springs (*15*) but are higher than steady-state H_2 concentrations in lake and river sediments (*16*). The lowest concentration threshold of H_2 utilization by *N. moscoviensis* was not determined here, but as shown recently, the high substrate affinity of group 2a [NiFe] hydrogenases of terrestrial actinomycetes allows even the scavenging of tropospheric H_2 (*11*).

Phylogenetically, Hup of *N. moscoviensis* clusters with group 2a [NiFe] hydrogenases of *Cyanobacteria* and nonphototrophic *Alpha-* and *Gammaproteobacteria* (fig. S5), although *Nitrospira* belong to a distinct bacterial phylum (*7*). Thus, the *hup* locus was likely acquired by *Nitrospira* through lateral gene transfer. Whether the absence of *hup* in "*Ca.* N. defluvii" results from secondary loss of the hydrogenase locus in this organism, or whether *hup* was laterally acquired only by *Nitrospira* lineage II (including *N. moscoviensis*), will remain unclear until genomic sequences of other *Nitrospira* become available.

Aerobic H_2 oxidation will be ecologically advantageous for NOB, as the amount of energy that can be gained ($\Delta G^{o'}$ = −237 kJ mol^{-1} H_2) is much larger than for nitrite oxidation ($\Delta G^{o'}$ = −74 kJ mol^{-1} NO_2^-). Low-potential electrons from H_2 also reduce the energy requirement for reverse electron transport, which is needed to fix CO_2 with nitrite as the electron donor. Addition of nitrite to H_2-oxidizing cultures, which were incubated with low levels of H_2, revealed that *N. moscoviensis* can oxidize both substrates simultaneously (fig. S4B). A lifestyle in which H_2 and O_2 are used as substrates, exclusively or in addition to aerobic nitrite oxidation, would increase the competitiveness of NOB in habitats where microbial processes provide H_2, such as in cyanobacterial mats, at oxic-anoxic interfaces, and in hypoxic pockets of soils, sediments, or biofilms, or at hydrothermal sites where upwelling fluids contain H_2 (*17*). Indeed, *Nitrospira* have been found in low-oxygen niches such as the basal zones of biofilms (*18*); in marine sediments, subsurface aquifers, and rice paddies; and also in deep-sea hydrothermal field sediment and hot springs (*19*, *20*). In such habitats, aerobic H_2 oxidation may provide extra energy and make (at least some) NOB independent of nitrite supplied by ammonia oxidizers or nitrate reducers.

Loci encoding putative hydrogenases of different types occur also in the genomes of NOB other than *Nitrospira*, indicating that H_2 utilization may be a widespread feature of these organisms. The marine nitrite oxidizer *Nitrospina gracilis* (phylum *Nitrospinae*) possesses the genes of a cytoplasmic group 3b bidirectional [NiFe] hydrogenase (*21*). A group 5 uptake [NiFe] hydrogenase was identified in the genome of *Nitrolancea hollandica* (phylum *Chloroflexi*), a nitrite-oxidizing bacterium isolated from activated sludge (*22*) (fig. S5).

The ability to switch their lifestyle would enable NOB to colonize new ecological niches and may stabilize nitrification by maintaining NOB populations during periods of nitrite depletion. The aerobic growth on H_2 of *N. moscoviensis* suggests that the contribution of NOB to chemolithoautotrophic CO_2 fixation in microbial communities is potentially greater than expected from the low energy yield of nitrite oxidation (*23*). Thus, a reassessment of their functional roles will be essential to more fully understand the ecology of NOB and to determine the impact of these almost ubiquitous microorganisms on the biogeochemical cycles of nitrogen and carbon in natural and engineered ecosystems.

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SUPPLEMENTARY MATERIALS

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MEMORY ENHANCEMENT

Targeted enhancement of cortical-hippocampal brain networks and associative memory

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The influential notion that the hippocampus supports associative memory by interacting with functionally distinct and distributed brain regions has not been directly tested in humans. We therefore used targeted noninvasive electromagnetic stimulation to modulate human cortical-hippocampal networks and tested effects of this manipulation on memory. Multiple-session stimulation increased functional connectivity among distributed cortical-hippocampal network regions and concomitantly improved associative memory performance. These alterations involved localized long-term plasticity because increases were highly selective to the targeted brain regions, and enhancements of connectivity and associative memory persisted for ~24 hours after stimulation. Targeted cortical-hippocampal networks can thus be enhanced noninvasively, demonstrating their role in associative memory.

