nature neuroscience

Article

https://doi.org/10.1038/s41593-023-01324-5

# Augmenting hippocampal–prefrontal neuronal synchrony during sleep enhances memory consolidation in humans

In the format provided by the authors and unedited

| ID | Age | Gender | Handedness | Seizure Onset | FDG-PET | MRI |
|---|---|---|---|---|---|---|
| **1** | 23 | W | R | Broad right fronto-temporal onset | RPHG and R-parietal hypometabolism | Normal |
| **2** | 33 | M | R | R-frontal lobe and R preSMA | Normal | Normal |
| **3** | 33 | W | R | Left mesial temporal lobe | LTL hypometabolism | Normal |
| **4** | 38 | M | L | R mesial temporal lobe | R-temporal and R-parietal hypometabolism | Structural abnormalities right superior parietal and temporal lobe |
| **5** | 47 | W | R | LITG | LTL hypometabolism | LTL structural abnormality |
| 6 | 34 | W | R | Right Occipital | R basal occipital and R-PNH hypometabolism | Bilateral PNH |
| **7** | 36 | M | R | R temporo-occipital | Normal | Normal |
| **8** | 34 | W | R | Bilateral temporal | Bilateral MTL hypometabolism | Bilateral hippocampal sclerosis |
| **9** | 29 | W | R | Bilateral temporal (R>L) | R-temporal hypometabolism | Normal |
| **10** | 44 | M | R | Broad R frontal and R parietal lobes, and RINS | R-parieto-occipital hypometabolism | Normal |
| **11** | 35 | M | R | LFSG and LINS | LTL hypometabolism | Normal |
| **12** | 31 | W | R | L SMA | Normal | Normal |
| **13** | 25 | W | R | R MTL | LTL hypometabolism | L-hippocampal sclerosis |
| **14** | 32 | M | R | Bilateral MTL | LTL hypometabolism | L-hippocampal sclerosis |
| **15** | 22 | W | R | Mesial LSTG, mesial LHSG | Normal | Normal |
| **16** | 25 | W | R | Bilateral temporal lobes | Left temporal hypometabolism | Subependymal gray matter heterotopia (periventricular) |
| **17** | 32 | W | R | Left temporal lobe | Normal | L-hippocampal sclerosis |
| **18** | 19 | M | R | Left frontal (heterotopia) | Left frontal | Left frontal heterotopia |

**Supplementary Table 1. Patient demographics and clinical information.** Columns: (i) Participant id, (ii) Age, (iii) Gender (self reported, M/W = Man/Woman), (iv) Handedness (R/L = Right/Left), (v) Seizure onset area; (vi) Imaging FDG-PET and (vii) MRI. Abbreviations: R = right hemisphere, L = Left hemisphere; AFSG – anterior fusiform gyrus, INS – insula, TL – temporal lobe, STG – superior temporal gyrus, HSG – Heschel's gyrus, MTL – medial temporal lobe, PHG –parahippocampal gyrus, PNH – periventricular nodular heterotopia, SMA – supplementary motor area.

