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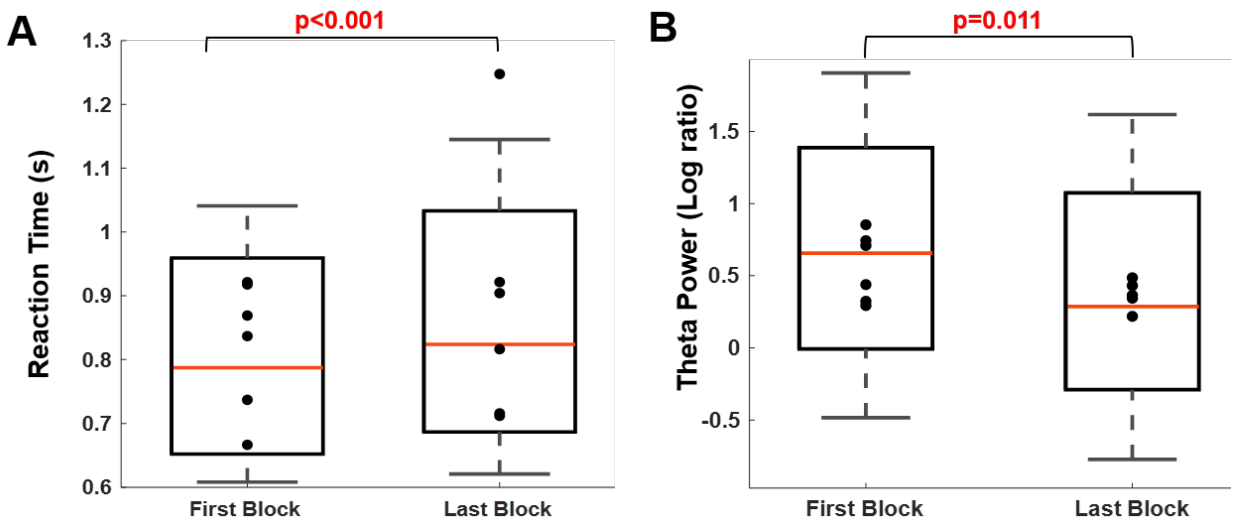
Supplementary information

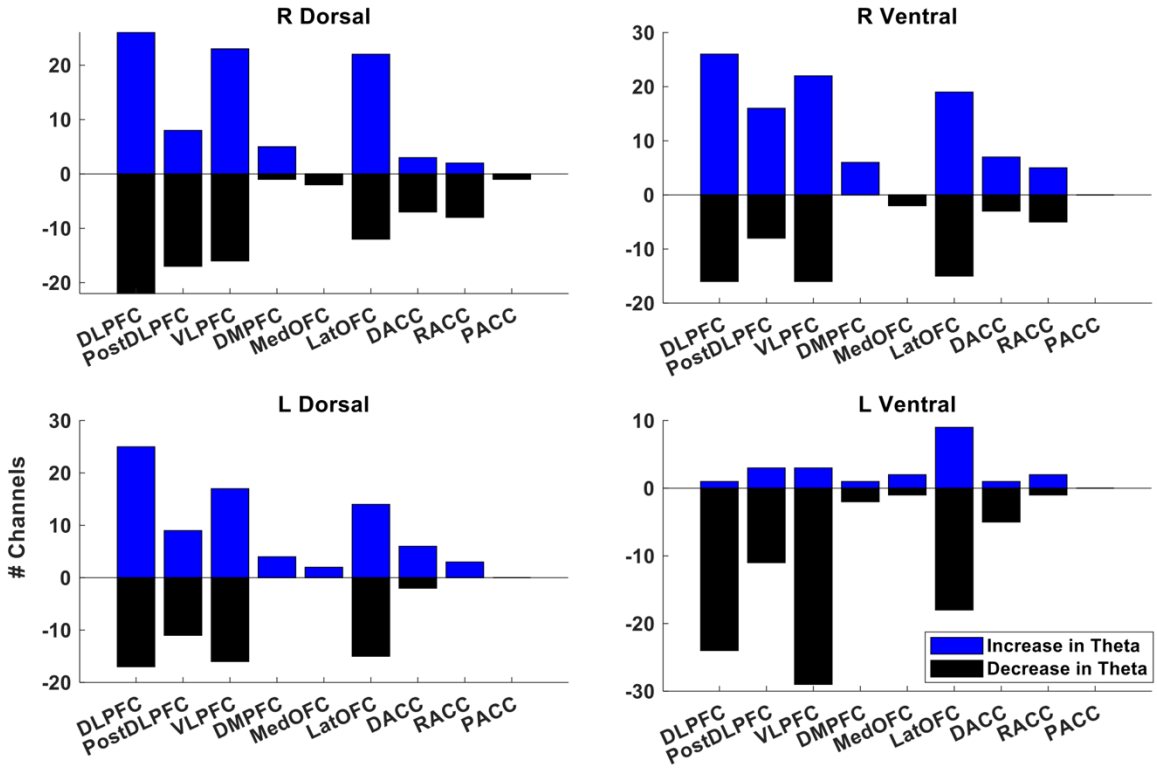
Closed-loop enhancement and neural decoding of cognitive control in humans

