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REPORT

Caudate stimulation enhances learning

Sarah K. Bick,[1] Shaun R. Patel,[2] Husam A. Katnani,[1] Noam Peled,[3] Alik Widge,[4] Sydney S. Cash[5] and Emad N. Eskandar[6]

Neuromodulation is a promising treatment modality for disorders of learning and memory, offering the possibility of precise alteration of disordered neural circuits. Studies to date have failed to identify an optimal target and stimulation paradigm. Six epilepsy patients with depth electrodes implanted for seizure localization participated in our study. We recorded local field potentials from implanted electrodes while subjects participated in an associative learning task requiring them to learn an association between presented images and a button press. Three subjects participated in stimulation sessions during which caudate or putamen stimulation was delivered for some images during feedback after correct responses. Caudate stimulation enhanced learning. Both caudate and dorsolateral prefrontal cortex demonstrated a beta power increase during the feedback period of the learning task that was greater following correct than incorrect trials. In dorsolateral prefrontal cortex, this difference increased with learning and persisted beyond the end of the feedback period. Caudate stimulation was associated with increased dorsolateral prefrontal cortex beta power following feedback. These findings suggest that temporally specific caudate stimulation is a promising neuromodulation strategy to improve learning in disorders of learning and memory.

1 Massachusetts General Hospital, Department of Neurosurgery, Boston, MA, USA
2 McCance Center for Brain Health, Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
3 Department of Radiology, MBGH/HST Martinos Center for Biomedical Imaging and Harvard Medical School, Boston, MA, USA
4 Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA
5 Massachusetts General Hospital, Department of Neurology, Boston, MA, USA
6 Albert Einstein College of Medicine, Montefiore Medical Center, Department of Neurosurgery, Bronx, NY, USA

Correspondence to: Sarah K. Bick
Wang 021
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114, USA
E-mail: SBick@partners.org

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Abbreviation: DLPFC = dorsolateral prefrontal cortex

Introduction

From Alzheimer's disease to traumatic brain injury, disorders of learning and memory have an enormous impact on our society, with large associated health, social, and financial burdens (Wimo *et al.*, 2017). Current medical treatment options non-specifically target diffuse neurotransmitter systems and have only modest impact on symptoms. Deep brain stimulation is a promising modality to treat disorders of learning and memory due to its ability to alter activity in disordered neural circuits. Initial trials of deep brain stimulation for improving memory in Alzheimer's disease targeting the fornix (Lozano *et al.*, 2016) and nucleus basalis of Meynert (Kuhn *et al.*, 2014)

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used a continuous stimulation paradigm and unfortunately had limited efficacy. Recently, closed loop stimulation of lateral temporal cortex in epilepsy patients with implanted depth electrodes showed more promising results for improving memory (Ezzyat *et al.*, 2018). Further optimization of stimulation target and delivery is needed to develop useful neuromodulation modalities for disorders of learning and memory.

Primate studies have demonstrated that the caudate nucleus plays an important role in learning (Williams and Eskandar, 2006). Caudate neurons encode information related to stimulus, action, and reward in learning tasks (Lau and Glimcher, 2007; Yanike and Ferrera, 2014), suggesting that the caudate may be important in associating learned actions with their resulting outcomes. Previous work demonstrated that primate caudate neural activity during the reinforcement period of an associative learning task correlated with learning rate, and that high frequency stimulation of the caudate during this time period following correct trials enhanced learning, while putamen stimulation impaired learning (Williams and Eskandar, 2006).

Dorsolateral prefrontal cortex (DLPFC) is also important in associative learning and may work in conjunction with the caudate. DLPFC has strong interconnections with the striatum (Haber *et al.*, 2006) and is well positioned to play a role in associative learning in conjunction with the caudate. DLPFC plays an important role in human learning (Barbey *et al.*, 2013), and patients with lesions of either caudate or DLPFC have learning deficits (Tricomi *et al.*, 2004). DLPFC neural firing carries information about stimulus, response, and outcomes in learning tasks (Seo *et al.*, 2007).

In this study we demonstrate that caudate stimulation delivered in conjunction with task events improves learning. Additionally, we show that caudate and DLPFC contain feedback-related power changes and that in the DLPFC, these changes increase with learning. Finally, we report that caudate stimulation may modulate DLPFC learning-related power changes.