| | | (iii) REAL-TIME CLOSED LOOP SESSION (CL) | | | | | | | | | | | (iv) UNDISTURBED SESSION (UD) | | | | | | | | | (v) Medications | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (i) Participant id | (ii) ORDER (CL = closed loop stimulation; UD = Undisturbed night; X Days delay between sessions) | 1. Vigilance test (PRE) | 2. Learning and baseline testing | 3. Image set version | 4. Sleep | 5. Stimulation session start | 6. Stim Duration (mins) | 7. Wake up | 8. Post sleep testing | 9. Vigilance test (POST) | 10. Time elapsed (min) - Evening learning to morning testing | 11. Time Elapsed (min) - waking up to morning testing | 1. Vigilance test (PRE) | 2. Learning and baseline testing | 3. Image set version | 4. Sleep | 5. Wake | 6. Post sleep testing | 7. Vigilance test (POST) | 8. Time elapsed (min) - Evening learning to morning testing | 9. Time Elapsed (min) - waking up to morning testing | 1. CL night | 2. UD night |
| **1*** | UD-CL (2D) | 10:15PM | 10:26PM | 2 | 11:45PM | 12:15AM | 90 | 7:43AM | 8:10 AM | 8:30AM | 584 | 27 | 11:00 PM | 11:30PM | 1 | 2:10AM | 8:10AM | 8:25AM | 8:35AM | 536 | 15 | Vimpat, Brivaracetam | Vimpat , Brivaracetam, Oxycodone |
| **2** | UD-CL (1D) | 9:05PM | 9:10PM | 1 | 11:45PM | 12:09AM | 90 | 5:15 AM | 6:10 AM | 6:30AM | 541 | 55 | 3:10PM | 3:31PM | 2 | 3:45PM | 5:30PM | 5:40PM | 5:56PM | 129 | 10 | Vimpat, Keppra | |
| **3** | UD-CL (3D) | 8:30PM | 8:45PM | 1 | 11:00 PM | 11:30PM | 120 | 5:50AM | 6:40 AM | 6:50AM | 607 | 50 | 8:45PM | 9:04PM | 2 | 10:00PM | 5:30 AM | 6:34AM | N/A | 570 | 65 | Oxcarbazepine | Onfi, Oxcarbazepine |
| **4** | CL-UD (1D) | 10PM | 11:15PM | 2 | 12:20AM | 2:00:00AM | 90 | 7:55AM | 8:45 AM | 8:55AM | 570 | 50 | 9:00 PM | 8:38PM | 3 | 2:30AM | 8:50AM | 9:15AM | N/A | 757 | 25 | Onfi, Keppra, Lamotrigine, Benadryl | Lamotrigine, Benadryl |
| **5** | CL-UD (5D) | 8:50PM | 9:15PM | 1 | 11:00 PM | 12:05AM | 90 | 9:00AM | 9:30 AM | N/A | 763 | 30 | N/A | 10:07PM | 2 | 10:30PM | 7:00AM | 10:20AM | N/A | 733 | 200 | | Dilantin, Oxycodone |
| **7** | CL-UD (3D) | 8:45PM | 9:10PM | 1 | 11:00 PM | 11:35PM | 150 | 6:15AM | 7:15 AM | 7:25AM | 605 | 60 | 8:10PM | 8:30PM | 3 | 10:00PM | 6:45AM | 7:20AM | 7:30AM | 650 | 35 | | |
| **8** | CL-UD (1D) | N/A | 8:40PM | 2 | 10:00 PM | 10:50PM | 160 | 8:10AM | 9:05 AM | N/A | 745 | 55 | 8:35PM | 8:55PM | 1 | 10:15PM | 9:15AM | 9:50AM | 10AM | 775 | 35 | Aptiom, Brivaracetam | |
| **9** | CL-UD (1D) | 9PM | 9:20PM | 2 | 10:00 PM | 11:00 PM | 120 | 8:30AM | 8:55 AM | 9:05AM | 695 | 25 | 7:30PM | 7:50PM | 1 | 10PM | 8:30AM | 9:30AM | 10:10AM | 820 | 60 | Oxcarbazepine | |
| **10** | UD**-CL-UD (1D) | 9:30PM | 9:45PM | 1 | 12:00 AM | 12:25AM | 100 | 7:15AM | 8:00 AM | 8:20AM | 615 | 45 | 9:05 PM | 9:10PM | 3 | 11:00 PM | 6:30AM | 8:30 AM | 8:50AM | 680 | 120 | Vimpat, Lamotrigine, Oxycodone | Vimpat, Lamotrigine, Oxycodone |
| **12** | CL-UD (4D) | 9:30PM | 9:40PM | 1 | 1:10AM | 2:15AM | 60 | 9:00 AM | 9:50 AM | 10:10 AM | 730 | 70 | 9:30PM | 9:45PM | 3 | 12:30AM | 8:35AM | 9:50AM | 10:05AM | 725 | 75 | Lamotrigine, Oxycodone | Brivaracetam, Lamotrigine, Oxycodone |
| **13*** | UD-CL (1D) | 11:30PM | 11:45PM | 3 | 1:15AM | 2:35AM | 60 | 8:30AM | 9:30AM | 9:45AM | 585 | 60 | 11:30PM | 11:40 PM | 2 | 12:00AM | 8:30AM | 9:50 AM | 11:07 AM | 610 | 80 | Hydroxygine | Hydromorphone, Oxycodone |
| **14** | CL-UD (1D) | 10:25PM | 10:50PM | 2 | 12:45AM | 3:45AM | 45 | 8:00 AM | 8:50AM | 9:05AM | 600 | 50 | 11:10PM | 11:30PM | 1 | 12:00AM | 8:15AM | 8:45AM | 9:05AM | 555 | 30 | Clobazam, Lamotrigine, Oxycodone | Clobazam, Lamotrigine, Oxycodone |
| **15** | UD-CL (3D) | 10:11AM | 10:22PM | 2 | 10:50PM | 12:05AM | 59 | 7:45AM | 9:19AM | 9:28AM | 657 | 94 | 8:35PM | 9:09PM | 1 | 10:00PM | 7:00AM | 8:43AM | 9:07AM | 694 | 103 | | |
| **16***** | UD-CL (9D) | 21:58PM | 10:15PM | 2 | 12:00AM | 12:15PM | 57 | 7:30AM | 8:15AM | 8:28AM | 600 | 45 | 9:36PM | 9:51PM | 3 | 11:00PM | 6:30AM | 7:44AM | 7:51 AM | 607 | 74 | Oxycodone | |
| **17*,***** | UD-CL (1D) | 23:33PM | 12:00AM | 1 | 12:25AM | 1:42AM | 35 | 9:05AM | 9:45AM | 9:56AM | 585 | 40 | 1:01AM | 01:46AM | 2 | 2:35AM | 8:50AM | 10:30AM | 10:38AM | 524 | 100 | Hydromorphone, Oxycodone, methoocarbomol | Hydromorphone, Oxycodone, methoocarbomol |
| **18** | CL-UD (1D) | 20:48PM | 09:00PM | 1 | 10:50PM | 12:04AM | 55 | 08:20AM | 10:08AM | 10:21AM | 788 | 110 | 10:32PM | 10:40PM | 2 | 12:30AM | 08:34AM | 09:40AM | 9:50AM | 660 | 66 | Oxycodone, fluoxetine | Fluoxetine |

