PSYCHIATRY

Using fMRI connectivity to define a treatment-resistant form of post-traumatic stress disorder

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A mechanistic understanding of the pathology of psychiatric disorders has been hampered by extensive heterogeneity in biology, symptoms, and behavior within diagnostic categories that are defined subjectively. We investigated whether leveraging individual differences in information-processing impairments in patients with post-traumatic stress disorder (PTSD) could reveal phenotypes within the disorder. We found that a subgroup of patients with PTSD from two independent cohorts displayed both aberrant functional connectivity within the ventral attention network (VAN) as revealed by functional magnetic resonance imaging (fMRI) neuroimaging and impaired verbal memory on a word list learning task. This combined phenotype was not associated with differences in symptoms or comorbidities, but nonetheless could be used to predict a poor response to psychotherapy, the best-validated treatment for PTSD. Using concurrent focal noninvasive transcranial magnetic stimulation and electroencephalography, we then identified alterations in neural signal flow in the VAN that were evoked by direct stimulation of that network. These alterations were associated with individual differences in functional fMRI connectivity within the VAN. Our findings define specific neurobiological mechanisms in a subgroup of patients with PTSD that could contribute to the poor response to psychotherapy.

INTRODUCTION

Extreme stress can exert long-lasting detrimental effects and is a precipitant of numerous manifestations of psychopathology in humans. The most severe of these is post-traumatic stress disorder (PTSD), a common, chronic, and disabling mental illness whose pathophysiology is both complex and poorly understood. PTSD, like all psychiatric disorders, is currently diagnosed on the basis of different combinations of clinical symptoms (*1*, *2*). As a consequence of this symptom-based diagnostic framework, the syndrome of PTSD contains extensive clinical heterogeneity, covering hundreds of thousands of different symptom combinations (*3*–*5*). Moreover, despite many years of pioneering work characterizing the brains, behavior, and physiology of individuals with PTSD, we still lack biological metrics for consistently partitioning clinical variation within the broad clinical syndrome of PTSD in a way that has both mechanistic implications for understanding disorder expression and demonstrable clinical relevance for the practitioner. Establishment of such metrics could provide a basis for targeted treatment selection and development of new therapeutics, much as has been achieved in other areas of biology and medicine (*6*).

Our approach draws on the premise that disruption in basic brain information-processing functions underlying cognition forms the foundation upon which various aspects of PTSD are built. For example, impaired declarative memory in PTSD, most evident for verbal learning and memory (*7*), may contribute to development of perturbed emotional memories acquired as a result of PTSD-producing

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traumas (*8*, *9*), and is relevant for treatment outcome (*7*, *9*–*12*). Memory intrusions are a classic PTSD symptom, and memory is a primary target for evidence-based treatments using therapeutic exposure to traumatic memories so that they can be controlled. Similarly, impairments in attention and higher-level executive function may result in difficulty disengaging from trauma-relevant stimuli and engaging with the task at hand (*13*). Moreover, given that only some PTSD patients display impaired cognition when compared to healthy individuals, the associated neural abnormalities may likewise be evident in only a portion of patients. Hence, cognitive deficits may allow us to understand clinically meaningful heterogeneity in PTSD by providing an opportunity to link dysfunction in core brain processes to the neurobiology of information-processing systems (*10*) and from there to account for heterogeneity in symptoms or treatment outcome.

At the neural level, widespread interactions within and across distributed brain networks are well documented to underlie cognitive processes (*14*–*19*). Individual differences in cognitive capacities have, in turn, been related to individual differences in connectivity of the frontoparietal, default-mode, dorsal attention, and ventral attention (i.e., "salience") networks using functional magnetic resonance imaging (fMRI) even under task-free resting-state conditions in healthy individuals (*20*, *21*). Neuroimaging studies in PTSD have also identified resting-state fMRI connectivity abnormalities in these large-scale neural networks in individuals with PTSD (*22*–*24*). As a clinical tool, resting-state connectivity carries additional advantages, such as its ease of semi-standardized acquisition and independence of performance requirements. Thus, examining deficits in cognition and related resting-state network interactions may help to objectively define clinically relevant phenotypes within the larger clinical syndrome of PTSD. This would further ground aspects of clinical heterogeneity in biological mechanisms. In addition, use of resting-state connectivity facilitates generalization of our findings, given that collection of these data is now commonplace in semi-standardized ways across human imaging studies.

Resting-state connectivity has been a major area of biomarker-related research because it has been presumed that abnormalities in resting-state fMRI connectivity reflect alterations in the interactions among different brain regions (i.e., in direct information flow) (*25*). However, because of the limitations of conventional neuroimaging with respect to causal inference, the relationship between identified abnormalities in network interactions in patients (e.g., using resting-state fMRI) and affected components of neural signal flow mechanisms has remained largely unknown. This knowledge is important not only for understanding the meaning of resting-state fMRI connectivity but also for driving a transition from a descriptive approach to psychiatric illness to a circuit-based mechanistic one that could also be used to directly guide much-needed new interventions (*26*). One way to address this challenge is to directly and noninvasively stimulate cortical regions using single pulses of transcranial magnetic stimulation (spTMS) while recording consequent brain activity with electroencephalography (EEG), thereby allowing interrogation of stimulation-evoked neural signal flow at a neural temporal scale (*27*–*31*). Each TMS pulse produces a series of EEG responses. Early phase-locked potentials (e.g., at 30 ms) likely reflect evoked excitatory activity, whereas later potentials (~50 to 400 ms) likely reflect a slow inhibitory rebound to stimulation unfolding over several hundred milliseconds (*30*, *32*–*35*). Changes in oscillatory power can outlast the phase-locked potentials, for which inhibitory processes have also been implicated (*36*). By stimulating various cortical regions with concurrent spTMS/EEG, one can therefore relate stimulation-driven effects on signal flow to differences in fMRI connectivity, thus grounding our understanding of fMRI connectivity in more specific neurophysiological mechanisms using noninvasive neurostimulation. Hence, concurrent spTMS/EEG not only offers an opportunity to understand how direct stimulation–evoked neural signal flow is associated with fMRI connectivity but also establishes brain loci and neurophysiological signals that may, in turn, become targets for remediation through plasticity-inducing repetitive TMS-based treatment.

Here, we investigated the biology underlying heterogeneity within the broader PTSD clinical syndrome by (i) identifying how deficits in basic cognitive function relate to abnormalities in resting-state fMRI connectivity in cognitive networks, (ii) testing whether phenotypes defined through cognition and network connectivity could be generalized across demographically and clinically distinct PTSD populations, (iii) delineating the clinical relevance of these phenotypes by examining their relationship to both individual differences in symptom expression as well as individual differences in capacity to benefit from evidence-based treatment, and (iv) interrogating alterations in neurostimulation-evoked neural signal flow using concurrent spTMS/EEG.

RESULTS

Mapping brain connectivity to behavioral deficits in PTSD

Our core hypothesis was that clinically meaningful biological heterogeneity within the broader clinical syndrome of PTSD could be explained by considering neuroimaging data in the context of cognitive task performance. Specifically, we posited that brain functional data acquired using resting-state fMRI connectivity might differ between patients with PTSD who had cognitive impairments and either healthy individuals or patients with PTSD whose cognitive performance was in the healthy range. We began by comparing performance on a battery of computerized neurocognitive tasks in healthy individuals and PTSD patients in study 1 (see patient characteristics in tables S1 and S2; the study design for studies 1 and 2 is shown in fig. S1). Given previous meta-analytic investigations of neurocognitive functioning in PTSD, we expected patients to show deficits in verbal learning and memory, attention, working memory, information-processing speed, and various executive functions (e.g., inhibition and flexibility) (*7*). To maximize the interpretability of our findings, we selected only unmedicated PTSD patients ($n = 36$ healthy controls; $n = 56$ patients). Looking at deficits in patients with respect to healthy individuals, only verbal memory delayed recall demonstrated a significant difference after controlling for a false discovery rate (FDR) of 0.05 (Wald $\chi^2 = 6.0$, $P = 0.014$, $P_{FDR} = 0.0431$; Fig. 1B and fig. S2). This small to medium effect size (Cliff's $\delta = 0.23$) was consistent with that reported in a meta-analyses of neurocognition in PTSD (*7*).

Given that our goal was to identify a candidate cognitive phenotype for dissecting heterogeneity within PTSD, we created a cutoff in delayed recall scores using a discriminant function that determined the optimal value for differentiating patients from healthy individuals. Patients with delayed recall scores below this cutoff (90% accuracy or lower; 26% of PTSD cases) were considered to be impaired relative to healthy individuals, whereas patients performing above this cutoff were considered to be cognitively intact. These groupings were then used for analysis of the neuroimaging data in studies 1 and 2. Median recall accuracies in the memory-impaired PTSD groups were 82.5 and 85% in studies 1 and 2, respectively,