In the format provided by the authors and unedited

Contents

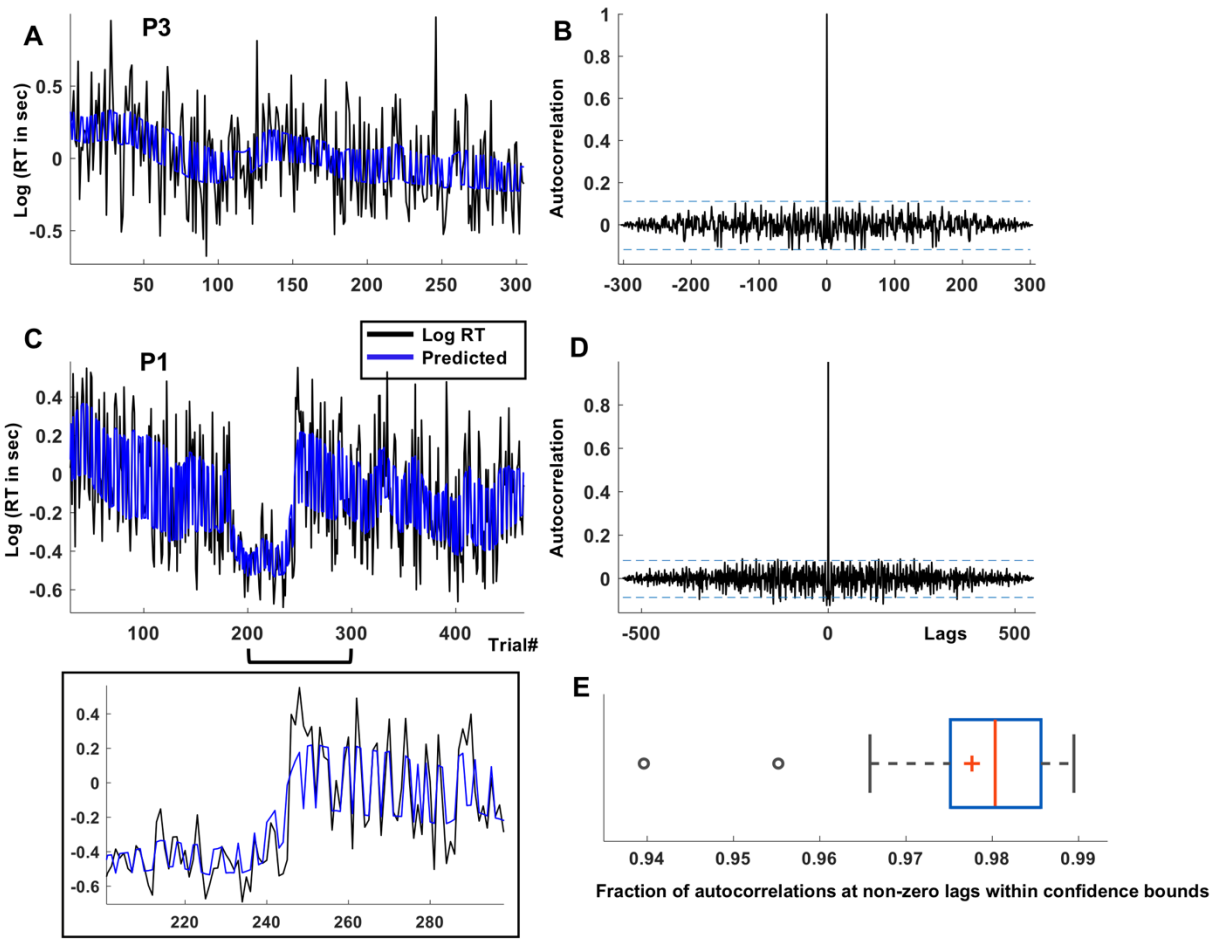


Supplementary Fig. 1: Open loop stimulation effects are not explained by practice or regression to the mean. Here we show the reaction time (A) and theta power (B) for the first and last MSIT block of each participant in the open loop experiment. Analysis windows, channel selection, and statistical testing follow main text Fig. 2. All p-values are Wald tests on coefficients from a generalized linear model with Block as the primary fixed effect. Both analyzed blocks contain only NS1 trials, meaning there is no stimulation on any of the trials. In this comparison, RT significantly worsens (increases) over the course of the experiment, while PFC theta decreases. This is the precise opposite of the stimulation effects reported in Fig. 2, verifying that those effects are attributable to the stimulation itself. We believe this RT increase and theta decrease represent fatigue and/or difficulty sustaining attention on task performance.



Supplementary Fig. 2: Behaviorally effective stimulation increases theta in brain regions related to cognitive control. The Y-axis plots the number of channels that are localized to the specified region, and that showed either an increase (above X-axis) or decrease (below axis) in theta power, using the same analysis window and baseline correction as in main text Fig. 2. Increases and decreases are based solely on numeric comparison, not on mass univariate t-testing. To demonstrate consistency of effects across the relatively large extent of the lateral PFC, and to account for the relatively large number of channels assigned to this region, we have fractionated DLPFC into anterior and posterior sub-portions.