Materials and methods

Subjects and task

Six patients with medically refractory epilepsy with intracranial depth electrodes placed for clinical seizure localization participated in our study. Areas targeted included the DLPFC and posterior orbitofrontal cortex. Posterior orbitofrontal cortex electrodes required a trajectory that traversed the internal capsule or striatum (Fig. 1A–D). The decision to perform invasive monitoring, electrode positioning, and length of monitoring were determined entirely by clinical considerations. All subjects provided written informed consent prior to participating in the study. The study was approved by the Institutional Review Board.

To identify caudate and DLPFC electrode contacts, we co-registered the postoperative CT scan for each patient with the preoperative high resolution MRI. We determined electrode locations corresponding to caudate and DLPFC by visual inspection of the resulting coregistered image. For further details see the Supplementary material.

Subjects participated in an associative learning task requiring them to learn an association between a presented image and a specific button press on a keyboard (Fig. 1E). Three subjects (Subjects 1–3) completed stimulated sessions and five (Subjects 2–6) completed non-stimulated sessions. Our study protocol required patients to be on their full home anti-epileptic regimen during stimulated sessions due to safety considerations, while non-stimulated sessions occurred when patients were on a variety of anti-epileptic medications. During stimulated sessions, three of the six images presented in each block were stimulated images and received stimulation during the 1-s feedback period following correct responses, while the other three images were non-stimulated images and never received stimulation. The task was presented using Psychtoolbox task presentation software. Continuous EEG was recorded during task presentation. Neural data were acquired using two Blackrock Neural Signal Processor units at 2000 Hz sampling rate.

Stimulation

Stimulation was bipolar. Stimulation contacts were chosen prior to stimulation sessions to maximize stimulation coverage of the dorsal caudate. Subjects 1 and 2 received bilateral caudate stimulation during the feedback period following correct responses. For Subject 3, the right posterior orbitofrontal cortex electrode trajectory was more laterally placed and passed through the putamen. This subject therefore received right putamen and left caudate stimulation. A digital trigger from the task presentation computer to a Blackrock Cerestim R96 initiated delivery of stimulation. Stimulation was delivered at 200 Hz, with pulse width of 0.2 ms and amplitude of 2 mA for 1000 ms. We chose 200 Hz stimulation following correct responses as previous primate work demonstrated this combination to be necessary to improve learning (Williams and Eskandar, 2006; Katnani *et al.*, 2016).

Analysis

Learning curves were calculated using a state space model incorporating both response accuracy and reaction time to estimate learning state, a method which has been previously published and validated (Smith *et al.*, 2004; Prerau *et al.*, 2009) (Supplementary material). Repeated measures ANOVA was used to test for significant difference in learning between stimulated and non-stimulated images within stimulation sessions for each subject. Repeated measures ANOVA was additionally used to determine whether learning occurred over time for individual subjects.

Local field potential analysis was performed using MATLAB. Data were down-sampled to 1000 Hz and aligned to behavioural events using digital events triggers. Data were bandpass filtered at 60 Hz to remove line noise. Power was calculated using Morlet wavelet time frequency transformation in Fieldtrip MATLAB toolbox (Oostenveld *et al.*, 2011).

Based on previous work, we were particularly interested in caudate power changes during the feedback period (Williams and Eskandar, 2006). We also examined power changes during a 500 ms post-feedback period from 250 to 750 ms

