Data Supplement for Philip et al., Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.18101160)

TABLE S1. Trauma Types

	Active TBS (n=25)	Sham TBS (n=25)
Life Events Checklist (LEC) Items, *n* (%)[a]		
Natural disaster	17 (68)	21 (84)
Fire/Explosion	16 (64)	19 (76)
Transportation accident	21 (84)	20 (80)
Serious accident at work, home, or during recreational activity	18 (72)	8 (32)
Exposure to toxic substance	12 (48)	15 (60)
Physical attack	22 (88)	21 (84)
Assault with a weapon	17 (68)	22 (88)
Sexual assault	13 (52)	7 (28)
Other unwanted/uncomfortable sexual experience	12 (48)	8 (32)
Combat/war-zone exposure	13 (52)	19 (76)
Captivity	1 (4)	1 (4)
Life-threatening illness/injury	18 (72)	13 (52)
Severe human suffering	16 (64)	16 (64)
Sudden violent death	15 (60)	12 (48)
Sudden accidental death	12 (48)	13 (52)
Serious injury, harm, or death you caused to someone else	11 (44)	10 (40)
Other very stressful event/experience(s)	20 (80)	17 (68)

[a] LEC items endorsed by subjects as "Happened to me" and/or "Witnessed" and/or "Part of my Job." Totals equal greater than 100% due to multiple responses.

A. Potential Impact of Medications and Adult versus Childhood Trauma on Outcomes

Of note, we performed many post-hoc tests of whether medications might differentially impact clinical outcomes. We were unable to find that medication classes reliably impacted clinical outcomes, but we did find some indication that benzodiazepines might be associated with poorer outcomes on the CAPS and SOFAS. This would be consistent with prior neurophysiology research indicating that benzodiazepines impact motor cortex excitability (e.g., reviewed in Ziemann et al., Clin Neurophysiol 2015). Yet, because these analyses are hampered by small sub-sample sizes, we interpret these results with caution and strongly encourage future studies to evaluate whether medications may impact clinical outcomes to iTBS in PTSD.

Furthermore, because the vast majority of participants (>85%) also reported some degree of childhood trauma, we are unable to determine whether there could be differential effects of iTBS on childhood versus adult trauma exposure.

B. Neuroimaging acquisition, preprocessing and data analyses

Acquisition

Structural and functional images were collected with 3T Siemens scanners (Siemens, Erlangen, Germany), either the Verio or Prisma models, using a 32-channel head coil. A mirror was affixed to the head coil which allowed subjects to view a digital display placed at the rear of the scanner bore. We collected a high-resolution T1-weighted anatomical image (TR = 1900ms, TE = 2.98ms, FOV=256mm^2, voxel=1 mm^3) and T2*-weighted gradient-echo echo-planar resting-state functional images (TR = 2500ms, TE = 28ms, flip angle = 90 deg., FOV = 64mm^2, 42 slices, voxel size = 3.0 mm^2; volumes=192) from each participant. We asked subjects to remain as still as possible during scanning. Subjects were instructed to keep their eyes open and focus their gaze on a white crosshatch displayed against a black foreground during acquisition of resting-state functional data. Subsequent runs of functional task data were collected during imaging sessions, but these data were not used in the current analyses.

MRI Preprocessing

All MRI data were converted from DICOM to NifTi format with the MRICron's dcm2nii utility (https://www.nitrc.org/projects/mricron). Subsequent preprocessing steps were carried out with the CONN Toolbox for functional connectivity (Whitfield-Gabrieli and Nieto-Castanon, 2012). Functional preprocessing included: 1) slice-time correction, 2) head motion estimation and correction, 3) segmentation and normalization to the Montreal Neurological Institute (MNI) atlas template, 4) artifact detection with Artifact Detection Tools (https://www.nitrc.org/projects/artifact_detect) as implemented in CONN, and 5) spatial smoothing with a 6 mm full-with half-max Gaussian kernel. The artifact detection analysis flagged high motion or global signal variance volumes (>0.5mm translational, >0.2 degrees rotational motion, signal variance >3 SD) for nuisance regression during functional connectivity preprocessing. Structural data underwent segmentation and normalization to MNI atlas space.

Additional functional connectivity preprocessing steps were applied to functional data to limit effects of motion and non-neuronal signal on connectivity estimates (Ciric *et al*, 2017; Power *et al*, 2012; Satterthwaite *et al*, 2013). Following the aCompCor method (Behzadi *et al*, 2007), blood oxygen-level dependent (BOLD) signal timecourses were extracted from the cerebral spinal fluid (CSF) and white matter and submitted to principle components analysis. Next, subject-level regression of: 1) a constant and linear term for each run, 2) six motion

parameters and their temporal derivatives, 3) five aCompCor principle components from both CSF and white matter, and 4) artefactual volumes were conducted. The resulting residuals were temporally filtered (0.008 - 0.1 Hz) after nuisance regression (Satterthwaite *et al*, 2013).

