Title: Thetaburst TMS to the posterior superior temporal sulcus decreases resting-state fMRI connectivity across the face processing network

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Abstract

Humans recognize faces using a network of face-selective regions distributed across the brain. Neuropsychological patient studies demonstrate that focal damage to nodes in this network can impair face recognition, but such patients are rare. We simulated the effects of damage to the face network in neurologically normal human participants using thetaburst transcranial magnetic stimulation (TBS). Multi-echo functional magnetic resonance imaging (fMRI) data were collected pre and post TBS delivery over the face-selective right superior temporal sulcus (rpSTS), or a control site in the right motor cortex. Results showed that TBS delivered over the rpSTS reduced resting-state connectivity across the extended face-processing network. This connectivity reduction was observed not only between the rpSTS and other face-selective areas, but also between non-stimulated face-selective areas across the ventral, medial and lateral brain surfaces (e.g. between the right amygdala and bilateral fusiform face areas and occipital face areas). TBS delivered over the motor cortex did not produce significant changes in resting-state connectivity across the face-processing network. These results demonstrate that disrupting a single node in a brain network can decrease the functional connectivity between the distributed nodes of that network that have not been directly stimulated.

Introduction

The ubiquitous presence of faces in our environment makes them a salient stimulus for studying the cognitive functions of the human brain. Functional magnetic resonance imaging studies have identified regions across the brain that exhibit a stronger neural response to faces, than to objects (Gauthier et al., 2000; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Phillips et al., 1997; Puce, Allison, Bentin, Gore, & McCarthy, 1998). These face-selective regions are linked to form distributed nodes of a face-processing network (Calder & Young, 2005; Haxby, Hoffman, & Gobbini, 2000). Neuropsychological patients with damage to these face-selective areas exhibit face-selective recognition impairments (Barton, 2008; Bouvier & Engel, 2006; Landis, Cummings, Christen, Bogen, & Imhof, 1986; Rezlescu, Barton, Pitcher, & Duchaine, 2014; Rossion et al., 2003), providing strong evidence that faces are processed in a specialized network. Despite the importance they have afforded the study of brain function, such patients are rare. In addition, the interpretation of the data they produce is limited by individual differences in pre-morbid ability (Farah, 2004), and compensatory effects of plasticity that may have occurred after the incident (Robertson & Murre, 1999).

In the present study we used thetaburst transcranial magnetic stimulation (TBS) in combination with multi-echo fMRI acquisition (Posse et al., 1999) during resting-state as a proxy for the impact of disruption of one node in the face network of neurologically normal experimental participants. Over two sessions, neurologically normal participants were scanned using multi-echo fMRI pre and post TBS delivery over the face-selective right superior temporal sulcus (rpSTS), the stimulation site of interest, or the hand area of the right motor cortex, the control site. Multi-echo fMRI denoising is a relatively new method that quantitatively identifies and removes non-blood oxygen-weighted noise from fMRI data

(Kundu et al., 2013). Prior to TBS, participants viewed 3-second videos of moving faces and objects (Pitcher, Dilks, Saxe, Triantafyllou, & Kanwisher, 2011) during fMRI scanning to functionally localize face-selective regions of interest (ROIs).

The face-selective areas in the rpSTS, the fusiform face area (FFA) (Kanwisher et al., 1997; McCarthy et al., 1997), and the occipital face area (OFA) (Gauthier et al., 2000) comprise the core nodes of the face processing network (Calder & Young, 2005; Haxby et al., 2000). In addition to these core nodes, fMRI studies have also identified face-selective voxels in the amygdala (Phillips et al., 1997). Face processing models propose these areas perform different cognitive functions (e.g. recognizing identity, facial expression or eye gaze direction), but share task relevant information. The existence of functional connections between face areas is supported by evidence showing that disruption to one of these areas can impair a range of face recognition tasks. For example, TMS delivered over the rpSTS disrupts the McGurk effect (Beauchamp, Nath, & Pasalar, 2010) as well as performance on face-processing tasks involving eye-gaze (Pourtois et al., 2004), trustworthiness judgments (Dzhelyova, Ellison, & Atkinson, 2011) and facial expressions (Pitcher, 2014; Sliwinska & Pitcher, 2018). Neuropsychological patients with lesions to the rpSTS also show face processing impairments. A patient with a lesion to the rpSTS and angular gyrus was impaired on an unfamiliar face matching task (Sakurai, Hamada, Tsugawa, & Sugimoto, 2016), while another patient with a lesion to right superior temporal gyrus was impaired at discriminating gaze detection (Akiyama et al., 2006).

While previous studies have shown TMS-induced face network activation changes during tasks (Pitcher, Duchaine, & Walsh, 2014; Pitcher, Japee, Rauth, & Ungerleider, 2017), we tested whether the same face network areas defined in those studies show correlation

decreases in response to TMS to the rpSTS, even in the absence of a face stimulus. If so, then this would build evidence that behaviorally defined face processing regions are part of a network whose nodes regularly communicate and interact with each other. Results demonstrated that TBS delivered over the rpSTS caused a reduction in correlations between the stimulated node and unstimulated nodes of the face processing network.

Results

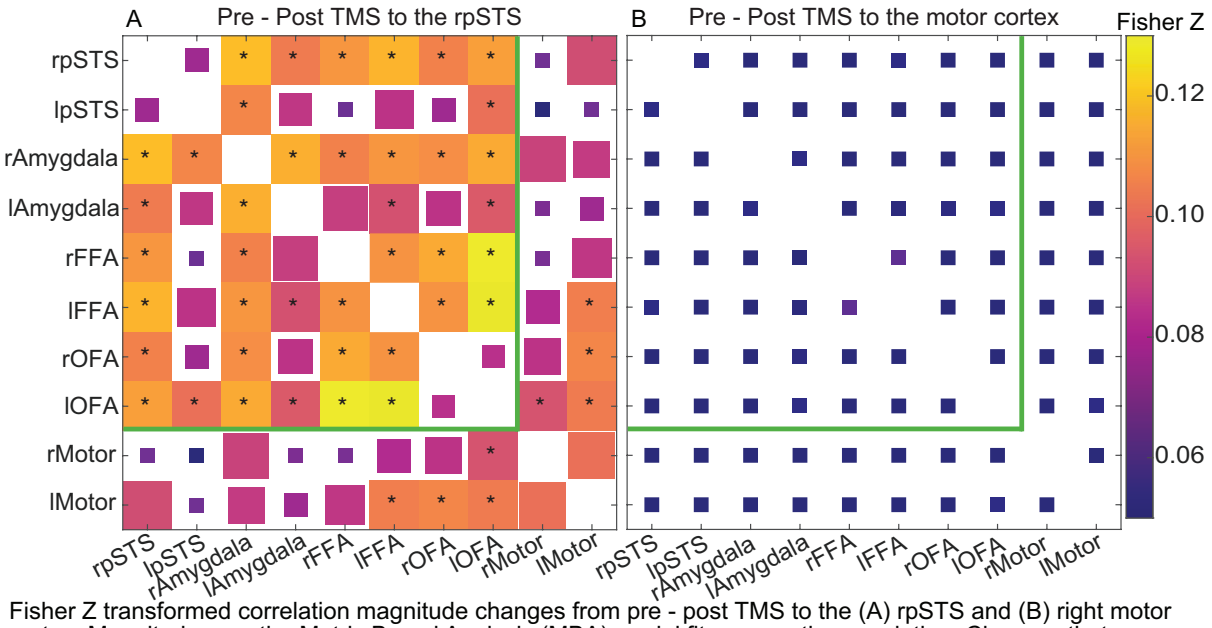
For each volunteer, face-selective regions of interest (ROIs) were localized using voxels with larger responses to face videos than to object videos for the left posterior superior temporal sulcus (lpSTS), bilateral fusiform face areas (FFA), bilateral occipital face areas (OFA) and bilateral amygdala. The right posterior superior temporal sulcus (rpSTS) ROIs were face-selective voxels in gray matter that were also within an 18mm diameter sphere centered on the stimulation site. This added restriction means the voxels in the rpSTS ROI were likely to have been directly affected by TBS stimulation. The simulation site was defined using the same functional localizer scan, but collected on a preceding session. The right hand motor stimulation site was anatomically defined using an anatomical scan from a preceeding session. ROIs for the bilateral hand areas were manually drawn following the gray matter anatomy of the hand knob in the precentral sulcus. The locations for the regions of interest are shown in Figure S1.

