PROJECT PROTOCOL
V1.3, 22.11.2016

Title: A clinical trial of theta burst stimulation to enhance social relating in autism spectrum disorder (ASD)

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Background

Autism spectrum disorder (ASD) is estimated to affect 1 in 45 children [1]. Despite the public health significance of ASD, we still lack a biomedical treatment that targets the core symptoms, such as social communication and social interaction. The impact of ASD on the quality of life of affected individuals and their families is greater than any other intellectual or developmental disability [2], and such a treatment is urgently needed.

The last decade has witnessed significant advances in our neurobiological understanding of ASD that create opportunities for research translation. For instance, ASD is now broadly considered a disorder of connectivity (e.g., reduced long-range connectivity) [3], evidently underpinned by dysfunction within specific neurotransmitter systems (e.g., gamma-amino-butyric-acid [GABA]) [4] and associated neuroplasticity mechanisms (e.g., long-term potentiation [LTP]) [5]. Thus, ASD essentially appears to be a disorder of aberrant synaptic transmission, with some brain regions and circuits particularly affected (e.g., frontoparietal pathways) [6].

Pharmacological approaches to treating specific neurochemistry have been unsuccessful in alleviating any of the core symptoms of ASD (although appears to have some benefit for associated behavioral and mood disorder; [7]). By contrast, many of these mechanisms can be selectively modulated by non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS, see Figure at right) and transcranial direct current stimulation (tDCS) [8]. These approaches are safe and efficacious in the treatment of several psychiatric disorders (most notably depression; [9]), and

there is increasing interest in whether NIBS might have a therapeutic application in ASD [10].

We have conducted seminal studies targeting the 'social brain' in ASD using transcranial magnetic stimulation. These studies have helped to better understand the cortical and network deficits associated with ASD [11-14], but more recently we have conducted clinical trials using rTMS to enhance neurophysiological function and core social symptoms in adolescents and adults with ASD [15-17]. We have also found that four weeks of daily high-frequency rTMS to dorsomedial prefrontal cortex (dmPFC) in adults with ASD results in (a) enhanced glucose metabolism within mid cingulate gyrus (part of the stimulated 'mentalizing' network), and (b) social symptom reductions that last for at least six months (as measured via the Social Responsiveness Scale). A manuscript describing these results is in preparation.

Thus, proof of concept appears to be clearly established with respect to both safety and efficacy. rTMS, however, presents challenges for an autistic population, particularly those younger or considered 'low- functioning.' This includes the time taken to deliver stimulation (typically 30+ minutes) and the auditory/tactile sensations of undergoing rTMS (many individuals with ASD experience significant sensory hypersensitivities). It is thus critical to transform rTMS for ASD into something that is feasible, tolerable, and has wide applicability.

One solution may be the use of a newer form of rTMS: theta burst stimulation (TBS). This involves very high- frequency, but reduced intensity stimulation that appears to have similar or greater benefits compared with standard rTMS [18]. Importantly, TBS treatments take only 1-3 minutes per day and are associated with significant reductions in tactile sensation, making it more suitable for young people, those with associated sensory/cognitive impairments, and those with intellectual disability . Experimental studies of TBS in ASD suggest that the autistic brain is particularly responsive to TBS, or 'hyperplastic' [19]. Although an emerging area, TBS is already suggesting efficacy for the treatment of depression [20].

Another important component of rTMS in ASD concerns the target brain site. As noted, we have generally targeted bilateral dmPFC, but our group's recent neuroimaging (fMRI) research indicates that right temporoparietal junction (rTPJ, see Figure at left) might be a better target for social cognitive dysfunction in ASD [21]. Indeed, our lab is currently conducting "proof of concept" work looking at neurocognitive, neurophysiological, and functional neuroimaging outcomes associated with NIBS of TPJ (including TBS and "high-definition" tDCS) [22].

The proposed study is a cross-over, head-to-head study comparing TBS to dmPFC (via an angulated figure-of-eight coil to achieve sufficient depth) with TBS to rTPJ (using the same angulated coil) among adolescents and young adults with ASD. As noted, there is enormous need for a biomedical treatment targeting social symptoms in ASD, and this age is particularly critical given the increasing

social complexities and need for independence. The approach suggested below is considered a better option for tolerability (and thus feasibility), and should address many of the potential barriers to treatment (e.g., sensory, attention, cognitive, and motor impairments).

