HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2021 January 11.

Published in final edited form as:

Biol Psychiatry. 2019 February 01; 85(3): e13–e14. doi:10.1016/j.biopsych.2018.07.002.

A Case for the Frontal Pole as an Empirically Derived Neuromodulation Treatment Target

Colleen A. Hanlon, **Noah S. Philip**, **Rebecca B. Price**, **Warren K. Bickel**, **Jonathan Downar**

Departments of Psychiatry and Neurosciences (CAH), Medical University of South Carolina, Charleston, South Carolina; Alpert Medical School at Brown University (NSP) and Center for Neurorestoration and Neurotechnology (NSP), Providence VA Medical Center, Providence, Rhode Island; Departments of Psychiatry and Psychology (RBP), University of Pittsburgh, Pittsburgh, Pennsylvania; Addiction Recovery Research Center (WKB), Virginia Tech Carillion Research Institute, Roanoke, Virginia; and the Department of Psychiatry (JD), University of Toronto, Toronto Western Hospital, Toronto, Ontario, Canada.

To the Editor:

Since 2015 there has been unprecedented growth in the development of noninvasive brain stimulation treatments for a variety of psychiatric diseases. This growth was catalyzed by the initial U.S. Food and Drug Administration clearance of transcranial magnetic stimulation (TMS) as a tool to treat pharmacoresistant major depressive disorder in 2008, widespread coverage by medical insurers throughout the United States, and the announcement of several high-profile Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative requests for noninvasive brain stimulation applications from the National Institutes of Health. As this field matures, one of the most formidable barriers to progress is identifying the most effective neural target to induce change in the distributed neural networks underlying psychopathology.

In the last year, several influential publications have suggested that the frontopolar cortex (FP) may be a fruitful, transdiagnostically relevant target. The FP is a critical neural hub whose connectivity to the rest of the brain is disrupted across multiple neuropsychiatric disorders (1). Functional connectivity with the FP is related to treatment outcome in major depressive disorder, posttraumatic stress disorder, and obsessive-compulsive disorder (2–4). The FP is a fixed anatomical landmark that represents one of three established subdivisions of Brodmann area 10, which has particularly extensive dendritic spine concentrations and arborization densities (5). Anatomically, this region overlaps with both the ventral medial prefrontal cortex and medial orbitofrontal cortex. Lastly, convergent evidence from lesion, stimulation, connectivity, and functional neuroimaging studies suggests that inhibition of the FP may be a viable therapeutic strategy for repetitive TMS in major depression.

It stands to reason that the noninvasive brain stimulation field should be developing innovative TMS strategies to modulate frontal pole connectivity in our patients. One of the

Address correspondence to Colleen A. Hanlon, Ph.D., Departments of Psychiatry and Neurosciences, Medical University of South Carolina, 67 President St., Charleston, SC 29425; hanlon@musc.edu.

first published TMS studies targeting the frontal pole demonstrated that 3600 pulses of continuous theta burst stimulation at 110% resting motor threshold decreased in frontostriatal connectivity in cocaine users and alcohol users (6). This lower frontostriatal connectivity was specifically observed during presentations of cues related to the drug of abuse (rather than neutral cues) in these alcohol users and cocaine users (7). In addition, in cigarette smokers, Bickel et al. (8) demonstrated that 5 days of this same FP continuous theta burst stimulation protocol decreases striatal reactivity to smoking cues and behavioral preference for cigarettes among smokers. The frontal pole is also being evaluated as a target for obsessive-compulsive disorder— wherein Price et al. are delivering intermittent or continuous theta burst stimulation at 110% resting motor threshold (https://clinicaltrials.gov/ct2/show/NCT03265015). Note that the aforementioned investigations have been funded in part by the National Institutes of Health, have been approved by institutional review boards, and have had no significant adverse events.

Why has the FP not caught on as a treatment target? In our experience, three perceived barriers have led to slow adoption of the frontal pole as a treatment target for psychiatric populations. They are 1) the difficulty of reaching this cortical site, 2) the discomfort for participants, and 3) concern that local review boards will not approve protocols because of the unconventional coil position. Regarding reaching this cortical site, although we agree that the scalp to cortex distance from the FP1 position (using the 10–20 electroencephalography system) is higher than the distance from C3 (motor) to the cortex, a recent paper demonstrated that the average distance from FP1 to the cortex and F3 to the cortex (dorsolateral prefrontal cortex target) was not significantly different in healthy control subjects or chronic cocaine users (many of whom have cortical atrophy) (9). Consequently, we recommend that all studies using TMS to the dorsolateral prefrontal cortex or frontal pole integrate scalp-to-cortex distance as a dosing factor, given that even small changes in distance have large effects on the dose (10). Regarding the discomfort to participants, given that the frontal pole (FP1 or FP2 via the 10–20 electroencephalography system) in most individuals is located dorsal to the medial aspects of the eyebrow, we would expect greater sensitivity compared to the dorsolateral prefrontal cortex, which is often covered by hair. That said, we have overcome this barrier by using a slow ramping of increased intensity for each session. These studies have used a ramping procedure that starts the participants at low intensity (0–30% machine output) and gradually amplifies the output through the session. This ramping procedure has been published in previous papers along with a full standard operating procedure and video (6). Regarding institutional review board concerns, the primary purpose of this correspondence is to increase awareness regarding the growing use of the frontal pole as a treatment target and in support of this scientific momentum. Table 1 lists the clinical populations who received frontal pole TMS, the TMS protocol, and the ramping procedure. To our knowledge, no seizures or other safety events related to frontal pole TMS have been reported.