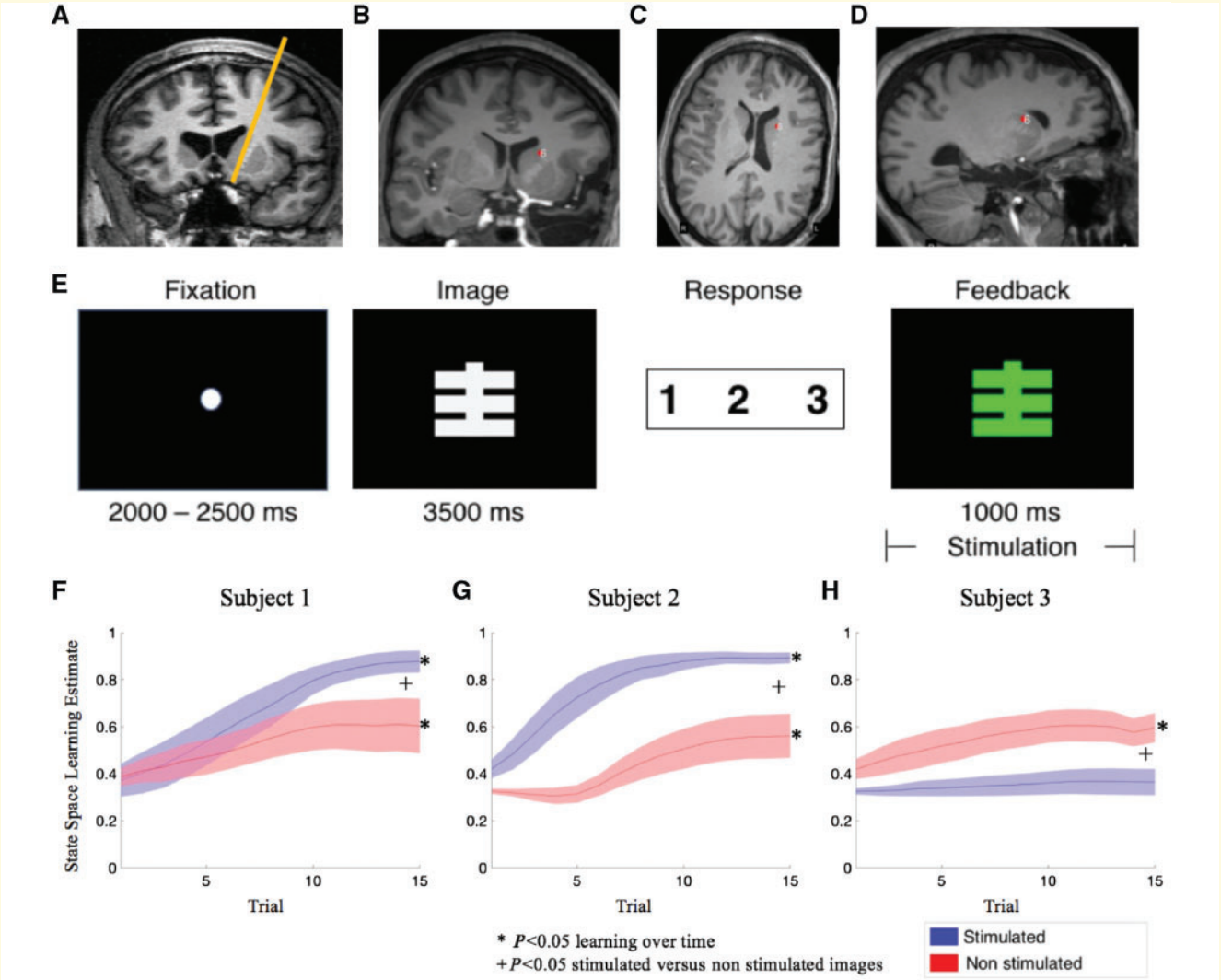

Figure 1 Striatal stimulation modulates learning. (**A**–**D**) Striatal electrode trajectory. Electrodes targeting posterior orbitofrontal cortex used a trajectory passing through anterior striatum or anterior internal capsule. (**A**) Representative electrode trajectory with electrode passing through striatum to target posterior orbitofrontal cortex. (**B**) Corontal, (**C**) axial, and (**D**) sagittal MRI slices depicting a caudate electrode contact in a second subject. (**E**) Schematic of the associative learning task. Following a fixation point indicating the start of the trial, subjects were presented with an image that they learned to associated with a specific button press through trial and error. Visual feedback indicated whether the response was correct or incorrect. In stimulated sessions, half of the presented images received bilateral caudate stimulation during feedback following correct responses. (**F**–**H**) Individual subject learning curves for the stimulated and non-stimulated images for the three subjects who completed stimulated sessions. Shaded bars represent standard error. (**F** and **G**) Bilateral caudate stimulation was performed in two subjects and significantly improved learning. (**F**) Subject 1 demonstrated learning over time for both stimulated and non-stimulated images ($P = 1.76 \times 10^{-30}$, F = 22.57, df = 14, and $P = 9.69 \times 10^{-9}$, F = 2.01, df = 14); however, learning was significantly enhanced by caudate stimulation ($P = 7.37 \times 10^{-5}$, F = 3.26, df = 14). (**G**) Subject 2 also demonstrated learning for both stimulated and non-stimulated images ($P = 9.25 \times 10^{-40}$, F = 33.70, df = 14, and $P = 2.64 \times 10^{-7}$, F = 4.81, df = 14, respectively), with caudate stimulation similarly improving learning ($P = 2.57 \times 10^{-8}$, F = 2.57, df = 14). (**H**) Subject 3 received right putamen and left caudate stimulation. While this subject displayed learning of non-stimulated images in the stimulation session ($P = 7.63 \times 10^{-9}$, F = 5.70, df = 14), the subject did not display learning of stimulated images ($P = 0.98$, F = 0.38, df = 14). The combination of right putamen and left caudate stimulation significantly impaired learning in this subject ($P = 2.32 \times 10^{-10}$, F = 5.94, df = 14).

