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Neurochemical profiles of the anterior temporal lobe predict response of repetitive transcranial magnetic stimulation on semantic processing

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ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique used to modulate cortical excitability in the human brain. However, one major challenge with rTMS is that the responses to stimulation are highly variable across individuals. The underlying reasons why responses to rTMS are highly variable between individuals still remain unclear. Here, we investigated whether the response to continuous theta-burst stimulation (cTBS) – an effective rTMS protocol for decreasing cortical excitability – is related to individual differences in glutamate and GABA neurotransmission. We acquired resting-state magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI) during semantic processing. Then, we applied cTBS over the anterior temporal lobe (ATL), a hub for semantic representation, to explore the relationship between the baseline neurochemical profiles in this region and the response to cTBS. We found that the baseline excitation-inhibition balance (glutamate + glutamine/GABA ratio) in the ATL was associated with individual cTBS responsiveness during semantic processing. Specifically, individuals with lower excitation-inhibition balance showed stronger inhibitory effect – poorer semantic performance. Our results revealed that non-responders (subjects who did not show an inhibitory effect of cTBS on subsequent semantic performance) had higher excitatory-inhibitory balance in the ATL, which led to up-regulated task-induced regional activity as well as increased ATL-connectivity with other semantic regions compared to responders. These results disclose that the baseline neurochemical state of a cortical region can be a significant factor in predicting responses to cTBS.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technique used to modulate cortical excitability in the human brain. Theta-burst stimulation (TBS), a repetitive TMS protocol induces effective modulation of cortical excitability in the stimulated region for up to an hour with a rather short period of stimulation (Huang et al., 2005). However, one major challenge with rTMS/TBS is that the responses to stimulation are highly variable across individuals. Recent studies demonstrated high inter-individual variability in response to rTMS/TBS in the motor system and suggest that about 50 ~ 70% of participants either did not respond or responded in an unexpected manner (Goldsworthy et al., 2014; Hamada et al., 2013; Hinder et al., 2014; Lopez-Alonso et al., 2014; Maeda et al., 2000a; Muller-Dahlhaus et al., 2008).

The underlying reasons why responses to rTMS/TBS are highly variable between individuals are not well understood, but several factors come into play, including age, gender, time of the day, regular activity, attention, previous history of plasticity, neuromodulation, and genetics (Ridding and Ziemann, 2010). In one of the first studies employing TBS protocols in a burst-firing pattern (3 pulses at 50Hz, total 600 pulses), Huang et al. (2005) reported that continuous TBS (cTBS) suppressed motor evoked potentials (MEPs), whereas intermittent TBS (iTBS delivering 2s train repeated every 10s for 20 repetitions) facilitated it in the human motor cortex (M1). To examine the inter-individual variation of the TBS responsiveness, Hamada et al. (2013) stimulated the M1 with a larger sample size (N = 56) and found approximatley one quarter of participants showed the expected response of the TBS protocols. They suggested that about 50% of this variation may be accounted for by differential recruitment of subtypes of cortical interneurons. Recent studies combining functional magnetic resonance imaging (fMRI) and TBS demonstrated that the differential recruitment of these interneurons correlated with the functional connectivity of the motor system

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(Volz et al., 2015) and the responsiveness to TBS depended on the pre-interventional network connectivity of the stimulated region (Cardenas-Morales et al., 2014; Nettekoven et al., 2015).

Moreover, the mechanism underlying rTMS/TBS effects on brain tissue are not clearly defined. Previous studies demonstrated that rTMS alters cortical excitability through changes in synaptic strength (Chen et al., 1997; Cooke and Bliss, 2006; Fitzgerald et al., 2006; Huang et al., 2005; Maeda et al., 2000b; Pascual-Leone et al., 1994). Animal models provide evidence that TBS protocols are more likely to induce long-term potentiation (LTP) and long-term depression (LTD) (Hess et al., 1996; Huemmeke et al., 2002; Vickery et al., 1997), which depend on the GABAergic and glutamatergic systems in the cortex (Funke and Benali, 2011; Lenz et al., 2016; Trippe et al., 2009). In the human, the effects of TBS on synaptic transmission have been measured indirectly, by administrating pharmacological agents (Huang et al., 2007). Recently, Stagg et al. (2009) used magnetic resonance spectroscopy (MRS) to measure local changes in the cortical concentrations of GABA and glutamate + glutamine (Glx). They demonstrated that cTBS increased the GABA concentrations at the target site. The study provides direct evidence of GABAergic interneuronal activity for the underlying mechanism of cTBS and suggests a possibility that the GABAergic system can also be an important factor in rTMS responsiveness.

Contrary to studies on the motor system, the inter-individual variability of rTMS responsiveness has not been investigated in higher cognitive functions such as language and memory. Some studies have excluded non-responders and only reported the results of responders (Pattamadilok et al., 2015; Sliwinska et al., 2015) or reported contrary results from the stimulation protocols (e.g., inhibitory 1Hz rTMS/cTBS inducing a facilitatory effect) (Andoh et al., 2006; Bonni et al., 2015). Given the dearth of information about the nature of individual differences in rTMS on higher cognition, in this study, we explored this use respect to semantic memory, a feature of human higher cognition by employing a combination of MRS, fMRI and rTMS.

Semantic memory is defined as the collective knowledge of the world including words, pictures, objects, people, and emotions. Converging evidence indicates that the anterior temporal lobe (ATL) is the site of a transmodal hub that generates coherent semantic representations by interacting with multiple modality-specific brain regions (Binney et al., 2010; Doeltgen et al., 2010; Patterson et al., 2007; Pobric et al., 2007; Sale et al., 2010; Todd et al., 2010a; Todd et al., 2010b; Visser et al., 2012). Thus, perturbing the ATL with inhibitory rTMS/TBS produces a temporal semantic impairment leading to slower reaction times in healthy participants (Jung and Lambon Ralph, 2016; Lambon Ralph et al., 2009; Pobric et al., 2010a, b; Pobric et al., 2007). Although ATL rTMS effects on semantic processing have been repeatedly demonstrated at the group level, there are often considerable individual differences in the rTMS effect.