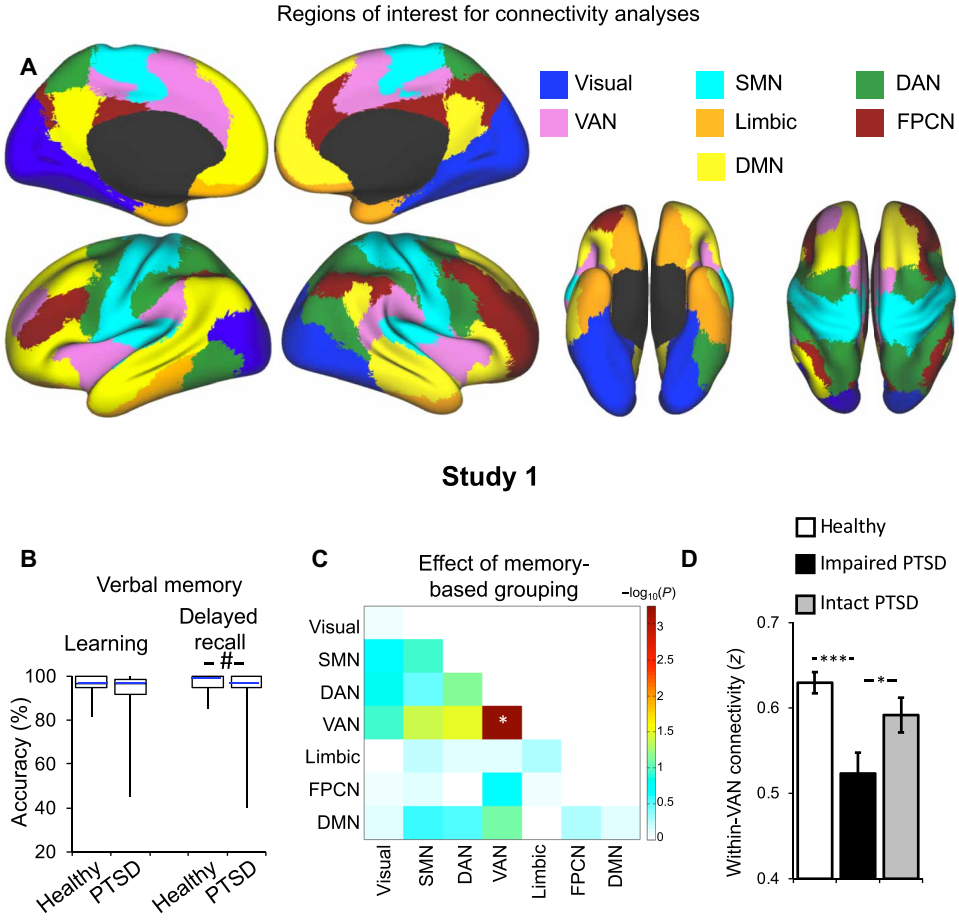

Fig. 1. Impaired verbal memory delayed recall is associated with poor within-VAN resting-state fMRI connectivity in patients with PTSD (study 1). (**A**) Three-dimensional renderings of fMRI images for a previously identified set of seven canonical cortical connectivity networks. SMN, somatomotor network; DAN, dorsal attention network; FPCN, frontoparietal control network; DMN, default mode network; VAN, ventral attention network. (**B**) Comparison of memory task performance between healthy individuals and PTSD patient groups. Only blunted verbal learning delayed recall in patients with PTSD survived FDR correction across the neurocognitive tests examined (group difference generalized linear mode, Wald $\chi^2 = 6.0$, $P = 0.014$, $P_{FDR} = 0.0431$; # represents FDR $P < 0.05$). (**C**) Group differences in fMRI connectivity within and between the labeled fMRI networks. Healthy individuals, PTSD patients with impaired memory, and PTSD patients with intact memory were compared using a generalized linear model. The plot shows $-\log_{10}(P \text{ value})$ of the effect of the three-level group comparison. Only within-VAN connectivity survived FDR correction (Wald $\chi^2 = 14.8$, $P = 0.0006$, $P_{FDR} = 0.015$; white asterisk). (**D**) Bar graph showing the group effect on within-VAN connectivity, demonstrating impaired connectivity only in the PTSD patients with impaired memory, relative to both the healthy group and the group of PTSD patients with intact memory. *$P < 0.05$, ***$P < 0.001$. Bar graphs present means and SEM for normally distributed variables; box and whisker plots show medians, interquartile ranges, minima, and maxima for variables with skewed distributions.

but 98 to 100% in the healthy control groups and intact memory PTSD groups.

We next examined whether functional connectivity abnormalities were observed selectively for the memory-impaired PTSD subgroup in resting-state fMRI analyses. Functional connectivity was calculated for each pair of cortical regions in a previously identified set of seven canonical cortical connectivity networks (Fig. 1A) (*37*, *38*). Pairwise connectivity values were then averaged on the basis of region-network assignments to obtain one within-network connectivity value for each network and one between-network connectivity value for each pair of networks. These measures were then entered into a three-level group factor generalized linear model [i.e., verbal memory impaired PTSD patients ($n = 12$), verbal memory intact PTSD patients ($n = 39$), healthy individuals ($n = 36$)] while controlling for age, gender, education, and head motion. After FDR correction for all pairwise network-level connections, only connectivity within the ventral attention network (VAN) was found to differ among the three groups (Wald $\chi^2 = 14.8$, $P = 0.0006$, $P_{FDR} = 0.015$; Fig. 1C). This network consists of regions located in the insula, dorsal anterior cingulate, anterior middle frontal gyrus, and supramarginal gyrus. A subsequent post hoc pairwise contrast between the groups (using a Sidak correction for multiple comparisons) revealed that the impaired PTSD group had lower within-VAN connectivity relative to both healthy individuals ($P = 0.0001$) and the intact PTSD group ($P = 0.03$), whereas cognitively intact patients with PTSD and healthy individuals did not differ (Fig. 1D).

These findings were not confounded by age, intelligence, or performance on other cognitive tests ($P < 0.001$ for the three-level group analyses controlling for these measures). Notably, whereas the impaired memory PTSD group was significantly older than the intact PTSD groups (Wald $\chi^2 = 7.4$, $P = 0.025$; table S3), neither including age as a covariate nor excluding participants >55 years old altered the within-VAN group difference. Age also did not correlate with within-VAN connectivity (Wald $\chi^2 = 0.9$, $P = 0.34$). Last, we also considered the possibility that connectivity differences within the VAN reflected more focal aspects of the signal fluctuation in VAN regions. Thus, we quantified the coefficient of variation within VAN regions but did not find a significant effect of memory-based grouping on this measure (Wald $\chi^2 = 2.9$, $P = 0.23$).

We next tested whether the brain-behavior findings in PTSD patients in study 1 could be generalized to a new cohort of patients and healthy controls. Study 1 used the DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition) manual for diagnosis of PTSD and was composed primarily of civilians. Study 1 participants were largely female, were all right-handed, and featured patients who developed PTSD most commonly after physical or sexual assault, and for whom fMRI data were acquired using a specific scanning protocol. Moreover, only unmedicated patients were used in our primary analyses in study 1. By contrast, study 2 used the DSM-5 manual for diagnosis of PTSD and was composed entirely of Iraq/Afghanistan-era military combat–exposed veterans. Study 2 participants were mostly male, included left-handed individuals, featured patients who developed PTSD almost exclusively

after combat-related events (n = 117 healthy controls; n = 128 PTSD participants), and employed a different fMRI scanning protocol. Study 2 participants were also more frequently medicated with a broader variety of medications (tables S1 and S2). Thus, given predominantly demographic differences, but similar neurocognitive and neuroimaging methodological approaches, the study 2 sample represented a prime opportunity for testing the generalization of our brain-behavior findings from study 1. As expected from study 1, the verbal memory impairment in study 2 was significantly more frequent among the PTSD group than healthy controls (33% of cases and 19% of controls; Fisher's exact test, P = 0.018; total n = 117 healthy controls and n = 123 PTSD patients).

We next examined the relationship of the a priori–derived verbal memory–based groupings on fMRI connectivity within the VAN in study 2. Using the generalized linear models and covariates defined in study 1, while additionally controlling for acquisition site, the different medication classes represented in our population, and handedness, we found a significant effect of verbal memory–based grouping on within-VAN connectivity (Wald χ^2 = 11.4, P = 0.003; Fig. 2A). Specifically, within-VAN connectivity was significantly lower in verbal memory–impaired PTSD cases, relative to healthy individuals (P = 0.042) and verbal memory–intact PTSD cases (P = 0.002), after Sidak correction for multiple comparisons (Fig. 2A). Similarly, when considering all within- and between-network connections, the within-VAN connectivity effect also passed the FDR significance threshold (Fig. 2B; P_{FDR} = 0.009). These results were likewise not confounded by age, intelligence, or performance on other cognitive tasks (P < 0.006 for the three-level group analyses controlling for these measures). Age in study 2 did not differ between memory-based groups (Wald χ^2 = 1.9, P = 0.39).

Association of impaired verbal memory and poor within-VAN connectivity with symptoms, comorbidities, and treatment outcome

We next asked whether clinical aspects of PTSD, or its common comorbidities, differed in patients as a function of verbal memory delayed recall, within-VAN connectivity, or their interaction. We found no relationships of any of these variables, across either study 1 or 2, to PTSD or depression severity (including PTSD symptom clusters and dissociative symptoms), comorbid diagnoses, alcohol use, traumatic brain injury, or quality of life (P > 0.08 without correction for multiple comparisons; fig. S2). It thus appeared that, from a cross-sectional clinical perspective, the neurobehavioral phenotype we had identified within the clinical syndrome of PTSD could not be distinguished by current symptoms or comorbidities (i.e., clinically "latent"). We therefore next asked whether this phenotype was predictive of clinical outcome when PTSD patients were treated with the best-supported intervention for the disorder, exposure-based psychotherapy.

Trauma-focused psychotherapy, such as prolonged exposure psychotherapy, is considered the gold-standard treatment for PTSD and involves therapeutic techniques that tap learning and memory (*12*, *39*). Within study 1, 66 patients entered a randomized clinical trial contrasting prolonged exposure psychotherapy (n = 36) to a control arm where patients were wait-listed for this treatment (n = 30) (fig. S3) (*40*, *41*). As expected (*39*), prolonged exposure psychotherapy resulted in a much greater reduction in PTSD symptoms, as assessed by the DSM-IV CAPS (Clinician-Administered PTSD Scale) score, than did wait-listing ($F_{2,113}$ = 20.0, $P = 4 \times 10^{-8}$; table S4), with no difference in dropout rates (Fisher's exact test, P = 0.14).

Using generalized linear mixed models in an intent-to-treat analysis, we next examined the potential moderating effects of verbal memory delayed recall and within-VAN functional connectivity (i.e., whether these factors differentially predicted outcome to prolonged exposure psychotherapy versus wait-list, as tested by a moderator by group by time interaction). When examined alone, neither verbal memory delayed recall impairment nor within-VAN functional connectivity significantly moderated treatment outcome (memory: $F_{2,90}$ = 2.0, P = 0.13; connectivity: $F_{2,108}$ = 0.2, P = 0.84). By contrast, when interactions were examined, there was a significant moderation effect on treatment outcome as a function of both verbal memory impairment and within-VAN connectivity ($F_{2,82}$ = 27.4, $P < 10^{-8}$). Figure 3A shows a median split on connectivity scores to illustrate the mixed model result. This model explained more treatment outcome variance than either single variable model alone (likelihood ratio test: ΔG^2 = 102.8, df = 6, P < 0.001). Moreover, when considering all within- and between-network connections, the moderation effect for within-VAN connectivity was also significant after FDR correction for multiple comparisons ($P_{FDR} = 10^{-7}$; Fig. 3B). When testing each arm alone, we found that significant outcome prediction as a function of both memory and connectivity was found only in the prolonged exposure psychotherapy arm (treatment: $F_{1,41}$ = 187.8, $P < 10^{-8}$; wait-list: $F_{1,41}$ = 1.0, P = 0.31). These effects were unrelated to any demographic variables, medication use, or baseline PTSD severity ($P < 10^{-7}$ controlling for these measures).