following feedback offset. We used the Kruskal-Wallis test to test for differences in beta power between correct and incorrect trials for individual subjects. For group level analysis, we averaged beta power during the feedback and post feedback periods across correct and incorrect trials within each session for each channel, and then used a Wilcoxon rank sum test to test for significant difference between average correct and incorrect trials across sessions. For stimulation sessions we averaged post feedback beta power across correct stimulated and correct non-stimulated trials within each session for each channel and similarly used a Wilcoxon rank sum test to compare post feedback beta power for correct stimulated and correct non-stimulated trials across sessions. Because of the small number of subjects we chose not to average beta power across channels

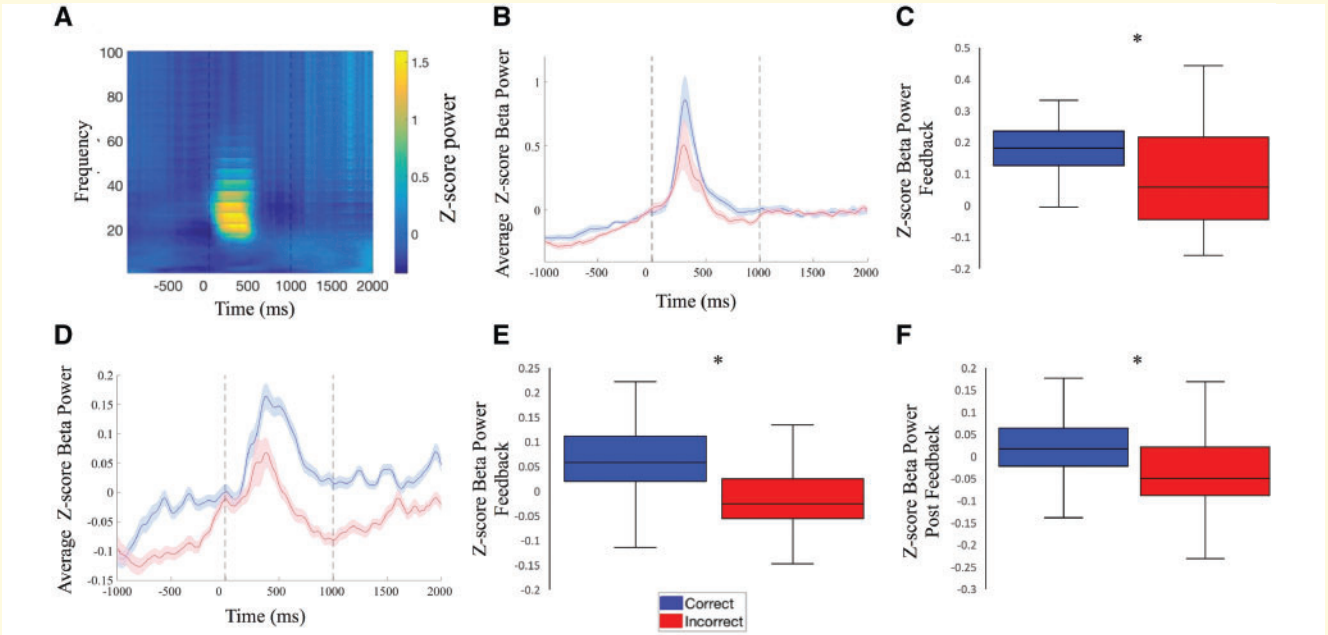

Figure 2 Caudate and DLPFC beta power changes during learning task. (**A**) Spectrogram of z-score power averaged over all trials from a representative single left caudate electrode, aligned to feedback onset. There was a significant increase in power during the feedback period centred in the beta band. (**B** and **C**) Caudate beta power changes during feedback. (**B**) Time courses of caudate z-score beta power averaged across subjects for all non-stimulated images during correct and incorrect trials, aligned to feedback onset. (**C**) Box-and-whisker summary of caudate z-score beta power during feedback. Caudate feedback beta power was higher following correct than incorrect trials (Wilcoxon rank sum test $P = 0.028$, z = 2.99, generalized linear mixed effects model $P = 0.042$, t = 2.034, df = 2338). (**D**–**F**) DLPFC beta power changes during feedback. (**D**) DLPFC z-score beta power time courses aligned to feedback onset for correct and incorrect trials for all non-stimulated images. (**E**) Box-and-whisker plot of DLPFC z-score beta power during feedback. DLPFC feedback beta power was greater following correct compared to incorrect trials (Wilcoxon rank sum test $P = 2.03 \times 10^{-13}$, z = 7.34, generalized linear mixed effects model $P = 1.59 \times 10^{-8}$, t = 5.66, df = 4858). (**F**) Box-and-whisker summary of DLPFC z-score beta power 250–750 ms following feedback offset. DLPFC post-feedback beta power was greater following non-stimulated correct compared to incorrect trials (Wilcoxon rank sum test $P = 3.12 \times 10^{-10}$, z = 6.29, generalized linear mixed effects model $P = 1.092 \times 10^{-8}$, t = 5.73, df = 4858). Shaded bars on time courses represent standard error between electrode contacts. Box-and-whisker plots depict median (horizontal line), interquartile interval (coloured boxes), and maximum and minimum values (vertical bars) of the data presented. Asterisks denote significance.