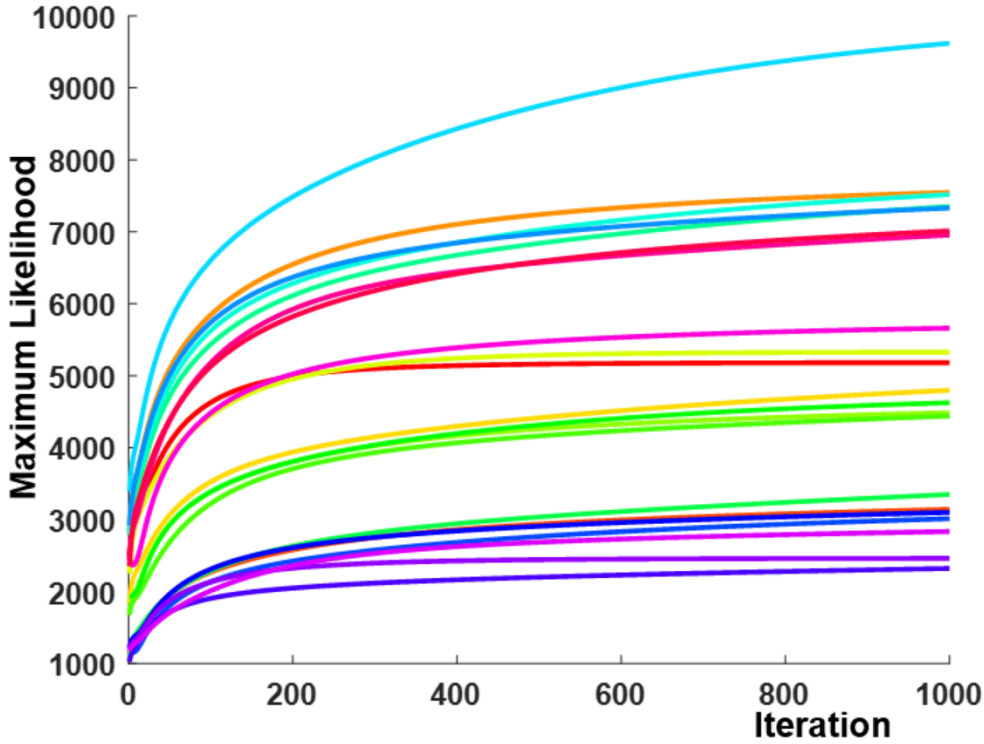
After stimulation at sites that were behaviorally effective (Left/Right Dorsal and Right Ventral capsule) channels with theta increases outnumbered those with decreases, specifically in regions known to be engaged by the Multi-Source Interference Task (DLPFC, VLPFC, and cingulate to a lesser degree). More importantly, after stimulation at the ineffective site (Left Ventral capsule), there were no regions where theta increases predominated. These results support a link between PFC theta augmentation and enhanced cognitive control, although they also emphasize the heterogeneity of this response and of PFC generally.



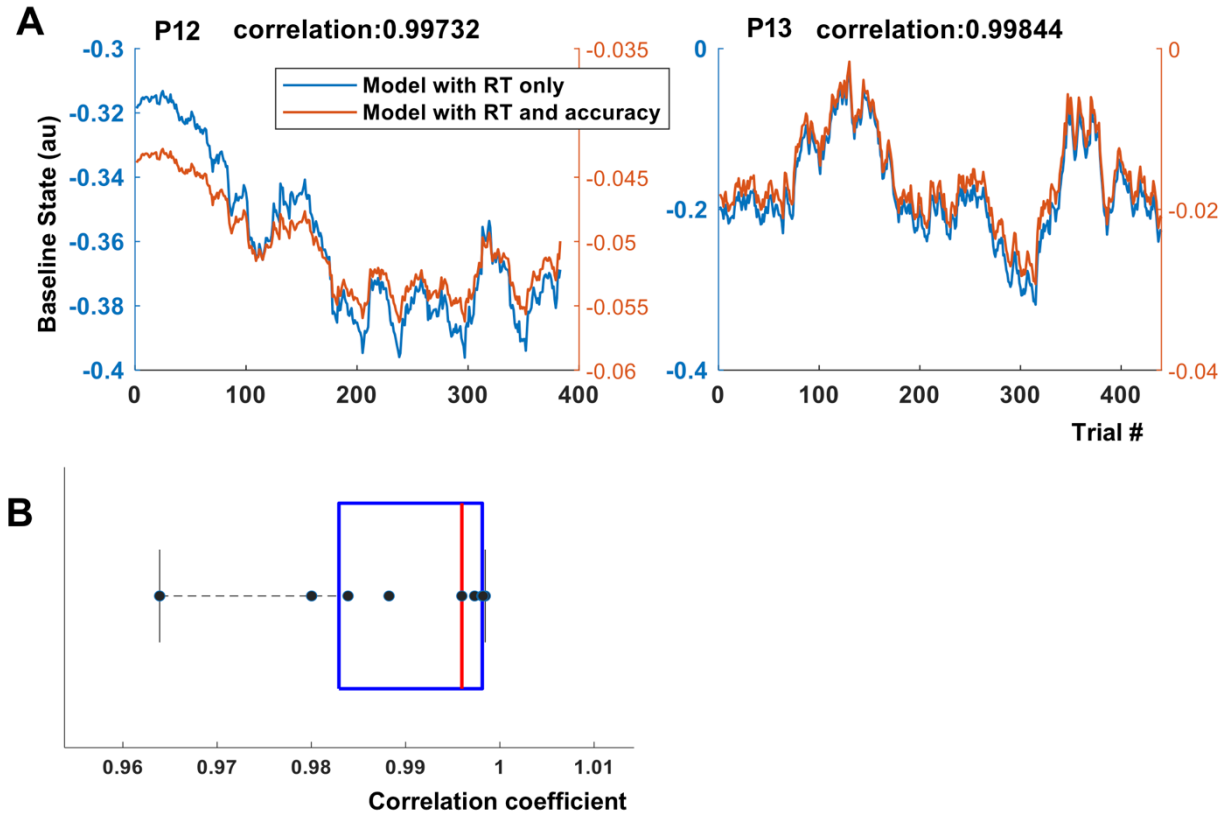
Supplementary Fig. 3: **State-space model goodness of fit.** A,C) Examples of actual log(RT) from one MSIT run in each of two participants (black), with model prediction superimposed (blue). The model captures both slow-scale fluctuations (primarily in x_{base}) and fast, conflict-driven fluctuations (through $x_{conflict}$) in RT. An inset below panel C provides zoomed-in detail of the two timeseries at an inflection point.

B,D) autocorrelation of residual error between measured and predicted log(RT), for the same participants. The dotted blue lines indicate the confidence bound for autocorrelation at non-zero lags for a white noise process (calculated as in https://nwfsc-timeseries.github.io/atsa-labs/sec-tslab-correlation-within-and-among-time-series.html).

