Perspectives on the Non-Human Primate Touch-Screen Self Ordered Spatial Search Paradigm

Jane Sutcliffe, Daniel Hutcheson

Neuroscience & CNS Research, Maccine Pte Ltd, Singapore.
jane.sutcliffe@maccine.com, daniel.hutcheson@maccine.com

Abstract

The self-ordered spatial search (SOSS) working memory task implemented as the computerised touch-screen task is a highly translatable platform providing a good comparison of human and non-human primate (NHP) cognitive performance measures. This communication describes how the manipulation of integral task components provides the ability to alter the dynamic range of range of performance suitable for the experimental approach being used. Accordingly, in the case of disruptors such as scopolamine for modelling cognitive decline and some aspects of brain disease states high baseline performances may be set to allow demonstration of disruption and reversal with potential new therapeutics. However, the SOSS task may be manipulated to obtain a large dynamic window of baseline performance optimised to detect the pure pro-cognitive impact of novel compounds.

Introduction

Rodents are an invaluable species for the evaluation of cognitive function during early drug development. However the use of non-human primates affords the ability to investigate complex behavioural processes that are more closely aligned with human function and disease with utility especially during the later stages of pharmaceutical drug lead optimization. Data derived from the NHP provides an invaluable, translatable link between data generated in rodents and in the human. Similarities in anatomy, neuronal circuitry, neurochemistry, functional and cognitive abilities exhibited between NHPs and humans provide an arguably more translatable approach to investigate higher cortical-mediated behaviours in particular, and allows for direct comparisons of cognitive function to be made using the same endpoints across species. The CAmbridge Neuropsychological Test Automated Battery (CANTAB) is a well established system for assessing cognitive function in patients across several neurodegenerative and psychiatric indications and for assessing responses to therapeutic agents. Touch-screen based cognitive tasks have been developed for use in NHP research from the early 1980's [1] and from conception the NHP-CANTAB tasks were adapted from the available clinical versions [2]. The SOSS task within the CANTAB battery shares obvious roots with the classic Hamilton search task [3-4], builds on the research of Mishkin [5-6] and is analogous to the rodent radial arm maze.

Methodology

In the clinic, the SOSS task is demonstrated as sensitive to frontal lobe damage [7] [8], disrupted in Schizophrenic patients [9] and in idiopathic Parkinson's disease [10] even when symptoms are mild [11]. Furthermore, Lange et al., 1992 [12] have demonstrated a distinct decline in SOSS performance in L-DOPA medicated Parkinsonian patients when "off" medication. The objective in the clinical version of the CANTAB spatial working memory task is to collect 'blue tokens' which are hidden beneath the boxes presented on the touch-screen and to then use the found tokens to fill an empty column present at the side of the screen. The subject must search by touching one box at a time to find the hidden token, on any one trial only one token is hidden. Once found, the next token will then become available in different location, the key feature of the task is that once a blue token has been discovered in one box location, that box location will not be used again to hide another token within that trial. Subjects are required to thus remember where they have found the previous token and not to return to that location. Non-verbal strategies have to be employed to train an NHP on the SOSS task and during initial training the NHP is gradually introduced to the concept of the task via the introduction of two coloured stimuli boxes. On touch selection of the stimuli the box may change colour or 'blink' to indicate that

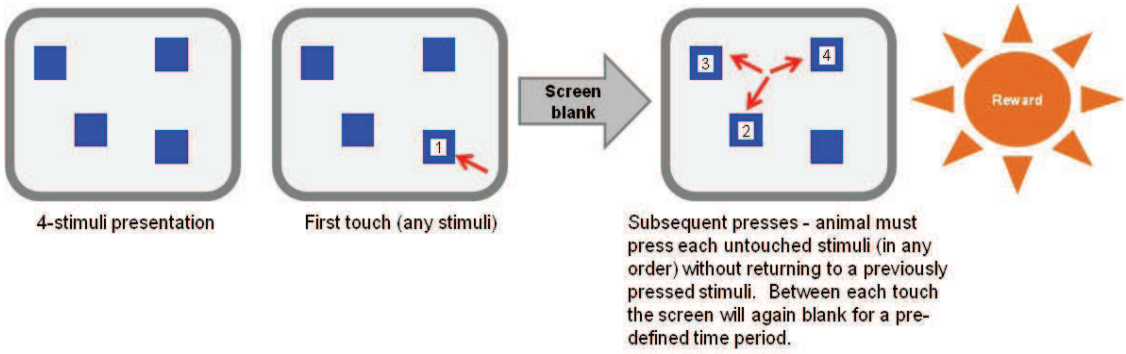

Figure 1. Schematic representation of the SOSS paradigm (4-stimulus trial).