Here, we investigated the inter-individual variability of rTMS responsiveness on semantic processing at the behavioural level as well as at a neural/neurochemical level using a combined MRS and fMRI-guided cTBS. Previously, we demonstrated that the neurochemical profiles of the ATL were associated with task-induced regional activity and task performance during semantic processing (Jung et al., 2017). Specifically, GABA concentrations in the ATL were positively correlated with semantic task performance and negatively associated with task-induced regional activity in the ATL during semantic processing. Here, we used the resting-state MRS and fMRI data from our previous study as the baseline neurochemical profiles including GABA, Glx concentrations, and Glx/GABA ratio (excitation and inhibitory balance: EIB). Then, we asked participants to attend following cTBS sessions. cTBS was delivered at the ATL through individually fMRI-guided TMS neuronavigation which maximizes rTMS effects at the behavioural level (Sack et al., 2009). Participants were assigned into two groups (responders and non-responders) based on their semantic performance changes after cTBS at the ATL. Based on previous studies showing the involvement of GABAergic and glutamatergic systems in rTMS effects (Funke and Benali, 2011; Lenz et al., 2016), we explored the relationship between ATL cTBS responsiveness in semantic processing and baseline neurochemical profiles including GABA, Glx, and EIB in the ATL. Then, we compared the baseline neurochemical profiles of the ATL between responders and non-responders. Our previous investigation demonstrated that the synchronization of the semantic network inclduing the ATL, prefrontal, and posterior temporal cortices were positively associated with the level of ATL GABA levels and semantic task performance (Jung et al., 2017). Nettkoven et al. (2015) demonstrated that pre-interventional nerual states predict the TBS responsiveness in the motor system, such that responders showed decreased functional connectivity in the motor network compared to non-responders. Thus, we hyphothesized that the neural state of the semantic network prior to the stimulation could be associated with rTMS responsiveness in semantic processing. Specifically, responders would show decreased connectivity in the semantic system including the ATL compared to non-responders.

2. Materials and methods

2.1. Subjects

Twenty healthy English native speakers (7 males, mean age = 23 years ± 4, range from 20 to 36 years) participated in this study. Right-handedness was confirmed using the Edinburgh Handedness Inventory (Oldfield, 1971). All subjects provided informed written consent. The study was approved by the local ethics committee.

2.2. Experimental design and procedure

All subjects had an fMRI and MRS at rest at the beginning of the study, which have been previously included in a previous publication (Jung et al., 2017). They performed a semantic association task and a picture matching task as a control task during fMRI. We used the picture version of semantic association task employed by previous studies (Pobric et al., 2010c; Visser et al., 2012). The semantic association task required subjects to select which of two pictures was more related in meaning to a probe picture. Three pictures were presented on the screen, a probe picture on the top, the target, and unrelated picture at the bottom (Fig. 1A left). In the control task, subjects had to select which of two patterns was identical to a probe pattern (Fig. 1A right). The items for the pattern matching task were created by scrambling the pictures used in the semantic association task. An fMRI scanning had 9 blocks of each task (interleaved order, A-B-A-B). Fixation blocks for 4000ms were interleaved with task blocks. A task block had 4 trials of each task and a trial started with 500ms fixation followed by the stimuli for the duration of 4500ms.

After the MRI, all subjects had two rTMS sessions on different days. In each session, subjects received rTMS stimulation at the left ATL or control site (occipital pole). The order of stimulation was counterbalanced across subjects. A session consisted of a baseline block (No-TMS) and the after TMS block (post cTBS). The baseline was performed before or 50mins after the stimulation. The order of blocks was counterbalanced across subjects. In each session, subjects performed the same semantic association task and the control task. Tasks had 63 trials and a trial started with 500ms fixation then the stimuli were presented until response or 3000ms. E-prime software (Psychology Software Tools Inc., Pittsburgh, USA) was used to display stimuli and to record responses.

2.3. fMRI-guided transcranial magnetic stimulation

To guide a TMS target site, we used the individual fMRI results of the contrast of interest (semantic > control). The maximal peak activation in the ATL (MNI coordinates) was selected and converted to the untransformed individual naïve space coordinate. The target site was used to guide the frameless sterotaxy, a Brainsight TMS-fMRI co-registration