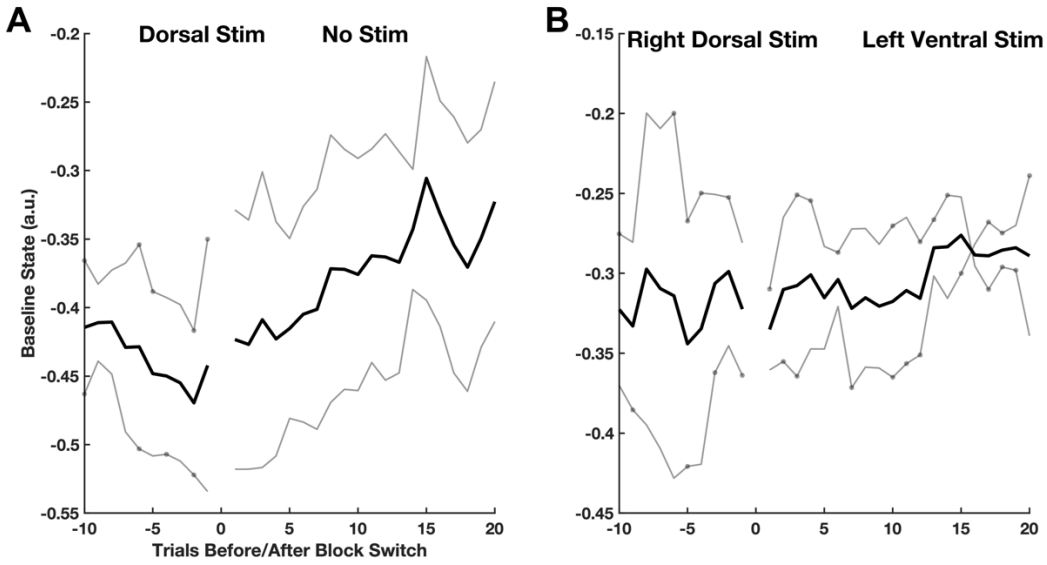
E) Fraction of autocorrelation values at non-zero lags (as in B,D) that lay within the confidence bounds of a white noise process, for all 21 participant datasets. These are all substantially greater than 90%, indicating that the two-variable state-space model captures the primary structured sources of variance within RT.



Supplementary Fig. 4: State-space modeling convergence. Each colored curve is the model likelihood, at each step of the expectation-maximization (EM) algorithm, for one participant (colors are arbitrary and do not relate to other figures). We applied a fixed termination criterion of 1000 EM iterations. By this point, all curves had reached an asymptotic maximum likelihood, and none was still in a phase of linear or supra-linear improvement.



Supplementary Fig. 5: Considering accuracy in addition to RT did not improve behavioral model fitting. A) example x_{base} trajectories for models fit using only continuous RT or both RT and accuracy, in two example participants. The curves are nearly identical to within a scaling factor, as evidenced by extremely high Pearson correlation coefficients between them (above figures). B) distribution of Pearson correlations between RT-only and RT-plus-accuracy models, for all participants. All correlations are above 0.96, and the majority are above 0.99. Adding accuracy to the model would not change our inferred states or any conclusions related to stimulation effects or decoding. It would, however, add multiple free parameters to the model fitting process, offering opportunities for overfitting. This strongly argued for the more parsimonious RT-only model, which we used in all further analyses.

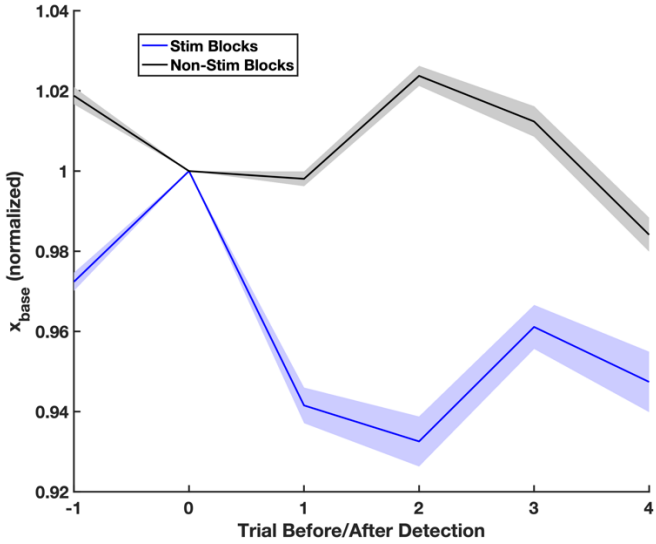


Supplementary Fig. 6: Stimulation effects had modest carry-over between blocks, but in a pattern that would not cause spurious detection of between-block differences. Each panel shows the maximum likelihood estimate of x_{base}, in light grey for individual participants and dark black for the mean of all participants (n=2 in each case, based on having experienced the required type of block transition). Markers on the individual-participant curves show trials on which stimulations were delivered.

A), transition from dorsal capsule stimulation (one left dorsal, one right dorsal) to the terminal non-stimulated block. x_{base} increases rapidly once stimulation ends, stabilizing at a higher value after about 10 trials. As noted in Supplementary Fig. 4 above, this led to a higher median RT in the final block than in the initial non-stimulated block, which we interpret as a fatigue effect.

