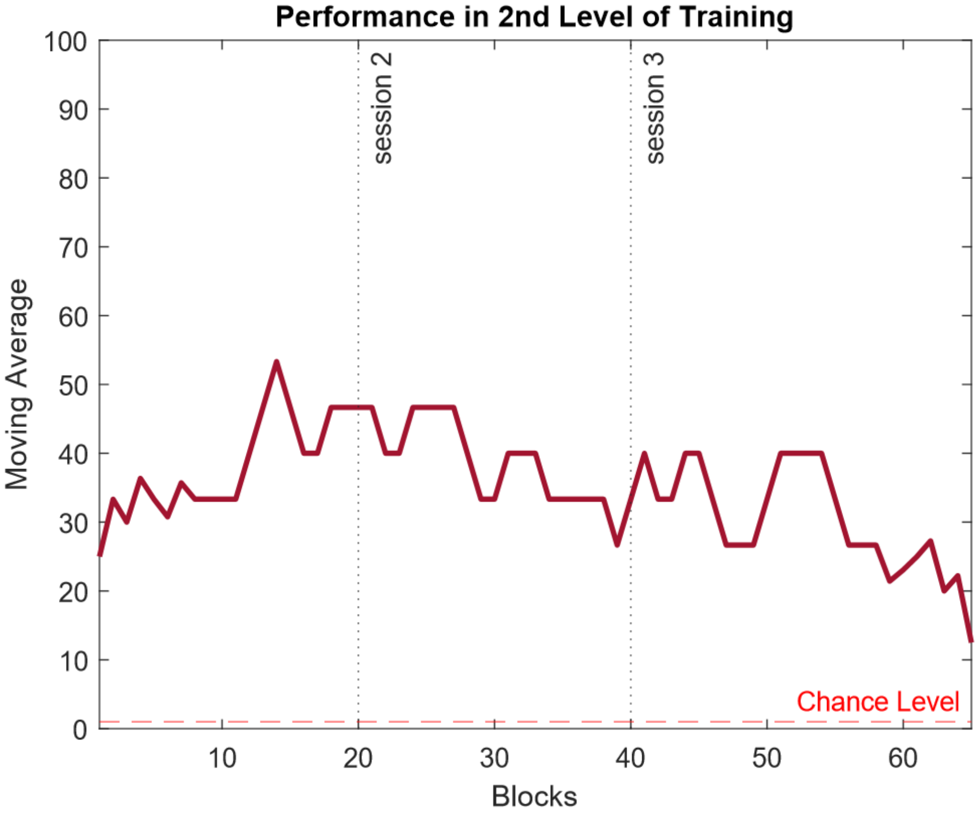

Figure 13. The moving average of performance (window of 15 blocks) in the second level of training; red dashed line represents the chance level for correct performance (.011); gray dotted lines distinguish training sessions; the moving average of performance for all sessions was above chance level.

A simple linear regression was used to predict the number of panel mistakes based on the training procedure. Figure 14 represents the fitted model to the data. The model explains 30% of the variance in data (R^2 =.3) and the regression coefficient was found to be significant (β = .134, 95%, C.I. (.008,.26), T =2.3, p < .03; Figure 10).