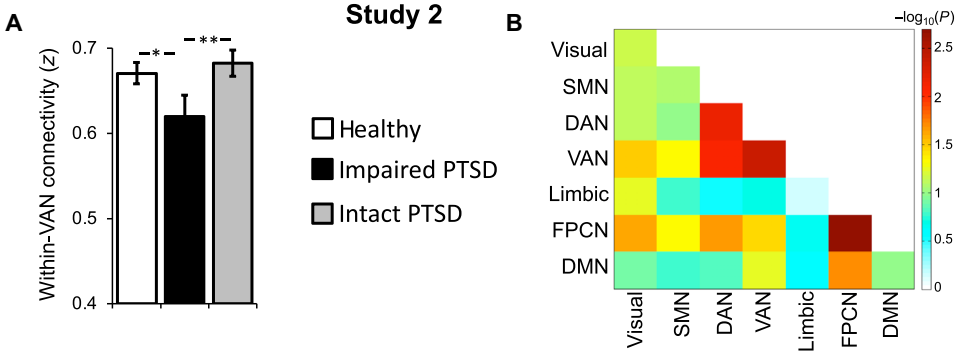

Fig. 2. Impaired verbal memory delayed recall is associated with poor within-VAN resting-state fMRI connectivity in patients with PTSD (study 2). (**A**) Group differences in within-VAN fMRI connectivity comparing healthy individuals, PTSD patients with impaired memory, and PTSD patients with intact memory in a generalized linear model. Study 2 used the same cutoffs and analytical approaches as study 1. As with study 1, there was a reduction in fMRI connectivity in the VAN only in the PTSD patients with impaired memory relative to both the healthy group and the PTSD patient group with intact memory (Wald χ^2 = 11.4, P = 0.003). (**B**) The memory-related impairment in within-VAN fMRI connectivity also survived FDR correction across all network pairs (P_{FDR} = 0.009). The plot shows $-\log_{10}(P$ value) of the effect of the three-level group comparison. *P < 0.05, **P < 0.01. Shown are means and SEM.

The significant interaction in the prolonged exposure psychotherapy arm arose from the poor treatment response of individuals with both impaired verbal memory and lower within-VAN connectivity (Fig. 3A). Having either intact verbal memory or normal within-VAN connectivity resulted in a robust treatment response. For context, a CAPS-IV score cutoff of 20 is considered symptom remission (*42*), which many of the individuals without both the memory and connectivity impairments were able to achieve. Thus, this biological stratification within the broader PTSD clinical syndrome may be of clinical significance.

To understand the individual-level predictive value of memory and connectivity, we next tested these two variables as potential predictors of treatment outcome (quantified as a binary response variable corresponding to a 50% decrease in symptoms) using support vector machine (SVM) classification with leave-one-out cross-validation within the prolonged exposure arm only. We found that treatment response could be predicted at 85% accuracy with a linear SVM (sensitivity, 80%; specificity, 87%; P = 0.009 using 5000 permutation tests) and at 90% accuracy with a nonlinear radial basis function SVM (sensitivity, 80%; specificity, 93%; P = 0.01). SVMs using only memory or only connectivity scores did not predict outcome (accuracies ≤ 65%, P > 0.18). Figure S4 shows individual data points for memory, connectivity, and treatment outcome as parallel coordinate plots.

In spite of the treatment-moderating effects of verbal memory and within-VAN connectivity, neither memory nor connectivity showed a significant change following prolonged exposure psychotherapy compared to the wait-list group (Fig. 4, A and B; group × time interactions for memory: $F_{2,91}$ = 2.3, P = 0.11; connectivity: $F_{2,111}$ = 0.02, P = 0.98). This is consistent with the expectation that individuals with the greatest impairments in both measures failed to respond to prolonged exposure psychotherapy, whereas those without both impairments who responded well to prolonged exposure psychotherapy were already within the healthy range on both measures.

Association of within-VAN fMRI connectivity with direct neurostimulation-evoked neural effects using spTMS/EEG

Although resting-state fMRI connectivity is a broadly used measure in both basic and clinical human neuroscience, which helped to motivate our examination of this metric in this study, its physiological meaning remains unclear. It is largely unknown how aspects of neurophysiology and directed information flow (as revealed by neurostimulation-evoked circuit perturbations) are reflected in individual differences in fMRI connectivity. By stimulating various cortical regions with concurrent spTMS/EEG, one can discover the directional influence of the stimulated region on downstream regions. We next sought to understand neurophysiological mechanisms that might account for variations in within-VAN connectivity. For this goal, we conducted concurrent spTMS/EEG circuit interrogation by stimulating a TMS-accessible region of the VAN in healthy individuals and in patients with PTSD. This VAN region was located in the anterior middle frontal gyrus (aMFG/VAN) (Fig. 5A). We contrasted results of VAN spTMS with stimulation of a nearby region in the posterior middle frontal gyrus located within the frontoparietal control network (pMFG/FPCN) (Fig. 5A), also termed the executive control network. In previous work using concurrent spTMS/fMRI, we found that spTMS applied to the right aMFG/VAN node resulted in increased within-VAN fMRI connectivity relative to spTMS applied to the right pMFG/FPCN node (*43*). We localized the VAN and FPCN nodes for neuronavigation in the same manner as in our previous work, although now both left-sided and right-sided spTMS sites were included. These experiments were added to study 2 after acquisition of fMRI and behavioral data had begun; thus, most, but not all, participants underwent both fMRI and spTMS/EEG.

EEG quantification of direct neural influence includes both phase-locked amplitude changes [TMS-evoked responses (TERs)] and changes in power of different frequency bands [event-related spectral perturbation (ERSP) changes]. To cast a broad net across potential neurophysiological mechanisms, we examined a broad range of TER measures (potentials at 30, 60, 100, and 200 ms after the TMS pulse) and ERSP measures (across theta, alpha, beta, and low gamma frequency ranges and in time bins extending up to 800 ms after the TMS pulse) (Fig. 5B). These were extracted from a spatial mask covering VAN regions using an EEG source localization algorithm (*44*). We then correlated each individual's within-VAN resting-state fMRI connectivity against each of the VAN-extracted TER and ERSP measures, correcting for multiple comparisons with FDR across the full set of correlations (i.e., each of four stimulation sites and all EEG measures). These analyses were done on

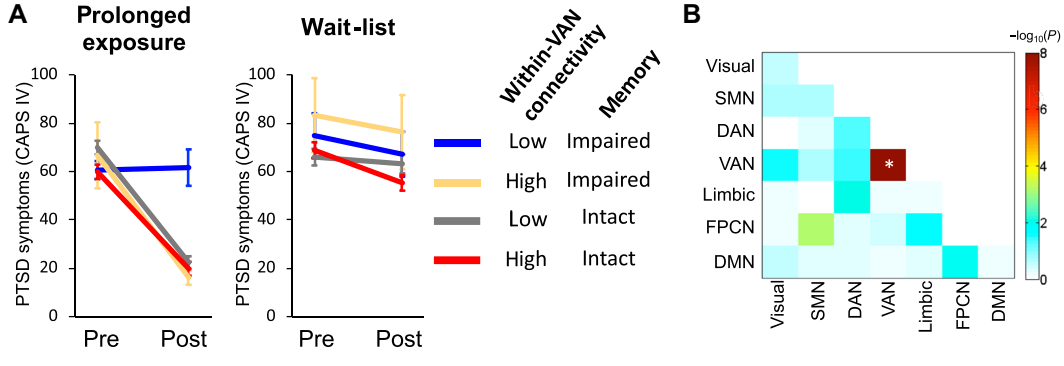

Fig. 3. Poor treatment outcome for patients with both impaired memory and within-VAN connectivity (study 1). Patients with PTSD in study 1 took part in a clinical trial in which they were randomized to an evidence-based psychotherapy treatment (prolonged exposure psychotherapy) or were wait-listed for this treatment (comparison arm). (**A**) Generalized linear mixed model in an intent-to-treat analysis revealed a moderation of treatment outcome by brain and behavioral metrics (i.e., a treatment group by memory by connectivity by time interaction). A median split on the fMRI connectivity variable is shown and illustrates the mixed model result (i.e., low/high fMRI connectivity in the VAN). (**B**) Within-VAN fMRI connectivity likewise survived FDR correction across all network pairs in the moderation of treatment outcome ($P_{FDR} = 10^{-7}$; white asterisk) based on the treatment group by memory by connectivity by time interactions term. The plot shows $-\log_{10}(P$ value) of the moderation term (i.e., treatment group by memory by connectivity by time interaction) for each network pair.

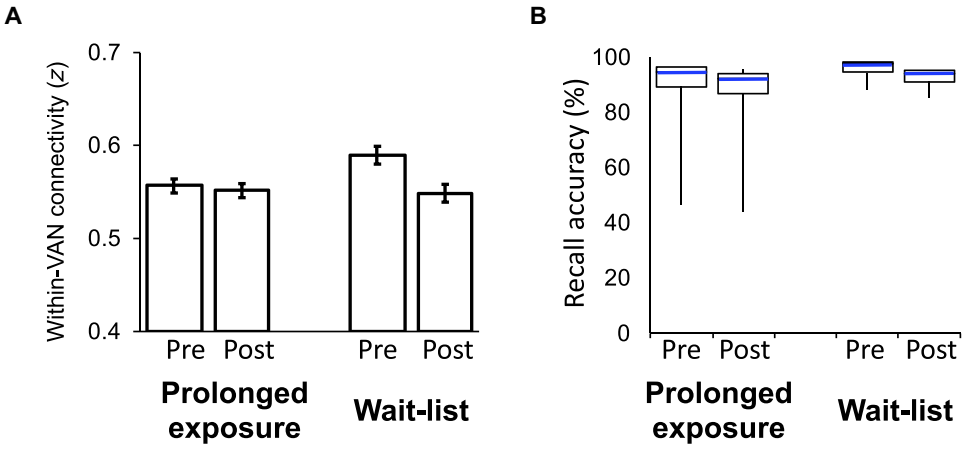

Fig. 4. Within-VAN fMRI connectivity and memory recall in PTSD patients before and after psychotherapy treatment. Within-VAN connectivity (**A**) and delayed recall of verbal memory (**B**) were assessed in study 1 patients with PTSD both before and after either prolonged exposure psychotherapy or being wait-listed for this treatment. No significant differences were observed in either measure as a function of treatment (prolonged exposure psychotherapy versus wait-list: group × time linear mixed models). Bar graphs show means and SEM for normally distributed variables; box and whisker plots show medians, interquartile ranges, minima, and maxima for variables with skewed distributions.

participants in study 2, a portion of whom additionally underwent spTMS/EEG (which was added after study recruitment had begun). As shown in table S5, there were no demographic differences between those study 2 patients who did and did not have spTMS/EEG data. Furthermore, spTMS/EEG data were processed by an automated artifact rejection algorithm we recently developed (*31*), thereby minimizing the biases in preprocessing possible with manual rejection of artifacts, as is typically done in spTMS/EEG research.