* Pts were excluded from cognitive analysis based on poor performance (Methods)
** First undisturbed-night morning follow-up not completed due to technical reasons
*** Pt excluded for low number of stimulations (Methods)

**Supplementary Table 2. Cognitive testing details**

Columns: (i) Participant-id of subset of participants with cognitive testing, asterisks denotes participants who were excluded from memory accuracy statistics but included in neurophysiology analysis (Methods, patients 1,13,16-17). (ii) Order of testing nights – CL = RTCL intervention night, UD = undisturbed night. In parentheses are the number of days between experimental nights. (iii) Sub-columns for each intervention experimental night – time of day (TOD) for (1) vigilance testing; (2) learning and testing in memory paradigm; (3) test version (3 different sets of images); (4) Sleep start TOD as recorded by an observer based on participant's EEG signals; (5) Stimulation session start TOD; (6) Stimulation session duration (comprised as intermittent stimulation and pause blocks as described in Fig. 1b); (7) Wake up TOD; (8) morning testing TOD; Time elapsed (min) between (9) evening learning to morning testing and (10) wake-up to testing. (iv) Sub-columns for each un-disturbed experimental night – same as (iii) without the stimulation-related columns. (v) Participant's drug regimen during (1) CL intervention nights and (2) undisturbed nights Shading corresponds to stimulation type (see Supplementary Table 4) – sync stimulation in orbitofrontal cortex (red) or other areas (brown), and mixed-phase stimulation (gray).