The hippocampus is necessary for associative (relational/declarative) memory (*1*, *2*). It is a neuroanatomical convergence zone for highly processed sensory information regarding qualities of objects and contexts and therefore could serve as a "hub" to support binding of information from distinct processing modules into associative memories (*1*–*4*). However, hippocampal interactivity with distributed brain regions has yet to be demonstrated as necessary for associative memory in humans. Few experiments have used functional magnetic

resonance imaging (fMRI) to identify hippocampal interactions with distributed cortical regions that are correlated with associative memory (*5*). Although brain-lesion studies have shown the necessity of an intact hippocampus for associative memory, they cannot readily demonstrate the necessity of hippocampal interactivity with other regions.

We therefore developed methods to modulate cortical-hippocampal brain networks in healthy adults (n = 16 subjects) in order to test their role in associative memory (*6*). We focused modulatory stimulation on the lateral parietal cortex component of a well-characterized cortical-hippocampal network (*4*) on the basis of hypothesized interactions between hippocampus and lateral parietal cortex in memory (*7*) as well as robust functional connectivity between these regions (*8*), which is likely mediated by lateral parietal projections to retrosplenial and parahippocampal cortex (*9*, *10*). We defined a target within the left hippocampus for each subject and used resting-state fMRI to identify a subject-specific left lateral parietal location that demonstrated high functional connectivity with the hippocampal target (Fig. 1A and fig. S1) (*6*). Noninvasive high-frequency repetitive transcranial magnetic stimulation (rTMS) (*6*) was delivered to the parietal location for 5 consecutive days on the basis of evidence that rTMS can induce changes in connectivity within stimulated networks (*11*, *12*) and that such effects can increase over multiple-day stimulation sessions (*13*).

We measured changes in cortical-hippocampal network fMRI connectivity and associative memory using pretreatment (baseline), midtreatment (Mid-Tx), and posttreatment (Post-Tx) assessments (Fig. 1B). Stimulation effects were measured relative to a sham-control condition involving the same parameters, but at subthreshold intensity for neural stimulation (*6*). Compared with sham, Post-Tx resting-state fMRI connectivity was significantly greater than that of the baseline in four regions, including (i) the precuneus/retrosplenial cortex, (ii) the fusiform/parahippocampal cortex, (iii) the superior parietal cortex, and (iv) the left lateral parietal cortex (Fig. 2A and table S1). These stimulation-responsive regions include elements of well-characterized hippocampal intrinsic connectivity networks (*8*) hypothesized to interact with the hippocampus to support associative memory (*4*, *14*, *15*), including the approximate location of lateral parietal cortex that was stimulated.

Increased fMRI connectivity was highly specific to the individual hippocampal target selected for each subject. By assessing Post-Tx versus baseline connectivity changes due to stimulation (relative to sham) along the anterior-posterior axis of the targeted hippocampus (*6*), we noted a rapid decline in stimulation effects on fMRI connectivity with increasing distance from the target (Fig. 2B). At average distances of 1.5 and 3.0 mm from the target in either direction, the T values of the change in whole-brain (global) connectivity from baseline were ~48 and ~17% of the connectivity change for the target, respectively, and were not statistically significant (Fig. 2B). Stimulation-induced changes in connectivity of the hippocampal target with the four stimulation-responsive regions were similarly selective (Fig. 2C). We found no reliable changes for right hippocampal locations that mirrored left hippocampal target locations and no reliable changes for the left hippocampus treated as a unit (*6*).