For ROI-based analyses, mean time series of the ten minute resting state fMRI data were calculated using the voxels within each ROI. The correlations between these ROIs were calculated for the resting runs pre and post TBS stimulation. The correlation coefficients were Fisher Z transformed. Since the ROIs are *apriori* selected from a network where we expect to see disruption (Pitcher et al., 2014; Pitcher et al., 2017) – with the hand motor

regions as a control, the statistical changes of interest will focus on the ROI analyses. A matrix based analysis (MBA) through Bayesian multilevel modeling was used to identify pairs of ROIs where a decrease in correlation magnitude was larger than expected along with a measure of statistical evidence (Chen et al., 2019). The advantage of this approach is that, instead of adopting a univariate GLM with the assumption that each ROI pair is an independent entity that shares no commonality or similarity with its peers, the contrast magnitude estimates and uncertainties of all ROI pairs are assessed as part of a single integrative model.

Figure 1 shows the effects of stimulation on the correlations pre – post TMS for all pairs of ROIs (bilateral STS, FFA, OFA, amygdala and hand motor cortices) using Baysian multilevel modeling. For rpSTS stimulation, multiple ROI pairs within the face processing network showed decreased connectivity that would be likely to be greater than zero with a posterior probability of at least 0.95 (Fig 1A). For pre – post TMS to the motor cortex (Fig 1B) and interaction effects, there was no strong evidence that any ROI pairs were likely to be greater than zero. All posterior probabilities were less than 0.85 and all effect sizes were less than 0.07 (Fig. S2).

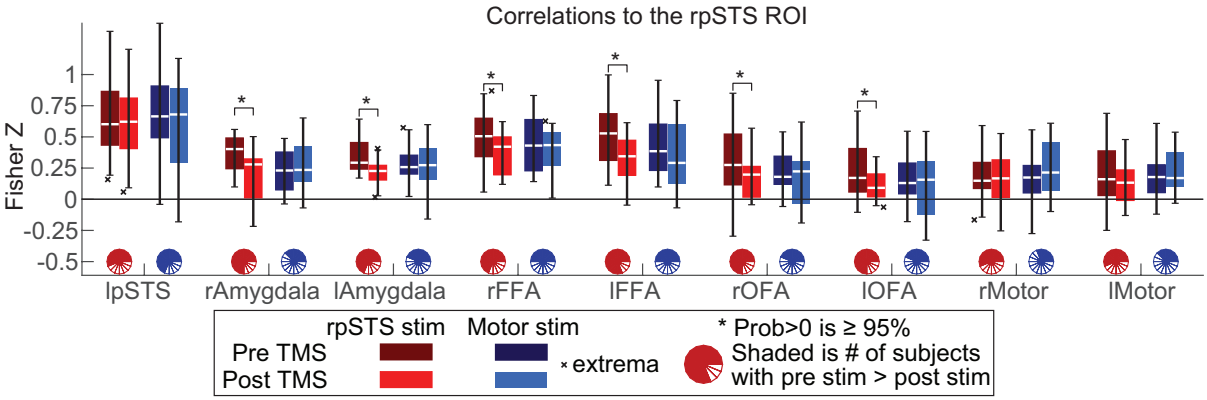
Figure 1



Fisher Z transformed correlation magnitude changes from pre - post TMS to the (A) rpSTS and (B) right motor cortex. Magnitudes are the Matrix Based Analysis (MBA) model fits across the population. Changes that are likely to be greater than 0 with a posterior probability of at least 95% are full squares and include an *. The squares' edge lengths decrease linearly to their minimum size for a 90% likelihood or less. The green line marks the ROI pairs that are within the pre-defined face-selective network. Fig. S2 contains an unthresholded version of this figure and the interaction effect.

To help visually compare the effect sizes for rpSTS vs motor stimulation, Figure 2 shows boxplots for the correlations between the rpSTS and the other ROIs for the runs pre and post TMS. The colored section of the pie charts in this figure show the number of volunteers that had a pre – post TMS correlation decrease. These pie charts show that 11-13 of the 16 volunteers showed a correlation decrease post rpSTS stimulation. The supplementary material includes boxplots for correlation magnitudes of all ROI pairs (Figs S3 and S4). Whether the correlation is between a pair of ROIs that includes the directly stimulated rpSTS or another pair of face network ROIs, the correlations to other ROIs in the face network decreased across the majority of volunteers when the rpSTS was stimulated.

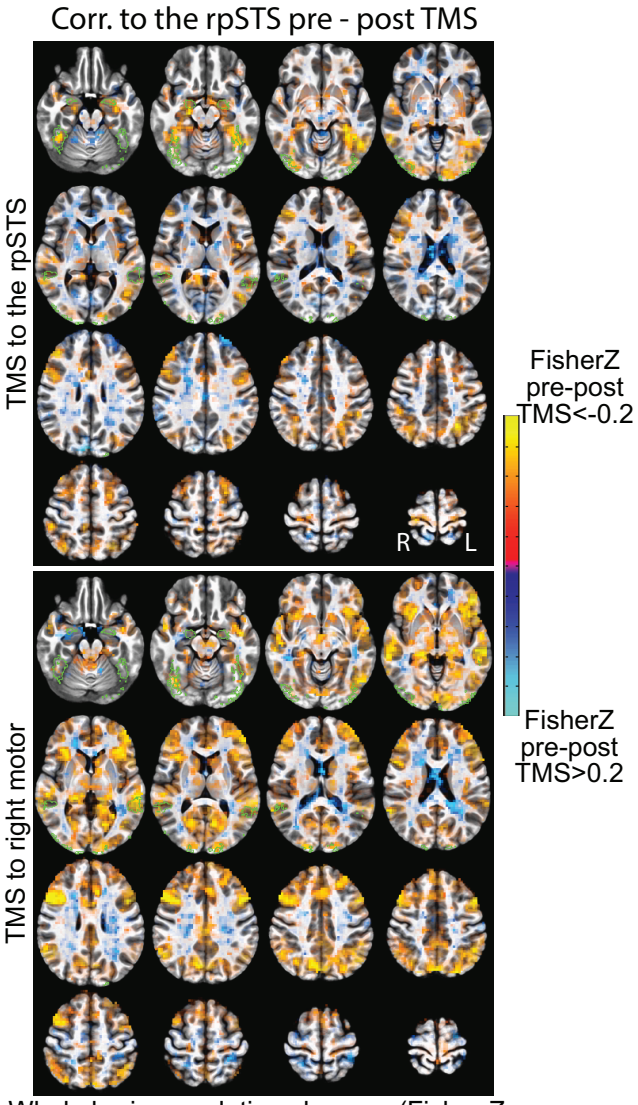
Figure 2



Correlations between the rpSTS ROI and ROIs in a pre-defined face network as well as the bilateral primary motor hand regions. These data correspond to the first row of the matrix in figure 1. The full matrix of bar plots in in Fig. S2. Magnitudes are the MBA model fits across the population for each condition. Boxplots show 25-75% of the distribution. The white line is the median. Whiskers are the maximum and minimum values excluding outliers. MBA used to calculate posterior probabilities that a difference is greater than 0. The correlations between the rpSTS and other face regions consistently decrease post rpSTS stimulation, but not post rMotor stimulation.

There is a possibility that TBS to the rpSTS would cause correlation decreases between the rpSTS and the entire brain. To test for this possibility, all subjects' data were aligned to each other and a group map was calculated with an ANOVA using multivariate modeling (Figure 3). While there are decreases in activity that do not all cross meaningful statistical thresholds both within and outside the face network, the correlation decreases post rpSTS stimulation are clearly not a global effect.