within a given region in order to increase power to detect a statistical difference. We additionally used a generalized linear mixed effects model to test for differences in caudate and DLPFC beta power in different conditions across all trials in all sessions (see Supplementary material for details).

To investigate whether beta power changes during the feedback period were related to learning, we used Spearman rank correlation to determine whether beta power during feedback averaged across caudate and DLPFC contacts for each subject was correlated with the state space learning estimate on a trial by trial basis. To perform group analysis, we first correlated beta power during the feedback period for each channel with state space learning estimate on a trial by trial basis, and then averaged the correlation coefficients across images learned by each subject. We then used a one-way *t*-test to determine whether the combined correlation coefficients from all subjects were significantly different than 0.

Data availability

The data that support the findings of this study are available from the corresponding author upon request.

Results

Six subjects participated in the study (Supplementary Table 1). There were a total of 20 caudate electrodes and 82 DLPFC electrodes included in our analysis (Supplementary Table 2 and Supplementary Fig. 1). Five subjects completed non-stimulated sessions (Supplementary Fig. 2).

We were able to perform caudate stimulation sessions in two subjects. Caudate stimulation significantly improved learning [$P = 7.37 \times 10^{-5}$, F = 3.26, degrees of freedom (df) = 14 and $P = 2.57 \times 10^{-8}$, F = 2.57, df = 14; Fig. 1F and G]. In Subject 3, the right electrode trajectory was more laterally placed and passed through putamen. In this subject, putamen stimulation significantly impaired learning ($P = 2.32 \times 10^{-10}$, F = 5.94, df = 14; Fig. 1H). We found that learning performance varied by session. However, within stimulated sessions caudate stimulation enhanced learning (Supplementary Fig. 3A and B) while right putamen and left caudate stimulation impaired learning (Supplementary Fig. 3C).

These results suggest striatal stimulation can modulate human learning in a temporally specific manner and that caudate is a promising target for neuromodulation for improving memory.

