Assessment of Behavioural Flexibility and Executive Function Using Novel Touch Screen Paradigms

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The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative has recently identified a NIMH consensus cognitive battery comprising seven major domains for use in clinical trials assessing cognitive impairment associated with schizophrenia (CIAS). Major cognitive domains identified include Attention/Vigilance (assessed using variants of the continuous performance test), Visual Learning and Memory (e.g., visuospatial memory tests), Working Memory (e.g., spatial span or delayed response tasks), Speed of Processing (e.g., trail-making) and Reasoning and Problem-Solving. There is a great need for a biologically and statistically-validated consensus cognitive test battery for rodents which can reliably translate to these CIAS clinical endpoints. Here we report on the development of three novel touchscreen-based tasks for the rodent – a 3-Stimulus Discrimination and Reversal test, a Continuous Performance test, and a Self-Ordered Working Memory test – that tap into several of the CIAS domains, and have responses requirements and outcome measures that are highly related or identical to those used in clinical assessment.

3-Stimulus Discrimination and Reversal Learning

Recent evidence suggests that schizophrenia patients are unimpaired in simple rule learning but appear inflexible when rules change, possibly reflecting difficulties in using negative feedback information and in switching attention [1]. Reversal learning is thus a promising target for translational studies because it is simple, specific, clinically-relevant, and putatively targets orbitofrontal dysfunction.

We have recently developed a 3-stimulus discrimination and reversal learning paradigm as a tool for measuring rule learning and flexibility for visual stimuli in rats. The basic task uses 3 stimuli randomly presented across 3 screen locations on the touchscreen. Data will be presented on two task variants in which, in addition to the S+ and S- included in standard 2-choice reversal learning paradigms, the third stimulus is included as an additional S-, or as a neutral distracting stimulus (So). The 3-stimulus paradigm was devised in effort to obtain 1) better discernment of stimulus perseveration versus avoidance through analysis of choices of the unchanged third stimulus (S- or So), 2) lower reinforcement of spatial biases (e.g., reinforced 33% versus 50%) 3) less possibility of solving the task through configural or other forms of learning (triplets vs pairs). The relative merits and difficulties of the 3-stimulus paradigm will be discussed in relation to comparable data acquired using a standard 2-stimulus procedure and with respect to its ability to detect effects within animal models of schizophrenia and in response to pharmacological agents.

Continuous Performance Test

The continuous performance test (CPT) is a paradigm comprising several procedural variants, some of which have proven reliable indicators for the presence of, and susceptibility to, schizophrenia [2,3]. In its basic form, the CPT involves rapid, externally-paced (e.g., not under subject control) presentation of a large number of consecutive stimuli, to which subjects are instructed to respond only upon detection of a designated target stimulus or sequence. Performance on the CPT is traditionally assessed by analyzing numbers of correct responses ("hits" or, inversely, omissions or "misses") and incorrect responses ("commission errors" or "false alarms"). Signal detection analysis can also be used to combine these traditional measures and extract d' (ability to discriminate signal from background) and B (bias toward responding). The CPT is generally considered

primarily as a measure of vigilance or sustained attention, with performance variables typically worsening as the session proceeds. However, CPT performance is also dependent on task parameters and may be designed to be more or less sensitive to elements of sustained attention, selective attention, impulsivity or executive control.

We report here on our development of an analogue of the CPT using the rat touchscreen. We trained rats to attend to a central location on the screen and presented stimuli every 3-7s (vITI) continuously throughout the task (the only pauses occurring after a correct response). Stimuli are presented for 1.5s stimulus duration and rats have 2s to respond to the stimulus after stimulus onset (limited hold). Initial probabilities are 50:50 for target (in example X) and nontarget (O,H,I) stimuli, where is never possible to have more than 4 targets or nontargets in a row (except correction trials). The stimulus presentation and response requirements were thus highly similar to the human version of the CPT. The basic version of the CPT task was acquired within 20 sessions. Task validation procedures confirmed detrimental effects on d' sensitivity measures using variable event rate, reduced stimulus duration and reduced stimulus contrast. Moreover, rats showed performance decrements toward the latter trials of the session suggestive of taxing vigilance processes. The results will be further discussed in relation to data collected on animal models of schizophrenia and in response to putative cognitive enhancing agents.

Self-Ordered Working Memory Task

Working memory dysfunction is a key aspect of cognitive impairment in schizophrenia where impairments have been reliably documented in schizophrenic patients, as well as back-translated to studies of primate and rodent models of schizophrenia. Evidence exists linking dopaminergic systems that may underlie schizophrenia-like working memory impairments in rhesus monkeys, with similar results found in rodents [4]. Moreover, visuospatial working memory (SWM) has been identified as a putative cognitive endophenotype of schizophrenia [5].

We have developed a self-ordered working memory task for rats in the touchscreen environment. In the basic version of the task, rats were trained on each trial to touch 3 spatially distinct squares on the touchscreen, receiving rewards for each new square touched. If a square was revisited within a trial, a negative feedback image was displayed and houselight illuminated. A trial was completed after all 3 squares had been touched once. A variable inter trial interval (25-45s) separated each trial. Rats were given up to 60 trials in a 60 min session. Rats were observed to progressively improved in the task, making fewer errors per trial than chance, and completing more than 42% perfect trials per session (chance performance = 22.2%). Probe tests to examine sequencing behaviour revealed that, despite some evidence for sequencing, rats continued to perform considerably better than chance when sequencing was discouraged (different forced starting squares). This suggests that the task may be reflective of spatial working memory. Further behavioural and pharmacological probe tests will be presented to illuminate putative underlying cognitive processes.

In summary, we have recently developed 3 novel cognitive tests in the rodent touchscreen apparatus (3-Stimulus Reversal; rodent CPT and rodent SOWM) that are highly similar to corresponding clinical paradigms (CANTAB visual discrimination; X-CPT and CANTAB spatial working memory tests) in terms of the stimuli, responses and outcome measures. Evidence suggests that these tasks can lead to reliable levels of performance (3-stimulus reversal has already been replicated across laboratories) that are sensitive to parametric behavioural manipulations that alter cognitive load. These tests are currently being validated in terms of their underlying neural substrates (e.g., medial and/or orbital prefrontal cortex lesions) and with respect to their sensitivity to detection of cognitive enhancing agents. These novel touchscreen tasks are highly promising for use in flexible translational battery with relevance to the examination of cognitive processes in schizophrenia.

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