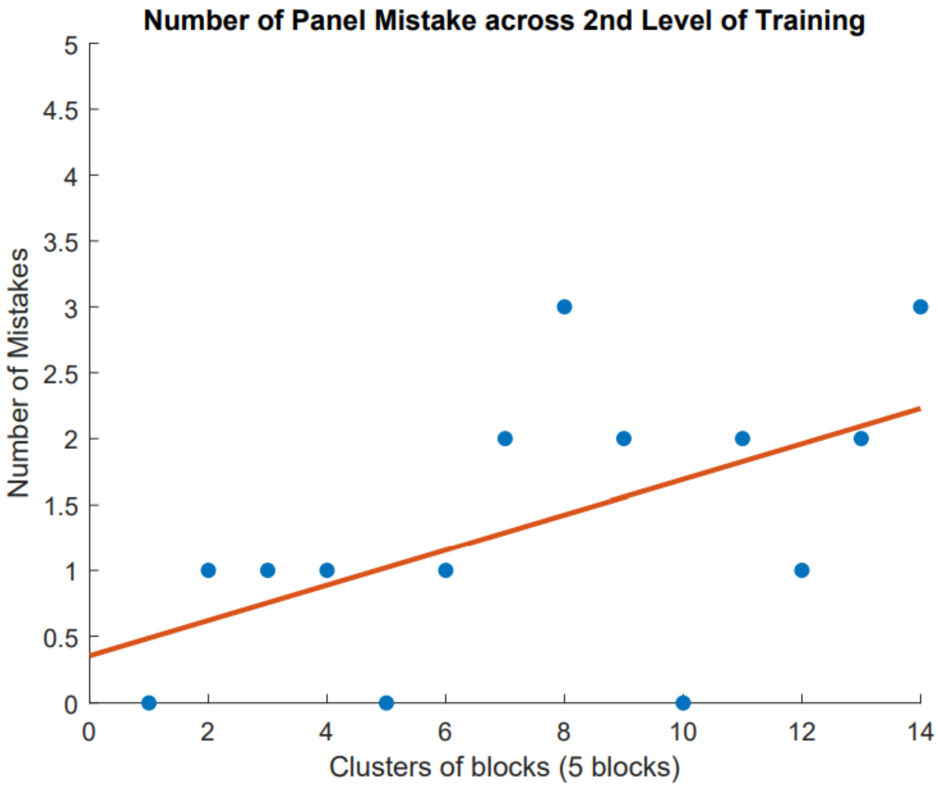

Figure 14. A simple linear regression model for the number of panel mistakes made in clusters of 5 blocks in the second level of training; a significant negative regression for the number of panel mistakes based on training procedure was observed (R^2= .3).

The number of panel mistakes type I, type II, and type III was calculated to investigate the significant increase of panel mistakes further. Figure 15 presents simple linear regressions to predict the number of panel mistakes type I, II, and III based on the training procedure. For panel mistakes type I, the model explains 40% of variance in data (R2 = .4) and the regression coefficient was found to be significant (*b* = .109, 95%, C.I. (.02,.194), *T* = 2.8, *p* < .01).

Perseverating on making panel mistakes indicated that the subject has difficulty understanding that each block is separate and requires specific organized response planning and/or the subject has difficulty inhibiting the perseverative responses to the previous panel. Performance on the second level of training showed that further training in this level was necessary to establish the panel rule. However, due to the lack of resources for further data collection, this project was stopped at this point.

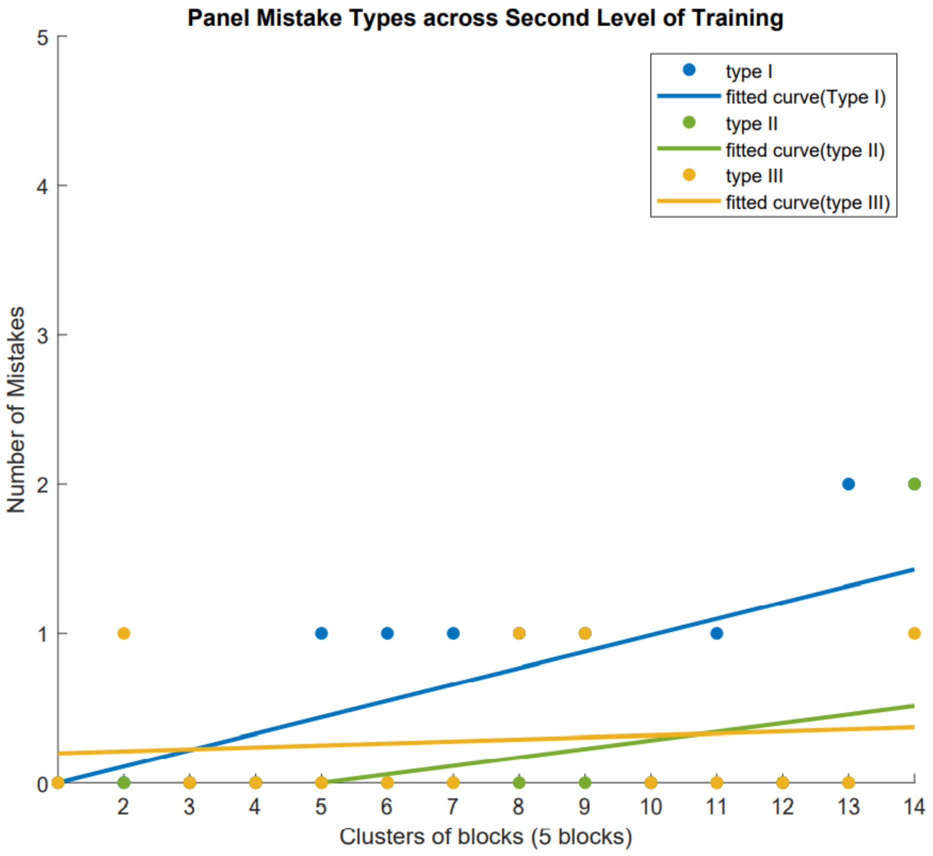

Figure 15. A simple linear regression model for the number of three types of panel mistakes in the second level of training; a significant regression for panel mistake type I based on the training procedure was observed (R2= .15). No significant regression was found for type II and type III panel mistakes.