Figure 3



Whole brain correlation changes (Fisher Z transformed) pre - post TBS stimulation. Voxel coloring shows the magnitude of the correlation difference. Voxels are opaque for p>=0.01 to transparent for p=0.The green outlines are voxels in the ROIs of the pre-defined face network in at least 3 volunteers. For TMS to the rpSTS, many of the larger signal drops are within the face network ROIs. TMS to right motor shows decreases across more of the brain that isn't localized to the face network.

Discussion

Models of the human face processing network propose that face-selective areas perform different functional roles but share task relevant information when processing faces (Calder & Young, 2005; Haxby et al., 2000). In the current study, we simulated the impact of disruption to the face network by delivering TBS over the face-selective area in the right

posterior superior temporal sulcus (rpSTS). The impact of the TBS stimuation was measured with resting-state fMRI. Our results demonstrated that disruption of the rpSTS reduced resting-state connectivity, measured by correlation, across the nodes of the face processing network. Figure 1 shows a reduction in connectivity between the rpSTS and bilateral FFA, OFA, and amygdala as well as between 14 of 21 pairs of ROIs in the face network that were not directly stimulated. This result demonstrates that disrupting a single face-selective area causes widespread connectivity decreases across the extended face processing network.

Figures 2, S3, and S4 visualize the effect of TBS across subjects to show that correlations between face network regions have correlation decreases for the majority of volunteers post rpSTS stimulation. This widespread pattern of distributed correlation decreases suggests that the nodes of the face network are tightly interconnected, and that distruption of one node can affect other notes in the network. Importantly, TBS delivered over the right motor cortex (which acted as a control site) didn't produce above chance reductions in functional connectivity across the face network. The observed network-wide drop in resting-state connectivity is consistent with models proposing that the rpSTS is a core component of the face-processing network (Calder & Young, 2005; Haxby et al., 2000). While we do show an effect of rpSTS stimulation and not an effect for motor stimulation, we do not observe a significant effect of motor cortex stimulation between motor ROIs, nor an interaction effect. One possible cause of that result was a post-stimulation observation of spatial variation between the hand motor ROI and the hand motor stimulation site (Fig S1). This variation in stimulation site may have led to an observed increase in variance of correlation changes post motor stimultion vs rpSTS stimulation (Fig S3 and S4). That added variance may have reduced the posterior probabilities involving motor stimulation data.

The reduction in network connectivity we observed between non-stimulated face-selective regions on the medial and ventral brain surfaces extends the findings of prior work. Our previous combined TBS/fMRI studies examined the impact of disruption in face-selective regions while participants viewed face videos (Pitcher et al., 2014; Pitcher et al., 2017). These studies showed that TBS delivered over the rpSTS reduced the neural response to faces in the rpSTS itself, as well as in other face-selective areas including the right fusiform face area (rFFA) (Pitcher, 2014) and face-selective voxels in the right amygdala (Pitcher et al., 2017). However, while these studies reported a reduction in the neural response to faces in remote face-selective areas, neither study was capable of detecting changes in functional connectivity between face-selective areas. While prior studies demonstrated functional connectivity between the FFA and the amygdala (Fairhall & Ishai, 2007; Herrington, Taylor, Grupe, Curby, & Schultz, 2011; Vuilleumier, Armony, Driver, & Dolan, 2001, 2003), our study shows that correlations between these areas are reduced post TBS delivery over a remote node in the network, in this case the rpSTS.

Non-human primate neuroanatomical studies in macaques report a cortical pathway projecting from the STS to dorsal sub-regions of the amygdala (Aggleton, Burton, & Passingham, 1980; Stefanacci & Amaral, 2000, 2002). In addition, neuroimaging and lesion studies of humans and macaques demonstrate that the amygdala is engaged in facial expression recognition (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs et al., 1999; Calder et al., 1996; Hadj-Bouziane et al., 2012; Hoffman, Gothard, Schmid, & Logothetis, 2007; Morris et al., 1996; Whalen et al., 1998). We previously proposed that humans have a cortical pathway projecting along the STS into the amygdala that processes changeable facial aspects (e.g expression), which was supported using combined TBS/fMRI during face, body, and object viewing (Pitcher et al., 2017). By replicating this effect using functional

connectivity and without a viewing task, we provide further support for a pathway between these regions.

Neuropsychological patients exhibiting face-selective recognition impairments were essential to the development of cognitive and brain models of face processing (Bruce & Young, 1986; Haxby et al., 2000). Studies of patients with right lateral lesions (in the area of the pSTS) showing impairments with eye gaze direction detection (Akiyama et al., 2006; Campbell, Heywood, Cowey, Regard, & Landis, 1990) and unfamiliar face identity matching (Sakurai et al., 2016) have been reported. However, propopagnosic patients with lateral lesions are less common than those with ventral lesions. Our study further demonstrates that transiently disrupting the brains of neurologically normal experimental participants with TMS offers an alternative, and safe proxy for modeling the effects of focal cortical disruption on cognitive networks. TMS can be combined with functional magnetic resonance imaging (fMRI) to study the networks that process scenes (Mullin & Steeves, 2013), faces (Rafique, Solomon-Harris, & Steeves, 2015; Solomon-Harris, Rafique, & Steeves, 2016), decision making (Rahnev, Nee, Riddle, Larson, & D'Esposito, 2016) and memory (Wang et al., 2014). Crucially, while we do see some decreases between a few face network ROIs and the motor ROIs (Fig 1), we examined the voxel-wise correlations across the brain to show that the largest distruptions of TBS to the rpSTS were in the face selective network. Still, the decreases in some connections to motor cortex ROIs hint at how altering a single node can potentially distrupt multiple distinct networks. Each brain region does not contribute to only one self-contained network of brain regions.

The results of the current study further demonstrate how TBS can be combined with neuroimaging to systematically study the effects of transient disruption across the brain.

Neurologists have studied the impact of focal brain lesions in patients for over two hundred years. The study of these patients has been highly influential and has produced insights into human cognition. However, patients with focal lesions in brain regions of interest are extremely rare. In addition, the interpretation of the data they produce is tempered by factors like individual differences in pre-morbid ability (Robertson & Murre, 1999) and the unknown effects of neural plasticity that may have occurred after their incident (Farah, 2004). TBS combined with rsfMRI has been used to study the default mode network (Abellaneda-Perez et al., 2019; Shang et al., 2019), attention (Anderkova et al., 2018), visualspatial neglect (Fu et al., 2017), cerebellar connectivity (Rastogi et al., 2017), mental illness, (Baeken, Duprat, Wu, De Raedt, & van Heeringen, 2017) and memory in humans (Mancini et al., 2017). These studies show that measuring transient TBS induced disruption with rsfMRI offers a systematic experimental methodology for extending more than two hundred years of neuropsychological research.

In conclusion, models propose that face-selective brain areas can be linked together to form the distributed components of a face processing network (Calder & Young, 2005; Haxby et al., 2000). The current findings support these models by showing that transient disruption to one of these components, the rpSTS, results in widespread correlation decreases across the distributed nodes of this network.

Materials and Methods

Participants

17 right-handed participants (11 females) with normal, or corrected-to-normal, vision gave informed consent as directed by the National Institutes of Health (NIH) Institutional Review Board (ClinicalTrials.gov identifier: NCT01617408). One participant was excluded due to

high motion (207 of 1200 volumes in the 4 resting runs censored due to motion vs 0-40 for all other volunteers).

Experimental Design

Procedure

Participants completed three separate fMRI sessions, each performed on a different day. The first session was an fMRI experiment designed to individually localize the TMS stimulation sites in each participant. Participants viewed face and object videos and a high resolution structural scan was also taken. The data collected in this initial session were used for TMS target site identification only. During the two subsequent fMRI sessions, participants were scanned pre and post receiving TBS stimulation of either the right posterior superior temporal sulcus (rpSTS) or the right primary motor cortex hand knob (rHK). Stimulation site order was balanced across participants. The two TBS sessions were 7 – 182 days apart (median=23). All the data presented were collected during these two TBS sessions.