A cross-over, head-to-head design is somewhat unusual, but this is an approach that is increasingly used in brain stimulation research, and with what might be considered an "active control" (i.e., the other stimulated region) will give a stronger sense of the need for precise neurobiological targets in rTMS for autism spectrum disorder. This approach was also selected as it is an extremely novel protocol, and evidence of efficacy will justify a large-scale follow-up study that does include an adequate placebo control. As the involvement of families is significant, there was also significant concern about the use of placebo/sham conditions, particularly where our previous trials have seen no change in such conditions.

Hypotheses

It is hypothesized that TBS will lead to improvements in clinical ratings, ASD-related neuropsychological function, and neural connectivity within social brain networks. Improvements are expected to be greater following stimulation of rTPJ compared with dmPFC.

Methods

Participants: n = 20

Inclusion criteria:

- DSM-5 diagnosis of autism spectrum disorder (ASD)*
- Aged 14-30
- Male or female
- Formal IQ assessment indicating FSIQ 55 or higher
- Social Responsiveness Scale (SRS) score in the clinical range (60 or above)

Exclusion criteria:

- Seizure history
- First degree relative with seizure disorder
- History of serious head injury
- Presence of ferromagnetic metal in the head outside the mouth
- Presence of implanted medical device
- Pregnant or lactating
- Current substance use disorder

*Participants or parents/guardians will be asked to provide a diagnostic report from the diagnosing clinician to verify their or their child's ASD status. As detailed in the consent form, if the participant is not able to provide a diagnostic report we will seek permission to contact the diagnosing clinician directly to verify the diagnosis of ASD.

- Neurological or psychiatric disorder other than common comorbid disorders (specifically, ADHD, depression, anxiety, OCD)
- Professional driver or machine operator

Requirements for TMS treatments:

- No recreational drugs or alcohol within past 24 hours
- No change in medication regime within past 4 weeks
- Typical sleep pattern (within 20%) previous 24 hours

Treatment arms:

Theta burst stimulation will be provided using the Neurosoft "Neuro-MS/D" stimulator, with the cooled, angulated figure-of-eight coil (AFEC-02-100-C).

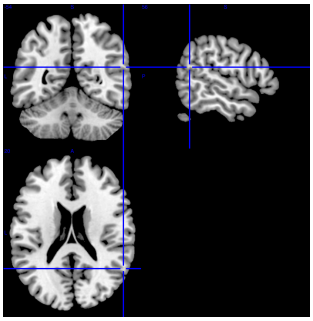
1. Intermittent TBS to rTPJ: 600 pulses, 3 pulses delivered at 50 Hz, repeated 5 times per second for 2 seconds at 70% resting motor threshold, 8 second inter-train interval (190s total). Week daily treatments for 4 weeks (20 treatments).

2. Intermittent TBS to dmPFC: 600 pulses, 3 pulses delivered at 50 Hz, repeated 5 times per second for 2 seconds at 70% resting motor threshold, 8 second inter-train interval (190s total). Week daily treatments for 4 weeks (20 treatments).

Participants will be randomly allocated to begin in one of the two treatment arms, but then will crossover to other condition 6 months after completion of last treatment.

Treatment regime: Week daily treatment for 4 weeks (20 treatments per arm). Participants will be monitored by medical staff for at least five minutes after each treatment session.

Treatment site: Posterior section of right temporoparietal junction (rTPJp, pictured), localized based on meta-analysis of brain regions activated during mentalising (Schurz et al., NBR, 2014) (MNI coordinates: 56, -56, 18).



ASSESSMENTS

[A1] Pre-treatment assessment (within week before first treatment):

Monash Biomedical Imaging:

- Structural and functional magnetic resonance imaging (T1, T2, mentalising triangles task)

MAPrc/Deakin:

- Autism Diagnostic Observation Schedule (ADOS)
- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery
- Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-2)

[A2-5] Treatment assessment (at the end of each treatment week; four in total):

- NIBS Post-stimulation survey
- NIH Toolbox Cognition Battery

Results for these assessments to be actively monitored by PI throughout treatment period.