Chapter 4

4 Discussion

Interference control, the ability to control irrelevant information and keep WM content intact, is essential for WM functioning and goal-directed behaviour (Semrani et al., 2019). Difficulty in interference control in WM in people with ADHD and ASD has been associated with PFC structure and function (Cornoldi et al., 2001; Geurts et al., 2014; Palladino & Ferrari, 2013).

Understanding the development of PFC in relation to interference control tasks, paves the way to understanding neurodevelopmental disorders. Non-human animal studies are essential to expanding our understanding of neurodevelopmental disorders beyond the limits of human studies. The marmoset monkey is a relatively new NHP model suggested for studying the development and deficits of executive functioning.

Few studies validated touchscreen SOST for the marmoset and showed the marmoset's ability to perform on this task. SOST resembles the n-back paradigm and requires interference control. Although SOST has been validated for use with the marmoset, the training period for this task is long relative to the duration of developmental stages in the marmoset. Developmental studies using the marmoset are timely and require special attention to the training time to ensure experiments can be conducted during the short time windows of each developmental stage.

In the current study we designed a self-paced version of SOST that required the foraging behaviour of marmosets, relying upon the existing literature on interference control in the marmoset. Foraging is a context in which monkeys have developed their memory, learning, and goal-directed behaviour during evolution. Here, a foraging environment was utilized to facilitate the training period.

Data was collected during pre-task training, the foraging SOST, and post-task training. Pre-task training was devised based on the shaping method. Pre-task training began with training our only subject on one blinking location in each block. We gradually increased the difficulty level upon improvement in performance by increasing the number of blinking locations. Performance on pre-task training was above chance level accuracy, which encouraged us to continue with collecting data on the foraging SOST. Thus, the foraging SOST was then implemented on one panel of the apparatus. However, the foraging SOST showed a below chance level performance accuracy.

Two confounding factors for poor performance on the foraging SOST were observed related to the task design and training procedure. First, the separation of blocks from each other was unclear. The task and training levels were devised to be implemented on two panels to resolve this issue. The change of panel associated with the change of blocks signified the start of a new block. Second, performance on the foraging SOST showed that the association of reward and light was disregarded. Administering visual cues for training levels established the association of light and reward. Turning off the blinking lights as soon as the reward was received was the visual cue to establish the association between light and reward. Modifications were applied in post-task training. Post-task training was a modified version of pre-task training, but following the shaping method to overcome these possible confounds and retrain the subject. This additional training was conducted in two levels.

Our results from the first level of training signified the effectiveness of modifications in task design and training. Above chance performance on blocks with two blinking locations showed that the association of light and reward was established. A significant decrease in the number of panel mistakes across training indicated the effectiveness of using two panels to differentiate blocks. The results from this level motivated moving to the second level of training. The above chance performance was observed for all blocks on the second level of training, which showed the establishment of light and reward association on blocks with three blinking locations. However, unlike the first level, a significant increase in panel mistakes was observed. The behaviour indicated that the monkey had difficulty differentiating blocks from each other. Since the subject received very limited training on the second level, it was possible to observe improvement in performance upon additional training. Therefore, administering additional training sessions was suggested to establish the distinction of blocks. Understanding the distinction of blocks was essential for correct performance on the task.

In summary, the data reported in this project for performance on the foraging SOST was based on administering the task on one panel of the apparatus only. We thought that low performance on the task using one panel could be related to difficulty the animal had differentiating the blocks from one another and, therefore, the inability to plan responses specific to each block. To address this issue, we trained the animal on the task administered on two panels to support the differentiation of the blocks. We planned to collect further data on the foraging SOST administered on two panels. However, data collection was abruptly terminated due to a lack of time and resources. Observing performance on the foraging SOST on two panels was necessary to investigate whether our modified training had been effective and to provide conclusive data on the performance on the foraging SOST and training time.

4.1 Caveats and Limitations

This project was limited to one previously trained subject on a memory task. Administering the task for a greater number of naïve subjects to the memory tasks is suggested to increase the generalizability of the results. In addition, we noticed reflections of the blinking locations on different places in the apparatus during the study. At certain angles, the animal could see the reflections in the glass that could be seen on unblinking locations. Our subject then could make mistakes unrelated to memory or interference control. This technical issue could be one reason for poor performance on the task. One way to prevent this confounding issue was to replace glass walls with metal mesh. However, non-transparent surfaces could disrupt motion-tracking cameras.

Moreover, the apparatus limited us in controlling for confounding variables. One potential confound could be animal disengagement from the task. A usual practice in studies using touch-screen tasks is to signify the start of trials by inserting fixation points (Nakamura et al., 2018; Yamazaki et al., 2016; Collin et al., 1998). Using fixation points before the start of trials forces the animal’s attention to the screen and encourages engagement in the task. However, we were limited in using fixation points to capture the subject’s attention and signify the start of each block because we did not use a touch screen apparatus. Modifying our task and implementing blocks on two apparatus panels was our way of addressing this confounding issue.