Stimulation also increased interconnectivity among stimulation-responsive regions. A correlation-weighted fMRI connectivity matrix formed from locations with at least minimal stimulation-related change in connectivity with the hippocampal target (*6*) indicated robust increases in regional interconnectivity (Fig. 3A and fig. S2). To test whether increases in regional interconnectivity were associated with the degree to which an anatomically defined region was part of the hippocampal resting-state network, the matrix was sorted by each region's baseline fMRI connectivity with the hippocampal target. The number of significant interregional links [$P < 0.05$, false discovery rate (FDR)–corrected] was significantly correlated with baseline fMRI connectivity with the hippocampal target [$R^2_{(adj)} = 0.27$, df = 69, $P < 0.0001$] (Fig. 3B). Lateral parietal cortex stimulation thus increased fMRI interconnectivity to a greater extent among regions that were more versus less strongly within baseline cortical-hippocampal networks.

We next tested for corresponding changes in associative memory. Stimulation increased associative memory performance (face-cued word recall) (Fig. 4A) from baseline to Post-Tx [$T_{(15)} = 3.05$, $P = 0.008$], whereas sham treatment caused no significant performance change [$T_{(15)} = 0.82$, $P = 0.425$] (Fig. 4B). The increase in performance for baseline to Post-Tx was greater for stimulation than for sham [$T_{(15)} = 2.21$, $P = 0.043$]. Using regionally constrained correlation analysis (*6*), we found that baseline to Post-Tx changes in performance because of stimulation (relative to sham) correlated significantly with corresponding changes in fMRI connectivity with the hippocampal target for a portion of treatment-responsive brain regions (Fig. 4, C and D). Subjects demonstrating larger stimulation-induced connectivity changes for these regions exhibited greater memory improvements. Targeted analysis of the left lateral parietal cortex identified the same relationship for a portion of this region (*6*), but at subthreshold size for the primary analysis. We administered a battery of additional cognitive tests (*6*) to assess selectivity of stimulation effects for associative memory. No such changes were observed on any of these tests (P = 0.33 to 0.99 for all pairwise Post-Tx versus baseline comparisons performed separately for each test).

A control experiment tested whether aforementioned stimulation effects could have resulted from nonspecific influences of above-threshold brain stimulation rather than targeted stimulation of cortical-hippocampal networks via lateral parietal cortex. Subjects receiving the same stimulation

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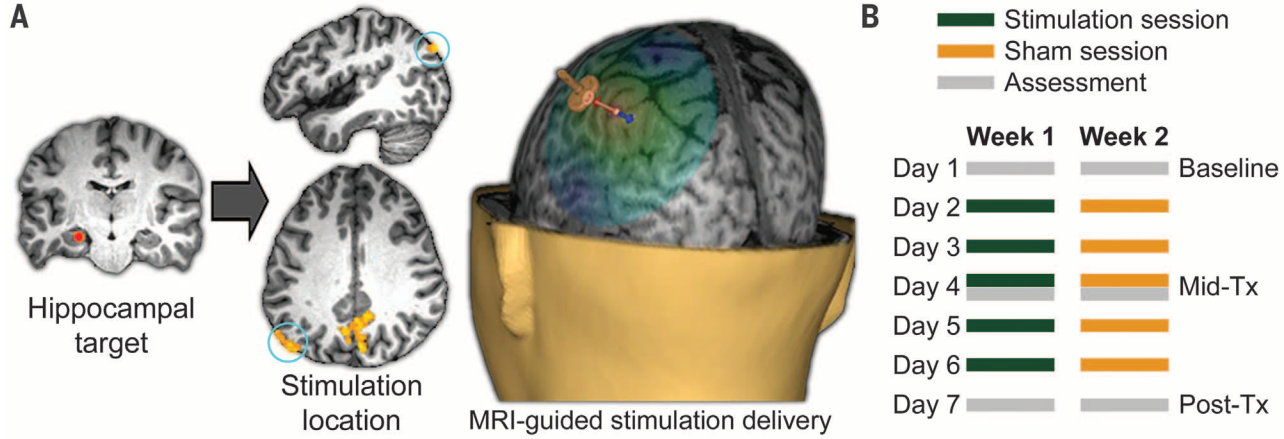

Fig. 1. Targeted cortical-hippocampal network stimulation. (**A**) For each subject, a parietal stimulation location was selected on the basis of maximum local fMRI connectivity with a hippocampal target, and stimulation was applied to this location under MRI guidance (*6*). (**B**) Timing of assessments and stimulation sessions for the stimulation and sham weeks, with week order counterbalanced (*6*). Post-Tx assessment was ~24 hours after the final stimulation session.

