Inter-individual variability of TMS responsiveness on semantic processing: a combined MRS and fMRI-guided cTBS study

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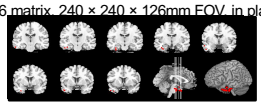
Introduction

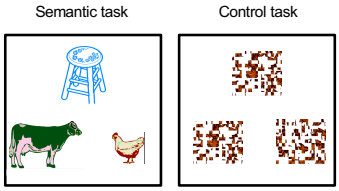
- Transcranial magnetic stimulation (TMS) is a non-invasive technique to modulate cortical excitability in human brain. However, one major challenge with TMS is that the response to stimulation is highly variable across individuals.
- Converging evidence indicates that the human anterior temporal lobe (ATL) is a semantic representational hub.
- We investigate the inter-individual variability of TMS responsiveness on semantic representation using a combined functional magnetic resonance imaging (fMRI)/magnetic resonanc spectroscopy (MRS) in order to measure the neural and neurochemical profiles of the ATL before stimulation and continuous theta-burst stimulation (cTBS) was delivered at the ATL t measure the TMS-responsiveness at behavioral level.

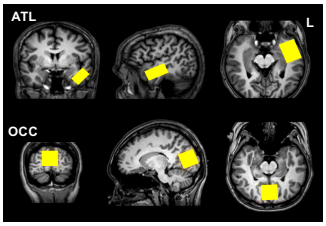
Methods

- 20 healthy right-handed participants (13 females, mean age = 23 year ± 4)
- Image acquisition
  - **Single voxel ^{1}H MRS** using a GABA-edited MEGA-PRESS spectra with the application of the MEGA inversion pulses at 1.95ppm (TR = 2000ms, TE = 68ms)
  - **T1-weighted image** using a 3D MPRAGE pulse sequence, with 200 slices, 256 x 256 matrix, in plane resolution 0.94 x 0.94 x 0.9 mm, TR = 8.4ms, TE = 3.9ms
  - **fMRI** using a dual-echo protocol[1], with 42 slices, 96 × 96 matrix, 240 × 240 × 126mm FOV, in plane resolution 2.5 × 2.5 × 3mm, TR = 2.8s, TE = 12 & 25ms
- TMS
  - cTBS at 80% resting-motor thresholds
  - mean intensity = 47% range from 42% to 60%



- Task & MRS localization





Results

- Definition of Responders

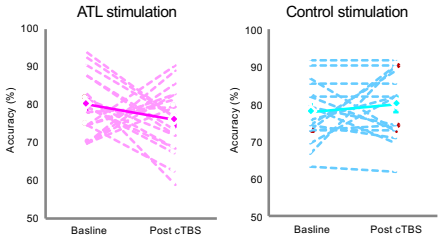


Fig. 1 cTBS-induced changes in the semantic task at individual level. A circle represents an individual and a diamond represents the mean of performance.

Individuals showing a decrease in task performance at the post cTBS compared to their baseline were defined as ***responders***, whereas participants showing no changes or an increase in their performance after the cTBS were defined as ***non-responders***.

- cTBS-induced plasticity in task performance

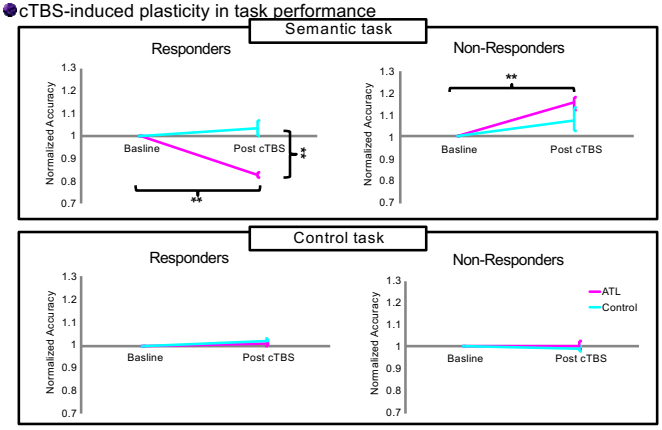


Fig.. 2 Changes in the normalized accuracy after cTBS. The normalized task performance was used by reflecting the individual variability in the baseline performance: individual performance was divided by the baseline performance. ATL stimulation leads to a significant decrease in the semantic task compared to the baseline and the control stimulation in ***responders***, whereas a significant increase in it compared to the baseline in ***non-responders***. ** p < 0.001