[A-6] Post-treatment assessment (within week after last treatment):

Monash Biomedical Imaging:

- Structural and functional magnetic resonance imaging (T1, T2, mentalising triangles task)

MAPrc/Deakin:

- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

[A-7] One-month assessment (one-month after last treatment):

MAPrc/Deakin:

- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)

- NIH Toolbox Cognition Battery

[A-8] Three-month assessment:

MAPrc/Deakin:

- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

[A-9] Six-month assessment (six-months after last treatment; will also serve as "pre" assessment when crossing over):

Monash Biomedical Imaging:

- Structural and functional magnetic resonance imaging (T1, T2, mentalising triangles task)

MAPrc/Deakin:

- Autism Diagnostic Observation Schedule (ADOS)
- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

[A-10-13] Treatment assessment (at the end of each treatment week; four in total):

- NIBS Post-stimulation survey
- NIH Toolbox Cognition Battery

Results for these assessments to be actively monitored by PI throughout treatment period.

[A-14] Post-treatment assessment (within week after last treatment):

Monash Biomedical Imaging:

- Structural and functional magnetic resonance imaging (T1, T2, mentalising triangles task)

MAPrc/Deakin:

- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)

- NIH Toolbox Cognition Battery

[A-15] One-month assessment (one-month after last treatment):

MAPrc/Deakin:
- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

[A-16] Three-month assessment:

MAPrc/Deakin:
- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

[A-17] Six-month assessment:

MAPrc/Deakin:
- Autism Diagnostic Observation Schedule (ADOS)
- Social Responsiveness Scale 2nd edition (SRS-2): parent and teacher report (child participants), parent and self report (adult participants)
- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)
- Yoni task (theory of mind)
- NIH Toolbox Cognition Battery

Adverse event reporting: Adverse events will be reported via the "Non-invasive Brain Stimulation Post-Stimulation Survey v.4," which is provided as an Appendix. This is a comprehensive measure that is used in all brain stimulation studies at Deakin University. As noted above, it will be completed at the end of each treatment week. Performance on the neuropsychological battery, the NIH Cognition Toolbox, which again will be completed at the end of each week of rTMS treatment, will also be closely monitored. In the case of serious adverse events (e.g., seizure), the PI will be notified immediately, and the ethics committees will be notified within 24 hours. A formal report will also be submitted. If necessary, the trial will be suspended and the protocol reviewed before recommencement.

Data Analyses

Neuroimaging data will be analysed using SPM v12 and CONN, which are Matlab-based software packages designed for analyzing functional magnetic resonance imaging blood-oxygen-level-dependent (BOLD) response, and associated neural connectivity (i.e., by examining coherence in the BOLD response across the brain). The statistical analyses will involve a series of repeated measures analysis of variance (RM ANOVA), with the primary factors being rTMS treatment site (right temporoparietal junction vs. dorsomedial prefrontal cortex) and time (pre, post, 1-month, 3-months, 6-months). This will be performed for each of the dependent measures, with family-wise corrections for multiple comparisons. The proposed sample size (n = 20) is based on our previous studies using rTMS in ASD [14, and *in preparation*], which uncovered moderate effect sizes (d = 0.5) and significant findings in n = 12 to 15 participants. A similar effect size will be sufficient to demonstrate a significant finding in 20 participants.

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Measures

- Autism Diagnostic Observation Schedule (ADOS)

The ADOS is a standardized observational measure of autistic symptomatology. It is considered a gold-standard assessment in autism diagnosis and research. The following description is provided by the "Autism Genetic Resource Exchange" (https://research.agre.org), and is adapted from the ADOS manual:

> **The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured assessment of communication, social interaction, and play (or imaginative use of materials) for individuals suspected of having autism or other pervasive developmental disorders. The ADOS consists of four modules, each of which is appropriate for children and adults of differing developmental and language levels, ranging from nonverbal to verbally-fluent.**
>
> **The ADOS consists of standardized activities that allow the examiner to observe the occurrence or non-occurrence of behaviors that have been identified as important to the diagnosis of autism and other pervasive developmental disorders across developmental levels and chronological ages. The examiner selects the module that is most appropriate for a particular child or adult on the basis of his/her expressive language level and chronological age. Structured activities and materials, as well as less structured interactions, provide standardized contexts in which social, communicative and other behaviors relevant to pervasive developmental disorders are observed. Within each module, the participant's response to each activity is recorded. Overall ratings are made at the end of the schedule. These ratings can then be used to formulate a diagnosis through the use of a diagnostic algorithm for each module. In effect, the ADOS provides a 30- to 45-minute observation period during which the examiner presents the individual being assessed with numerous opportunities to exhibit behaviors of interest in the diagnosis of autism/PDD through standard 'presses' for communication and social interaction. 'Presses' consist of planned social occasions in which it has been determined in advance that a behavior of a particular type is likely to appear (Murray, 1938).**
>
> **The modules provide social-communicative sequences that combine a series of unstructured and structured situations. Each situation provides a different combination of presses for particular social behaviors. Module 1 is intended for individuals who do not consistently use phrase speech (defined as non-echoed. three-word utterances that sometimes involve a verb and that are spontaneous, meaningful word combinations). Materials for Module 1 have been selected for young children, but materials from other modules may be substituted if desired. Module 2 is intended for individuals with some phrase speech who are not verbally fluent. Module 3 is intended for verbally fluent children for whom playing with toys is age-appropriate (usually up to 12 - 16 years of age). Verbal fluency is broadly defined as having the expressive language of a typical four-year-old child: producing a range of sentence types and grammatical forms, using language to provide information about events out of the context of the ADOS, and producing some logical connections within sentences (e.g., "but" or "though"). Module 4 includes the many of the tasks in Module 3 (some of which are optional), as well as additional interview items about daily living. It is intended for verbally-fluent adolescents and adults. The difference between Modules 3 and 4 lies primarily in whether information about social-communication is more appropriately acquired during play or a conversational interview.**
>
> **The four modules overlap in activities, but together contain a variety of tasks ranging from observing how a young child requests that the examiner continue**

blowing up a balloon in Module 1 to a conversation about social relationships at school or work in Module 4. Modules 1 and 2 will often be conducted while moving among different places around a room, reflecting the interests and activity levels of young children or children with very limited language; Modules 3 and 4 take place sitting at a table and involve more conversation and language without a physical context. Though the superficial appearance of the different modules is quite varied, the general principles involving the deliberate variation of the examiner's behavior using a hierarchy of structured and unstructured social behaviors are the same.

Because the focus of the ADOS is on observation of social behavior and communication, the goal of the activities is to provide interesting, standardized contexts in which interactions occur. Standardization lies in the hierarchy of behavior employed by the examiner and the kinds of behaviors taken into account in each activity during the overall ratings. The activities serve to structure the interaction; they are not ends in themselves. The object is not to test specific cognitive abilities or other skills in the activities, but to have tasks that are sufficiently intriguing that the child or adult being assessed will want to participate.

In general, each module should stand on its own in providing a range of tasks and social presses. If in doubt as to which module to choose, it is better to err in choosing a module that requires fewer language skills than an individual possesses than to risk confounding language difficulties with the social demands of the instrument. The order of tasks, pacing and materials can be varied, depending on the needs of the individual being assessed.

Many of the ratings made at the end of each schedule are similar across modules, with some identical items and some that are relevant only for a subset of modules. Separate algorithms for the different modules have been generated and are presented at the end of each scoring booklet. Adequate inter-rater reliability for items has been established for all modules.

The ADOS offers clinicians and researchers the opportunity to observe social behavior and communication in standardized, well-documented contexts. These contexts are defined in terms of the degree to which the examiner's behavior structures the individual participant's response and social initiative. For purposes of diagnosis, use of this instrument should be accompanied by information from other sources, particularly a detailed history from parents whenever possible (see Lord, Rutter & Le Couteur, 1994). Its goal is to provide standardized contexts in which to observe the social-communicative behaviors of individuals across the life span in order to aid in the diagnosis of autism and other pervasive developmental disorders. For this reason, it may not be a good measure of response to treatment or developmental gains especially in the later modules. On the other hand, some items have been deliberately included across several modules, even though they have diagnostic utility only in one (e.g., response to joint attention). It may be that developmental or treatment gains will be measurable using these items. An alternative strategy to measure absolute gains is to re-administer the same modules over time, as well as administering the developmentally-appropriate module.

- Social Responsiveness Scale 2nd edition (SRS-2): parent report (child participants), parent/spouse/relative and self-report (adult participants)

The SRS-2 is a questionnaire that asks a series of questions assessing autistic symptomatology. It is considered the premier such questionnaire, and is used extensively in the literature. For child participants, a parent will complete the SRS in relation to their child. For adult participants, a parent, spouse, or relative will complete the SRS-2 about the participant, but the participant will also complete a self-report version of the SRS-2. The different versions of the SRS are all very similar, but changed for language (e.g., 1st person or 3rd person). A copy of the SRS-2 items is attached.