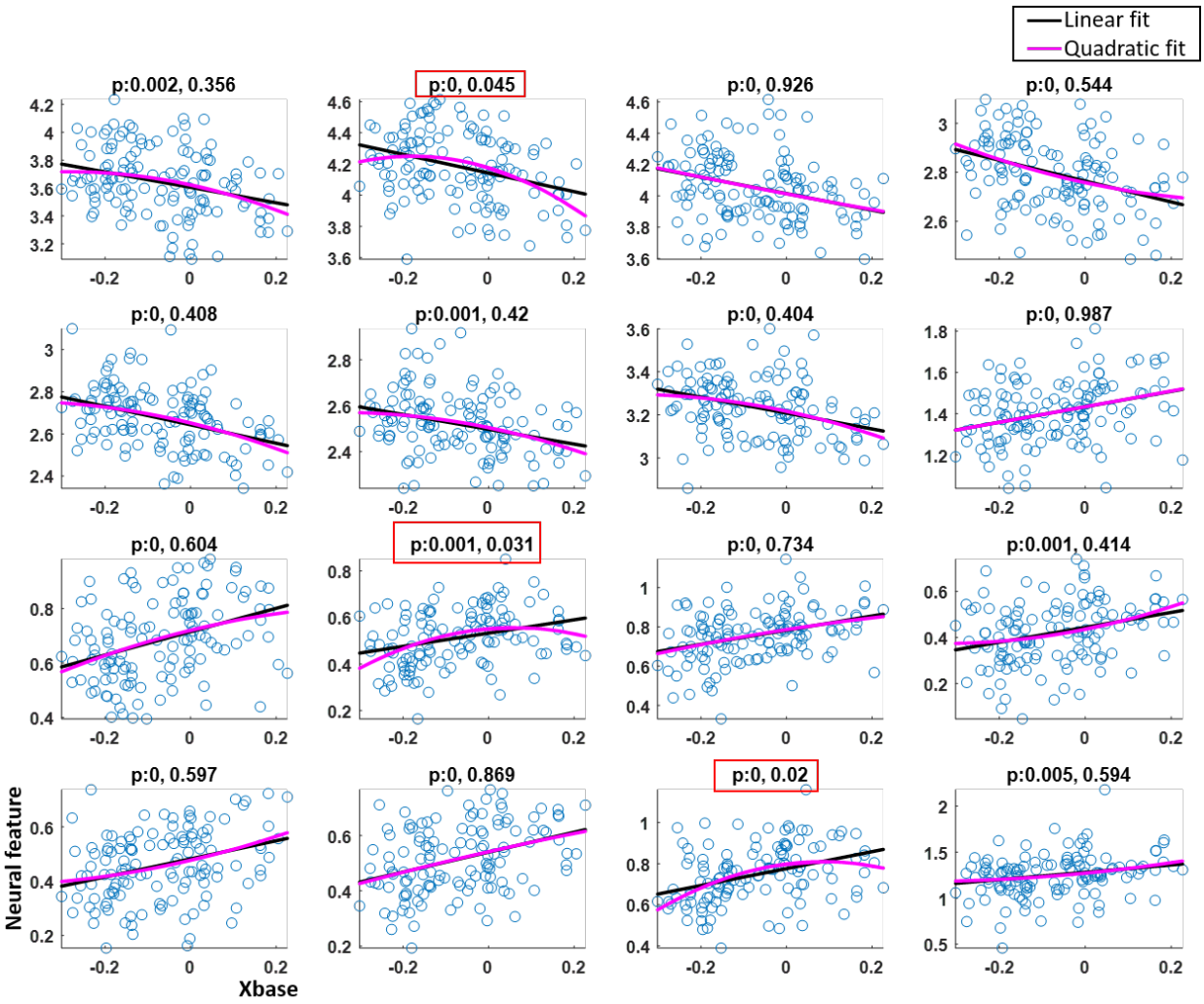
B), transition from right dorsal stimulation (our most effective condition) to left ventral stimulation (the only condition found to be ineffective in the RT analysis of main text Fig. 2). For clarity, we included only participants where right dorsal stimulation was clearly different from their baseline and where this specific transition occurred (P9 and P12). Here, there appears to be some carry-over – even though left ventral stimulation was not effective in the group-level analysis, x_{base} does not rapidly increase (at best, a very subtly upward trend is visible).

We emphasize that persisting effects between blocks would not explain the behavioral or neural effects described in the main text, because these persisting/carry-over effects would tend to decrease the statistical significance and numeric size of any detected between-block differences. That is, they actively bias against the conclusions we report, suggesting that the true effects might be larger in a different experimental design.

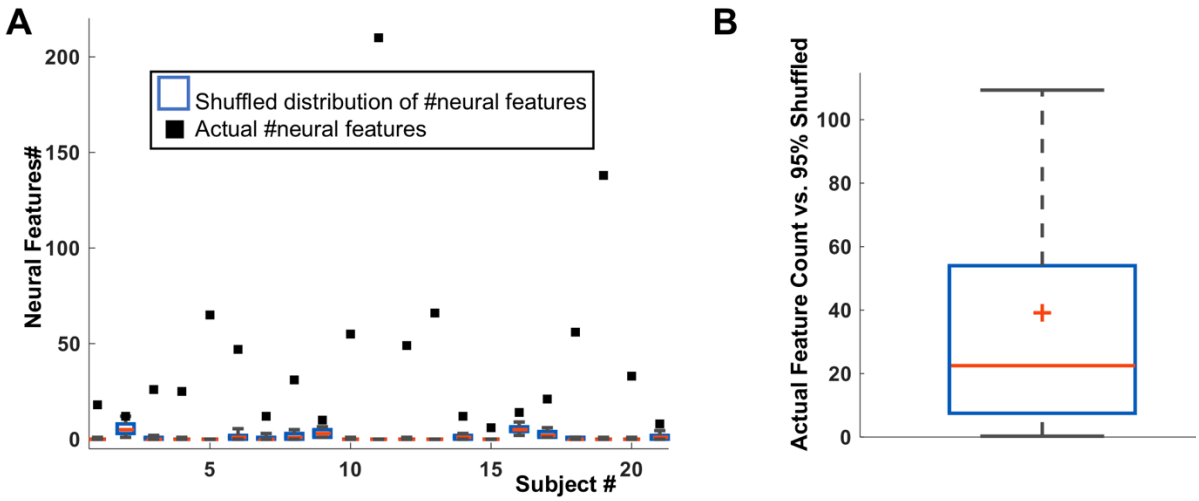


Supplementary Fig. 7: Closed loop stimulation effects cannot be explained by regression to the mean. For the 3 participants included in closed loop experiments, we examined the non-stimulated blocks they performed prior to closed-loop work. (These were the same blocks of behavior data used to train the closed loop model.) We applied the threshold that was used for actual closed loop work in that participant, then detected points in the non-stimulated blocks where our closed loop detector would have triggered (i.e., where x_{base} was above threshold). We compared these trials to the trials during closed loop stimulation, where the detector actually did trigger and stimulation was delivered. For these two sets of trials, we plot x_{base} before and after the detection event. The curves show this "stimulation triggered average", for blocks where stimulation was delivered (blue) or was not (black). The line represents the grand mean over all such events and patients, while shading represents standard error of the mean. To enable averaging over trials and patients (and to highlight changes), we normalized all data such that the detection trial always had a state value of 1.

