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Variability in response to theta burst TMS for PTSD: The role of epigenetic mediation

Dear editor:

Neurostimulation is an increasingly implemented treatment for a range of psychiatric disorders [1]. Population and disorder specific approaches to brain stimulation continue to be documented, such as the utility of intermittent theta-burst stimulation (iTBS) for post-traumatic stress disorder (PTSD) [2,3]. Philip et al., 2019 [4] conducted the first sham-controlled trial of iTBS in Veterans with PTSD, finding statistically significant improvement in social and occupational function, and clinically meaningful, albeit non-significant, reductions in PTSD symptoms following two-weeks of active iTBS treatment. Despite the growing body of literature demonstrating efficacy of iTBS, response variability persists, highlighting the need to identify inter-individual predictors of treatment outcomes [5].

Genetic and epigenetic factors may represent biomarkers for the prediction of TMS response. Polymorphisms of two candidate genes, catechol-*o*-methyltransferase (*COMT*) and brain-derived neurotrophic factor (*BDNF*) have been previously identified as moderators of TMS response [6,7]. Evidence of genotypic moderation implicates the potential for genetic screening in clinical decision making, however the complexity of molecular processes involved in gene expression brings to question whether epigenetic systems further mediate TMS outcomes. Low level magnetic stimulation has been linked to DNA methylation, a regulatory mechanism of gene suppression, in human neural cells [8]. The impact of magnetic stimulation on DNA methylation coupled with evidence of genetic moderation for TMS response warrants the study of whether DNA methylation contributes to TMS treatment response variability observed in clinical samples.

To explore the relationship between epigenetic markers (particularly *COMT* and *BDNF* methylation) on iTBS treatment response, DNA samples from whole blood were obtained from a subset ($n = 23$) of Veterans enrolled in Philip et al., 2019 [4] at baseline and end of two-week double-blind treatment phase. Treatment response was operationalized via change across the following measures obtained at both time points: Clinical Administered PTSD Scale for DSM-5 (CAPS), PTSD Checklist for DSM-5 (PCL-5), Social and Occupational Functioning Assessment Scale (SOFAs), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) and Inventory of Depressive Symptomatology Self-Report (IDS-SR). Pyrosequencing across two *COMT* and three *BDNF* CpG sites were completed. The average across the *COMT* and *BDNF* sites were used to create *COMT* average and *BDNF* average scores with positive values representing a reduction in methylation over time and therefore a putative increase in genetic expression, and negative values denoting an increase in methylation and putatively greater genetic suppression.

Statistical analyses included a series of linear regressions in which change on each self-report measure was predicted by treatment group (active ($n = 11$) vs. sham ($n = 12$)) and change in epigenetic values (Table 1). Additional models controlled for epigenetic interaction effects. The significant benefit of iTBS over sham on change in IDS-SR scores reported by Philip et al., 2019 [4] was reproduced in the subsample ($\beta = -8.6$, $p = 0.049$) with further significant changes in CAPS ($\beta = -5.9$, $p = 0.02$) and SOFAS ($\beta = 7.2$, $p = 0.03$) scores observed between treatment groups for those participants with epigenetic data. No main effects of change in *BDNF* average or change in *COMT* average values were found. However, a crossover interaction was detected in the PSTD model, indicating that for those in the active treatment group, a greater change in *COMT* average was related to an attenuation of PSTD symptom reduction at the end of the treatment phase when compared to those with lower change in *COMT* average values ($\beta = 2.9$, $p = 0.007$). Once controlling for this interaction, we saw significant main effects of treatment group ($\beta = -23.3$, $p = 0.01$) and change in *COMT* average ($\beta = -2.1$, $p = 0.02$). In contrast, within the sham condition, greater change in *COMT* average was associated with a modest increase in PCL-5 scores over time. Overall, active iTBS treatment and greater change in average *COMT* values (signifying a reduction in DNA methylation over time) resulted in greater PCL-5 improvement.