the alternate stimuli must be sequentially selected (touched) in order to obtain the reward. As an individual's performance improves, the difficulty of the task is increased in a step wise manner: stimuli remain on screen, (no colour change or blinking) and the screen blanking is lengthened until terminal conditions are obtained. Importantly, during training care is taken to ensure rule comprehension and also that motivation to complete the task remains high. The training protocol for the cynomolgus macaque is adapted from the available rhesus macaque [13] and marmoset [14] literature. In this case up to six small coloured boxes (stimulus) may be displayed on the touch-screen in up to sixteen different screen locations. A set of stimuli are presented together at the start of each individual trial. The subject must touch each presented stimulus box without returning to a stimulus already selected for each trials set of stimuli presented in order to receive a reinforcer fruit food pellet (Figure 1). The trial is completed when the animal has either touched all boxes without repetition (correct), touched a box that had previously been selected in that trial (error), or failed to touch a box within 30 seconds of stimulus presentation (omission). After an inter-trial interval of 3 or more seconds, a new trial is presented with randomised stimuli of each selected difficulty level in newly allocated screen positions.

The SOSS task is very amenable to manipulation of the dynamic range of performance appropriate to demonstrate either the pro-cognitive impact of novel compounds or to conduct disruptor studies (e.g. scopolamine, ketamine). Disruptor induced reductions in performance must ensure easy level performance remains similar to control levels (i.e. providing an unaltered measure of global behaviour), but with working memory deficits apparent at the higher difficulty levels. This may be attained by starting with a higher baseline performance level which can be achieved by overtraining the subjects, using fewer stimuli, or minimising the inter-response screen blanking. Due to the flexible manipulations the SOSS task allows one to run studies at both high performance levels (for disruptor studies) and in separate sessions to create a large window of performance ranges (as low as 10-20% correct and stepwise up to >80%) in order to detect pure pro-cognitive changes in the same group of subjects.

Case Study

Scopolamine has been shown to disrupt cognitive performance on a wide range of memory tasks in numerous species including rats [15-17], nonhuman primates [18-20] and humans [21-25]. This effect is believed to be mediated through antagonism of the muscarinic subtype of the cholinergic receptor, and thus, the amnestic action produced in animals by scopolamine has been widely used pre-clinically as a model to characterize the potential cognition-enhancing influence of compounds. The SOSS task has previously shown sensitivity to scopolamine insults [26] in the young male rhesus macaque (~4 years) resulting in the proportion of correctly completed trials in the SOSS task being reduced with increasing trial difficulty (increasing the number of boxes in a trial) and by increasing dose levels of scopolamine. Importantly, performance on the 'easy' level condition (2-stimuli) was preserved with increasing dose levels of scopolamine whereas performance on the 3- and 4-stimulus was significantly impaired. The impact of scopolamine on the SOSS task has been investigated in our laboratory using the middle-aged (~15 years) and mature (~6 year) female cynomolgus macaque with similar effects observed when compared to the rhesus literature. During scopolamine titration studies extreme care must be

taken to obtain an appropriate, individual, cognitive deficit without adversely affecting global behaviour. When using scopolamine to evaluate its actions on the central nervous system, particularly regarding memory, pretesting intervals of 30–45 min should be enforced since shorter pretest intervals may result in dominant peripheral anti-muscarinic side effects which will hinder task performance. In all cases the observed scopolamine deficit was replicated 2 or 3 times per individual prior to initiating reversal pharmacology. A robust, partial reversal of the scopolmaine induced cognitive deficit is observed with Donepezil pretreatment, confirming the clinical experience that cognitive improvements in Alzheimers disease after cholinesterase inhibitor administration exerts variable, often limited, responses in patient populations.

Conclusion

The NHP SOSS task is a highly translatable and sensitive neuropsychological paradigm which enables the pre-clinical researcher to model certain aspects of neurological disease states associated with cognitive decline. While a rodent touch-screen model of the SOSS task does not yet exist, its development would further aid translation across species.

Ethical Statement

All experimental procedures were conducted in an AAALAC accredited facility and approved by the Institutional Animal Care and Use Committee of Maccine Pte Ltd.

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