After quality control of processed spTMS/EEG data, we had ~110 participants with both spTMS/EEG and resting-state fMRI data across both healthy and PTSD groups (right aMFG/VAN, $n = 52$ healthy and $n = 58$ PTSD; left aMFG/VAN, $n = 50$ healthy and $n = 63$ PTSD; right pMFG/FPCN, $n = 56$ healthy and $n = 64$ PTSD; left pMFG/FPCN, $n = 50$ healthy and $n = 48$ PTSD). Correlation analyses between fMRI connectivity and spTMS/EEG response were done across both healthy individuals and patients with PTSD to identify generalizable neurostimulation-evoked signals in the spTMS/EEG data that may account for within-VAN fMRI connectivity under the assumption that such a relationship is not specific to a distinct clinical diagnosis. We subsequently tested whether clinical group moderated these findings.

Multiple relationships between within-VAN fMRI connectivity and spTMS/EEG measures survived FDR correction, all of which were in response to stimulation of the right aMFG/VAN node (Fig. 5C). All of these relationships were positive correlations and related to ERSP measures occurring largely after the phase-locked TER ended. For example, as illustrated in Fig. 5D, those individuals with lower within-VAN fMRI connectivity displayed profound VAN-localized alpha frequency range desynchronization, that is, reduction in alpha power below baseline (defined as −300 to −100 ms) in the 400- to 600-ms post-spTMS pulse period. In contrast, study 2 participants with higher fMRI connectivity showed either more modest or no desynchronization. To visualize these multiple fMRI-spTMS/EEG relationships, Fig. 5E shows ERSP plots for the individuals in the top third of the within-VAN fMRI connectivity distribution and those within the bottom third. There was profound and prolonged desynchronization in individuals with lower within-VAN fMRI connectivity extending until the end of the 800-ms time period across which we quantified ERSP measures. Thus, the neurophysiological response to an spTMS pulse ended by ~400 ms for individuals with higher within-VAN connectivity but persisted for at least 800 ms in those with lower within-VAN connectivity.

These fMRI connectivity–spTMS/EEG relationships were unchanged if we accounted for diagnostic group (healthy versus PTSD; Wald $\chi^2 > 8.4$, $P < 0.004$). Moreover, these findings were specific for the right aMFG/VAN stimulation site. Covarying for the equivalent ERSP measure in response to right pMFG/FPCN or left aMFG/VAN stimulation did not eliminate the relationships between within-VAN fMRI connectivity and the various VAN ERSP responses to right aMFG/VAN spTMS (Wald $\chi^2 > 6.4$, $P < 0.012$). In particular, the alpha desynchronization effect at 400- to 600-ms post-spTMS pulse shown in Fig. 5D survived both of these analyses at Wald $\chi^2 > 11.9$, $P < 0.0006$.

DISCUSSION

Here, we have identified a neurobehavioral phenotype within the broader clinical syndrome of PTSD, characterized by impairments in the delayed recall of verbal memory and resting-state fMRI connectivity in the VAN. This phenotype was identified in two independent and demographically/clinically distinct populations of patients with PTSD compared to healthy individuals. This phenotype was associated with poor treatment outcome, despite being unrelated in the absence of treatment to symptoms or comorbidities (hence clinically latent). Moreover, using concurrent spTMS/EEG to interrogate direct neurostimulation-evoked neural signal flow, we identified a neurophysiological circuit response that was associated with the degree of within-VAN fMRI connectivity. Specifically, we found that poorer within-VAN connectivity was reflected in a more prolonged circuit perturbation to single TMS pulses delivered to a right-sided anterior prefrontal VAN region; this took the form of profound alpha-range below-baseline desynchronization. From a clinical perspective, these findings help to ground clinically meaningful variation within the syndrome of PTSD in objective and quantifiable features. From a translational perspective, by identifying neurophysiological direct stimulation–evoked signal flow correlates for altered within-VAN fMRI connectivity, we can start to elucidate what, at least within-VAN, resting fMRI connectivity may indicate.

Previous neuroimaging and behavioral studies have generally treated PTSD as a single clinical group, contrasting PTSD cases with healthy participants (although DSM-5 now recognizes a dissociative subtype) (*45*). This has resulted in substantial inconsistencies in the literature. In the case of the VAN, for example, various authors have argued for overactivity or overconnectivity of the VAN in PTSD, by virtue of its response to salient stimuli such as threat cues (*46*, *47*). However, results regarding resting-state VAN connectivity have been

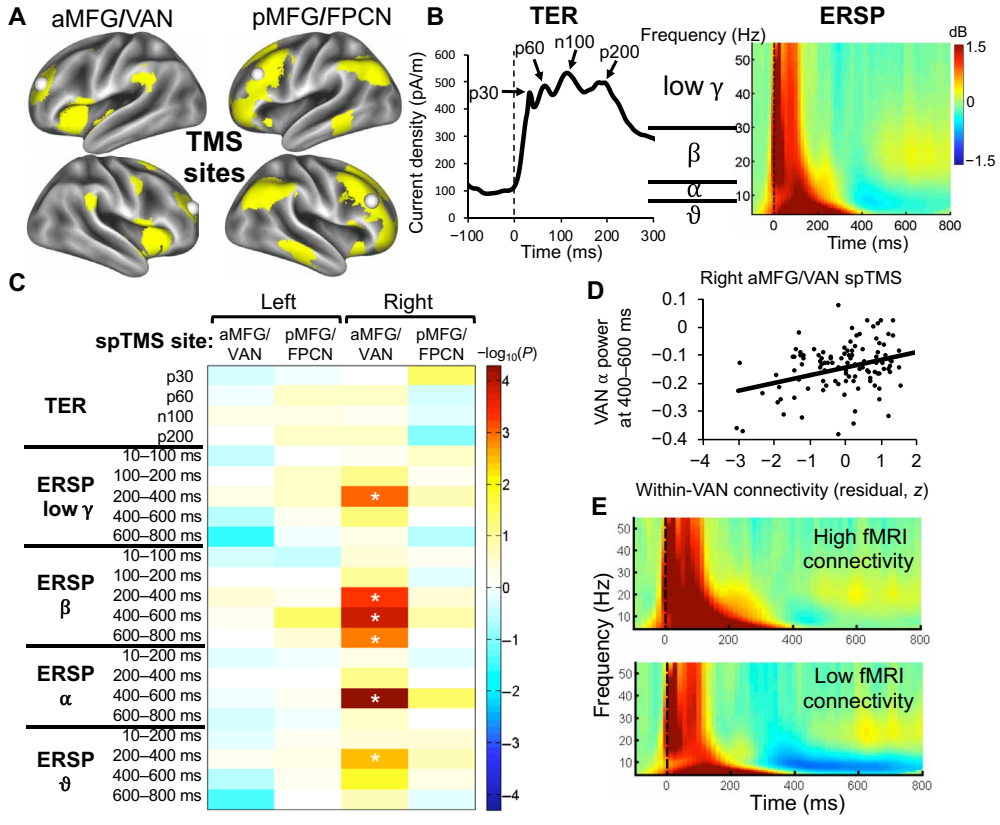

Fig. 5. Within-VAN resting-state fMRI connectivity and EEG responses after single TMS pulses. Individual differences in fMRI connectivity were correlated with the neural responses to noninvasive transcranial magnetic brain stimulation of different brain regions in healthy individuals and patients with PTSD. (**A**) A TMS pulse was delivered to one of the brain stimulation sites. These sites were identified on the basis of independent component analyses of resting-state fMRI data from a separate group of participants (shown in yellow). The TMS targets (white spheres) were either in the anterior middle frontal gyrus (aMFG, part of the VAN) or posterior middle frontal gyrus (pMFG, part of the FPCN). (**B**) Quantification of EEG signals in response to spTMS covering both TER and ERSP. Dashed line indicates the timing of the TMS pulse. (**C**) A significance plot of the generalized linear models relating individual differences in within-VAN fMRI connectivity across all participants (healthy individuals and patients with PTSD) to differences in each EEG measure. This is shown for each of the stimulation sites (i.e., left and right aMFG/VAN and left and right pMFG/FPCN). To derive each EEG measure, an average was taken of that measure for each of the source-localized vertices comprising the VAN. Thus, each participant's single within-VAN fMRI connectivity measure was correlated with single measures of each participant's EEG responses after TMS stimulation within the VAN (evoked at each stimulation site). Only ERSP measures for right aMFG/VAN stimulation survived FDR correction (denoted by asterisks). The plot shows $-\log_{10}(P)$ for the correlation of within-VAN fMRI connectivity with spTMS/EEG measures. (**D**) Scatter plot of one of the FDR-significant relationships, demonstrating that individuals with lower within-VAN fMRI connectivity had greater alpha-range desynchronization 400 to 600 ms after the TMS pulse (i.e., below-baseline alpha power). (**E**) ERSP plots showing the correlation in (D). ERSP values were averaged for participants in the top and bottom third of the within-VAN fMRI connectivity distribution to visualize the correlation findings across the whole time-frequency range. The data show prolonged alpha-range desynchronization from ~400 to ~800 ms after the TMS pulse delivered to the right aMFG/VAN in those individuals with reduced within-VAN fMRI connectivity.

inconsistent, with evidence of both increased (*48*) and decreased (*23*, *49*, *50*) within-VAN connectivity. It has also been noted that abnormalities associated with PTSD are typically greater when comparing patients to trauma-naïve healthy controls but diminished, or even absent, when comparing them to well-matched trauma-exposed healthy controls (*51*, *52*).