Regions-of-interest (ROIs) Localizer Session

For the independent localizer runs used to identify face-selective regions of interest (ROIs), participants viewed 3-second video clips of faces, objects, and scrambled objects. There were sixty movie clips for each category in which distinct exemplars appeared multiple times. Movies of faces were filmed on a black background, and framed close-up to reveal only the faces of 7 children as they danced or played with toys or adults (who were out of frame). Fifteen different moving objects were selected that minimized any suggestion of animacy of the object itself or of a hidden actor pushing the object (these included mobiles, windup toys, toy planes and tractors, balls rolling down sloped inclines). Within each block, stimuli were randomly selected from within the entire set for that stimulus category. This meant that the

same actor or object could appear within the same block. These stimuli were used in a previous fMRI study of face perception (Pitcher et al., 2011) and previous combined TBS/fMRI studies (Pitcher et al., 2014; Pitcher et al., 2017).

The rpSTS was identified using a contrast of faces greater than objects. The rpSTS stimulation target was the peak voxel in the significant cluster in the pSTS. A T1 weighted anatomical scan was also collected during this session and the right motor cortex was the most superior location on the motor cortex hand knob. A posthoc re-examination identified two vounteers where the motor stimulation zone may not have directly stimulated the hand motor region (Fig S1). This may have contributed to a greater variance of responses to hand motor stimulation across the population and thus the lower posterior probabilities for correlation decreases post motor stimulation and interaction effects between the stimulation sites.

Combined fMRI/TBS sessions

Data acquisition: Participants were scanned using a GE 3-Tesla MR 750 scanner at the National Institutes of Health (NIH). fMRI images were acquired using a 32-channel head coil (36 slices, 3 × 3 × 3 mm, FOV=21.6 cm, grid = 72x72, flip angle = 77°, ASSET=3, TR = 2 s, TEs = 14.8, 27.1, & 39.5 ms). In addition, high-resolution MPRAGE anatomical scans (T1-weighted, 1 x 1 x 1 mm resolution) were acquired to anatomically localize functional activations and register functional data between sessions.

Before each MRI session, the stimulation site (either rpSTS or rHK) was located using the BrainSight system (Rogue Research) and marked. During the MRI session, two 10-minute resting-state scans (310 volumes) were acquired followed by functional localizer scans similar to those used for the ROI session and then an MPRAGE anatomical scan. The

volunteers were then removed from the scanner. TBS was delivered using a MagStim Super Rapid stimulator with figure-eight coil (wing diameter 70 mm). Stimulation was delivered over the rpSTS or rHK at 30% of machine output with 3 pulses at 50Hz repeated at 200ms intervals for 60 seconds (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005). As soon as simulation ended, volunteers were returned to the MRI where they received a localizer scan, slice placement that was visually similar to the pre-TMS scan, an ASSET calibration scan, and two 10-minute resting-state scans. The resting scans began 2.5-5 minutes after the last TMS pulse was delivered depending on how quickly the participant was able to be loaded into the scanner. After the resting scan, another MPRAGE anatomical scan was acquired. Three of the 34 MRI sessions did not include an anatomical scan during the post-TMS part of the session due to time constraints. The second 10-minute resting scans both pre and post TMS had more head motion in many subjects. For 14 of the 64 pre or post TMS run pairs, there was at least 5 more motion censored volumes in the second run, versus 1 for first run – second run. Similarly the median delta motion (frame-to-frame difference) was larger for 49 of the second runs vs first runs. The average median delta motion difference between run pairs was 0.01 larger in the second runs. The average median delta motion was 0.05 so this was a 19% increase in median motion. There was only a 7% difference in median delta motion for the first and third runs, which were used in these analyses. While these are subtle differences, the systematic nature of this difference added a confound that made these data difficult to interpret, so the second runs were excluded from all analyses.

Data processing

Data were processed using AFNI (Cox, 1996). For each fMRI run: The first four pre-steady state volumes were removed; Data were despiked to remove non-biological large signal fluctuations and slice time corrected. Spatial alignment transforms for motion correction

within runs and registration across runs were calculated using the middle echo (TE=27.1ms) time series. Non-uniformity of image intensity for the first volume of this time series was corrected using the bias correction code in SPM8. This reference fMRI volume was aligned to the MPRAGE anatomical from the same pre or post TMS session, if available. Otherwise, it was aligned to the anatomical scan from the same day. The anatomical scans were aligned to each other and averaged to make a single, higher quality anatomical volume per volunteer. Registration quality for each pair of anatomical scans and for each fMRI to anatomical alignment were visually inspected for accuracy. The motion correction and alignment transforms were combined into a single affine transform matrix and applied to fMRI time series for all echoes so that fMRI data from each subject was in a single subject-specific space across sessions.

The multi-echo data were then denoised using the MEICA algorithm. MEICA uses the expected properties of signal changes across multiple echoes times to identify and remove signal fluctuations that are unlikely to reflect the blood oxygenation differences that are central to fMRI. By doing this, MEICA has been shown to increase the signal-to-noise ratio and remove data artifacts (Kundu et al., 2013; Kundu, Inati, Evans, Luh, & Bandettini, 2012). The version of the denoising code that we used is available at: https://bitbucket.org/BenGutierrez/me-ica. We will refer to the output of the full MEICA algorithm as "denoised" data. The denoised data will be used for all analyses in this manuscript.

Univariate statistical maps and correlations were calculated within subjects. For functional localizer runs, time series were intensity normalized by dividing by the mean value in each run. For resting-state runs, volumes when the first derivative Euclidian norm of the 6 motion

parameters was greater than 0.2 were censored. The motion parameters and their first derivatives were regressed from the time series. In the same step, signals from a Cerebral Spinal Fluid (CSF) ROI and a white matter ROI that excluded voxels within 8 voxels of either stimulation site were averaged and regressed from the data. The resting-state data were bandpass filtered (0.01-0.1Hz) with censoring and the data were spatially smoothed with a 5-mm full-width-half-maximum Gaussian kernel.

Cross session imaging alignment and ROIs for TBS sessions

Freesurfer was used to create subject-specific anatomical face-selective ROIs of the fusiform gyri, lateral occipital gyri, and amygdala. Any fMRI voxel which included at least 50% the Freesurfer defined ROI was included in the ROI. These anatomical ROIs were intersected with faces>objects functional activation maps from the localizer scans collected during the TMS sessions (false-discovery-rate threshold $q<0.05$). If 10% of the voxels in the anatomical ROI, or 10 voxels for anatomical ROIs with less than 100 voxels did not cross this threshold, then the threshold was increased until this threshold of faces>objects voxels was crossed. In 5 subjects, this threshold was not crossed in the amygdala ROIs, which has a mean of 51 voxels in the anatomical ROIs. In 4 of these subjects, the same volunteers participated in a separate study that included the identical functional localizer task with more significant faces>objects voxels in the regions of interest (Pitcher et al., 2017). Those localizers were used to define the functional ROIs in those 4 volunteers. The voxels in the fusiform with face>objects contrast were designated the Fusiform Face Area (FFA) ROI and the voxels in the lateral occipital gyri were the Occipital Face Area (OFA) ROI. The left and right hand knob motor ROIs were hand drawn on each volunteers structural scan by a single person and checked for accuracy by a second person. For whole-brain analyses, the within-subject aligned anatomical volumes

from each subject were registered to a standard MNI space and then nonlinearly, iteratively warped to each other to make a within-study anatomical template (Figure 3 and S1).