During active stimulation, x_{base} decreases (RT improves) on the very next trial, and remains low. In the absence of stimulation, it remains effectively flat, perhaps oscillating around a baseline. This clear difference between trajectories demonstrates that, in the absence of stimulation, our observed performance improvements are highly unlikely.



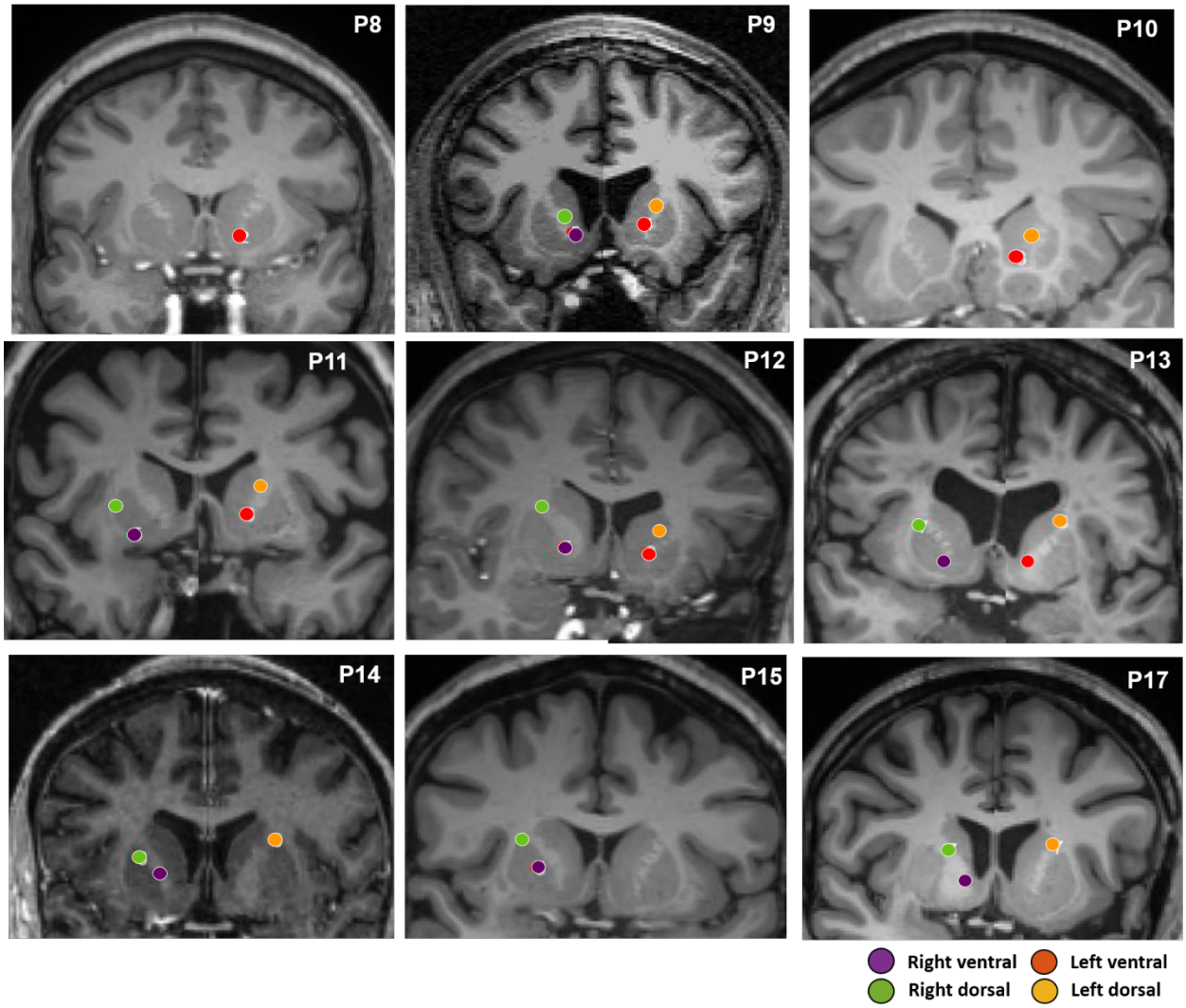
Supplementary Fig. 8: Scatter plot of x_{base} and neural features in an example dataset. The p-values corresponding to each subplot correspond to the linear and quadratic coefficients in the model Y~1+X and Y~1+X+X^2 respectively. Most features show a linear relationship (significant linear coefficient only). The features that show both significant linear and quadratic coefficients are boxed in red. In each of those cases, the linear model is still a better fit to the data.



Supplementary Fig. 9: Comparison of neural decoding vs. chance performance. Our neural decoding and variable selection algorithm automatically prunes the feature set to only those LFP power variables that are strongly correlated with the behavioral outcomes (here, x_{base} and $x_{conflict}$). As in ref. 70, we tested whether these correlations could occur by chance. We randomly shuffled the order of the behavior trials, then re-ran the decoder variable selection. We repeated this process 100 times for each participant, and on each step, counted the number of features (power bands in specific channels) that were selected. This provides a distribution of the number of significant encoding features expected in purely random data.