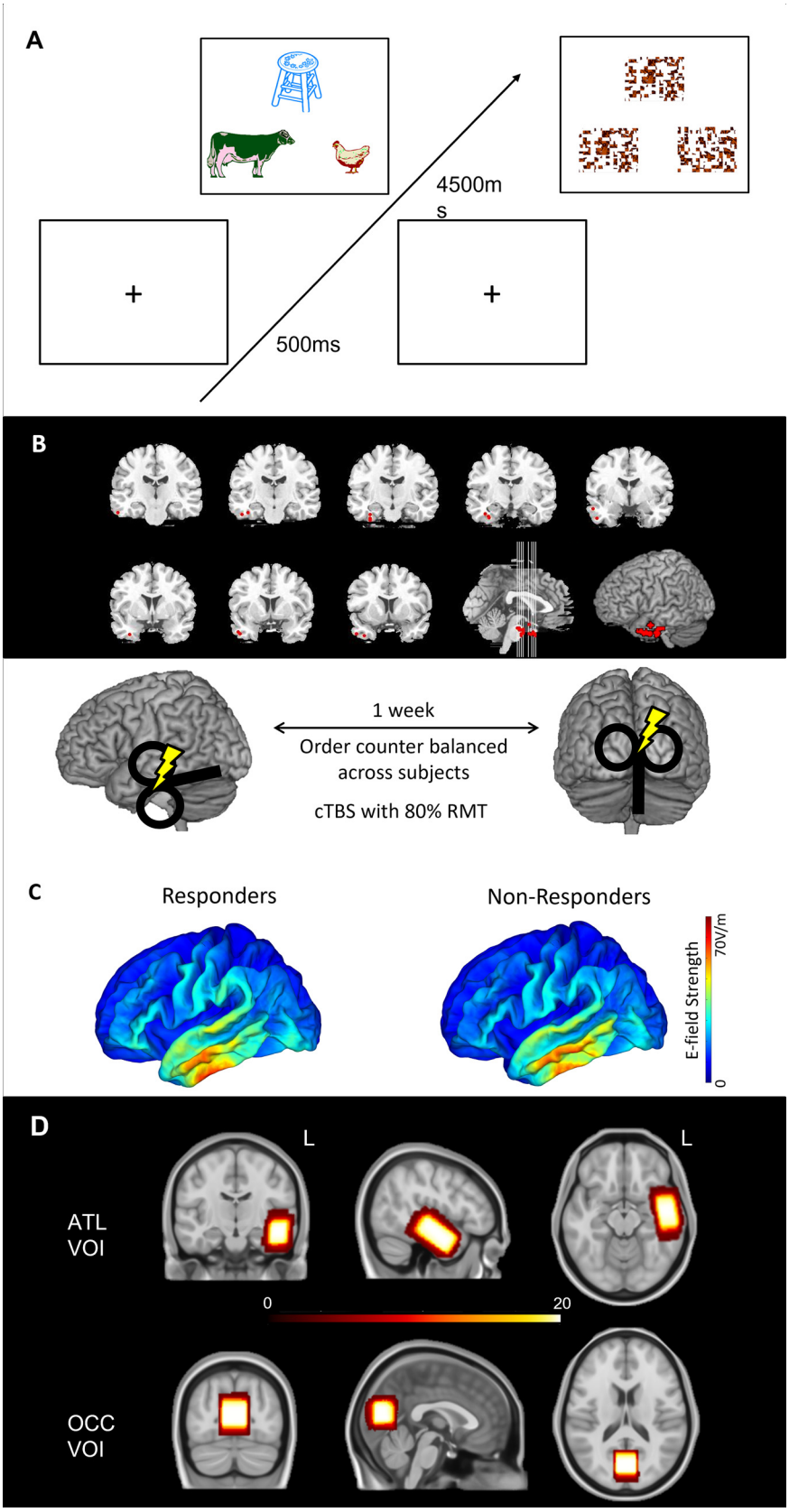

Fig. 1. **A.** Experimental design. Left: semantic association task, Right: pattern matching task. **B.** The procedures of cTBS sessions. fMRI-guided individual TMS sites. Red dots indicate individual peak coordinates in the ATL during semantic processing. C. The averaged ATL TMS E-fields for responders (left) and non-responders (right). **D.** The location of volume of interest (VOI) for MRS: ATL and OCC. The colour bar indicates the overlapping number of subjects.

Table 1
fMRI-guided TMS sites for individuals.

	Maximal peak coordinates		
	X	y	z
sub01	-32	-10	-34
sub02	-38	-10	-28
sub03	-48	-16	-29
sub04	-33	-13	-38
sub05	-57	-19	-26
sub06	-45	5	-35
sub07	-48	5	-32
sub08	-33	-13	-29
sub09	-45	11	-32
sub10	-36	8	-38
sub11	-39	-16	-26
sub12	-33	-10	-32
sub13	-33	2	-36
sub14	-33	-13	-29
sub15	-54	-1	-20
sub16	-48	17	-32
sub17	-48	8	-35
sub18	-33	-13	-35
sub19	-33	-13	-35
sub20	-48	-1	-35

system (Rogue Research, Montreal, Canada). TMS target sites were located within the left anterior/ventrolateral ATL. Table 1 and Fig. 1B summarise the maximal peak activation and the actual TMS target site on the normalized brain (the lateral view). occipital pole (Oz) was used as a control site using international 10-20 system.

2.4. Theta-burst stimulation

cTBS was delivered over the left ATL using a Magstim Super Rapid stimulator with a figure-of-eight coil (70mm standard coil, MagStim Company, Whitland, UK) according to Huang et al. (2013).xxxx cTBS was applied at 80% of the resting motor threshold (RMT). RMT was defined as a minimal intensity of stimulation inducing motor evoked potentials in the contralateral FDI muscle in at least 5 of 10 stimulation trials at the optimal scalp position. The average stimulation intensity (80% RMT) was 47% ranging from 34% to 60%.

We used SimNIBS v 3.2 to calculate individual electric field of cTBS (Thielscher et al., 2015). The individual head models were generated from T1 images using the pipeline by Nielsen and colleagues (Nielsen et al., 2018). The head model consisted of five tissue types comprising grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), skull, and scalp. We applied the fixed conductivity values implemented in the SimNIBS: 0.275 S/m (GM), 0.126 S/m(WM), 1.654 S/m (CSF), 0.01 S/m (skull), and 0.465 S/m (scalp). Employing Saturnio and colleagues' procedure (2019), the electric field interpolation was conducted to determine the electric field at the target (ATL) within grey matter and computed the electrical field at the centre of grey matter. Then, we averaged the individual electric field according to responders and non-responders (Fig. 1C). There was no significant difference in the e-field strength between responders and non-responders ($p = 0.24$).

2.5. Definition of responders

The aim of this study was to investigate whether inter-individual differences in the behavioural performance response to cTBS were related to the different neural profiles of the stimulated region and the related-brain network before the stimulation. Therefore, responders and non-responders were classified according to their semantic performance changes after the ATL stimulation: subjects showing a decrease in task performance at the post ATL cTBS compared to the baseline were defined as responders; whereas subjects showing no changes or an increase in their task performance after the ATL cTBS were defined as non-responders. This criterion ensured that responders had task-specific rTMS effect (inhibitory) as expected by the stimulation protocol.

2.6. fMRI data acquisition and analysis

fMRI images were acquired on a 3T Philips Achieva scanner using a 32-channel head coil with a SENSE factor 2.5 using a dual-echo sequence with the following parameters: 42 slices, 96 × 96 matrix, 240 × 240 × 126mm FOV, in-plane resolution 2.5 × 2.5, slice thickness 3mm, TR = 2.8s, TE = 12ms and 35ms, 258 volumes. The sequence was developed to maximise signal-to-noise (SNR) in the ATL by Halai et al. (2014). A high-resolution T1-weighted structural image was acquired using a 3D MPRAGE pulse sequence with following parameters: 200 slices, in-planed resolution 0.94 × 0.94mm slice thickness 0.9mm, TR = 8.4ms, TE =3.9ms. fMRI data were analysed using Statistical Parametric Map (SPM8, http://www.fil.ion.ucl.ac.uk/spm/). First, dual gradient echo images were realigned to the mean image of each time series and corrected for slice timing by shifting the signal measured in each slice relative to the acquisition of the middle slice. Then, the dual gradient echo images were averaged using in-house MATLAB code developed by Halai et al. (2014). The mean EPI volumes were coregistered with the structural T1-weighted image. All images were spatially normalized to the MNI template using the DARTEL (diffeomorphic anatomical registration through an exponentiated lie algebra) toolbox (Ashburner, 2007) and smoothed with an isotropic Gaussian kernel of 8mm full-with at half-maximum.

A general linear model (GLM) was used for statistical analyses. The three experimental conditions (semantic, control, and fixation) were modelled using boxcar stimulus functions convolved with a canonical hemodynamic response function. Six head motion parameters resulting from the realignment were entered as covariates to remove movement-related variance. The time series of each voxel were high-pass filtered at 1/128Hz. A contrast of interest (sematic > control) for each participant were calculated. Voxels were considered significant on the individual level if passing a threshold of $p_{\text{uncorrected}} < 0.001$ (for the TMS target site). For the group-level analysis, the estimations of the contrast of interest were entered into one-sample t-tests. Clusters were considered significant when passing a threshold of $p_{\text{FWE-corrected}} < 0.05$, with at least 100 contiguous voxels.