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References

Abellaneda-Perez, K., Vaque-Alcazar, L., Vidal-Pineiro, D., Jannati, A., Solana, E., Bargallo, N., . . . Bartres-Faz, D. (2019). Age-related differences in default-mode network connectivity in response to intermittent theta-burst stimulation and its relationships with maintained cognition and brain integrity in healthy aging. *NeuroImage, 188*, 794-806. doi:10.1016/j.neuroimage.2018.11.036

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372*(6507), 669-672. doi:10.1038/372669a0

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A., . . . Damasio, A. R. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37*(10), 1111-1117. doi:10.1016/s0028-3932(99)00039-1

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (Macaca mulatta). *Brain Res, 190*(2), 347-368. doi:10.1016/0006-8993(80)90279-6

Akiyama, T., Kato, M., Muramatsu, T., Saito, F., Umeda, S., & Kashima, H. (2006). Gaze but not arrows: a dissociative impairment after right superior temporal gyrus damage. *Neuropsychologia, 44*(10), 1804-1810. doi:10.1016/j.neuropsychologia.2006.03.007

Anderkova, L., Pizem, D., Klobusiakova, P., Gajdos, M., Koritakova, E., & Rektorova, I. (2018). Theta Burst Stimulation Enhances Connectivity of the Dorsal Attention Network in Young Healthy Subjects: An Exploratory Study. *Neural Plast, 2018*, 3106918. doi:10.1155/2018/3106918

Baeken, C., Duprat, R., Wu, G. R., De Raedt, R., & van Heeringen, K. (2017). Subgenual Anterior Cingulate-Medial Orbitofrontal Functional Connectivity in Medication-Resistant Major Depression: A Neurobiological Marker for Accelerated Intermittent Theta Burst Stimulation Treatment? *Biol Psychiatry Cogn Neurosci Neuroimaging, 2*(7), 556-565. doi:10.1016/j.bpsc.2017.01.001

Barton, J. J. (2008). Prosopagnosia associated with a left occipitotemporal lesion. *Neuropsychologia, 46*(8), 2214-2224. doi:10.1016/j.neuropsychologia.2008.02.014

Beauchamp, M. S., Nath, A. R., & Pasalar, S. (2010). fMRI-Guided transcranial magnetic stimulation reveals that the superior temporal sulcus is a cortical locus of the McGurk effect. *J Neurosci, 30*(7), 2414-2417. doi:10.1523/JNEUROSCI.4865-09.2010

Bouvier, S. E., & Engel, S. A. (2006). Behavioral deficits and cortical damage loci in cerebral achromatopsia. *Cereb Cortex, 16*(2), 183-191. doi:10.1093/cercor/bhi096

Bruce, V., & Young, A. (1986). Understanding face recognition. *British Journal of Psychology, 77*(3), 305-327. doi:10.1111/j.2044-8295.1986.tb02199.x

Calder, A. J., & Young, A. W. (2005). Understanding the recognition of facial identity and facial expression. *Nat Rev Neurosci, 6*(8), 641-651. doi:10.1038/nrn1724

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial emotion recognition after bilateral amygdala damage: Differentially severe impairment of fear. *Cognitive Neuropsychology, 13*(5), 699-745. doi:10.1080/026432996381890

Campbell, R., Heywood, C. A., Cowey, A., Regard, M., & Landis, T. (1990). Sensitivity to eye gaze in prosopagnosic patients and monkeys with superior temporal sulcus ablation. *Neuropsychologia, 28*(11), 1123-1142. doi:10.1016/0028-3932(90)90050-x

Chen, G., Burkner, P. C., Taylor, P. A., Li, Z. H., Yin, L. J., Glen, D. R., . . . Pessoa, L. (2019). An integrative Bayesian approach to matrix-based analysis in neuroimaging. *Human Brain Mapping, 40*(14), 4072-4090. doi:10.1002/hbm.24686

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res, 29*(3), 162-173. doi:10.1006/cbmr.1996.0014

Dzhelyova, M. P., Ellison, A., & Atkinson, A. P. (2011). Event-related repetitive TMS reveals distinct, critical roles for right OFA and bilateral posterior STS in judging the sex and trustworthiness of faces. *J Cogn Neurosci, 23*(10), 2782-2796. doi:10.1162/jocn.2011.21604

Fairhall, S. L., & Ishai, A. (2007). Effective connectivity within the distributed cortical network for face perception. *Cereb Cortex, 17*(10), 2400-2406. doi:10.1093/cercor/bhl148

Farah, M. J. (2004). *Visual agnosia* (2nd ed.). Cambridge, Mass.: MIT Press.

Fu, W., Cao, L., Zhang, Y., Huo, S., Du, J., Zhu, L., & Song, W. (2017). Continuous theta-burst stimulation may improve visuospatial neglect via modulating the attention network: a randomized controlled study. *Top Stroke Rehabil, 24*(4), 236-241. doi:10.1080/10749357.2016.1253139

Gauthier, I., Tarr, M. J., Moylan, J., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). The fusiform "face area" is part of a network that processes faces at the individual level. *J Cogn Neurosci, 12*(3), 495-504. doi:10.1162/089892900562165

Hadj-Bouziane, F., Liu, N., Bell, A. H., Gothard, K. M., Luh, W. M., Tootell, R. B., . . . Ungerleider, L. G. (2012). Amygdala lesions disrupt modulation of functional MRI activity evoked by facial expression in the monkey inferior temporal cortex. *Proc Natl Acad Sci U S A, 109*(52), E3640-3648. doi:10.1073/pnas.1218406109

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends Cogn Sci, 4*(6), 223-233. doi:10.1016/S1364-6613(00)01482-0

Herrington, J. D., Taylor, J. M., Grupe, D. W., Curby, K. M., & Schultz, R. T. (2011). Bidirectional communication between amygdala and fusiform gyrus during facial recognition. *NeuroImage, 56*(4), 2348-2355. doi:10.1016/j.neuroimage.2011.03.072

Hoffman, K. L., Gothard, K. M., Schmid, M. C., & Logothetis, N. K. (2007). Facial-expression and gaze-selective responses in the monkey amygdala. *Curr Biol, 17*(9), 766-772. doi:10.1016/j.cub.2007.03.040

Huang, Y. Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. doi:10.1016/j.neuron.2004.12.033

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci, 17*(11), 4302-4311. doi:10.1523/JNEUROSCI.17-11-04302.1997

Kundu, P., Brenowitz, N. D., Voon, V., Worbe, Y., Vertes, P. E., Inati, S. J., . . . Bullmore, E. T. (2013). Integrated strategy for improving functional connectivity mapping using multiecho fMRI. *Proc Natl Acad Sci U S A, 110*(40), 16187-16192. doi:10.1073/pnas.1301725110

Kundu, P., Inati, S. J., Evans, J. W., Luh, W. M., & Bandettini, P. A. (2012). Differentiating BOLD and non-BOLD signals in fMRI time series using multi-echo EPI. *NeuroImage, 60*(3), 1759-1770. doi:10.1016/j.neuroimage.2011.12.028

Landis, T., Cummings, J. L., Christen, L., Bogen, J. E., & Imhof, H. G. (1986). Are unilateral right posterior cerebral lesions sufficient to cause prosopagnosia? Clinical and radiological findings in six additional patients. *Cortex, 22*(2), 243-252. doi:10.1016/s0010-9452(86)80048-x

Mancini, M., Mastropasqua, C., Bonni, S., Ponzo, V., Cercignani, M., Conforto, S., . . . Bozzali, M. (2017). Theta Burst Stimulation of the Precuneus Modulates Resting State Connectivity in the Left Temporal Pole. *Brain Topogr, 30*(3), 312-319. doi:10.1007/s10548-017-0559-x

McCarthy, G., Puce, A., Gore, J. C., & Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *J Cogn Neurosci, 9*(5), 605-610. doi:10.1162/jocn.1997.9.5.605

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J., & Dolan, R. J. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383*(6603), 812-815. doi:10.1038/383812a0

Mullin, C. R., & Steeves, J. K. (2013). Consecutive TMS-fMRI reveals an inverse relationship in BOLD signal between object and scene processing. *J Neurosci, 33*(49), 19243-19249. doi:10.1523/JNEUROSCI.2537-13.2013

Phillips, M. L., Young, A. W., Senior, C., Brammer, M., Andrew, C., Calder, A. J., . . . David, A. S. (1997). A specific neural substrate for perceiving facial expressions of disgust. *Nature, 389*(6650), 495-498. doi:10.1038/39051

Pitcher, D. (2014). Facial expression recognition takes longer in the posterior superior temporal sulcus than in the occipital face area. *J Neurosci, 34*(27), 9173-9177. doi:10.1523/JNEUROSCI.5038-13.2014

Pitcher, D., Dilks, D. D., Saxe, R. R., Triantafyllou, C., & Kanwisher, N. (2011). Differential selectivity for dynamic versus static information in face-selective cortical regions. *NeuroImage, 56*(4), 2356-2363. doi:10.1016/j.neuroimage.2011.03.067

