Neural circuit mapping of waiting impulsivity and proactive inhibition with convergent evidence from fMRI and TMS

Introduction

- Waiting and stopping are essential and distinct elements of appropriate behavioural control with its dysfunction implicated in various impulsivity related mental disorders
- Waiting impulsivity is operationally defined as the tendency to respond before target onset after a reward-predicting cue in the 5 Choice Serial Reaction Time Task (5CSRTT) (1)
- In humans, waiting impulsivity is associated with decreased connectivity of STN with ventral striatum and subgenual cingulate (2)
- Preparing to stop plays a role in appropriate response inhibition. Proactive inhibition depends on participants’ strategy and knowledge of task contingencies as shown in studies using stop-signal paradigms i.e. measuring reactive stopping (3,4)
- No studies have investigated how preparing to stop affects waiting impulsivity where no stop-signal occurs

Aim

We conducted two separate, but hierarchical studies

1st study
We aimed to map the neural circuit involved in waiting impulsivity and proactive stopping by:
- using an adapted human version of the 5CSRTT, the 1CSRTT, which included extensive overtraining in the fixed cue-target interval, which was not implemented in previous human studies
- developing a new proactive stopping paradigm with a baseline similar structure to the 1CSRT task
  - using fMRI
  - in healthy volunteers, N=41 (24f: 17m)

2nd study
Based on our fMRI study data showing a strong association between LIFG activity and variability in waiting impulsivity in the 1CSRT task, we then attempted to investigate possible causation between LIFG and waiting impulsivity.
We used:
- an adapted 1CSRTT
- an inhibitory off-line TMS protocol called continuous theta burst stimulation (cTBS) stimulation increased premature responses in the testing session of the adapted 1CSRTT after controlling for covariates, p= .034
  - The stimulation group also showed more premature responses compared to the sham group during the testing session, p <.05
  - Premature responses presented as proportion (i.e. premature responses/total number of trials in both training and testing sessions)

Method

A. fMRI study

- Pre-scan training session had 500 non-delayed trials with a fixed cue-target interval.
- FMRI testing session had 300 test trials, of which 120 non-delayed trials and 80 delayed trials, and 80 null trials
- The cue-target interval differs between non-delayed trials (fixed) and delayed trials (variable)

Structure of the 1CSRT task

(a) Pre-scan training session had 350 non-delayed trials with a fixed cue-target interval. FMRI test session had 200 test trials, of which 120 non-delayed trials and 80 delayed trials, and 80 null trials
(b) The cue-target interval differs between non-delayed trials (fixed) and delayed trials (variable)

B. Human 1CSRT trial types

- Non-delayed trials: no stop-signal occurs
- Delayed trials: in 25% of these trials, participants were required not to release the left button when the stop target appeared
- Baseline trials: punished if participants did not press the button upon appearance of the green circle as in the baseline trials (Go-trials)

Experimental trial design in the proactive inhibition task

(a) Baseline trials with same structure as the 1CSRT non-delayed trials
(b) Proactive inhibition trials with red fixation cross indicating possibility of stop-signal; 40% of these trials, participants were required to release the left button when the stop target appeared (No-Go target)
(c) cTBS stimulation increased premature responses in the testing session of the adapted 1CSRTT after controlling for covariates, p= .034
(d) The stimulation group also showed more premature responses compared to the sham group during the testing session, p <.05

Results

Premature responses in the fMRI 1CSRTT

- Premature responses were significantly decreased in 25% of the proactive inhibition trials with No-Go target. RTs of correct responses were increased in the proactive inhibition task and this increase was negatively correlated with the premature responding rate in these trials.

Neural basis of internal inhibition in 1CSRTT and proactive inhibition tasks

- Premature responses presented as proportion (i.e. premature responses/total number of trials in both training and testing sessions).

Conclusion

- Validation of the 1CSRTT as a translational analogue for human neuroimaging studies
- Development of novel proactive inhibition task with promise for translational significance
- We showed a causal role of LIFG in waiting impulsivity
- We established causality with subsequent cTBS study
- Provided further insight into waiting impulsivity with tasks of translational significance among animal and human studies

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References