Our findings argue that these inconsistencies and lack of generalization across cohorts or studies may stem from a failure to account for the biological heterogeneity within the syndrome of PTSD, as well as an uncontrolled differential sampling of the heterogeneity that occurs in each study. Rather, consistent mechanistically meaningful and clinically meaningful neurobiological phenotypes in PTSD could emerge by anchoring stratification of PTSD clinical populations on objectively quantifiable factors, such as verbal memory and within-VAN functional connectivity. Neurocognitive impairments have been frequently found in PTSD (*7*), with verbal memory representing one of the areas of greatest impairment; however, many PTSD patients nonetheless perform within the healthy range. Hence, we focused our analyses on a differentiation of patients with PTSD, first looking at those who were impaired in verbal memory (defined as performing outside of a discriminant-determined healthy range). Then, we compared these individuals to those patients with PTSD who performed similarly to healthy controls on the verbal recall task and who would be expected to have similar fMRI connectivity patterns. Notably, if we had solely used subjectively reported or clinician-rated symptoms to identify this behavioral phenotype, we would have failed because it was not consistently associated with differences in symptom expression. Thus, our findings are consistent with recent proposals to shift away from defining PTSD through symptoms and rather do so using brain information processing–based approaches (*53*).

Consistent with our findings, a role of the VAN in verbal memory is suggested by multiple previous findings. Neuroimaging meta-analysis of activation during performance of memory tasks has found that activity in the VAN is associated with increased familiarity of remembered items (*16*), as well as memory of verbal over pictorial stimuli (*54*). Resting-state fMRI within-VAN connectivity has also been found to predict delayed recognition memory (*55*). Memory impairments observed as part of "cognitive aging" have also been associated with decreased within-VAN connectivity (*56*, *57*), although other findings have also implicated aberrant connectivity across a broader set of brain networks in memory impairment (*17*).

We found that verbal memory–impaired patients with PTSD had lower within-VAN fMRI connectivity than did either trauma-exposed

control individuals or verbal memory–intact patients with PTSD.This suggested that impairments in memory and aberrant within-VAN connectivity are likely to be two related but independent measures of what may be a core deficit in an underlying information-processing capacity. An interaction between these two factors was critical for effectively predicting treatment outcome. Whereas most individuals with poor delayed recall of verbal memory in study 1 also showed reduced within-VAN fMRI connectivity and poor treatment outcome, there were some memory-impaired individuals with healthy-range within-VAN fMRI connectivity who displayed favorable treatment outcomes. Therefore, there may be an inconsistency between our association of memory impairments with poor within-VAN connectivity and the necessity of using both measures to predict treatment outcome rather than just one measure. However, poor delayed recall of verbal memory may occur for multiple reasons, not all of which are related to the within-VAN memory processes implicated here (e.g., distractibility, attention, and fatigue). These other reasons may reflect unrelated circuitry characteristics. Because memory tasks require the interaction of multiple cognitive networks (*16*), within-VAN connectivity may be impaired in some individuals but memory performance may remain intact. Likewise, factors related to variations in individual cognitive processes during resting state, as well as simple measurement error, may result in lower within-VAN connectivity for reasons not related to their relationship to verbal memory. That is, each measure contains statistical "noise" relating to multiple factors that do not reflect the core neurocircuitry deficit characterizing subtype treatment resistance. Thus, only in those individuals who have both poor memory and low within-VAN connectivity (i.e., in whom there is confluence of measures mapping the core deficit) is treatment ineffective. This is not the case for individuals in whom these measures may diverge in the core deficit due to noise or variance from other factors.

Future work can build on these findings in several ways. We examined resting-state connectivity, but different relationships may emerge when looking at memory task–related fMRI connectivity. It may also be that a free recall-based verbal memory test may prove more sensitive to within-VAN connectivity abnormalities in PTSD as it suffers less from an accuracy ceiling effect than the recognition-based recall task used here. Moreover, given the role of the VAN in a range of cognitive operations (*58*, *59*), other tasks that tap into these elements of VAN function may similarly be able to capture the phenotype we report here. It is also important to consider that every metric has its own test-retest reliability, and although verbal memory recall and fMRI connectivity both have relatively good reliability, their covariation and treatment outcome prediction capacity is nonetheless gated by the reliability of each, as well as that of the outcome measure. Additional work is therefore necessary to refine which aspects of verbal memory (or related constructs) and within-VAN resting fMRI connectivity are closely tied to one another to better understand this brain-behavior relationship. Last, it will be important to test in future research whether both the relationship between within-VAN connectivity and verbal memory, and their joint relationship to treatment outcome, is specific to PTSD. Previous work has found associations between VAN function and memory unrelated to PTSD (*55*–*57*). There have also been implications of verbal memory alone in predicting outcome in disorders as diverse as bipolar disorder, psychosis, and drug addiction (*60*–*63*). We have found that disruptions in VAN are a feature common to many major psychiatric disorders (*64*, *65*). Thus, we cautiously speculate that the VAN-memory relationship could be generalized to other conditions and could be used to predict poor treatment outcome in other contexts.

In the current study, we sought to go beyond a correlative characterization of the behavioral phenotype using resting-state fMRI. Rather, we aimed to identify potential neurophysiological mechanisms that could account for differences in within-VAN fMRI connectivity. To do this, we interrogated the concurrent EEG responses to single TMS pulse stimulation of bilateral VAN regions located in the anterior middle frontal gyrus of patients with PTSD and healthy control individuals. We compared these EEG responses to those from a nearby posterior middle frontal region that is part of the frontoparietal control network. In previous spTMS/fMRI work, we had found that stimulation of the same right VAN region, but not the right frontoparietal control network region, resulted in increased TMS-evoked fMRI connectivity within the VAN (*43*).

We now report that reduced within-VAN fMRI connectivity was associated with below-baseline alpha-range desynchronization for hundreds of milliseconds (~400 to 800 ms) after the TMS pulse was administered. These findings open a new window into understanding the neurophysiological meaning of differences in fMRI resting connectivity. We found this relationship after rigorous correction for multiple comparisons and in a generalizable manner that was independent of clinical state. Thus, we anticipate that these findings may be of broad relevance to fMRI research. Our spTMS/EEG results reveal that causal signal flow within a network may relate to within-VAN fMRI-measured network connectivity. Our findings could help to establish spTMS/EEG as a brain mapping tool for understanding the neural basis of resting-state fMRI network measures when applied across other networks and stimulation sites in the brain.

Normal within-VAN resting-state fMRI connectivity (e.g., that typical of memory-intact patients with PTSD or healthy controls) potentially could make the VAN resilient to perturbation by a TMS pulse. In individuals with normal within-VAN connectivity, the phase-locked response (i.e., TER) and oscillatory power changes (i.e., ERSP) largely returned to baseline by ~400 ms after the TMS pulse. By contrast, the same network may be more susceptible to perturbation by the TMS pulse in individuals with lower within-VAN connectivity (e.g., that typical of memory-impaired patients with PTSD), wherein the oscillatory power changes continued for at least 800 ms after the end of the TMS pulse. These results may have implications for therapeutic repetitive TMS on network neurophysiology in individuals with different within-VAN fMRI connectivity. Individuals with low fMRI connectivity may, for example, show a greater impact of the previous TMS pulse on the next TMS pulse by virtue of the prolonged period of alpha-range desynchronization from one pulse interacting with the next one.

This late alpha-range desynchronization has been reported with motor cortex stimulation and may reflect a non–phase-locked aspect of the spTMS/EEG response that may be sensitive to agonists of either γ-aminobutyric acid type A ($GABA_A$) or $GABA_B$ receptors (*36*). Alpha desynchronization is increased by drugs that stimulate either $GABA_A$ or $GABA_B$ receptors (*36*), suggesting that the increased and prolonged alpha-range desynchronization observed in individuals with lower within-VAN connectivity may reflect a larger inhibitory response to spTMS stimulation of the VAN. This interpretation contrasts with a common view of alpha-range oscillatory power in task and resting-state contexts, which argues that alpha desynchronization reflects local inhibitory processing (*66*) and an increase might actually mean less inhibition. However, the relationship between task and resting-state alpha oscillations and spTMS-induced late alpha desynchronization remains

to be investigated. Future work should examine the relationship between VAN alpha power at rest and spTMS-induced late alpha desynchronization because altered alpha power has been observed in PTSD (*67*), and pre-spTMS alpha power has been found to predict aspects of the response to the spTMS pulse (*68*).

Identification of the right anterior middle frontal VAN node as a brain target that when stimulated evokes fMRI connectivity–correlated EEG responses within the VAN has potential clinical implications. Specifically, this region may be a potential target for remediating the within-VAN fMRI connectivity deficit found in memory-impaired patients with PTSD. This possibility is further supported not only by our previous spTMS/fMRI work (*43*) but also by a recent finding that examined the impact of high-frequency repetitive TMS stimulation of either the right or left side of the anterior middle frontal gyrus VAN (*69*). In that study, repetitive stimulation at 10 Hz, which is thought to increase neuronal excitability (*34*), resulted in increased within-VAN resting-state fMRI connectivity but only after stimulation of the right side of the VAN target. Although we do not know why the correlation with fMRI connectivity was lateralized to the right side of the VAN in our study, our findings are nonetheless consistent with those of the 10-Hz repetitive TMS study. The vast majority of repetitive TMS treatment studies for PTSD have targeted a right-sided prefrontal region in the vicinity of our VAN region (*70*–*73*) and have reported clinical efficacy. Likewise, TMS manipulations of nearby right-sided prefrontal regions have been found to alter memory encoding or recall (*74*, *75*). TMS treatment optimization could be guided by monitoring changes in spTMS/EEG responses to right anterior middle frontal VAN node stimulation.

There are several limitations to our study. Although we identified consistent patterns of biological heterogeneity across two independent cohorts of patients with PTSD that were clinically and demographically diverse, our findings need to be replicated in other patient cohorts. Likewise, fMRI may be less well suited to ultimate clinical translation than EEG, as EEG data are cheaper to acquire and can be done at point-of-care rather than in a hospital setting. Going beyond correlational neuroimaging research requires the ability to perturb circuits to gain inferential power. Combining an understanding of clinical heterogeneity in neurobiological terms, and perturbation-based imaging approaches, holds promise for elucidating the factors underlying clinical heterogeneity and variability in treatment response and for uncovering disease mechanisms in PTSD.