Pitcher, D., Duchaine, B., & Walsh, V. (2014). Combined TMS and FMRI reveal dissociable cortical pathways for dynamic and static face perception. *Curr Biol, 24*(17), 2066-2070. doi:10.1016/j.cub.2014.07.060

Pitcher, D., Japee, S., Rauth, L., & Ungerleider, L. G. (2017). The Superior Temporal Sulcus Is Causally Connected to the Amygdala: A Combined TBS-fMRI Study. *J Neurosci, 37*(5), 1156-1161. doi:10.1523/JNEUROSCI.0114-16.2016

Posse, S., Wiese, S., Gembris, D., Mathiak, K., Kessler, C., Grosse-Ruyken, M. L., . . . Kiselev, V. G. (1999). Enhancement of BOLD-contrast sensitivity by single-shot multi-echo functional MR imaging. *Magn Reson Med, 42*(1), 87-97. doi:10.1002/(sici)1522-2594(199907)42:1<87::aid-mrm13>3.0.co;2-o

Pourtois, G., Sander, D., Andres, M., Grandjean, D., Reveret, L., Olivier, E., & Vuilleumier, P. (2004). Dissociable roles of the human somatosensory and superior temporal cortices for processing social face signals. *European Journal of Neuroscience, 20*(12), 3507-3515. doi:10.1111/j.1460-9568.2004.03794.x

Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *J Neurosci, 18*(6), 2188-2199. doi:10.1523/JNEUROSCI.18-06-02188.1998

Rafique, S. A., Solomon-Harris, L. M., & Steeves, J. K. (2015). TMS to object cortex affects both object and scene remote networks while TMS to scene cortex only affects scene networks. *Neuropsychologia, 79*(Pt A), 86-96. doi:10.1016/j.neuropsychologia.2015.10.027

Rahnev, D., Nee, D. E., Riddle, J., Larson, A. S., & D'Esposito, M. (2016). Causal evidence for frontal cortex organization for perceptual decision making. *Proc Natl Acad Sci U S A, 113*(21), 6059-6064. doi:10.1073/pnas.1522551113

Rastogi, A., Cash, R., Dunlop, K., Vesia, M., Kucyi, A., Ghahremani, A., . . . Chen, R. (2017). Modulation of cognitive cerebello-cerebral functional connectivity by lateral cerebellar continuous theta burst stimulation. *NeuroImage, 158*, 48-57. doi:10.1016/j.neuroimage.2017.06.048

Rezlescu, C., Barton, J. J., Pitcher, D., & Duchaine, B. (2014). Normal acquisition of expertise with greebles in two cases of acquired prosopagnosia. *Proc Natl Acad Sci U S A, 111*(14), 5123-5128. doi:10.1073/pnas.1317125111

Robertson, I. H., & Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychol Bull, 125*(5), 544-575. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10489541

Rossion, B., Caldara, R., Seghier, M., Schuller, A. M., Lazeyras, F., & Mayer, E. (2003). A network of occipito-temporal face-sensitive areas besides the right middle fusiform

gyrus is necessary for normal face processing. *Brain, 126*(Pt 11), 2381-2395. doi:10.1093/brain/awg241

Sakurai, Y., Hamada, K., Tsugawa, N., & Sugimoto, I. (2016). Ventral simultanagnosia and prosopagnosia for unfamiliar faces due to a right posterior superior temporal sulcus and angular gyrus lesion. *Neurocase, 22*(1), 122-129. doi:10.1080/13554794.2015.1066827

Shang, Y., Chang, D., Zhang, J., Peng, W., Song, D., Gao, X., & Wang, Z. (2019). Theta-burst transcranial magnetic stimulation induced functional connectivity changes between dorsolateral prefrontal cortex and default-mode-network. *Brain Imaging Behav*. doi:10.1007/s11682-019-00139-y

Sliwinska, M. W., & Pitcher, D. (2018). TMS demonstrates that both right and left superior temporal sulci are important for facial expression recognition. *NeuroImage, 183*, 394-400. doi:10.1016/j.neuroimage.2018.08.025

Solomon-Harris, L. M., Rafique, S. A., & Steeves, J. K. (2016). Consecutive TMS-fMRI reveals remote effects of neural noise to the "occipital face area". *Brain Res, 1650*, 134-141. doi:10.1016/j.brainres.2016.08.043

Stefanacci, L., & Amaral, D. G. (2000). Topographic organization of cortical inputs to the lateral nucleus of the macaque monkey amygdala: a retrograde tracing study. *J Comp Neurol, 421*(1), 52-79. doi:10.1002/(sici)1096-9861(20000522)421:1<52::aid-cne4>3.0.co;2-o

Stefanacci, L., & Amaral, D. G. (2002). Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol, 451*(4), 301-323. doi:10.1002/cne.10339

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2001). Effects of attention and emotion on face processing in the human brain: An event-related fMRI study. *Neuron, 30*(3), 829-841. doi:10.1016/S0896-6273(01)00328-2

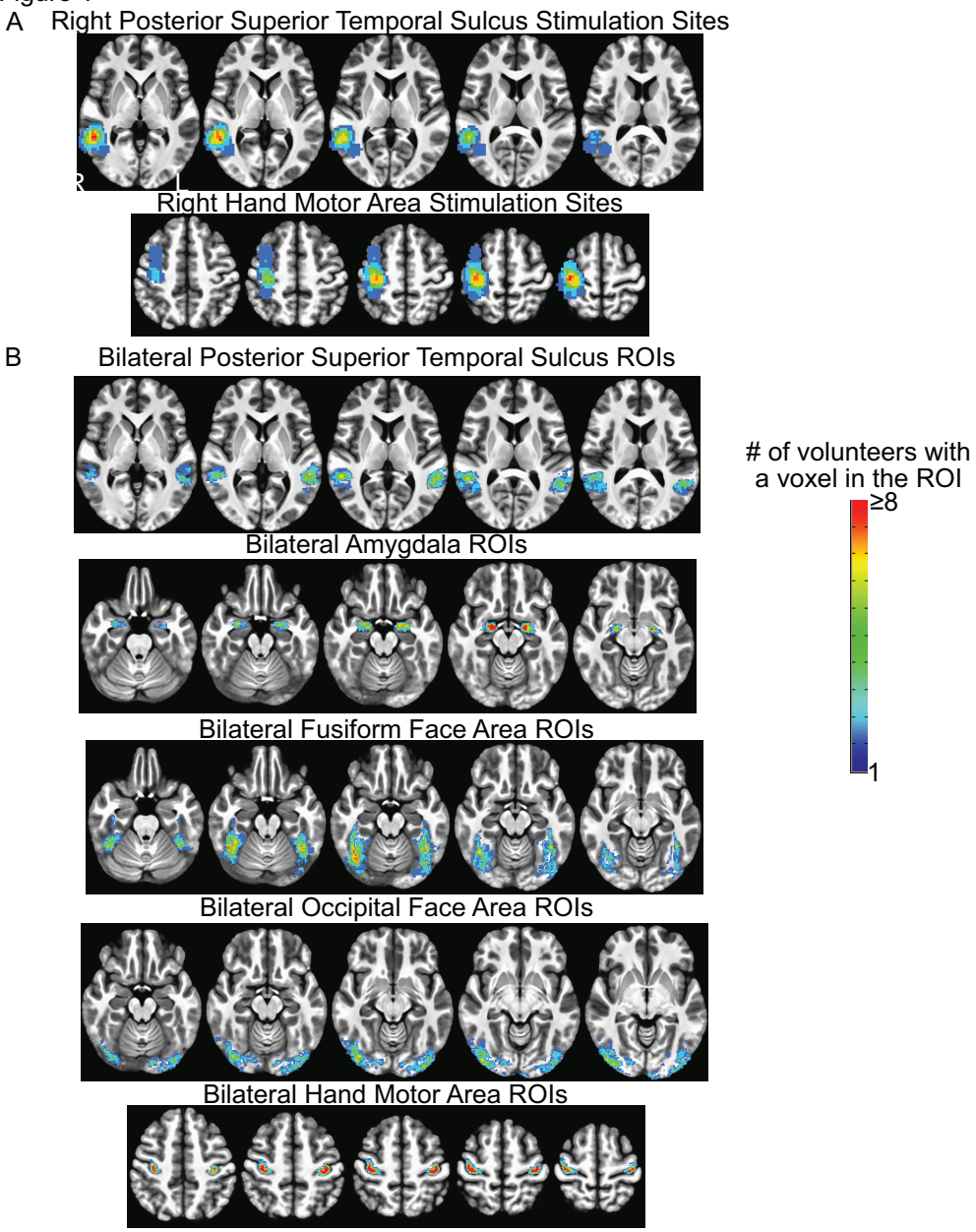
Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2003). Distinct spatial frequency sensitivities for processing faces and emotional expressions. *Nature Neuroscience, 6*(6), 624-631. doi:10.1038/nn1057