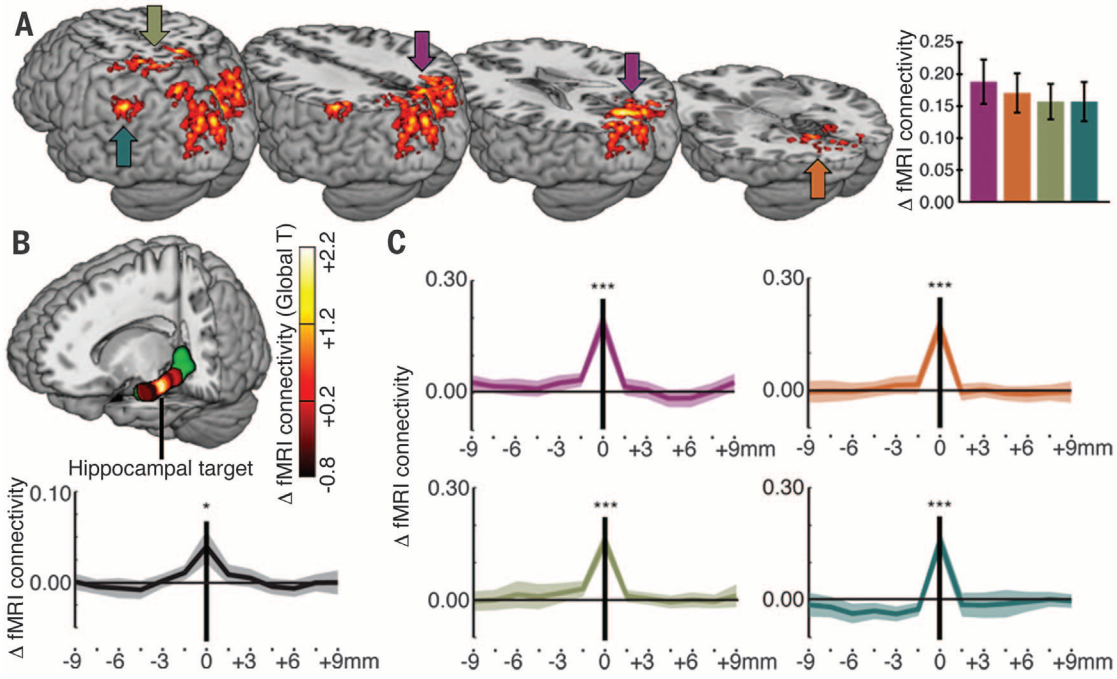

Fig. 2. Stimulation-induced fMRI connectivity increases selectivity to hippocampal targets. (**A**) Regions showing significant change in fMRI connectivity with the hippocampal target (Post-Tx versus baseline for stimulation compared with sham) (*6*) shown on a template brain viewed from the back left. (**B**) Stimulation-induced changes in whole-brain fMRI connectivity (*T* values of differences in global average connectivity) are colorized for the target and other locations along the anterior-posterior axis of the left hippocampus (which is displayed in green on the rendered brain) (*6*). The plot shows changes in fMRI connectivity values for the subject-specific hippocampal target (0 mm) and for 1.5-mm steps along the anterior-posterior hippocampal axis (negative values indicate anterior to the target). (**C**) The same change values are plotted for the four stimulation-responsive regions shown in (A). *$P < 0.05$ versus zero; ***$P < 0.001$ versus zero. Error bars and line shading indicate SEM.