MATERIALS AND METHODS

Study design

Our study included both cross-sectional and longitudinal clinical trial components. In our cross-sectional analyses, we studied two independent cohorts of patients with PTSD and healthy participants (studies 1 and 2) and examined the relationship between impaired cognitive task performance and fMRI connectivity. Patients in study 1 were additionally randomized to treatment with prolonged exposure psychotherapy or were in a wait-list comparison arm (clinicaltrials.gov, NCT01507948), allowing us to examine the clinical relevance of differences in task performance and fMRI connectivity among patients. Study 2 included EEG measurements concurrent with single-pulse TMS stimulation of the VAN or FPCN regions. This allowed us to determine how individual differences in variations in resting-state fMRI connectivity were related to neural signal flow when directly stimulating that brain network, providing a greater mechanistic understanding of clinically relevant network connectivity differences.

Figure S1 shows an overview of the experimental design. Study 1 included 112 primarily civilian participants (36 trauma-exposed healthy controls and 76 patients with PTSD), who underwent clinical, fMRI, and behavioral assessments. Of these patients, 66 went on to a randomized controlled trial comparing prolonged exposure psychotherapy treatment to a no delayed intervention comparison arm (i.e., wait-list control). The prolonged exposure psychotherapy protocol followed well-described procedures and was supervised by an expert in this area (B.O.R.). Study 2 included 245 Iraq/Afghanistan-era combat veterans (117 trauma-exposed healthy veterans and 128 with PTSD). These participants underwent the same assessments as those in study 1. In addition, they received concurrent EEG with single-pulse TMS stimulation to probe neural excitability consequent to direct noninvasive stimulation. Study 2 participants did not get study-provided treatment (such as the prolonged exposure psychotherapy in study 1). Both studies were approved by the respective institutional review boards, and all participants provided written informed consent.

The behavioral assessments were conducted through a computerized neurocognitive battery of tests that probed verbal memory, attention, working memory, and response inhibition. The key verbal memory test used here entailed learning lists of words, followed by a test of delayed recall. The fMRI consisted of an 8-min resting-state fMRI scan conducted either using spiral in-out imaging at Stanford University (study 1) or as a two-site study using echoplanar imaging at Stanford University and New York University (study 2). Stanford University used a General Electric 750 3 T scanner; New York University used a Siemens Skyra 3 T scanner. Preprocessing and connectivity assessments followed conventional procedures.

The TMS/EEG assessment involved stimulation with a single TMS pulse to several sites within the prefrontal cortex, localized to either the VAN or FPCN, while measuring concurrent EEG responses. Preprocessing was accomplished through an automated artifact rejection algorithm previously published by our group (*31*). EEG source localization followed conventional procedures. We quantified both phase-locked neural responses, that is, TER, and non–phase-locked spectral responses, that is, ERSP.

Statistical analyses

All statistical analyses were conducted in SPSS software (IBM Corporation) and primarily used generalized linear models, with the exception of the treatment outcome prediction analyses, which used generalized linear mixed models. All tests and post hoc analyses were corrected for multiple comparisons using two-sided tests. A memory-based division of patients with PTSD was established on the basis of the cutoff in a discriminant analysis that compared performance of the PTSD groups with that of healthy individuals on the verbal memory test. The same cutoff was used for all analyses in studies 1 and 2. Analysis of treatment outcome prediction in the randomized clinical trial followed an intent-to-treat framework that incorporated all randomized study participants in the analysis.

SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1. Overview of the experimental design.

Fig. S2. Neurocognitive task performance in patients with PTSD.

Fig. S3. No relationship between the memory/connectivity-related phenotype and symptoms in patients with PTSD (studies 1 and 2).
Fig. S4. CONSORT diagram for the study 1 treatment component.
Fig. S5. Individual data points for verbal memory delayed recall, within-VAN fMRI connectivity, and percent change in CAPS total scores with treatment in study 1 participants completing the prolonged exposure psychotherapy arm.
Table S1. Demographic and clinical characteristics of participants in studies 1 and 2.
Table S2. Details of traumas for study 1 and 2 participants.
Table S3. Demographic and clinical characteristics of participants according to memory-based groupings.
Table S4. Demographic and clinical characteristics of participants for the intent-to-treat analysis of treatment outcome and its moderation by verbal memory impairment and within-VAN fMRI connectivity.
Table S5. Demographic and clinical characteristics of participants in study 2 who underwent spTMS/EEG.
References (*76*–*95*)

REFERENCES AND NOTES

1. APA, *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Press, ed. 4, 1994).
2. APA, *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Press, ed. 5, 2013).
3. I. R. Galatzer-Levy, R. A. Bryant, 636,120 ways to have posttraumatic stress disorder. *Perspect. Psychol. Sci.* **8**, 651–662 (2013).
4. C. W. Hoge, R. Yehuda, C. A. Castro, A. C. McFarlane, E. Vermetten, R. Jetly, K. C. Koenen, N. Greenberg, A. Y. Shalev, S. A. M. Rauch, C. R. Marmar, B. O. Rothbaum, Unintended consequences of changing the definition of posttraumatic stress disorder in *DSM-5*: Critique and call for action. *JAMA Psychiatry* **73**, 750–752 (2016).
5. D. J. Stein, K. A. McLaughlin, K. C. Koenen, L. Atwoli, M. J. Friedman, E. D. Hill, A. Maercker, M. Petukhova, V. Shahly, M. van Ommeren, J. Alonso, G. Borges, G. de Girolamo, P. de Jonge, K. Demyttenaere, S. Florescu, E. G. Karam, N. Kawakami, H. Matschinger, M. Okoliyski, J. Posada-Villa, K. M. Scott, M. C. Viana, R. C. Kessler, DSM-5 and ICD-11 definitions of posttraumatic stress disorder: Investigating "narrow" and "broad" approaches. *Depress. Anxiety* **31**, 494–505 (2014).
6. R. Rosell, T. G. Bivona, N. Karachaliou, Genetics and biomarkers in personalisation of lung cancer treatment. *Lancet* **382**, 720–731 (2013).
7. J. C. Scott, G. E. Matt, K. M. Wrocklage, C. Crnich, J. Jordan, S. M. Southwick, J. H. Krystal, B. C. Schweinsburg, A quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychol. Bull.* **141**, 105–140 (2015).
8. M. R. Milad, S. P. Orr, N. B. Lasko, Y. Chang, S. L. Rauch, R. K. Pitman, Presence and acquired origin of reduced recall for fear extinction in PTSD: Results of a twin study. *J. Psychiatr. Res.* **42**, 515–520 (2008).
9. M. M. Rigoli, G. R. Silva, F. R. Oliveira, G. K. Pergher, C. H. Kristensen, The role of memory in posttraumatic stress disorder: Implications for clinical practice. *Trends Psychiatry Psychother.* **38**, 119–127 (2016).
10. A. Etkin, A. Gyurak, R. O'Hara, A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues Clin. Neurosci.* **15**, 419–429 (2013).
11. M. J. Nijdam, G.-J. de Vries, B. P. R. Gersons, M. Olff, Response to psychotherapy for posttraumatic stress disorder. *J. Clin. Psychiatry* **76**, e1023–e1028 (2015).
12. B. O. Rothbaum, M. Davis, Applying learning principles to the treatment of post-trauma reactions. *Ann. N. Y. Acad. Sci.* **1008**, 112–121 (2003).
13. R. L. Aupperle, A. J. Melrose, M. B. Stein, M. P. Paulus, Executive function and PTSD: Disengaging from trauma. *Neuropharmacology* **62**, 686–694 (2012).
14. J. S. Siegel, L. E. Ramsey, A. Z. Snyder, N. V. Metcalf, R. V. Chacko, K. Weinberger, A. Baldassarre, C. D. Hacker, G. L. Shulman, M. Corbetta, Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E4367–E4376 (2016).
15. A. M. Schedlbauer, M. S. Copara, A. J. Watrous, A. D. Ekstrom, Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans. *Sci. Rep.* **4**, 6431 (2014).
16. H. Kim, Dissociating the roles of the default-mode, dorsal, and ventral networks in episodic memory retrieval. *NeuroImage* **50**, 1648–1657 (2010).
17. M. Y. Chan, D. C. Park, N. K. Savalia, S. E. Petersen, G. S. Wig, Decreased segregation of brain systems across the healthy adult life span. *Proc. Natl. Acad. Sci. U.S.A.* **111**, E4997–E5006 (2014).
18. J. R. Cohen, M. D'Esposito, The segregation and integration of distinct brain networks and their relationship to cognition. *J. Neurosci.* **36**, 12083–12094 (2016).
19. K. A. Tsvetanov, R. N. A. Henson, L. K. Tyler, A. Razi, L. Geerligs, T. E. Ham, J. B. Rowe, Cambridge Centre for Ageing and Neuroscience, Extrinsic and intrinsic brain network connectivity maintains cognition across the life span despite accelerated decay of regional brain activation. *J. Neurosci.* **36**, 3115–3126 (2016).
20. V. Menon, Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn. Sci.* **15**, 483–506 (2011).
21. R. L. Buckner, F. M. Krienen, B. T. T. Yeo, Opportunities and limitations of intrinsic functional connectivity MRI. *Nat. Neurosci.* **16**, 832–837 (2013).
22. A. C. Chen, A. Etkin, Hippocampal network connectivity and activation differentiates post-traumatic stress disorder from generalized anxiety disorder. *Neuropsychopharmacology* **38**, 1889–1898 (2013).
23. Y. Zhang, F. Liu, H. Chen, M. Li, X. Duan, B. Xie, H. Chen, Intranetwork and internetwork functional connectivity alterations in post-traumatic stress disorder. *J. Affect. Disord.* **187**, 114–121 (2015).
24. A. MacNamara, J. DiGangi, K. L. Phan, Aberrant spontaneous and task-dependent functional connections in the anxious brain. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* **1**, 278–287 (2016).
25. C. J. Keller, S. Bickel, L. Entz, I. Ulbert, M. P. Milham, C. Kelly, A. D. Mehta, Intrinsic functional architecture predicts electrically evoked responses in the human brain. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 10308–10313 (2011).
26. A. Etkin, Addressing the causality gap in human psychiatric neuroscience. *JAMA Psychiatry* **75**, 3–4 (2018).
27. M. Hallett, R. di Iorio, P. M. Rossini, J. E. Park, R. Chen, P. Celnik, A. P. Strafella, H. Matsumoto, Y. Ugawa, Contribution of transcranial magnetic stimulation to assessment of brain connectivity and networks. *Clin. Neurophysiol.* **128**, 2125–2139 (2017).
28. A. Giovanni, F. Capone, L. di Biase, F. Ferreri, L. Florio, A. Guerra, M. Marano, M. Paolucci, F. Ranieri, G. Salomone, M. Tombini, G. Thut, V. Di Lazzaro, Oscillatory activities in neurological disorders of elderly: Biomarkers to target for neuromodulation. *Front. Aging Neurosci.* **9**, 189 (2017).
29. S. Bestmann, E. Feredoes, Combined neurostimulation and neuroimaging in cognitive neuroscience: Past, present, and future. *Ann. N. Y. Acad. Sci.* **1296**, 11–30 (2013).
30. N. C. Rogasch, P. B. Fitzgerald, Assessing cortical network properties using TMS-EEG. *Hum. Brain Mapp.* **34**, 1652–1669 (2013).
31. W. Wu, C. J. Keller, N. C. Rogasch, P. Longwell, E. Shpigel, C. E. Rolle, A. Etkin, ARTIST: A fully automated artifact rejection algorithm for single-pulse TMS-EEG data. *Hum. Brain Mapp.* **39**, 1607–1625 (2018).
32. A. T. Hill, N. C. Rogasch, P. B. Fitzgerald, K. E. Hoy, TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in nonmotor brain regions. *Neurosci. Biobehav. Rev.* **64**, 175–184 (2016).
33. S. W. Chung, N. C. Rogasch, K. E. Hoy, P. B. Fitzgerald, Measuring brain stimulation induced changes in cortical properties using TMS-EEG. *Brain Stimul.* **8**, 1010–1020 (2015).
34. V. Kozyrev, U. T. Eysel, D. Jancke, Voltage-sensitive dye imaging of transcranial magnetic stimulation–induced intracortical dynamics. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 13553–13558 (2014).
35. I. Premoli, N. Castellanos, D. Rivolta, P. Belardinelli, R. Bajo, C. Zipser, S. Espenhahn, T. Heidegger, F. Müller-Dahlhaus, U. Ziemann, TMS-EEG signatures of GABAergic neurotransmission in the human cortex. *J. Neurosci.* **34**, 5603–5612 (2014).
36. I. Premoli, T. O. Bergmann, M. Fecchio, M. Rosanova, A. Biondi, P. Belardinelli, U. Ziemann, The impact of GABAergic drugs on TMS-induced brain oscillations in human motor cortex. *NeuroImage* **163**, 1–12 (2017).
37. A. Schaefer, R. Kong, E. M. Gordon, T. O. Laumann, X.-N. Zuo, A. J. Holmes, S. B. Eickhoff, B. T. T. Yeo, Local-global parcellation of the human cerebral cortex from intrinsic functional connectivity MRI. *Cereb. Cortex* **28**, 3095–3114 (2018).
38. B. T. Yeo, F. M. Krienen, J. Sepulcre, M. R. Sabuncu, D. Lashkari, M. Hollinshead, J. L. Roffman, J. W. Smoller, L. Zöllei, J. R. Polimeni, B. Fischl, H. Liu, R. L. Buckner, The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J. Neurophysiol.* **106**, 1125–1165 (2011).
39. IOM, *Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence* (The National Academies Press, 2008).
40. G. A. Fonzo, M. S. Goodkind, D. J. Oathes, Y. V. Zaiko, M. Harvey, K. K. Peng, M. E. Weiss, A. L. Thompson, S. E. Zack, S. E. Lindley, B. A. Arnow, B. Jo, J. J. Gross, B. O. Rothbaum, A. Etkin, PTSD psychotherapy outcome predicted by brain activation during emotional reactivity and regulation. *Am. J. Psychiatry* **174**, 1163–1174 (2017).
41. G. A. Fonzo, M. S. Goodkind, D. J. Oathes, Y. V. Zaiko, M. Harvey, K. K. Peng, M. E. Weiss, A. L. Thompson, S. E. Zack, C. E. Mills-Finnerty, B. M. Rosenberg, R. Edelstein, R. N. Wright, C. A. Kole, S. E. Lindley, B. A. Arnow, B. Jo, J. J. Gross, B. O. Rothbaum, A. Etkin, Selective effects of psychotherapy on frontopolar cortical function in PTSD. *Am. J. Psychiatry* **174**, 1175–1184 (2017).
42. F. W. Weathers, T. M. Keane, J. R. T. Davidson, Clinician-Administered PTSD Scale: A review of the first ten years of research. *Depress. Anxiety* **13**, 132–156 (2001).
43. A. C. Chen, D. J. Oathes, C. Chang, T. Bradley, Z.-W. Zhou, L. M. Williams, G. H. Glover, K. Deisseroth, A. Etkin, Causal interactions between frontoparietal central executive and default-mode networks in humans. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 19944–19949 (2013).
44. M. S. Hämäläinen, R. J. Ilmoniemi, Interpreting magnetic fields of the brain: Minimum norm estimates. *Med. Biol. Eng. Comput.* **32**, 35–42 (1994).