Wang, J. X., Rogers, L. M., Gross, E. Z., Ryals, A. J., Dokucu, M. E., Brandstatt, K. L., . . . Voss, J. L. (2014). Targeted enhancement of cortical-hippocampal brain networks and associative memory. *Science, 345*(6200), 1054-1057. doi:10.1126/science.1252900

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *J Neurosci, 18*(1), 411-418. doi:10.1523/JNEUROSCI.18-01-00411.1998

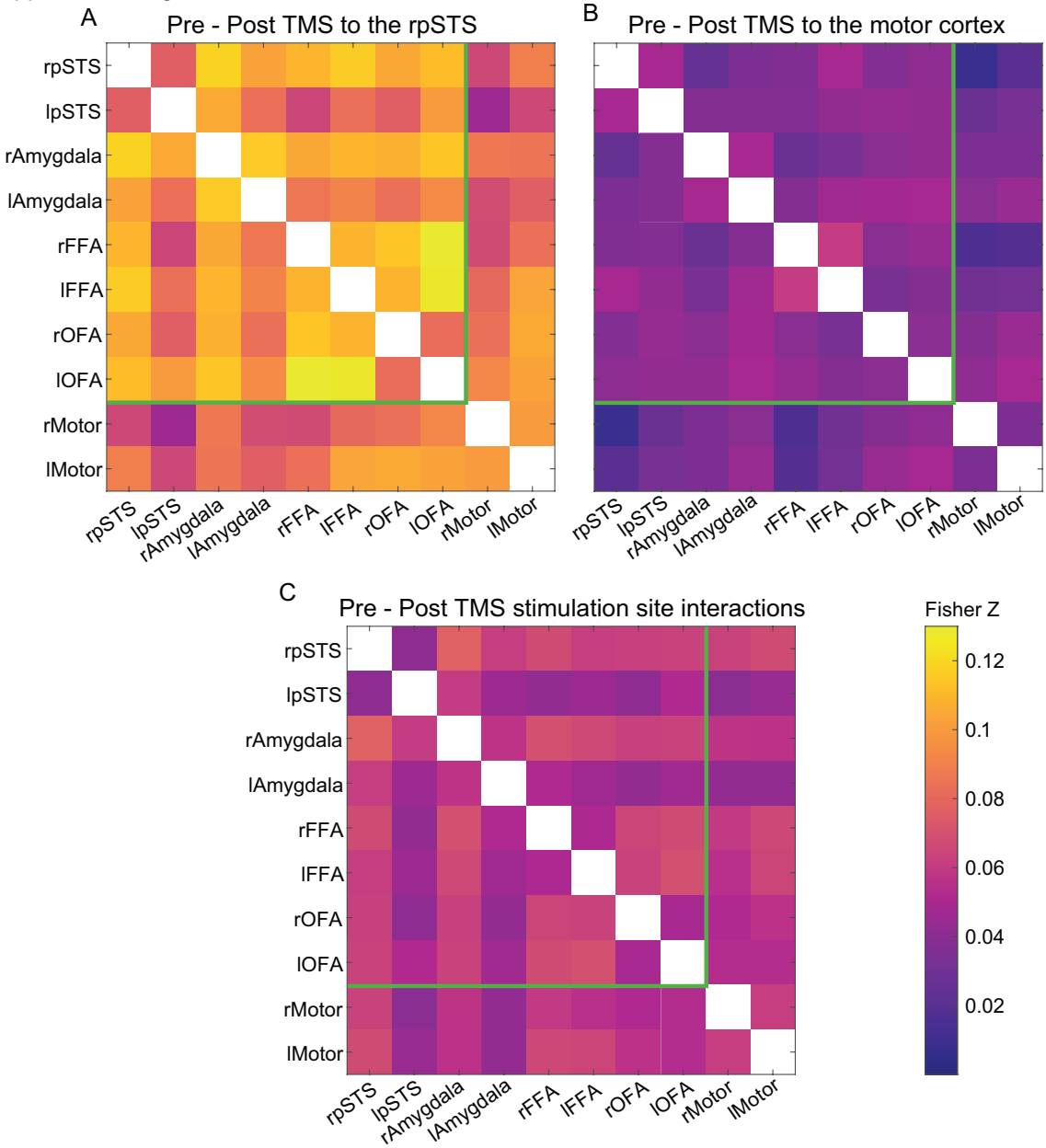
Supplemental Figures

Supplemental Figure 1



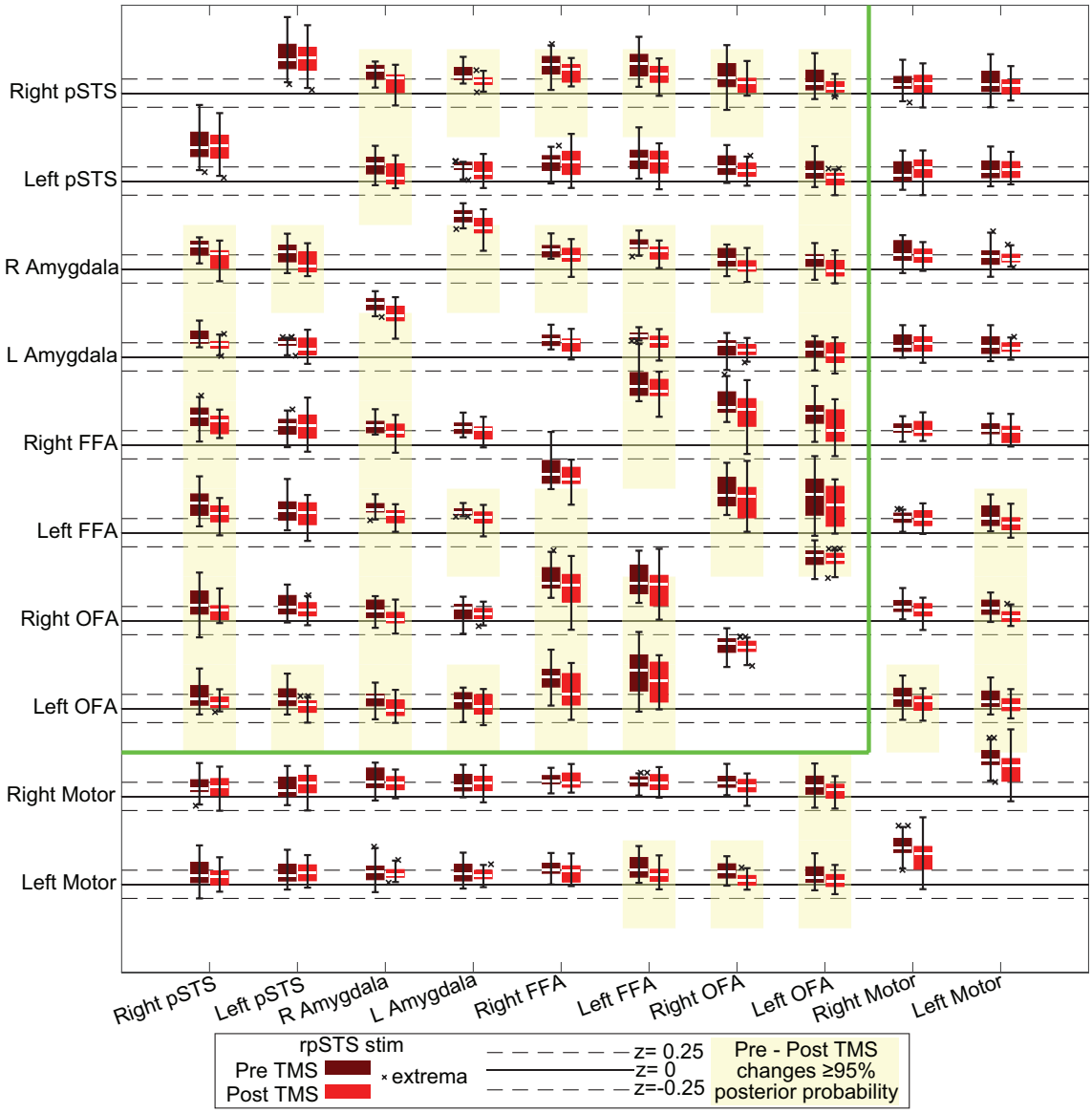
Union of the stimulation sites and ROI locations across volunteers. The anatomical underlay is the average of the aligned anatomical scans from the volunteers in this study. The overlay is the sum of all the volunter's ROIs. (A) The two stimulation sites across the subjects. The stimulation sites for each volunteer are visualized as a 1cm radius sphere centered on the stimulation site. The ROIs were individually localized for each stimulation site. The rpSTS stimulation site used a functional localizer and the motor stimulation site was defined using subject-specific anatomical landmarks. A re-examination of anatomical motor areas in each volunteer shows that the focus of the motor stimulation site was outside of the hand motor area for 5 volunteers with the focus being greater than 1 cm from the hand motor area in two volunteers. (B) Bilateral ROIs used for all connectivity analyses in this manuscript. All ROIs except for the hand motor areas were defined using the intersection of a Freesurfer-defined anatomical ROI and a Faces>Objects functional localizer