Subject-level functional connectivity analysis

We adopted a region-of-interest or ROI-to-ROI approach for all subsequent analyses. A 6-mm sphere ROI was constructed for 38 regions in the DMN, FPN, VLPFC, and SN using the MarsBaR ROI Toolbox (http://marsbar.sourceforge.net/) (Supplemental Table 2). DMN ROI center coordinate selections were guided by the tripartite DMN fractionation of Andrews-Hanna et al. (Andrews-Hanna *et al*, 2010) and the Neurosynth database (http://neurosynth.org/). MNI coordinates for the remaining ROIs were also generated with the Neurosynth meta-analytic database. Briefly, terms functionally related to these networks were used to generate a term association map and peak coordinates were used as ROI sphere center coordinates. Sphere ROI locations were then compared to several existing resting-state network parcellations (Shirer *et al*, 2012; Yeo *et al*, 2011) to confirm that they were generally consistent with current network theory. BOLD timecourses for each ROI were then extracted from subjects' filtered residuals, cross-correlated with all other ROIs in the ROI matrix, and the resulting Pearson's correlation coefficients underwent Fisher's R-to-Z transformation.

Group-level functional connectivity analysis

To evaluate whether ROI-to-ROI functional connectivity at baseline was predictive of later symptom improvement, we examined the unique association between percent change in scale score after completion of two weeks of active TMS after controlling for age and scanner differences. For subjects randomized to the active group, we computed percent change in scale score between the end of the blinded phase and baseline. For the sham group subjects, percent change was based on differences in scores at the end of the open-label phase and at baseline. Percent change scores were then converted to z-scores. See Limitations paragraph in the manuscript document for caveats related to equality of non-specific effects across blind and open-label phases. Correlations between ROIs were considered significant if the Fisher-transformed correlation coefficient p-value <.05 after seed-level false discovery rate correction. We ran additional regressions to ensure that significant findings were not driven by individual differences in data quality or sex by entering these potential confounders as independent variables during post hoc testing. To better characterize the relationship between connectivity at baseline and later symptom response, we computed mean Pearson's R-values for the 11 patients that experienced above-average decrease in symptoms (z-transformed percent change in score<0), and for the 15 patients experiencing below-average change in symptoms after treatment.

TABLE S2: Region of Interest Definitions

Functional Network	*Subnetwork*	*Subregion*	*MNI Coordinate*	*Neurosynth Term*
Default	DMN-Core	Ant.mPFC	-2,50,-6	default
		PCC	0 -52 28	default
	DMN-DMPFC	DMPFC	0 54 24	beliefs
		R.LTC	60 -2 -30	default
		L.LTC	-62 -14 -18	default
		L.TPJ	-54 -56 20	tom
		R.TPJ	54 -56 20	tom
		R.Ant.TC	50 16 -28	tom
		L.Ant.TC	-44 12 -24	tom
	DMN-MTL	R.PHG	22 -20 -20	episodic
		L.PHG	-22 -20 -22	episodic
		R.HPC	30 -12 -20	episodic
		L.HPC	-30,-12,-20	episodic
		R.Retrosplenial	18 -52 10	episodic
		L. Retrosplenial	-6 -50 10	episodic
		R.AG	50 -52 28	episodic
		L.AG	-44 -70 32	episodic
		SGACC	-2 26 -16	value
Cognitive Control				
	FPN	R.Ant.DLPFC	38 50 10	cognitive control
		L.Ant.DLPFC	-40 52 10	externally
		R.DLPFC	44 38 26	working memory
		L.DLPFC	-44 30 26	working memory
		R.IPS	40 -48 48	working memory
		L.IPS	-38 -50 44	working memory
	VLPFC	L.Orbitalis	-46 30 -10	comprehension
		L.Triangularis	-48 30 8	semantic
		R.Orbitalis	48 32 -6	empathy
		L.Opercularis	-48 16 22	language
		R.Triangularis	48 30 14	memory
		R.Opercularis	52 18 10	inhibition

Salience	R. Amygdala	22 -2 -20	fear
	L. Amygdala	-22 -2 -20	fear
	R. Ant.Insula	38 14 2	pain
	L. Ant.Insula	-36 14 -10	pain
	R. Ant.DLPFC	26 50 24	noxious
	L. Ant.DLPFC	-30 50 18	noxious
	R. Dorsal ACC	6 28 26	pain
	L. Dorsal ACC	-6 28 26	pain

Abbreviations: tom, Theory of mind

Supplemental References

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