Marsbar (Brett et al., 2002) was used for region of interest (ROI) analysis. Six ROIs based on the result of group level analysis were defined as a sphere with a radius of 5mm from the contrast of interest (semantic > control). The ROIs defined as the semantic network included the ATL (peak activation left: -36, -6, -36; right: 33, -6, -36), vlPFC (peak activation left: -48, 21, 24; right: 57, 24, 21), and pMTG (peak activation left: -57, -48, -3; right: 54, -69, 12).

Functional connectivity toolbox (CONN) (http://web.mit.edu/swg/software.htm) was used for computing temporal correlation between the defined ROIs. Pre-processed fMRI images were registered into the toolbox with the six ROIs. Connectivity analyses provided ROI-to-ROI functional connectivity estimations for the experimental conditions (semantic, control, and baseline). The head motion parameters were entered as regressors and all voxels were filtered ($0.01 < f < \text{Inf}$) to decrease the effect of low-frequency drift. CompCor strategy implemented in the toolbox removed several sources of noise from white matter, cerebral fluid, and the others. Functional connectivity (Fisher's Z-transformed Pearson correlation coefficient) among ROIs was averaged for network-level analyses.

2.7. MRS data acquisition and analysis

GABA-edited MEGA-PRESS spectra were acquired from an ATL voxel (35 × 25 × 15mm) and an occipital control voxel (30 × 30 × 30mm). The ATL voxel was positioned on the left anterior/lateral temporal lobe, excluding hippocampus (Fig. 1D). The occipital voxel was aligned with

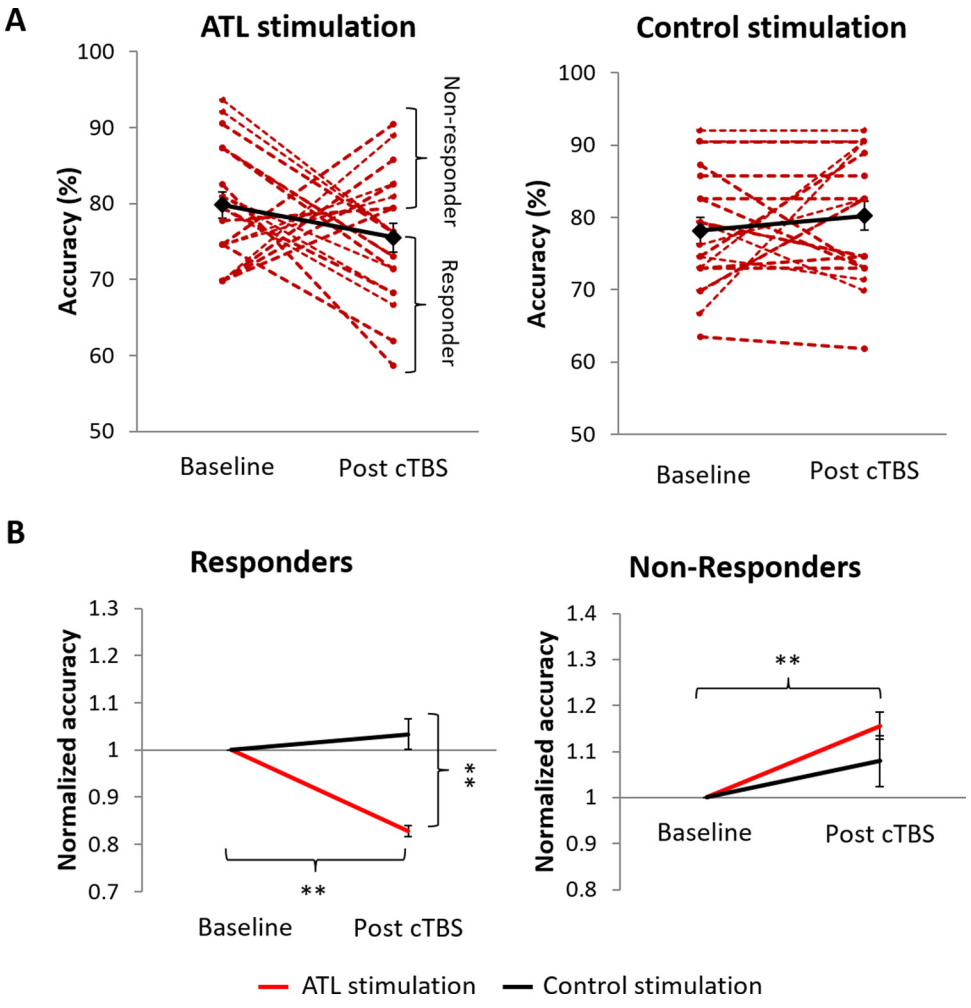

Fig. 2. **A.** cTBS-induced changes in the semantic task. A red circle represents an individual performance and a black diamond represents the mean of performance. **B.** cTBS-induced changes in normalized accuracy of the semantic task. Red lines present the ATL stimulation. Black lines indicate the control stimulation. Error bar represents standard error. ** $p < 0.005$.

the occipital midline covering both hemispheres (Fig. 1D). The following parameters were used: repetition time = 2000ms, echo time = 68ms. Spectra were acquired in interleaved blocks of 4 scans with application of the MEGA inversion pulses at 1.95 ppm to edit the GABA signal and at 7.45 ppm as control; 79 repeats at the ATL and 74 repeats at the OCC. A total of 1024 sample points were collected at a spectral width of 2 kHz. Each MRS voxel took approximately 10mins to complete. Quantification was conducted using the Advanced Magnetic Resonance (AMARES) in the Java-based magnetic resonance user's interface (jMRUI.1, EU project www.jmrui.eu) (Naressi et al., 2001). The water resonance was removed using the Hankel Lanczos Singular Valve Decomposition (HLSVD) algorithm (van den Boogaart et al., 1994). To improve the display of the spectra, line broadening of 7 Hz was used. No time-domain filtering was performed on the data before analysis by AMARES. All metabolite resonances were measured and a ratio was calculated for NAA, GABA and Glx (a combined measure of glutamate and glutamine). No correlations of GABA and Glx levels between the ATL and OCC were found (ps > 0.47).