Supplemental Figure 2



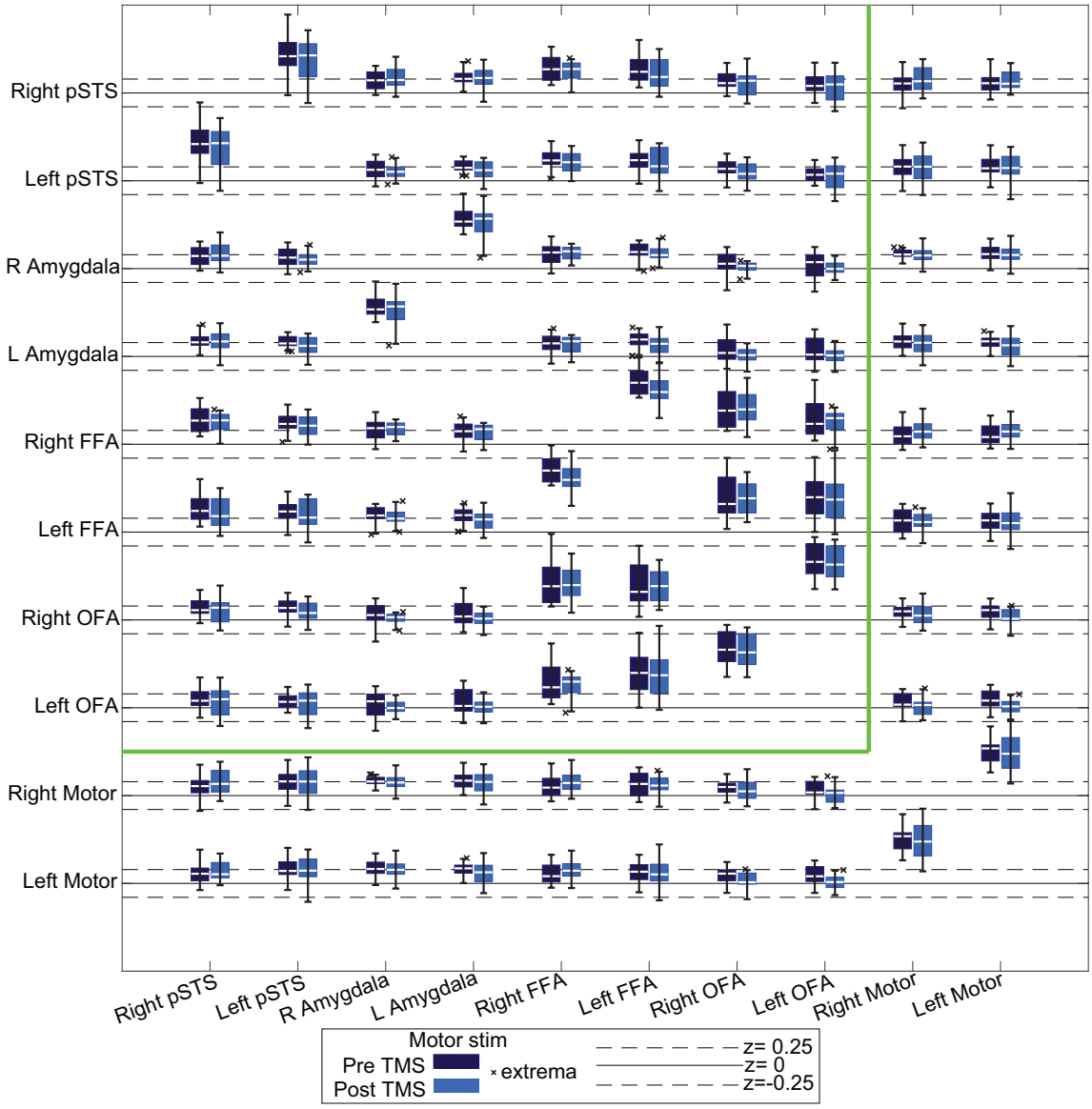
Fisher Z transformed correlation magnitude changes from pre - post TMS (A) To the rpSTS (B) To the the motor cortex, and (C) Pre - post stimulation & simulation site interaction effect. Magnitudes are the Matrix Based Analysis (MBA) model fits across the population. These are the results of the same analysis presented just for TMs to the rpSTS in Figure 1. Unlike Figure 1, the sizes of the squares are not scaled by their posterior probability. For the Motor cortex effect and the interaction effect, all posterior probabilities were less than 85%. The minimum value of the color scale is Z=0 rather than 0.2 in Figure 1 to better visualize the very small magnitude variations for motor stimulation and the interaction effects. The green line marks the ROI pairs that are within the pre-defined face-selective network.

Supplemental Figure 3



Correlations between the all pairs of ROIs in a pre-defined face network (within green line) as well as the bilateral primary motor hand regions. These boxplots correspond to the same data as the rpSTS stimulation box plots in Figure 2 but for the entire matrix of ROI pairs as in Figure 1. The first row directly corresponds to the rpSTS correlations shown in Figure 2. The solid and dashed black lines demarcate -0.25<z<0.25 for each row. Magnitudes are the MBA model fits across the population for each condition. Boxplots show 25-75% of the distribution. The white line is the median. Whiskers are the maximum and minimum values excluding outliers. MBA was used to calculate posterior probabilites that a difference is greater than 0. The ROI pairs with a yellow background show when the posterior probability was greater than 95% (Same as * in Figure 1)

Supplemental Figure 4



Correlations between the all pairs of ROIs in a pre-defined face network (within green line) as well as the bilateral primary motor hand regions. These boxplots correspond to the same data as the motor stimulation box plots in Figure 2 but for the entire matrix of ROI pairs as in Figure 1. The first row directly corresponds to the rpSTS correlations shown in Figure 2. The solid and dashed black lines demarcate -0.25<z<0.25 for each row. Magnitudes are the MBA model fits across the population for each condition. Boxplots show 25-75% of the distribution. The white line is the median. Whiskers are the maximum and minimum values excluding outliers. MBA was used to calculate posterior probabilites that a difference is greater than 0. None of the pre - post TMS to right motor cortex changes are above 85% posterior probability.