- *ANOVA with site (ATL vs. Control) × TMS (Baseline vs. post cTBS) × Task (Semantic vs. Control) × Group (Responder vs. Non-responder)*
  - *Main effect of the site ($F_{1, 17}$ = 34.29, p < 0.001)*
  - *Interactions: task × group ($F_{1, 17}$ = 25.86, p < 0.001), site × task × group ($F_{1, 17}$ = 25.17, p < 0.001), TMS × task × group ($F_{1, 17}$ = 17.92, p < 0.001) , site × TMS × task × group ($F_{1, 17}$ = 15.57, p < 0.001)*
- ***Responders*** *showed a decrease in semantic task accuracy: inhibitory TMS effects*
- ***Non-responders*** *showed an increase in semantic task accuracy: facilitatory TMS effects*

- Neural differences between responders and non-responders

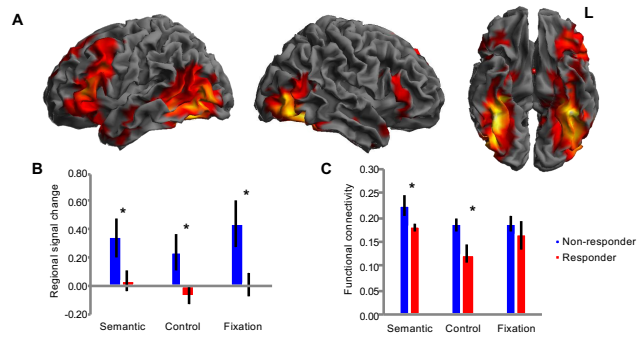


Fig. 3 (A) Brain activation map for the contrast of interest (semantic > control) (B) ATL regional activity differences between responders and non-responders (C) Functional connectivity differences of semantic network between responders and non-responders across the task conditions, * p < 0.05

- ***Non-responders*** *compared to* ***responders*** *showed significantly increased regional activation in the ATL and the functional connectivity of the semantic network across the task conditions.*

- Neurochemical profiles of ATL and TMS responsiveness

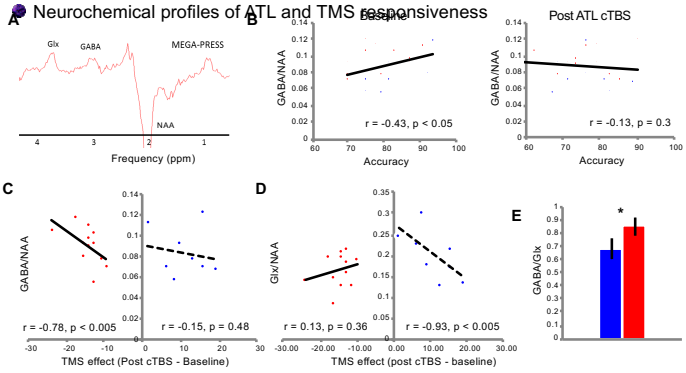


Fig. 4 (A) A representative MRS spectrum with estimated peaks (B) Relationship between the ATL GABA levels and task performance (C) ***Responders*** showed a significant correlation between the ATL GABA and TMS effects (D) ***Non-responders*** shows a significant correlation between ATL Glx and TMS effects (E) GABA/Glx (inhibitory/excitatory ratio) was higher in ***responders*** compared to ***non-responders.*** * p <0.05

Conclusion

- Responders and non-responders differed in cTBS-induced aftereffects on task performance: responders showed a task-specific inhibitory TMS effects in their task performance, whereas non-responders showed a paradoxical facilitatory effects.
- cTBS non-responders compared to responders featured higher pre-interventional levels of the ATL activity and the functional connectivity in the semantic network: high pre-interventic levels of neural profiles could preclude a further change in cortical excitability and functional connectivity.
- Only in responders, the steady-state GABA concentrations in the ATL predicted cTBS-induced aftereffects: responders with higher GABA levels showed stronger TMS effects.
- Responsiveness to cTBS on semantic processing may be strongly linked to the pre-interventional neural and neurochemical profiles of the ATL.

References

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2. Nettekoven C, Volz LJ, Leimbach M, Pool EM, Rehme AK, Eickhoff SB, Fink GR, Grefkes C (2015) Inter-individual variability in cortical excitability and motor network connectivity following multiple blocks of rTMS. Neuroimage 118:209-218.4
3. Duncan, N.W., Wiebking, C. & Northoff, G. Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans-A review of multimodal imaging studies. *Neurosci Biobehav R* **47**, 36-52 (2014)