To examine partial volume effects on MRS VOIs, the T1-weighted anatomical images were segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using SPM8. Then voxel registration was performed using custom-made scripts developed in MATLAB by Dr. Nia Goulden, which can be accessed at http://biu.bangor.ac.uk/projects.php.en. The scripts generated a mask for voxel location by combining location information for the Philips SPAR file with orientation and location information contained within the T1 image. The calculation of partial volume within the voxels provided the percentage of each tissue type within the relevant voxels. Partial correlation analyses were performed with the percentage of each tissue (GM, WM) as covariates accounting for the partial volume effects in the voxels.

3. Results

3.1. cTBS-induced plasticity in task performances

Subjects performed the same fMRI tasks at baseline and following the cTBS. Then, based on the semantic task performance changes caused by cTBS, twelve of the subjects were classified as responders and eight as non-responders (Fig. 2A). A four-way repeated measures ANOVA with site (ATL vs. Oz), TMS (baseline vs. post cTBS), and task (semantic vs. control) as within subject factors and group (responders vs. non-responders) as a between subject factor in accuracy revealed a significant main effect of the site ($F_{1, 17} = 34.29$, $p < 0.001$) and an interaction effect between task × group ($F_{1, 17} = 25.86$, $p < 0.001$), site × task × group ($F_{1, 17} = 25.17$, $p < 0.001$), TMS × task × group ($F_{1, 17} = 17.92$, $p < 0.001$), and site × TMS × task × group ($F_{1, 17} = 15.57$, $p < 0.001$). In order to assess semantic performance differences after cTBS between responders and non-responders, we conducted three-way repeated measures ANOVA with TMS, site and group for each task. In the semantic task, we found a significant main effect of site ($F_{1, 17} = 5.23$, $p < 0.05$) as well as an interaction between TMS × group ($F_{1, 17} = 25.21$, $p < 0.001$) and site × TMS × group ($F_{1, 17} = 28.04$, $p < 0.001$) (Supplementary Fig. S1). Post-hoc t-tests were performed on the normalized task performance thereby reflecting the individual variability in the baseline performance (Fig. 2A): individual performance was divided by the base-

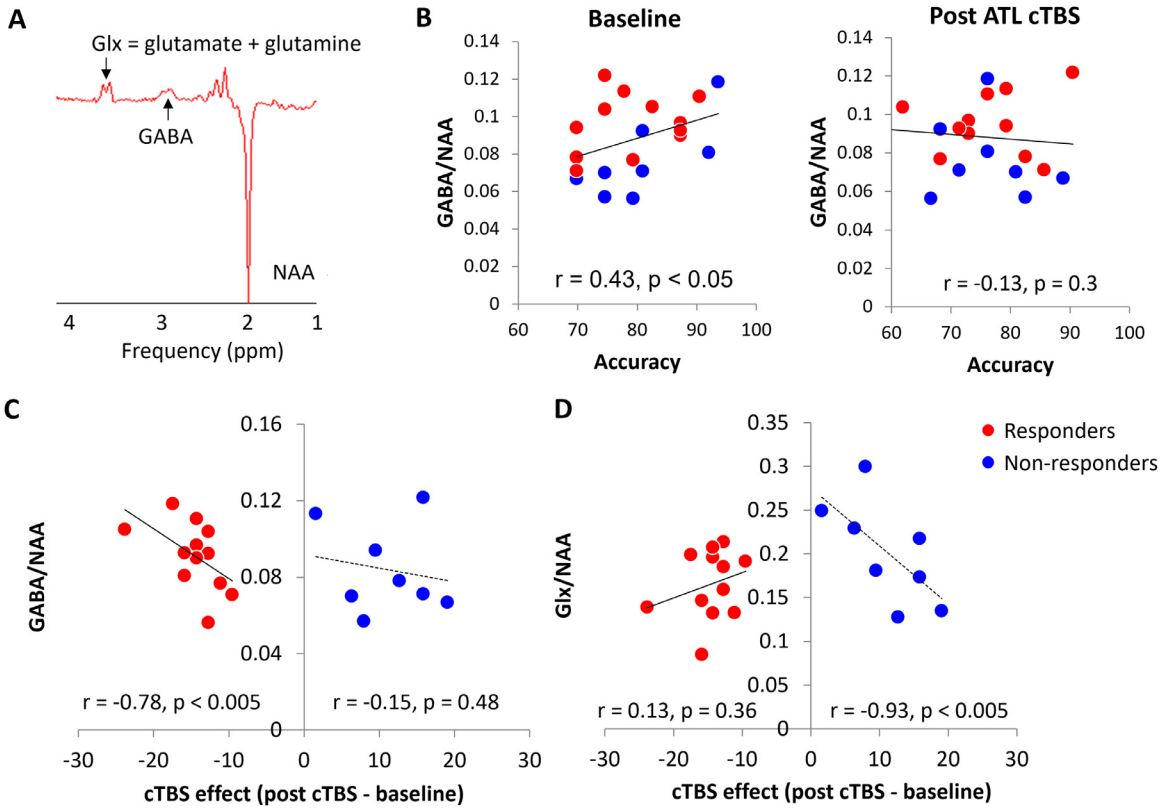

Fig. 3. ATL GABA and Glx concentrations and TMS responsiveness. **A.** A representative MRS spectrum with estimated peaks. NAA: N-acetylaspartate **B.** Relationship between ATL GABA concentrations and task accuracy with and without ATL cTBS. Semantic task accuracy was from the cTBS sessions. **C.** Responders showed a significant correlation between ATL GABA concentrations and cTBS effects, whereas non-responders did not. **D.** Non-responders showed a significant correlation between ATL Glx concentrations and cTBS effects. Red circles represent responders. Blue circles represent non-responders.

line performance, so the normalized baseline was always '1'. cTBS over the ATL reduced the accuracy in responders when compared to its baseline ($t = 14.47$, $p < 0.001$) as well as the accuracy after the control stimulation ($t = -5.12$, $p < 0.001$) (Fig. 2B). Also, responders revealed a significant decrease in accuracy compared to non-responders ($t = 5.83$, $p < 0.001$). On the contrary, cTBS at the ATL increased the accuracy in non-responders compared to the baseline ($t = -5.26$, $p < 0.001$) but no difference in it compared to the control stimulation ($p > 0.55$) (Fig. 2B). That is, responders showed a task-specific inhibitory ATL cTBS effect in accuracy, whereas the non-responders demonstrated a paradoxical facilitatory effect. There was no other significant effect found in accuracy during the control task or after the control stimulation (Supplementary Fig. S2) and in RT (Supplementary Fig. S3).