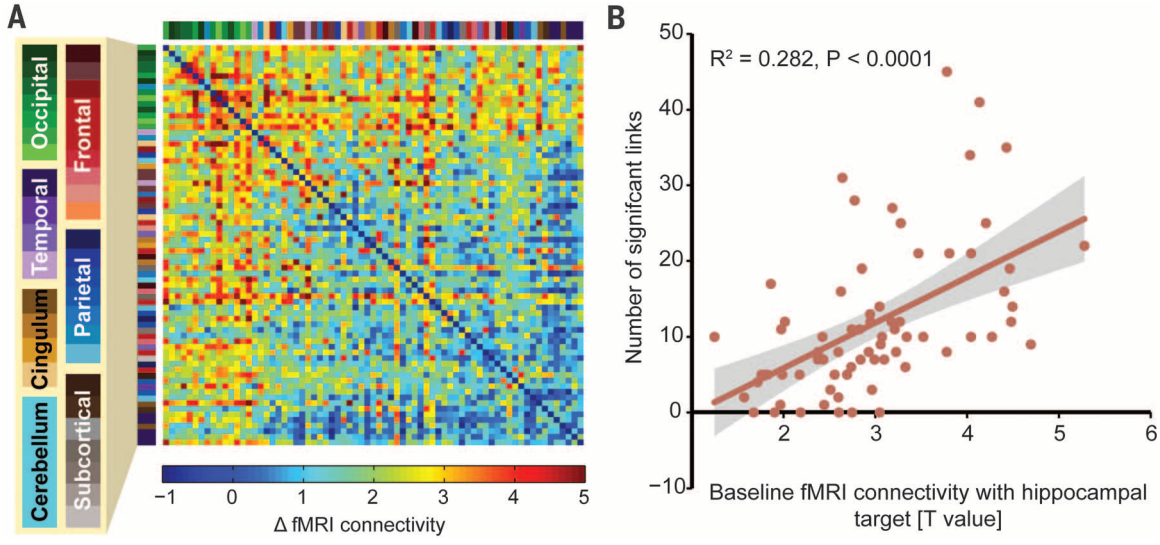

Fig. 3. Stimulation-induced fMRI regional interconnectivity scales with baseline connectivity with hippocampal targets. (**A**) Coloration indicates the effect of stimulation (Post-Tx versus baseline for stimulation relative to sham, *T* value) on fMRI connectivity among stimulation-responsive regions (*6*). Regions are sorted by baseline fMRI connectivity with hippocampal targets (top rows and left columns are highest). Region labels are colorized and expanded in fig. S2. (**B**) The degree of interconnectivity for a region (number of significant links with other regions surviving; $P < 0.05$ with FDR correction) correlated with the strength of baseline connectivity with hippocampal targets for the region. Shading indicates 95% confidence interval.

protocol to a primary motor cortex region that is not reliably included in cortical-hippocampal networks did not exhibit any reliable changes in cortical-hippocampal connectivity or associative memory performance (fig. S4) (*6*).

These findings confirm the proposed role of cortical-hippocampal interactions in associative memory (*1*–*4*). Enhanced memory via neurosurgical (invasive) stimulation of entorhinal cortex (the primary input to hippocampus) has been reported (*16*), although effects were specific to the material studied during stimulation, and network-level function was not tested. Our findings thus demonstrate persistent memory changes and substantiate fMRI correlative evidence for cortical-hippocampal network involvement in associative memory (*5*).

Although effects of noninvasive stimulation on neurophysiology are not fully characterized, findings that resemble *N*-methyl-D-aspartate–receptor–dependent long-term potentiation (LTP) of hippocampal circuits (*17*, *18*) have been observed by using rTMS parameters similar to those reported here (*13*, *19*). fMRI connectivity changes due to stimulation could reflect LTP-like effects throughout cortical-hippocampal networks (*20*). Indeed, changes were evident ~24 hours after stimulation (Post-Tx), indicating long-term plasticity. Alternatively, nonspecific physiological effects [such as neuromodulatory, neurochemical,