To investigate the mechanism underlying the observed learning improvements with caudate stimulation we sought to identify neurophysiological correlates of stimulation induced behavioural changes. We first examined caudate and DLPFC learning related power changes in non-stimulated sessions to better understand the role of these structures in associative learning. Beta (15–30 Hz) power has been linked to learning (Ruiz *et al.*, 2014), and is known to play an important role in motor planning and execution (Sanes and Donoghue, 1993), making it an excellent candidate for encoding learned actions. We averaged caudate z-score power over all trials and found that there was an increase in beta power during feedback (Fig. 2A). We found that the increase in beta power during the feedback period was greater following correct versus incorrect trials ($P = 0.0028$, $z = 2.99$ Fig. 2B and C). Similarly, when we examined DLPFC beta power changes we found that average DLPFC beta power during feedback following correct trials was significantly greater than that following incorrect trials ($P = 2.03 \times 10^{-13}$, $z = 7.35$; Fig. 2D and E). Unlike the caudate, this difference persisted beyond the end of feedback into the post feedback period ($P = 3.12 \times 10^{-10}$, $z = 6.29$; Fig. 2D and F). Individual subject results followed a similar trend (Supplementary Fig. 4). These findings suggest that caudate and DLPFC beta power changes encode outcome related information that may contribute to learning.

To examine whether caudate and DLPFC beta power changes were related to learning rather than to reward or another property associated with feedback, we examined whether average caudate and DLPFC beta power during the feedback period for each trial was correlated with the state space learning estimate for that trial. We found that caudate beta power during the feedback period of the five non-stimulated sessions was not correlated with learning (Fig. 3A; Spearman correlation coefficient 0.13, $P = 0.23$, $t = -1.12$, $df = 15$). However, DLPFC feedback and post feedback beta power were positively correlated with learning (Fig. 3B and C; Spearman correlation coefficient 0.27, $P = 8.71 \times 10^{-6}$, $t = 4.83$, $df = 65$ and Spearman correlation coefficient 0.17, $P = 3.74 \times 10^{-17}$, $t = 11.40$, $df = 65$, respectively). This was also true for stimulated sessions (Supplementary Fig. 5; Spearman correlation coefficient 0.061, $P = 0.049$, $t = 2.04$, $df = 31$). Individual subject correlation results are provided in Supplementary Fig. 6.

Next, we investigated power changes associated with stimulation-induced learning improvement. Stimulation artefacts precluded us from evaluating the feedback period of stimulated trials. We therefore chose to examine stimulation related power changes during the post-feedback period, which demonstrated persistent learning related beta power changes in DLPFC in non-stimulated trials (Fig. 2F).