In summary, stimulation of the FP appears to be a promising new area of noninvasive brain stimulation research and is applicable to various patient populations and disorders. The transdiagnostic relevance of the FP opens new opportunities for clinical trial development in multiple neuropsychiatric disorders. We hope that this perspective and these methodological suggestions will be taken into consideration and referenced by the Safety of TMS Consensus

Group to revise guidelines during the fall 2018 meeting in Sienna, Italy. Furthermore, we invite other investigators with data on frontal pole TMS to contact us so that we can add your information to the growing list of research in this area. We are also happy to supply information regarding regulatory documentation and standard operating procedures.

Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

References

1. Fettes PW, Downar J (2018): Identifying prefrontal networks for disease vulnerability versus acute illness in major depression. Biol Psychiatry Cogn Neurosci Neuroimaging 3:308–310. [PubMed: 29628062]
2. Philip NS, Barredo J, van't Wout-Frank M, Tyrka AR, Price LH, Carpenter LL (2018): Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. Biol Psychiatry 83:263–272. [PubMed: 28886760]
3. Fonzo GA, Goodkind MS, Oathes DJ, Zaiko YV, Harvey M, Peng KK, et al. (2017): Selective effects of psychotherapy on frontopolar cortical function in PTSD. Am J Psychiatry 174:1175–1184. [PubMed: 28715907]
4. Jacobs B, Schall M, Prather M, Kapler E, Driscoll L, Baca S, et al. (2001): Regional dendritic and spine variation in human cerebral cortex: A quantitative golgi study. Cereb Cortex 11:558–571. [PubMed: 11375917]
5. Moody TD, Morfini F, Cheng G, Sheen C, Tadayonnejad R, Reggente N, et al. (2017): Mechanisms of cognitive-behavioral therapy for obsessive-compulsive disorder involve robust and extensive increases in brain network connectivity. Transl Psychiatry 7:e1230. [PubMed: 28872637]
6. Hanlon CA, Dowdle LT, Correia B, Mithoefer O, Kearney-Ramos T, Lench D, et al. (2017): Left frontal pole theta burst stimulation decreases orbitofrontal and insula activity in cocaine users and alcohol users. Drug Alcohol Depend 178:310–317. [PubMed: 28686990]
7. Kearney-Ramos TE, Dowdle LT, Lench DH, Mithoefer OL, Devries WH, George MS, et al. (2018): Transdiagnostic effects of ventromedial prefrontal cortex transcranial magnetic stimulation on cue reactivity. Biol Psychiatry Cogn Neurosci Neuroimaging 3:599–609. [PubMed: 29776789]
8. Bickel W, Snider S, Hanlon C, Stein J (2017): Continuous theta burst TMS as a tool to change decision-making in smokers [abstract]. Brain Stim 10:487.
9. Hanlon CA, Dowdle LT, Moss H, Canterberry M, George MS (2016): Mobilization of medial and lateral frontal-striatal circuits in cocaine users and controls: An interleaved TMS/BOLD functional connectivity study. Neuropsychopharmacology 41:3032–3041. [PubMed: 27374278]
10. Summers PM, Hanlon CA (2017): BrainRuler-a free, open-access tool for calculating scalp to cortex distance. Brain Stim 10:1009–1010.

Table 1.

Frontal Pole Theta Burst Stimulation (TBS): Feasibility and Tolerability[a]

	Real TBS	Sham TBS[b]
Medical University of South Carolina		
Participants, *n*[c]	137	106
Sessions, *n*[d]	466	402
Ramp	30%–120% at rate tolerated	
Pulses/session, *n*	600 and 3600	
Populations	Individuals with cocaine and alcohol use disorder, individuals with chronic pain taking opiates, tobacco smokers, control subjects	
Virginia Tech Carillion Research Institute		
Participants, *n*[c]	31	23
Sessions, *n*[d]	127	96
Ramp	80%–110% at rate tolerated	
Pulses/session, *n*	3600	
Populations	Tobacco smokers, obese individuals	
University of Pittsburgh		
Participants, *n*[c]	19	19
Sessions, *n*[d]	19	19
Ramp	1 %–110% at rate tolerated	
Pulses/session, *n*	1200 total (including 600 for ramp)	
Populations	Individuals with obsessive-compulsive disorder	

[a] Record of sessions as of June 2018.

[b] Sham stimulation intensity is matched to real stimulation intensity. These data support for the tolerability of these protocols. Note: There have been no serious adverse events associated with these protocols.

[c] Individuals who received at least one complete session of intermittent TBS or continuous TBS.

[d] A predefined dose of TBS, defined by pulse number.