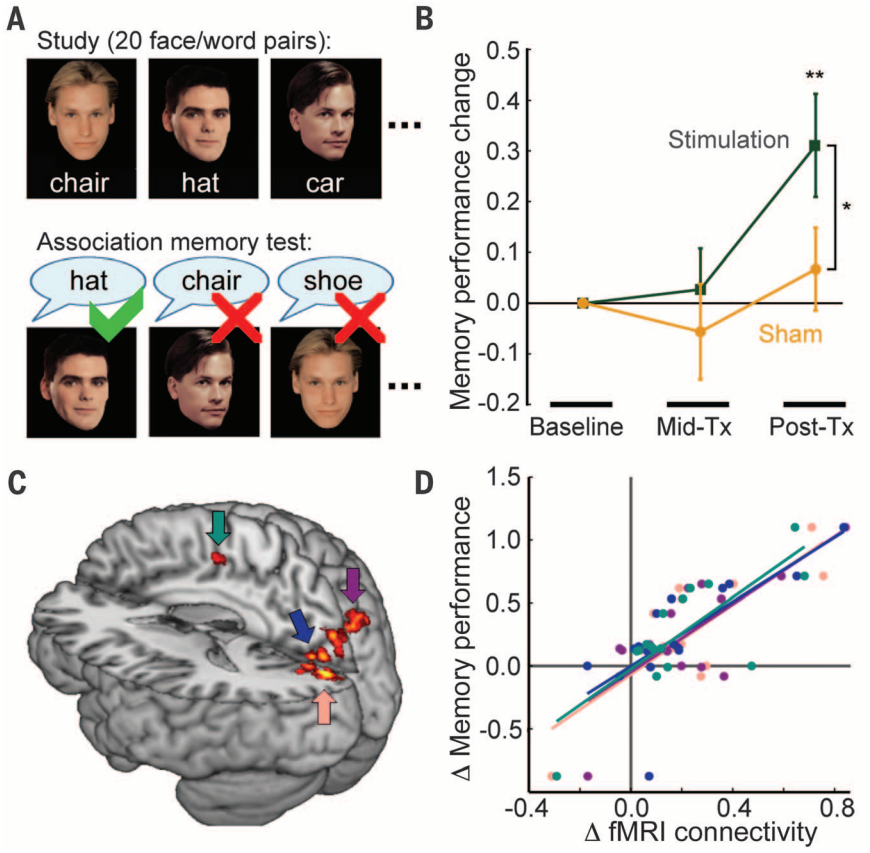

Fig. 4. Stimulation-induced associative memory enhancement. (**A**) Structure of the face-cued word recall test of associative memory, involving recall during test of words arbitrarily paired with faces at study (*6*). Different word-face pairs were used for each assessment. (**B**) Stimulation increased memory, whereas sham did not. Mean performance change for each assessment is expressed as a proportion of baseline. (**C**) Subset of treatment-responsive regions that demonstrate significant correlation between stimulation-induced fMRI connectivity change with hippocampal targets and memory improvement. (**D**) Plot of memory-improvement values (Post-Tx versus baseline for treatment relative to sham) and corresponding values of fMRI connectivity increase with respect to hippocampal targets from each subject for the four areas indicated in (C). *P < 0.05 stimulation versus sham; **P < 0.01 versus zero.

or other more global processes (*13*, *19*)] and/or psychological factors (such as memory recall during fMRI, effort during memory testing, or placebo effects) could have changed connectivity and memory. However, fMRI connectivity changes were remarkably specific for hippocampal targets (Fig. 2, B and C), were significantly correlated with associative memory improvements (Fig. 4, C and D), and did not occur when a motor-cortex region distinct from cortical-hippocampal networks was stimulated in the control experiment, providing strong evidence against these possible nonspecific influences. Additional research is required to determine whether other cortical-hippocampal networks can be modulated with similarly high specificity and to identify neurophysiological mechanisms.

Although memory-related processing by cortical-hippocampal networks is relevant for many cognitive domains (such as attention, language, and executive control) (*21*, *22*), there were no stimulation effects on standardized measures of those domains. However, the instruments were not designed to provide specificity to cortical-hippocampal network influences (*6*). Specialized tests could potentially be used to identify broader effects of stimulation on cognition. Stimulation-responsive regions and the hippocampus are elements of a network that shows high interconnectivity even during periods of quiescence [the "default-mode" network (*23*)], further underscoring the potential broader influences of stimulation-induced changes on cognition.

After hippocampal damage, residual tissue might retain function (*24*) and assume functions previously supported by damaged tissue (*25*). Further, cortical-hippocampal network dysfunction has been implicated in various memory disorders (*26*). The methods reported here potentially could be modified to treat memory disorders by targeting residual hippocampal tissue to improve impaired cortical-hippocampal networks.

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SUPPLEMENTARY MATERIALS

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