3.2. Neurochemical profiles of ATL and rTMS responsiveness

In order to investigate whether GABA and Glx concentrations in the ATL predict the rTMS responsiveness, we quantified metabolite concentrations from MRS (Fig. 3A). First, we correlated the baseline GABA concentrations with semantic task accuracy with and without the ATL stimulation accounting for the partial volume effects. A significant relationship (positive correlation) with semantic task accuracy was only found for baseline GABA (pre-intervention) (Fig. 3B) (Jung et al., 2017). After cTBS over the ATL, this correlation between GABA and accuracy disappeared. The control stimulation showed positive correlations between the ATL GABA concentration and semantic task accuracy regardless of the stimulation (Supplementary Fig. S4). Then, partial correlation analyses were conducted between the GABA concentrations and rTMS effects (Post cTBS – baseline) for responders and non-responders. A significant correlation was observed in responders only: responders with higher GABA concentrations showed bigger rTMS effects (Fig. 3C). Non-responders revealed no significant relationship in this analysis. Second, we correlated the baseline Glx concentrations with semantic task performance with and without the ATL cTBS and found no significant correlations (Supplementary Fig. S5). Then, partial correlation analyses were performed between the ATL Glx levels and rTMS effects according to the group. We found a significant negative correlation only for non-responders; higher Glx concentrations were associated with reduced rTMS effects in non-responders (Fig. 3D). However, there was no difference in the baseline GABA and Glx concentrations between responders and non-responders (ps > 0.35) (Supplementary Fig. S6). It is noted that no significant correlations between the OCC GABA and Glx concentrations and behavioural results were found (all ps > 0.20).

Our findings showed that both GABA and Glx concentrations seem to be associated with TMS responsiveness. In order to explore the neurochemical differences between groups, we used the Glx/GABA ratio for further analysis, potentially a suitable measure for reflecting excitation-inhibition balance in the cortex. We correlated the Glx/GABA ratio with rTMS effects and found a positive correlation ($p < 0.01$) (Fig. 4A). Non-responders had a significantly higher Glx/GABA ratio than responders ($t = 2.30$, $p < 0.05$) (Fig. 4B). There was no difference in the OCC Glx/GABA ratio between groups ($p > 0.13$). The neurochemical profiles of the ATL between responders and non-responders illustrated that they are not homogenous groups. We examined the baseline task performance in order to probe whether this neurochemical difference would reflect in semantic behaviours. A two-way repeated measures ANOVA with site (ATL vs. Oz) as a within subject factor and group (responders vs. non-responders) as a between subject factor in the baseline semantic accuracy revealed a significant main effect of group ($F_{1, 18} = 8.92$, $p < 0.005$) (Fig. 4C). Non-responders performed the semantic task poorer than responders even in the baseline, without stimulation. It is noted

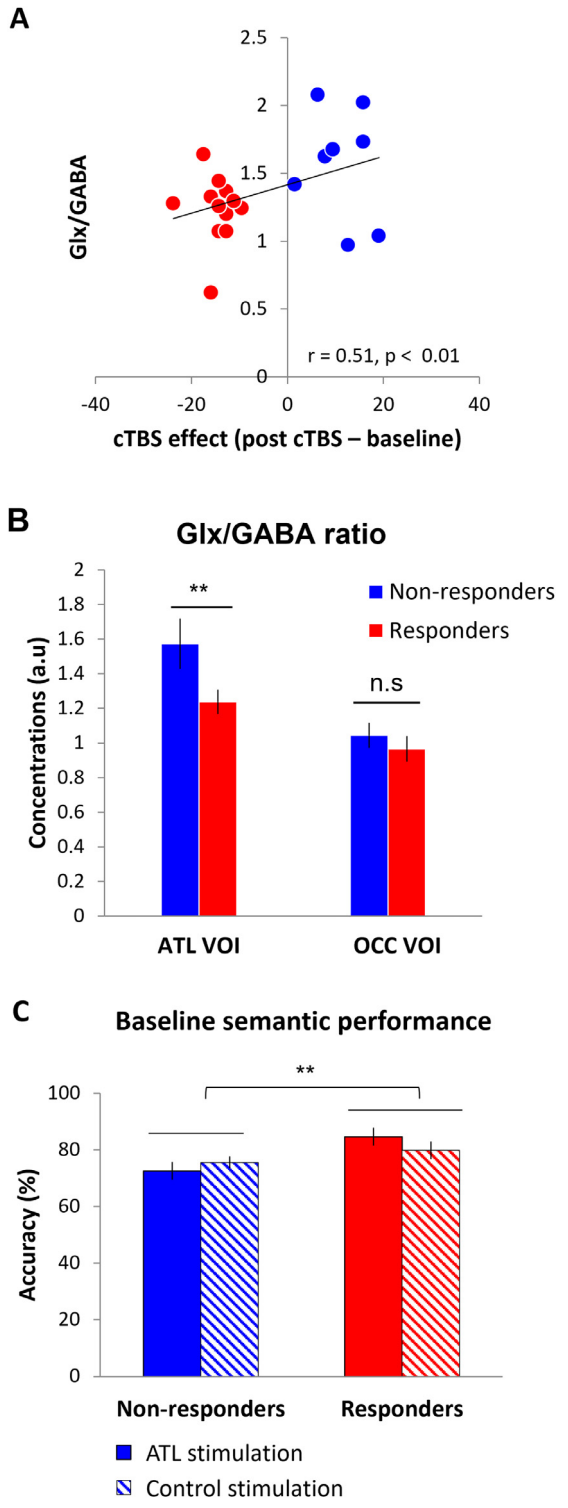

Fig. 4. A. The relationship between Glx/GABA ratio and cTBS effects during semantic processing **B.** Glx/GABA ratio difference between responders and non-responders **C.** Baseline semantic task performance between groups. Error bar represents standard error. ** $p < 0.005$.

that there was no significant effect in the control task performance at the baseline (all ps > 0.43) (Supplementary Fig. 7).