These findings preliminarily indicate an interaction between epigenetic change in *COMT* methylation and verum iTBS response, such that an increase in DNA methylation over time was associated with poorer response. These interpretations require caution given the small sample size and relatively narrow assessment of DNA methylation. More comprehensive and costly analytic procedures, such as methylome wide association studies, might serve to better classify the biomarkers implicated in response variability. These caveats aside, to our knowledge this is the first indication of a relationship between iTBS and changes in epigenetic status, indicating novel mechanism(s) related to TMS. Once precise epigenetic markers are identified, they have the potential to inform the development of pharmacological adjuncts that either bolster iTBS response or result in a similar effect. An additional line of inquiry involves the dose-dependent nature of neurostimulation. Philip et al., 2019 [4] reported the majority of iTBS benefit was observed within the first week of treatment. Earlier and more frequent DNA collection may aid in our understanding of whether epigenetic changes are implicated in the temporal track of treatment response. In summary, epigenetic mechanisms are associated with TMS

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Table 1
Clinical outcomes comparing active iTBS versus sham, using mixed models.

Outcomes: Difference (Post-pre) Those with epigen data (N = 23)	Clinician-Administered PTSD Scale for DSM-5				PTSD Checklist for DSM-5				Social and Occupational Functioning Assessment Scale				Quality of Life Enjoyment and Satisfaction Questionnaire				Inventory of Depressive Symptomatology–Self-Report			
	Beta	95%CI		p	Beta	95%CI		p	Beta	95%CI		p	Beta	95%CI		p	Beta	95%CI		p
Group (Active compared to SHAM)	−5.92	−20.76	−1.08	0.0188 *	−8.71	−19.54	2.13	0.11	7.19	0.71	13.67	0.0313 *	0.19	−0.28	0.66	0.41	−8.59	−17.16	−0.03	0.0494 *
R2	0.24				0.12				0.20				0.03				0.17			
Controlling for epigenetic data (N = 23)	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|
Group (Active compared to SHAM)	−5.41	−10.61	−0.22	0.042 *	−8.52	−20.20	3.20	0.14	6.07	−0.68	12.82	0.08	0.16	−0.34	0.65	0.52	−7.79	−16.62	1.04	0.08
Epigenetic variables*																				
COMT average	−0.20	−0.68	0.29	0.41	−0.15	−1.25	0.94	0.77	0.39	−0.24	1.02	0.21	0.01	−0.04	0.05	0.77	−0.43	−1.25	0.40	0.29
BDNF average	−0.07	−0.72	0.57	0.81	−0.44	−1.89	1.01	0.53	−0.03	−0.86	0.80	0.94	−0.02	−0.08	0.04	0.44	−0.72	−1.81	0.37	0.18
R2	0.26				0.14				0.28				0.08				0.26			
Controlling for epigenetic interaction effects (N = 23)	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|	Estimate	95%CI		Pr > |t|
Group (Active compared to SHAM)	−4.27	−0.15	5.34	0.36	−23.39	−41.28	−5.49	0.0135 *	0.00	−12.26	12.26	1.00	0.28	−0.64	1.19	0.53	−12.57	−26.55	1.41	0.07
Epigenetic variables*																				
COMT average	−0.27	−1.20	0.66	0.55	−2.11	−3.84	−0.38	0.0199 *	0.02	−1.17	1.21	0.97	0.04	−0.05	0.12	0.40	−0.03	−2.70	0.01	0.0521 *
group(active)*COMTavg	0.23	−0.86	1.32	0.66	2.93	0.90	4.96	0.0072 **	0.32	−1.07	1.71	0.63	−0.05	−0.16	0.05	0.31	1.52	−0.07	3.10	0.06
BDNF average	0.24	−0.69	1.17	0.60	−0.96	−2.69	0.78	0.26	−0.76	−1.95	0.42	0.19	−0.04	−0.12	0.05	0.41	−0.54	−1.90	0.81	0.41
group(active)*BDNFavg	−1.00	−2.37	0.37	0.14	−0.84	−3.40	1.72	0.50	1.71	−0.04	3.46	0.06	0.07	−0.06	0.20	0.27	−1.61	−3.61	0.38	0.11
R2	0.39				0.51				0.42				0.25				0.55			

*Averages over markers of pre-post differences in methylation %.
Statistical model (*p < 0.05, **p < 0.01).
Note: CAPS, SOFAS and QLESQ obtained at the end of every two weeks. PCL-5 and IDS-SR obtained at the end of every week (Data from Phillips et al., 2019).

response variability and therefore may represent a novel target for combined neurostimulation and pharmacological interventions in those with psychiatric disorders.

Declaration of interest

The authors declare that there are no known conflicts of interest.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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