- Autism spectrum quotient (AQ): parent report (14-16 year-old participants), self-report (17+ year-old participants)

The Autism Spectrum Quotient (AQ) is a 50-item questionnaire that assesses characteristics and behaviors synonymous with autism spectrum disorder. It is the most widely used measure for determining someone's place on the "autism spectrum," and is used in both clinical and non-clinical research. Parents of 14-16 year-old participants will complete the parent report version, while all other participants will complete the self-report version. As with the SRS-2, the AQ versions are very similar, but changed for language (e.g., 1st person or 3rd person). Copies of the AQ are attached.

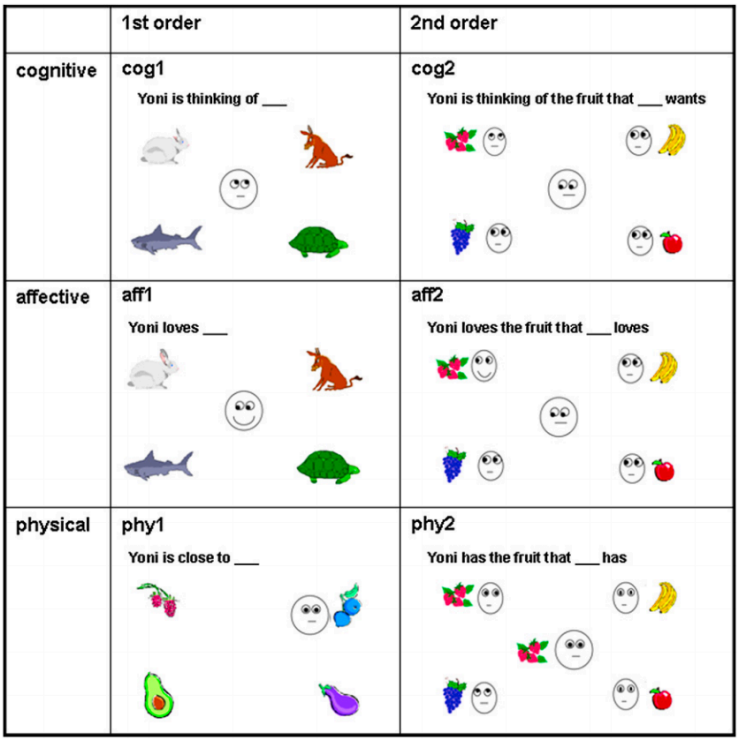
- Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-2)

The WASI-2 is a standardized measure of cognitive function/intelligence that takes about 20 minutes to complete. Participants complete four tasks that involve: i. Recreating patterns with blocks; ii. Providing definitions of common words; iii. Identifying patterns from pictures, and; iv. Describing similarities between two objects or concepts. This allows a determination of verbal, non-verbal, and overall intelligence relative to same-aged peers.

- Yoni task (theory of mind)

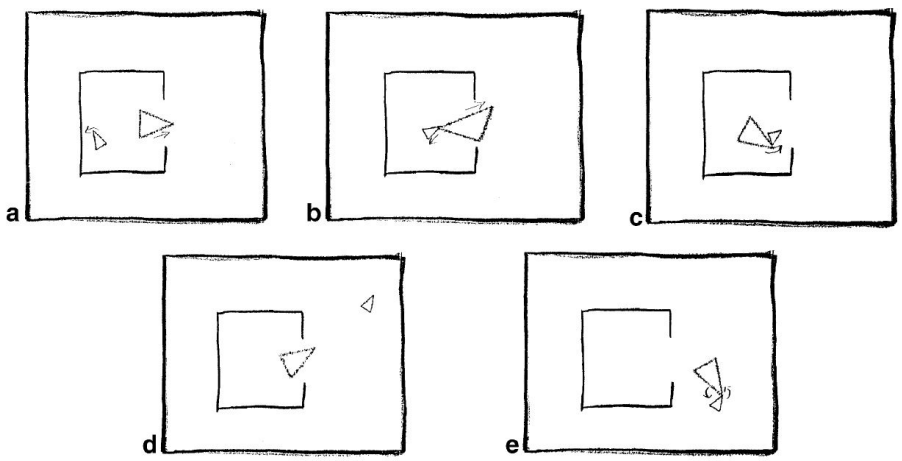
The Yoni task is a computerized assessment of "theory of mind," or the ability to deduce other people's mental and emotional states. While many theory of mind tests are designed for very young individuals, the Yoni is considered more challenging. It is also considered highly sensitive, as it allows a determination of both accuracy and speed.