45. R. J. Fenster, L. A. M. Lebois, K. J. Ressler, J. Suh, Brain circuit dysfunction in post-traumatic stress disorder: From mouse to man. *Nat. Rev. Neurosci.* **19**, 535–551 (2018).
46. I. Liberzon, J. L. Abelson, Context processing and the neurobiology of post-traumatic stress disorder. *Neuron* **92**, 14–30 (2016).
47. T. J. Akiki, C. L. Averill, C. G. Abdallah, A network-based neurobiological model of PTSD: Evidence from structural and functional neuroimaging studies. *Curr. Psychiatry Rep.* **19**, 81 (2017).
48. R. K. Sripada, A. P. King, R. C. Welsh, S. N. Garfinkel, X. Wang, C. S. Sripada, I. Liberzon, Neural dysregulation in posttraumatic stress disorder: Evidence for disrupted equilibrium between salience and default mode brain networks. *Psychosom. Med.* **74**, 904–911 (2012).
49. Y. Zhang, B. Xie, H. Chen, M. Li, X. Guo, H. Chen, Disrupted resting-state insular subregions functional connectivity in post-traumatic stress disorder. *Medicine* **95**, e4083 (2016).
50. Y. Liu, L. Li, B. Li, N. Feng, L. Li, X. Zhang, H. Lu, H. Yin, Decreased triple network connectivity in patients with recent onset post-traumatic stress disorder after a single prolonged trauma exposure. *Sci. Rep.* **7**, 12625 (2017).
51. J. A. DiGangi, A. Tadayyon, D. A. Fitzgerald, C. A. Rabinak, A. Kennedy, H. Klumpp, S. A. M. Rauch, K. L. Phan, Reduced default mode network connectivity following combat trauma. *Neurosci. Lett.* **615**, 37–43 (2016).
52. M. Kennis, A. R. Rademaker, S. J. H. van Rooij, R. S. Kahn, E. Geuze, Resting state functional connectivity of the anterior cingulate cortex in veterans with and without post-traumatic stress disorder. *Hum. Brain Mapp.* **36**, 99–109 (2015).
53. T. Insel, B. Cuthbert, M. Garvey, R. Heinssen, D. S. Pine, K. Quinn, C. Sanislow, P. Wang, Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am. J. Psychiatry* **167**, 748–751 (2010).
54. H. Kim, Differential neural activity in the recognition of old versus new events: An activation likelihood estimation meta-analysis. *Hum. Brain Mapp.* **34**, 814–836 (2013).
55. J. M. Andreano, A. Touroutoglou, B. C. Dickerson, L. F. Barrett, Resting connectivity between salience nodes predicts recognition memory. *Soc. Cogn. Affect. Neurosci.* **12**, 948–955 (2017).
56. V. La Corte, M. Sperduti, C. Malherbe, F. Vialatte, S. Lion, T. Gallarda, C. Oppenheim, P. Piolino, Cognitive decline and reorganization of functional connectivity in healthy aging: The pivotal role of the salience network in the prediction of age and cognitive performances. *Front. Aging Neurosci.* **8**, 204 (2016).
57. F. W. Sun, M. R. Stepanovic, J. Andreano, L. F. Barrett, A. Touroutoglou, B. C. Dickerson, Youthful brains in older adults: Preserved neuroanatomy in the default mode and salience networks contributes to youthful memory in superaging. *J. Neurosci.* **36**, 9659–9668 (2016).
58. J. Downar, D. M. Blumberger, Z. J. Daskalakis, The neural crossroads of psychiatric illness: An emerging target for brain stimulation. *Trends Cogn. Sci.* **20**, 107–120 (2016).
59. V. Menon, L. Q. Uddin, Saliency, switching, attention, and control: A network model of insula function. *Brain Struct. Funct.* **214**, 655–667 (2010).
60. E. Aharonovich, D. S. Hasin, A. C. Brooks, X. Liu, A. Bisaga, E. V. Nunes, Cognitive deficits predict low treatment retention in cocaine-dependent patients. *Drug Alcohol Depend.* **81**, 313–322 (2006).
61. A. Faerden, E. A. Barrett, R. Nesvåg, S. Friis, A. Finset, S. R. Marder, J. Ventura, O. A. Andreassen, I. Agartz, I. Melle, Apathy, poor verbal memory, and male gender predict lower psychosocial functioning one year after the first treatment of psychosis. *Psychiatry Res.* **210**, 55–61 (2013).
62. T. Deckersbach, A. T. Peters, C. Shea, A. Gosai, J. P. Stange, A. D. Peckham, K. K. Ellard, M. W. Otto, S. L. Rauch, D. D. Dougherty, A. A. Nierenberg, Memory performance predicts response to psychotherapy for depression in bipolar disorder: A pilot randomized controlled trial with exploratory functional magnetic resonance imaging. *J. Affect. Disord.* **229**, 342–350 (2018).
63. I. E. Bauer, M. Hautzinger, T. D. Meyer, Memory performance predicts recurrence of mania in bipolar disorder following psychotherapy: A preliminary study. *J. Psychiatr. Res.* **84**, 207–213 (2017).
64. M. Goodkind, S. B. Eickhoff, D. J. Oathes, Y. Jiang, A. Chang, L. B. Jones-Hagata, B. N. Ortega, Y. V. Zaiko, E. L. Roach, M. S. Korgaonkar, S. M. Grieve, I. Galatzer-Levy, P. T. Fox, A. Etkin, Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* **72**, 305–315 (2015).
65. L. M. McTeague, J. Huemer, D. M. Carreon, Y. Jiang, S. B. Eickhoff, A. Etkin, Identification of common neural circuit disruptions in cognitive control across psychiatric disorders. *Am. J. Psychiatry* **174**, 676–685 (2017).
66. W. Klimesch, P. Sauseng, S. Hanslmayr, EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Res. Rev.* **53**, 63–88 (2007).
67. J. Dayan, G. Rauchs, B. Guillery-Girard, Rhythms dysregulation: A new perspective for understanding PTSD? *J. Physiol. Paris* **110**, 453–460 (2016).
68. V. Romei, V. Brodbeck, C. Michel, A. Amedi, A. Pascual-Leone, G. Thut, Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cereb. Cortex* **18**, 2010–2018 (2008).
69. R. S. Schluter, J. M. Jansen, R. J. van Holst, W. van den Brink, A. E. Goudriaan, Differential effects of left and right prefrontal high frequency rTMS on resting state fMRI in healthy individuals. *Brain Connect.* **8**, 60–67 (2017).
70. M. T. Berlim, F. Van Den Eynde, Repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex for treating posttraumatic stress disorder: An exploratory meta-analysis of randomized, double-blind, and sham-controlled trials. *Can. J. Psychiatr.* **59**, 487–496 (2014).
71. C. Clark, J. Cole, C. Winter, K. Williams, G. Grammer, A review of transcranial magnetic stimulation as a treatment for post-traumatic stress disorder. *Curr. Psychiatry Rep.* **17**, 83 (2015).
72. P. S. Boggio, M. Rocha, M. O. Oliveira, S. Fecteau, R. B. Cohen, C. Campanhã, E. Ferreira-Santos, A. Meleiro, F. Corchs, S. Zaghi, A. Pascual-Leone, F. Fregni, Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *J. Clin. Psychiatry* **71**, 992–999 (2010).
73. H. Cohen, Z. Kaplan, M. Kotler, I. Kouperman, R. Moisa, N. Grisaru, Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: A double-blind, placebo-controlled study. *Am. J. Psychiatry* **161**, 515–524 (2004).
74. M. Sandrini, S. F. Cappa, S. Rossi, P. M. Rossini, C. Miniussi, The role of prefrontal cortex in verbal episodic memory: rTMS evidence. *J. Cogn. Neurosci.* **15**, 855–861 (2003).
75. P. Turriziani, D. Smirni, M. Oliveri, C. Semenza, L. Cipolotti, The role of the prefrontal cortex in familiarity and recollection processes during verbal and nonverbal recognition memory: An rTMS study. *NeuroImage* **52**, 348–357 (2010).
76. D. D. Blake, F. W. Weathers, L. M. Nagy, D. G. Kaloupek, F. D. Gusman, D. S. Charney, T. M. Keane, The development of a Clinician-Administered PTSD Scale. *J. Trauma. Stress* **8**, 75–90 (1995).
77. M. B. First, A practical prototypic system for psychiatric diagnosis: The ICD-11 clinical descriptions and diagnostic guidelines. *World Psychiatry* **11**, 24–25 (2012).
78. F. Weathers, B. Litz, D. Herman, J. Huska, T. Keane, paper presented at the International Society For Traumatic Stress Studies, San Antonio, TX, 1993.
79. A. T. Beck, R. A. Steer, G. K. Brown, *Manual for Beck Depression Inventory-II* (Psychological Corporation, 1996).
80. E. B. Foa, E. A. Hembree, B. O. Rothbaum, *Prolonged Exposure Therapy for PTSD* (Oxford Univ. Press, ed. 1, 2007).
81. S. M. Skevington, M. Lotfy, K. A. O'Connell, WHOQOL Group, The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. *Qual. Life Res.* **13**, 299–310 (2004).
82. D. Wechsler, *Wechsler Abbreviated Scale of Intelligence* (The Psychological Corporation: Harcourt Brace & Company, 1999).
83. J. D. Corrigan, J. Bogner, Initial reliability and validity of the Ohio State University TBI identification method. *J. Head Trauma Rehabil.* **22**, 318–329 (2007).
84. S. M. Silverstein, S. Berten, P. Olson, R. Paul, L. M. Williams, N. Cooper, E. Gordon, Development and validation of a World Wide Web–based neurocognitive assessment battery: WebNeuro. *Behav. Res. Methods* **39**, 940–949 (2007).
85. R. H. Paul, J. Lawrence, L. M. Williams, C. C. Richard, N. Cooper, E. Gordon, Preliminary validity of "INTEGNEURO": A new computerized battery of neurocognitive tests. *Int. J. Neurosci.* **115**, 1549–1567 (2009).
86. A. Etkin, B. Patenaude, Y. J. C. Song, T. Usherwood, W. Rekshan, A. F. Schatzberg, A. J. Rush, L. M. Williams, A cognitive-emotional biomarker for predicting remission with antidepressant medications: A report from the iSPOT-D trial. *Neuropsychopharmacology* **40**, 1332–1342 (2015).
87. G. H. Glover, S. Lai, Self-navigated spiral fMRI: Interleaved versus single shot. *Magn. Reson. Med.* **39**, 361–368 (1998).
88. D.-H. Kim, E. Adalsteinsson, G. H. Glover, D. M. Spielman, Regularized higher-order in vivo shimming. *Magn. Reson. Med.* **48**, 715–722 (2002).
89. G. H. Glover, T.-Q. Li, D. Ress, Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magn. Reson. Med.* **44**, 162–167 (2000).
90. L. Friedman, G. H. Glover, Report on a multicenter fMRI quality assurance protocol. *J. Magn. Reson. Imaging* **23**, 827–839 (2006).
91. G. H. Glover, B. A. Mueller, J. A. Turner, T. G. M. van Erp, T. T. Liu, D. N. Greve, J. T. Voyvodic, J. Rasmussen, G. G. Brown, D. B. Keator, V. D. Calhoun, H. J. Lee, J. M. Ford, D. H. Mathalon, M. Diaz, D. S. O'Leary, S. Gadde, A. Preda, K. O. Lim, C. G. Wible, H. S. Stern, A. Belger, G. McCarthy, B. Ozyurt, S. G. Potkin, Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. *J. Magn. Reson. Imaging* **36**, 39–54 (2012).