3.3. Neural differences between responders and non-responders

Consistent with past studies, the fMRI demonstrated that the semantic task relative to the control task evoked increased activation in bilateral prefrontal, anterior and posterior temporal cortices as well as cerebellum (Fig. 5A). First, we explored the relationship between rTMS effects and baseline task-induced BOLD signal changes in the ATL during semantic processing. We found a significant positive correlation between them ($r = 0.63$, $p < 0.005$): individuals with less task-induced ATL BOLD signal changes showed stronger inhibitory cTBS effect (Fig. 5B). Then, we compared regional BOLD signal changes in the left ATL between responders and non-responders. A repeated measure ANOVA with experimental condition (semantic vs. control) according to the group (responders vs. non-responders) revealed a significant main effect of the experimental condition ($F_{1, 18} = 43.35$, $p < 0.001$) and group ($F_{1, 18} = 5.36$, $p < 0.05$) as well as an interaction between factors ($F_{1, 19} = 3.53$, $p < 0.05$). *Post-hoc* t-tests demonstrated that non-responders had stronger ATL BOLD signals than responders regardless of the experimental condition (semantic: $t = 2.01$, $p = 0.054$, control: $t = 2.46$, $p < 0.05$) (Fig. 5C). The same analysis was conducted at the network-level (the averaged functional connectivity of semantic network). The analysis showed a main effect of the experimental condition ($F_{1, 18} = 10.57$, $p < 0.005$) and the group ($F_{1, 18} = 7.65$, $p < 0.05$). *Post-hoc* t-tests also revealed that non-responders showed stronger functional connectivity than responders in the semantic and control conditions (semantic: $t = 2.18$, $p < 0.05$, control: $t = 2.24$, $p < 0.05$) (Fig. 5D).

4. Discussion

rTMS has been widely used to modulate human cognitive functions in healthy and clinical populations. However, only in recent years the inter-individual variation of rTMS responsiveness has become a focus of research in neuroscience. The current study investigated whether the pre-interventional neural state of the stimulated region is related to the inter-individual rTMS-responsiveness on human semantic function. cTBS non-responders had higher Glx/GABA ratios compared to responders, leading to up-regulated task-induced activity in the ATL as well as relatively stronger ATL-connectivity within the semantic network comprising bilateral prefrontal cortex and posterior middle temporal gyrus. Furthermore, responders and non-responders differed in cTBS-induced effects on semantic task performance as well as in the neurotransmitters related to the cTBS-effects: only responders showed a decrease in semantic task performance and a negative correlation between GABA concentrations in the ATL and cTBS effects, whereas non-responders showed an increase in the task performance and a negative correlation between Glx concentrations and cTBS effects. Our findings suggest that the baseline level of local neurotransmitters in a cortical region can have a significant impact on rTMS effects.

As noted in the Introduction, there are many factors contributing to the high inter-individual variability observed in response to rTMS/TBS such as previous history of activation and the current state of the stimulated cortex, daytime, or genetic polymorphism (Li et al., 2015; Ridding and Ziemann, 2010). Recently, Nettekoven et al. (2015) showed a higher baseline resting-state functional connectivity between M1 and premotor areas in non-responders compared to responders when classifying their participants into responders and non-responders based on their MEPs changes after the stimulation. They suggested that high baseline levels of functional connectivity can preclude further changes evoked by rTMS – a ceiling effect. Likewise, we found a significantly higher ATL-connectivity as well as ATL activity in non-responders compared to responders during a semantic task. This ceiling effect has been reported in other studies with a variety of patients (Huang et al., 2010; Koch et al., 2008; Quartarone et al., 2003; Salomons et al., 2014). In particular, Salomons et al. (2014) demonstrated that a high baseline of resting-state cortico-thalamic-striatal connectivity was associated with poorer rTMS treatment outcome in patients with major depressive disorder. These studies have suggested that ceiling effects in neural connectivity might underlie absent intervention effects found in non-responders.