Additionally, touch-screen tasks allow for more control over the presentation of trial events and intertrial intervals and impose restrictions for marmoset's movement. Because of this, touch-screen tasks are more reliable for measuring reaction times. However, our apparatus required the marmoset to move and explore freely inside the apparatus so they could engage in foraging behaviour. Freely moving behaviour limited our control over movement, which created difficulty in obtaining a reliable reaction time measure. Therefore, we could not use reaction time as a behavioural measure representing WM ability as we see in previous studies (Dudchenco et al., 2012).

4.2 Future Directions

By referring to the previous studies in marmoset WM studies using SOST, we borrowed ideas to improve the training procedure to establish the foraging SOST for the marmoset. The procedure we developed, and the following ideas can be utilized in future studies that aim to incorporate training in a foraging environment. Below is a discussion of previous works and further modifications to improve training procedures.

First, in studies using SOST for the marmoset, the use of touch-screen apparatus enabled researchers to have more control over the design of the experiment. In the studies carried out by Collins et al. (1998) and Alexsson et al. (2021), a sequence was terminated prematurely if the monkey made a mistake. Termination of a block was followed by displaying a blank screen, playing a noise associated with an incorrect response, and turning off the house light for 5 s. Terminating the block when the monkey made a mistake, enabled the animal to better learn and understand the task rule. The rule was that no stimuli should be selected twice. Although in our study, the foraging environment did not allow us to terminate the block by remove all the locations and by eliminating the possibility of making any response, we still can apply some solutions that signify the termination of a block. Therefore, we could terminate the block after an incorrect response, although the locations were not removed. For example, we could modify the task so that the wrong response leads to termination of the block followed by a number of cues. We could, after terminating the block, provide a time out accompanied by a sound associated with an incorrect response and turning off house lights. More specifically, turning off the house lights could darken the space and potentially prevent the subject from exploring inside the space and visiting locations.

Second, it is important to know what kind of mistakes the marmosets are making in order to improve the training. One type of error often observed in the monkeys is perseverative errors. Perseverative errors are errors in which the subject continues to emit behaviours that have been previously rewarded but are no longer appropriate. Another type of error is when the subject makes random errors. It is essential to distinguish between these two types of errors because helping the monkey overcome a particular error requires insight into the type of error occurring. Our coding for this task did not differentiate these two types of errors. It would be beneficial to modify the coding of the task in a way that would enable us to differentiate these two types of errors.

Third, Axelsson et al. (2021) improved the effectiveness of their training by introducing a vanish time. Whenever a stimulus was selected correctly, that same stimulus vanished for a specific duration of time. The vanish time prevented selecting a stimulus twice consecutively and eliminated the possibility of making perseverative mistakes. The vanish time was decreased as performance improved. Unfortunately, introducing the vanish time into the foraging task was not applicable because, as mentioned, our apparatus did not allow us to remove the selected location to eliminate the possibility of visiting that location twice. However, we can train the subject on the foraging SOST by immediately turning off the light for the visited location and gradually decreasing the time that the light is off (quiet time) as the performance increases.

Introducing quiet time can be added to the training as an extra step and be implemented after the second level of training. In our study, during the second level of training, as soon as the reward was delivered, the light for that location went off until the end of the block. Turning off the light for the visited location was used to establish the association of light and reward in blocks with three rewarding locations. The second level of training did not require WM as the monkey performed based on the visual cue. Before moving to data collection on the foraging SOST on two panels, it would have been beneficial to train the monkey on a version of the task that requires WM. Introducing quiet time is a way to add the WM component to the task while preventing the subject from making perseverative errors. WM is required because the subject needs to keep track of visited locations and not rely on visual cues.

Fourth, previous studies delivered the reward after successful termination of a sequence that is proven effective in training the marmoset on SOST (Collins et al.,1998; Alexsson et al., 2021). We could apply this way of training in our apparatus. However, delivering the reward only at the end of the sequence of responses on our apparatus changes the nature of the task fundamentally. The foraging apparatus requires delivery of the reward after each search and represents how foraging works in the natural environment. Delivery of the reward once after several searches is not consistent with what the animal would experience in the natural environment, and the task would no longer be a foraging task.

The data from the foraging SOST could set the stage to pursue several next steps. One potential next step would be to conduct a longitudinal study of WM in the common marmoset across development. The second would be to leverage the proposed method to gain insight into mechanisms underlying problematic behaviours related to WM. Changes in morphology at the macroscale and mesoscale levels could be explored, and the developed task could measure the relationship between those changes with changes in the basic functions.

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