A), individual-level data. Each black square shows the actual number of features selected by the decoder construction algorithm. The box plot (blue/red; in many cases small due to compression near 0) shows the numbers of features selected by the same algorithm on randomly shuffled data. When the actual number of features is well outside this permutation null distribution, it indicates that the decoder is leveraging actual information present in the dataset. This is visibly true, with a very large separation, for almost all participants in the dataset.

B), aggregate data. This boxplot shows the difference between the actual number of features selected (black squares in panel A) and the 95th quantile of the null distribution (top of the blue box in panel A), aggregated across participants. There is a median gap of 20 features, with a confidence interval excluding 0, again demonstrating that the decoding models are capturing true structure in the data.



Supplementary Fig. 10: **Capsular electrode placements in 9 participants, derived from post-operative CT registered to pre-operative MRI**. The last row corresponds to participants who performed the closed loop MSIT experiment, and the first two rows to participants in the open loop experiment.

Supplementary Table 1: Clinical characteristics of participants. Age is rounded to nearest decade to mask participant identity. Seizure focus represents the area ultimately targeted for resection or responsive neurostimulator implant based on clinical consensus after acute monitoring. Neuropsychiatric diagnoses were, when available, taken from neuropsychological testing performed prior to implant. The “Depression Score” is the score on the Beck Depression Inventory (BDI-II). The “Anxiety Score” is the Beck Anxiety Inventory (BAI). In cases where the testing neuropsychologist chose to use a different scale, the name of that scale is given in parentheses. The listed anti-seizure medications are those that were being given at the time of stimulation experiments. Clonazepam is listed either as an anti-seizure or “other” medication depending on whether it was being used to reduce seizure frequency or manage anxiety.

ADHD: Attention Deficit Hyperactivity Disorder

GAD: Generalized Anxiety Disorder scale

PHQ: Personal Health Questionnaire

PMDD: Pre-Menstrual Dysphoric Disorder

PSWQ: Penn State Worry Questionnaire

PTSD: Post-Traumatic Stress Disorder

P#	Age	Seizure Focus	Prior Neuro-Psychiatric Diagnoses	Depression Score	Anxiety Score	Anti-Seizure Medications	Other CNS Medications
1	40	Right mesial temporal	None	14	38 (PSWQ)	Lamotrigine, zonisamide	Clonazepam
2	40	Left inferior temporal/ superior temporal	None	36	14	Oxcarbazepine	Mirtazapine
3	30	Left temporal	None	N/A	N/A	Ezogabine, Levetiracetam	Hydromorphone
4	60	Left insula	Depression, suicidality, visual hallucinations	N/A	N/A	Carbamazepine, levetiracetam, zonisamide	N/A
5	20	Right frontal region and left superior parietal lobule	None	1	1	Clobazam, cannabidiol, lacosamide,	N/A
6	50	Bitemporal	None	Score not recorded (normal)	Score not recorded (normal)	Levetiracetam	Oxycodone
7	20	Left temporo-occipital	ADHD	N/A	N/A	Lamotrigine, oxcarbazepine, zonisamide	N/A
8	20	Right frontotemporal	"at risk" for attentional disorder	7	4	Lacosamide, topiramate	N/A
9	40	Multifocal (mainly right temporal)	None	21	15	Levetiracetam, phenytoin	Clonazepam
10	20	Right mesial temporal	Depression	8	3	Lacosamide, lamotrigine	Clonazepam
11	60	Left anterior mesial temporal lobe	Depression, insomnia	25	20	Clobazam, eslicarbazepine, lamotrigine	Hydromorphone, oxycodone
12	20	Left anterior cingulate	Depression	0	3	Gabapentin, lacosamide,	N/A

						lamotrigine	
13	50	Bitemporal (left more than right)	None	8	2	Gabapentin, levetiracetam, zonisamide,	Oxycodone
14	50	Bilateral hippocampal	PMDD	11	5	Clobazam, levetiracetam	N/A
15	40	Left posterior mesial temporal	None	12	12	Lamotrigine	N/A
16	30	Left temporal	None	0	2	Lamotrigine, zonisamide	N/A
17	40	Bitemporal	ADHD, depression, anxiety, PTSD, substance abuse	33	32	Clonazepam, gabapentin, lamotrigine	Acetaminophen-butalbital-caffeine, oxycodone
18	40	Multifocal: left orbitofrontal region, right mesial frontal, right lateral temporal, right middle temporal	None	N/A	N/A	Lamotrigine, valproate	N/A
19	30	Right frontotemporal parietal	Bulimia nervosa, depression	2	4	Clobazam, topiramate	N/A
20	30	Multifocal: primarily right posterior	Depression, suicidality	27 (PHQ-9)	20 (GAD-7)	Lamotrigine, levetiracetam	N/A
21	40	Bilateral mesial temporal	None	5	1	Lamotrigine, zonisamide	N/A

Supplementary Table 2: Order of stimulation blocks in participants who received open-loop and closed loop (CL) capsular stimulation. (DC: Dorsal Capsule, VC: Ventral Capsule, L:Left, R:Right)

P#	8	9	10	11	12	13	14 (CL)	15 (CL)	17 (CL)
Blocks	L VC	R VC L DC R DC L VC	L DC L VC L DC	R VC R DC L VC L DC	R VC R DC L VC L DC R DC	R VC R DC L VC L DC	R DC L DC L DC R VC R DC	R DC R DC R VC	R DC R DC L DC R VC R DC R DC R VC

Supplementary Table 3a: Regression coefficients for reaction time (RT) in the open-loop stimulation experiments, from a generalized linear mixed-effects model, with a log-normal distribution and identity link function.