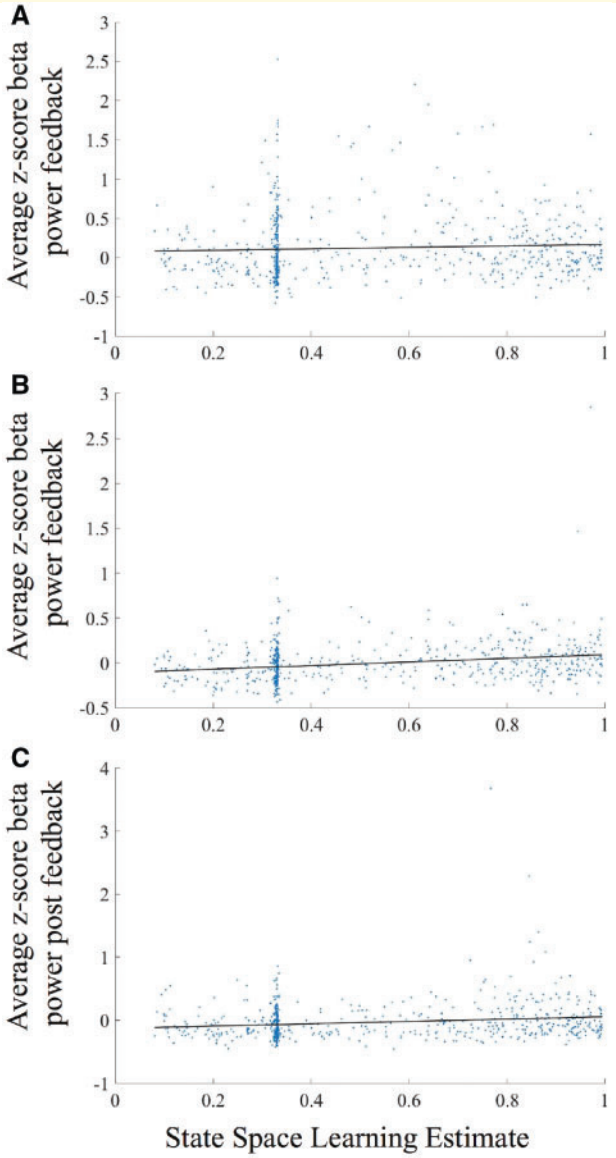

Figure 3 Caudate and DLPFC beta power correlation with learning. (**A**) Average caudate beta power during the feedback period of non-stimulated sessions did not correlate with the state space learning estimate (Spearman correlation coefficient 0.13, $P = 0.23$, $t = -1.12$, $df = 15$). (**B**) Average DLPFC beta power during the feedback period of non-stimulated sessions correlated with the state space learning estimate (Spearman correlation coefficient 0.27, $P = 8.71 \times 10^{-6}$, $t = 4.83$, $df = 65$). (**C**) Average DLPFC beta power during the post feedback period of non-stimulated sessions was also positively correlated with the state space learning estimate (Spearman correlation coefficient 0.17, $P = 3.74 \times 10^{-17}$, $t = 11.40$, $df = 65$).

Although these results did not quite reach statistical significance, DLPFC beta power trended towards being greater following correct stimulated trials than correct non-stimulated trials (Fig. 4, $P = 0.070$, $z = 0.82$), suggesting that caudate stimulation may alter DLPFC learning-related activity.

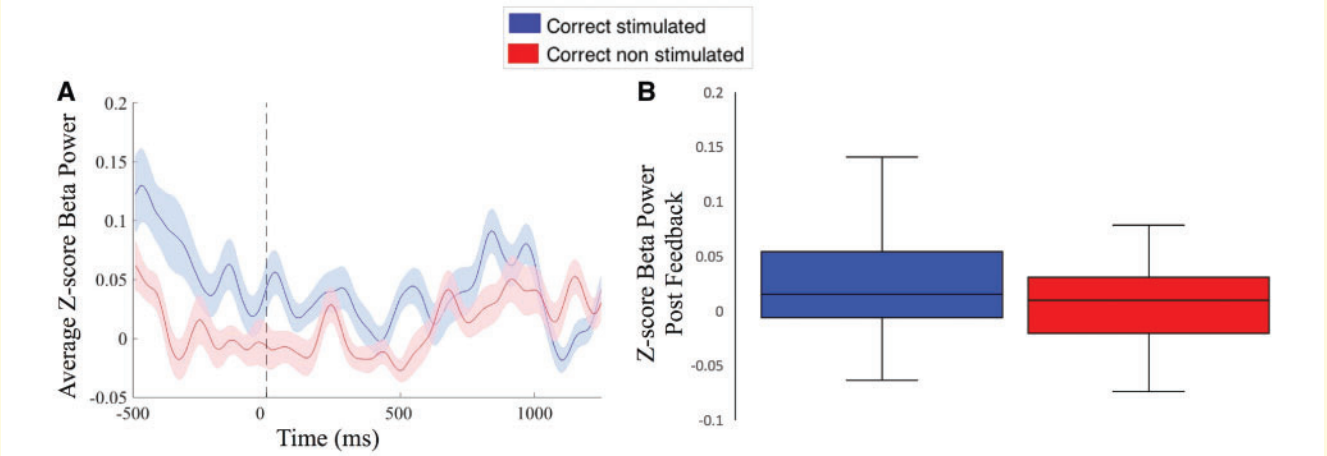

Figure 4 Stimulation-related power changes. Data were included from DLPFC contacts with ipsilateral caudate stimulation (bilateral DLPFC for Subjects 1 and 2 and left DLPFC for Subject 3). DLPFC beta power following stimulated correct trials trended towards being greater than beta power following non-stimulated correct trials, although results did not reach statistical significance. (**A**) Time course of average DLPFC z-score beta power for correct stimulated versus correct non-stimulated trials in stimulated sessions, aligned to feedback offset. (**B**) Box-and-whisker summary of DLPFC z-score beta power 250–750 ms following feedback offset for correct stimulated versus correct non-stimulated trials in stimulated sessions (Wilcoxon rank sum test $P = 0.070$, $z = 0.82$, generalized linear mixed effects model $P = 0.057$, $t = 1.91$, $df = 8446$). Shaded error bars on time course represent standard error between electrode contacts. Box-and-whisker plots depict median (horizontal line), inter-quartile interval (coloured boxes), and maximum and minimum values (vertical bars) of the data presented.