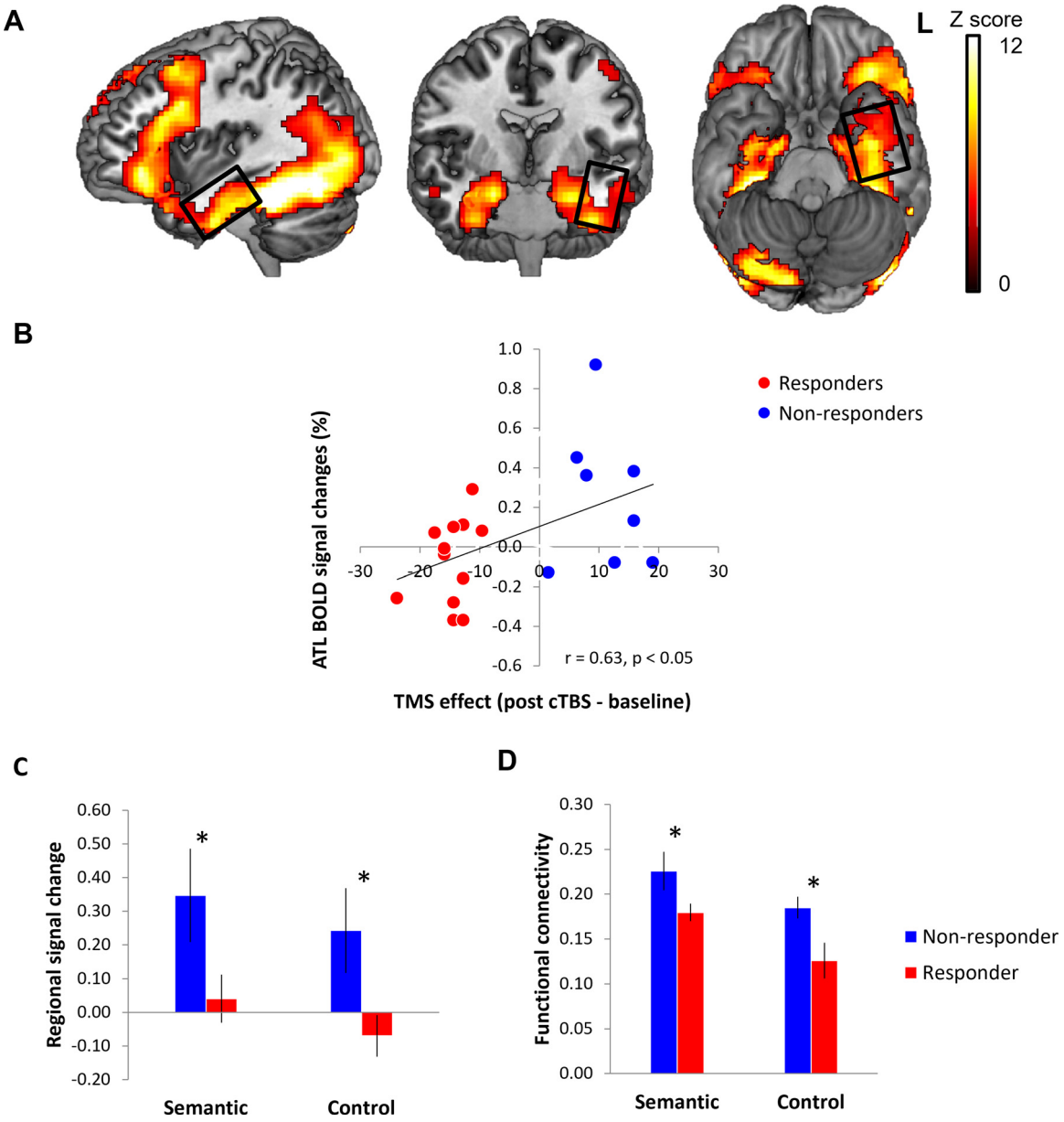

Fig. 5. **A.** Brain activation map for the contrast of interest (semantic > control). The black box indicates the ATL MRS VOI. **B.** The relationship between ATL BOLD signal changes and rTMS effects during semantic processing. **C.**ATL regional activity differences between responders and non-responders across task conditions. **D.** Functional connectivity differences of semantic network between responders and non-responders across task conditions. Error bar represents standard error. * $p_{FDR\text{-}corrected} < 0.05$.

Here, we further investigated the baseline neurochemical traits of a cortical region in relation to rTMS-responsiveness. First, we demonstrated that the relationship between the baseline ATL GABA concentrations and semantic task performance was modulated by cTBS. Stagg et al. (2009) demonstrated that cTBS increased regional GABA concentrations at the target site. cTBS over the ATL might change the regional level of GABA, resulting in disappearance of the positive relationship between the GABA concentrations and baseline semantic task performance. Thus, our findings support the contention that cTBS can modulate GABA neurotransmission in the cortex (Funke and Benali, 2011; Stagg et al., 2009; Trippe et al., 2009). Secondly, cTBS effects were associated with differential effects on glutamate and GABA according to the groups: responders showed a correlation with the GABA concentrations, whereas non-responders showed an association with the Glx concentrations. Specifically, higher GABA concentrations in responders were associated with a stronger cTBS effect and higher Glx concentrations in non-responders was associated with a weaker cTBS effect. The neurochemical differences between responders and non-responders became more prominent when the ratio of glutamate to GABA (excitatory and inhibitory balance) was used: responders had more GABA relative to Glx; whereas non-responders showed the reverse. In a similar manner to the neurochemical profiles, non-responders showed ceiling effects in the ATL activity -connectivity, which could possibly be driven by a higher Glx/GABA ratio compared to responders. Moreover, these neural and neurochemical differences influence the baseline task performance. Responders performed the semantic task better than non-responders at the baseline. Our findings suggest that there is a difference in neurochemical profiles of ATL between responders and non-responders, resulting in neural, behavioural and TBS-related differences.

In terms of baseline level factors related to rTMS-responsiveness, a recent study explored the relationship between genetic variation and rTMS-responsiveness (Cheeran et al., 2008). They examined the brain-

derived neurotrophic factor gene (BDNF) with respect to several non-invasive brain stimulation protocols. Subjects with the Val66Met polymorphism of the BDNF gene (non-responders) showed a reduced or absent response to both cTBS and iTBS, whereas Val66Val carriers (responders) exhibited expected responses following the TBS protocols. BDNF is involved in a significant role in promoting changes in synaptic efficacy by modulating N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDAR)-dependent LTP and LTD (Bramham, 2008; Figurov et al., 1996; Lu et al., 2005). As a glutamate receptor, NMDAR plays a critical role in synaptic plasticity and memory (Tsien et al., 1996) and the effects of TBS may rely on NMDARs in the human cortex (Huang et al., 2007). Moreover, recent animal studies have demonstrated that rTMS-induced postsynaptic changes are NMDAR-dependent (Tokay et al., 2014; Vlachos et al., 2012). Other human and animal studies have shown that TBS effects were associated with the glutamate and GABA systems in the cortex (Funke and Benali, 2011; Huang et al., 2007; Lenz et al., 2016; Trippe et al., 2009).

Recent studies on human motor cortex report that the effects of TBS protocols differ from those originally reported (Goldsworthy et al., 2012; Hasan et al., 2012; Martin et al., 2006) and that individual responses can be variable, resulting in no group-level effect of TBS on cortical excitability (Di Lazzaro et al., 2011; Gentner et al., 2008; Hamada et al., 2013; Lopez-Alonso et al., 2014; Zafar et al., 2008). Here, we firstly attempted to demonstrate the inter-individual variability of TBS-responsiveness in a higher cognitive domain: semantics. Although in our cohort of participants 60% were classified as responders, we did not find a significant decrease in semantic task performance across the entire sample after cTBS ($p = 0.09$). Previous work on the motor cortex reported 50% ~ 70% of their subjects to respond as expected after TBS protocols (Goldsworthy et al., 2014; Hamada et al., 2013; Hinder et al., 2014). The response rates observed in our study is similar to previous studies, although our data was driven from different measurements used to define responders and non-responders. Studies on the M1 used the MEP as a physiological measurement of cortical excitability. However, there is no direct way to measure the cortical excitability for other brain regions, especially areas related to higher cognitive functions. Here, we used behavioural changes induced by cTBS to determine responders and non-responders. A previous study demonstrated that cTBS over the ATL reduced semantic task-induced regional activity and semantic task performance (Jung and Lambon Ralph, 2016). Therefore, our approach to measure the inter-individual variability of rTMS-responsiveness can reflect the ATL cortical excitability.

Taken together, our data suggest that the responsiveness to cTBS depends on the baseline level of local glutamate and GABA balance in the ATL, at least partially, a potential biomarker for individual responsiveness to TBS. The baseline of neurochemical profiles of a cortical region also influences neural traits including task-induced regional activity as well as functional connectivity (Duncan et al., 2014). Our findings may imply a clinical use of non-invasive brain stimulation – predicting positive rTMS intervention treatment outcomes according to patients.

Author contributions

J.J and M.A.L.R designed the experiment. S.R.W developed the MRS protocol and supervised acquisition and analysis of MRS data. J.J collected and analysed data. F.S.N. performed the MRS brain segmentations. J.J, S.R.W and M.A.L.R were involved in writing the manuscript.

Data code

The data that support the findings of this study are available on request from the corresponding author, J.J and M.A.L.

Declaration of Competing Interest

The authors declare no competing financial interests.

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