The Yoni task consists of 120 items, which show a character, "Yoni," surrounded by four objects. Participants must use the computer mouse to answer a question about Yoni's relationship to the items, and in some instances this requires them to make an inference about mental and emotional states. Example items are provided below.



- Animations Task (during MRI session)

fMRI data will be collected whilst watching a series of silent animations depicting interactions between two geometric shapes, a large red triangle and a small blue triangle. In some cases these interactions are goal directed while in others the shapes drift about the screen randomly. Participants are required to metalize about and infer the social relationship of the two objects. E.g.: dancing, coaxing, and drifting. Participants will be asked by the experimenter to explain their interpretation of the interaction between the objects. This task will be adapted for presentation in the MRI scanner using a standard projector, screen and mirror arrangement so that the subject is able to respond to the task via a button press whilst undergoing the scanning procedure. This task takes about 12 minutes to complete.



Five stills taken from one of the animations scripted as Coaxing (mother and child) (a) Mother tries to interest child in going outside. (b) Child is reluctant to go out. (c) Mother gently nudges child towards door. (d) Child explores outside. (e) Mother and child play happily together.

- NIH Toolbox Cognition Battery

The NIH Toolbox Cognition Battery (http://www.nihtoolbox.org/WhatAndWhy/Cognition/Cognition%20Battery/Pages/default.aspx) is a series of simple, computerized neuropsychological tests that provide measures of the following:

- Executive Function
- Attention
- Episodic Memory
- Language
- Processing Speed
- Working Memory

Each of the tests involves responding to simple images and words on a tablet screen. Example images are provided below. The battery takes approximately 20 minutes to administer.

The NIH Cognition Toolbox has extensive normative data available, allowing us to track participant's cognitive function relative to their own performance, but also relative to performance of same-aged peers.

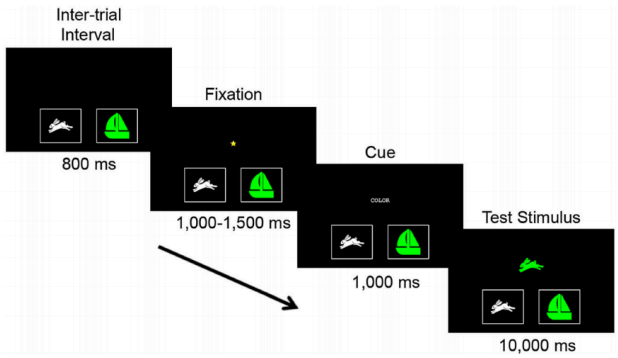


FIGURE 1.—Trial sequence for the Toolbox Dimensional Change Card Sort Test (with practice stimuli). © 2006–2012 National Institutes of Health and Northwestern University.

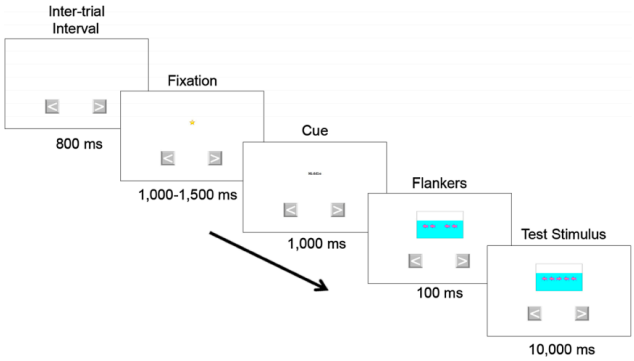


FIGURE 2.—Trial sequence for the Toolbox Flanker Inhibitory Control and Attention Test (fish block). © 2006–2012 National Institutes of Health and Northwestern University.

- NIBS Post-stimulation survey

The NIBS Post-stimulation survey is a measure used across all brain stimulation studies conducted at Deakin University. It is intended to provide a comprehensive assessment of side-effects experienced from brain stimulation. A copy of this measure is attached.