Discussion

Neuromodulation is a promising treatment for disorders of learning and memory; however, to date an optimal target and stimulation paradigm has not been identified. In this study we show that bilateral caudate high frequency stimulation during feedback following correct trials in an associative learning task improved learning. We also demonstrate that caudate and DLPFC have feedback related power changes which are correlated with learning in DLPFC and that caudate stimulation may modulate these signals in DLPFC. These findings suggest that the caudate is a promising target for neuromodulation for disorders of learning and memory and support a role for a targeted stimulation paradigm when devising neuromodulation strategies for improving memory.

The third subject to receive stimulation in our study had a more laterally placed right-sided electrode and therefore received right putamen and left caudate stimulation. In this subject, stimulation impaired learning. Previous primate work has suggested that putamen stimulation during the feedback period following correct responses impairs learning (Williams and Eskandar, 2006). This may explain the findings of impaired learning with stimulation in this subject. However, given that these findings were observed in a single subject and that this subject received both caudate and putamen stimulation, further work is needed to clarify the impact of putamen stimulation on associative learning. Furthermore, this subject found it difficult to complete the task and did not demonstrate learning in the non-stimulated session, perhaps contributing to these findings.

Our findings confirm previous functional MRI study findings suggesting a role for the caudate in human learning. Caudate activity has been shown to correlate with both learning and reward (Haruno, 2004), and may require an action reward pairing to be activated, suggesting that caudate is involved in the reinforcement of actions (O'Doherty *et al.*, 2004; Tricomi *et al.*, 2004). Our finding of beta power changes during the feedback period that differ with feedback valence supports this model. Caudate pathology has been linked to memory dysfunction in several disease states. In patients with Huntington's disease, decreased caudate volume correlates with worse learning and memory performance (Misiura *et al.*, 2017). In advanced Parkinson's disease, memory performance is correlated with caudate dopaminergic function (Holthoff-Detto *et al.*, 1997). Our findings suggest a new therapeutic target for memory dysfunction in these disorders.

The role of the caudate in memory may be related to dopaminergic reward prediction error, a key feature of reinforcement learning (Schultz *et al.*, 1997). Caudate dopamine binding correlates with learning related activation in DLPFC, hence caudate may provide information about stimulus value to DLPFC, which in turn selects actions (Seo *et al.*, 2012). Caudate high-frequency stimulation has been shown to increase local dopamine release in a temporally specific manner (Gale *et al.*, 2013). A leading potential mechanism for our observed behavioural effects is a transient increase in dopamine release during the feedback period enhancing the normal dopaminergic reward prediction error signal. Importantly, caudate stimulation at this amplitude was not intrinsically rewarding in primate studies (Williams and Eskandar, 2006). Our finding that

caudate feedback beta power is correlated with response accuracy but does not increase with learning over time while DLPFC is both correlated with response accuracy and increases with learning, supports the model of caudate providing value information to the DLPFC, which contains learning related information to select actions. Changes in striatal beta power may also contribute to the observed learning improvement. In rodents, striatal beta power during the reward period of a learning task has been associated with brief episodes of coordinated inhibition of projection neurons by excited interneurons, allowing resetting of striatal networks to reflect successful performance (Lee *et al.*, 2017). As high-frequency stimulation is generally believed to inhibit neural activity, a similar mechanism may explain why high frequency caudate stimulation improves learning. Further work will better elucidate the mechanisms of the learning and beta power changes we observed.

There are several limitations to our study. Our sample size is small, limited by clinical considerations. We were not able to control the order of non-stimulated and stimulated sessions or anti-epileptic status of subjects in our study. Differing anti-epileptic medications are a confounder that could impact the beta power changes seen in our study. The performance of sessions on different days likely contributed to the different learning performance seen for non-stimulated sessions and non-stimulated images within stimulated sessions. Because we compared stimulated and non-stimulated images within the same session, these confounding factors of practice, anti-epileptic status, and mental state should not contribute to our findings about the effect of caudate stimulation on learning. We did not test delayed recall in our study, therefore further work is needed to determine whether caudate stimulation would be beneficial for long term memory. Finally, the subjects in our study all had epilepsy but did not have symptomatic neurodegenerative processes. Caution must be taken in applying our findings to a learning and memory disorders patient population.

To our knowledge this is the first report of human caudate stimulation improving learning. Our findings suggest that the caudate is a promising target to consider for neuromodulation for disorders of learning and memory.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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