92. W. R. Shirer, S. Ryali, E. Rykhlevskaia, V. Menon, M. D. Greicius, Decoding subject-driven cognitive states with whole-brain connectivity patterns. *Cereb. Cortex* **22**, 158–165 (2012).
93. F. Tadel, S. Baillet, J. C. Mosher, D. Pantazis, R. M. Leahy, Brainstorm: A user-friendly application for MEG/EEG analysis. *Comput. Intell. Neurosci.* **2011**, 879716 (2011).
94. A. Gramfort, T. Papadopoulo, E. Olivi, M. Clerc, OpenMEEG: Opensource software for quasistatic bioelectromagnetics. *Biomed. Eng. Online* **9**, 45 (2010).
95. B. Fischl, M. I. Sereno, A. M. Dale, Cortical surface–based analysis II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage* **9**, 195–207 (1999).

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Author contributions: A.E. conceived the study, conducted the analyses, wrote the paper, and provided funding. All study 1 data were collected by Y.V.Z., K.K.P., G.A.F., M.S.G., E.W., D.J.O., S.E.L., and B.A.A. Study 1 treatment was administered by A.T. and S.Z. and supervised by B.O.R. All study 2 data were collected by E.S., P.L., R.T.T., B.G., R.E., J.C., I.A., R.H., S.M., K.D., S.H.B., F.E.B., A.G., J.A., J.N., and D.A.-A. fMRI data from both studies were analyzed by A.M.-K., G.A.F., J. Huemer, B.P., and P.E.V. EEG data were analyzed by W.W. and C.J.K. Clinical outcome data were analyzed by G.A.F., J.R., J.R.-C., N.C., J. Hallmayer, and S.F. B.O.R., C.R.M., E.T.B., and R.O. contributed to data analysis and interpretation, as well as manuscript preparation. C.R.M. provided additional funding. **Competing interests:** E.T.B. is employed 50% by the University of Cambridge and 50% by GlaxoSmithKline (GSK) in which he holds stock. E.T.B. is a paid editor at *Biological Psychiatry* and received royalties from Academic Press and Short Books. A.E. has consulted for and owns equity in Akili Interactive and Mindstrong Health, and has consulted for Brainsway, Cervel, Takaeda, Posit, Acadia, Otsuka, Lundbeck, and Janssen. A.E. received a grant from Brain Resource and is a paid editor at *Neuropsychopharmacology*. B.O.R. receives royalties from Oxford University Press, Guilford, APPI, and Emory University and received advisory board payments from Genentech, Jazz Pharmaceuticals, Nobilis Therapeutics, Neuronetics, and Aptinyx. J.R. holds stock in Siemens Healthcare AG. F.E.B. has received research funding from Siemens Healthcare and General Electric Healthcare. S.H.B. owns equity in Magnitend. J.R. received a portion of his salary from Siemens Healthcare, in which he also holds stock. S.H.B. has previously received research funding from Merck Sereno. C.R.M. has served as a fellow for the George W. Bush Institute and has consulted for and has equity in Receptor Life Sciences Inc. A.E. and C.R.M. have a pending patent (WO2017172487A1) entitled "Detecting or treating post-traumatic stress syndrome." **Data and materials availability:** All data associated with this study are in the paper or Supplementary Materials. Full datasets for studies 1 and 2 are managed under Data Use Agreements administered by Stanford University and Stanford University/New York University, respectively.

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Using fMRI connectivity to define a treatment-resistant form of post-traumatic stress disorder

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PTSD's secrets hidden in a VAN

Post-traumatic stress disorder (PTSD) is a severe psychiatric illness. Psychotherapy is the only effective treatment for PTSD but only works in a portion of patients. Etkin and colleagues now report a neuroimaging and behavioral signature in a subgroup of PTSD patients who failed to respond to psychotherapy. This signature was associated with impairments in fMRI connectivity in the brain's ventral attention network and a deficit on a word list learning task. Use of noninvasive brain stimulation in combination with neuroimaging identified a brain location in which network connectivity correlated with the effects of stimulation. This work may help to define a target for future noninvasive brain stimulation approaches for treating patients with PTSD who are refractory to psychotherapy.