Formula: RT ~ Conflict + blockNum + blockStim + (1 | Participant)

Fixed effects coefficients (95% CIs):

Name	Coefficient	SE	tstat	DF	p-value	FDR corrected p-value
Intercept	-0.30293	0.053981	-5.6118	1729	2.3279e-08	
Interference	0.24921	0.010086	24.708	1729	0	
blockNum	0.0022368	0.0018076	1.2374	1729	0.2161	
blockStim L VC	-0.024254	0.014045	-1.7269	1729	0.08437	0.0844
blockStim L DC	-0.041956	0.015824	-2.6515	1729	0.0080879	0.0162
blockStim R VC	-0.042092	0.018596	-2.2635	1729	0.023729	0.0316
blockStim R DC	-0.07421	0.01735	-4.2772	1729	1.9964e-05	0.0001

Supplementary Table 3b: Regression coefficients for theta power in the open-loop stimulation experiments, from a generalized linear mixed-effects model, with a log-normal distribution and identity link function.

Formula: Theta ~ blockStim + (1 | Participant)

Fixed effects coefficients (95% CIs):

Name	Coefficient	SE	tstat	DF	p-value	FDR corrected p-value
Intercept	0.40052	0.096427	4.1536	1191	3.5064e-05	
blockStim L VC	-0.055692	0.10777	-0.51676	1191	0.60542	0.6054
blockStim L DC	0.26118	0.11337	2.3038	1191	0.021406	0.0428
blockStim R VC	0.52333	0.13807	3.7902	1191	0.000158	0.0006
blockStim R DC	0.1937	0.12793	1.5141	1191	0.13028	0.1733

Supplementary Table 4: Qualitative comments made by 2 participants during and after stimulated MSIT sessions, demonstrating relief of anxiety and greater ability to redirect attention.

Participant	Comments
P10 (OL)	At the end of a DC open loop stimulation block, participant comments: "So, what I am experiencing in a way is that when I am usually doing the task, I think earlier, I was counting the numbers out loud in my head and then figuring, sort of like which one am I searching for right now? Right now, I feel like it just comes automatically." On being probed further, comments: "Increased sense of flow, being in the zone and sort of automatically knowing exactly what to do."
P17 (CL)	After VC stimulation, Participant comments "I almost felt like I have a hangover headache, but I shouldn't like in general. But it is probably because I didn't drink enough water yesterday." During DC stimulation: "I don't know how to explain it. I just feel lighter headed." On asked what kind of light headed, participant comments: "Usually I can't multi-task and talk and do things at the same time like this, but may be its also just because I am really used to this task. I don't even pay attention to it. But I know for a fact I couldn't… when I first did this number thing last week, a couple days ago… There is no way I could have had a conversation and been doing it at the same time." After the block was done, participant was asked to elaborate more on the earlier comments about being light headed. "Literally I just literally felt lighter headed. And also a sensitivity to light too. But also just felt lighter. I don't know how else to explain it." On asked if it was emotionally lighter, she comments further: "Yeah, I mean, not as weighed down, I guess you could say emotionally. Not as much. I have had multiple burdens on my mind. Maybe that you don't realize till its lifted. I felt lighter, like a weight off my shoulders for a second. At the same time, I felt calmer than I tend to. It didn't make me feel concerned or weird to speak, it felt different all of a sudden, which is also kind of great." Further goes on to say: "I am notorious for being my own worst critic, for over thinking to the point that it is counterproductive. I am nervous about everything, it gets hold of me instead of me controlling it." Asked if that sense of being nervous felt different, she comments: "Yeah, it just couldn't get to me." During a following unstimulated block, she spontaneously reports: "It feels more distracted, like I have more on my mind than I did a few minutes ago. Not by choice, it's the way I am, less focused, more burdened. " Debriefing after entire experiment, asked if the subjective experience of stimulation was desirable: "The only reason it was good is because at the same time, I was able to focus. It was bizarre, it sort of tuned out the rest of the world. Whatever I was trying to do, it made it easy, so I wasn't over-thinking it. I don't know how to explain, it was bizarre, so I would think perks and losses."

Supplementary Table 5: Self-report of positive emotional effects from capsular neurostimulation compared with prior self-report of self-control. As part of a broader study in which these experiments were embedded (Widge et al., 2017), participants completed a variety of self-report measures. These were compared against a companion dataset of 36 healthy controls, and are expressed as Z-scores for each participant relative to the healthy population. The Effortful Control subscale of the Adult Temperament Questionnaire (ATQ, 77-item short form) reports a respondent's capability to focus attention and shift behavior when appropriate. The two participants in Table S3 who reported subjective positive effects of stimulation are highlighted in bold. They also had the most negative (impaired) scores on ATQ Effortful Control. We did screen other questionnaires and did not observe this pattern; this was not a pre-planned analysis.

P#	8	9	**10**	11	12	13	14	15	**17**
ATQ	-1.505	-0.758	**-1.804**	0.363	0.213	-1.281	-0.384	-1.057	**-1.580**

Supplementary Table 6: Number of trials used for training, validation and testing of the encoder-decoder model in each participant. Note that the Train/Validate/Test columns will add to more than the overall number of trials, because there was overlap between Train and Validate sets. The Test set was fully disjoint from both Train and Validate. For P3, an encoder model could not be estimated for $x_{conflict}$ even when using 70% of the available trials.

P#	Total Trials	Baseline			Conflict		
		Train	Validate	Test	Train	Validate	Test
1	192	128	80	48	144	83	35
2	383	153	114	114	194	137	160
3	304	153	126	101	NA	NA	NA
4	304	152	114	114	205	128	70
5	250	166	111	63	166	111	63
6	304	204	135	75	204	135	75
7	304	204	135	75	204	135	75
8	312	159	111	94	132	111	135
9	305	169	118	102	169	118	102
10	250	117	69	66	175	54	64
11	223	141	80	72	141	80	72
12	310	144	95	143	144	95	143
13	337	213	130	100	165	106	135
14	287	140	114	103	140	114	103
15	241	105	97	91	105	97	91
16	394	178	197	108	178	197	108
17	296	110	144	86	110	144	86
18	270	170	118	75	180	120	67
19	258	172	114	64	170	113	63
20	444	256	158	94	128	96	96
21	372	184	165	115	200	284	284