| | UNDISTURBED NIGHT | | | | | | | | | | | INTERVENTION NIGHT | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Evening Test | | | | Morning Test | | | | | | | Evening Test | | | | Morning Test | | | | | | | |
| Pt ID | imageCorrectPairEve | imageFalsePairEve | imageCorrectRecognitionEve | imageFalseDetectionEve | imageCorrectPairMor | imageFalsePairMor | imageCorrectRecognitionMor | imageFalseDetectionMor | Mem Acc evening | Mem Acc morning | diff | imageCorrectPairEve | imageFalsePairEve | imageCorrectRecognitionEve | imageFalseDetectionEve | imageCorrectPairMor | imageFalsePairMor | imageCorrectRecognitionMor | imageFalseDetectionMor | Mem Acc evening | Mem Acc morning | diff | diff of nights |
| 2 | 10 | 4 | 23 | 0 | 9 | 7 | 20 | 0 | 0.92 | 0.80 | -0.12 | 15 | 3 | 24 | 0 | 10 | 8 | 24 | 0 | 0.96 | 0.96 | 0.00 | 0.12 |
| 3 | 6 | 10 | 25 | 0 | 3 | 8 | 23 | 0 | 1.00 | 0.92 | -0.08 | 3 | 12 | 20 | 1 | 2 | 15 | 19 | 1 | 0.73 | 0.69 | -0.04 | 0.04 |
| 4 | 0 | 0 | 16 | 0 | 0 | 0 | 11 | 3 | 0.64 | 0.24 | -0.40 | 8 | 3 | 13 | 0 | 3 | 4 | 10 | 0 | 0.52 | 0.40 | -0.12 | 0.28 |
| 5 | 4 | 3 | 20 | 1 | 3 | 5 | 17 | 3 | 0.73 | 0.48 | -0.25 | 9 | 8 | 22 | 1 | 2 | 4 | 15 | 4 | 0.81 | 0.33 | -0.48 | -0.23 |
| 7 | 9 | 0 | 23 | 0 | 8 | 0 | 18 | 1 | 0.92 | 0.65 | -0.27 | 11 | 0 | 23 | 0 | 8 | 0 | 20 | 1 | 0.92 | 0.73 | -0.19 | 0.08 |
| 8 | 0 | 13 | 13 | 1 | 1 | 13 | 14 | 2 | 0.45 | 0.43 | -0.03 | 1 | 15 | 16 | 2 | 2 | 18 | 20 | 8 | 0.51 | 0.27 | -0.24 | -0.21 |
| 9 | 5 | 11 | 18 | 1 | 2 | 12 | 16 | 2 | 0.65 | 0.51 | -0.15 | 1 | 14 | 15 | 1 | 2 | 9 | 11 | 0 | 0.53 | 0.44 | -0.09 | 0.05 |
| 10 | 15 | 10 | 24 | 0 | 11 | 14 | 25 | 0 | 0.96 | 1.00 | 0.04 | 17 | 8 | 25 | 0 | 15 | 10 | 25 | 2 | 1.00 | 0.87 | -0.13 | -0.17 |
| 12 | 13 | 3 | 16 | 0 | 9 | 4 | 14 | 0 | 0.64 | 0.56 | -0.08 | 12 | 3 | 23 | 0 | 6 | 4 | 17 | 1 | 0.92 | 0.61 | -0.31 | -0.23 |
| 14 | 12 | 5 | 20 | 0 | 8 | 9 | 17 | 1 | 0.80 | 0.61 | -0.19 | 9 | 2 | 19 | 1 | 8 | 4 | 15 | 1 | 0.69 | 0.53 | -0.16 | 0.03 |
| 15 | 11 | 12 | 24 | 1 | 10 | 11 | 24 | 2 | 0.89 | 0.83 | -0.07 | 12 | 9 | 23 | 0 | 10 | 13 | 23 | 1 | 0.92 | 0.85 | -0.07 | 0.00 |
| 18 | 12 | 7 | 20 | 0 | 9 | 6 | 19 | 2 | 0.80 | 0.63 | -0.17 | 12 | 7 | 20 | 0 | 9 | 4 | 20 | 1 | 0.80 | 0.73 | -0.07 | 0.11 |

**Supplementary Table 3. Cognitive testing (Raw data).** Columns: (1) Participant-id of a subset of participants included in the cognitive testing cohort (exclusion criteria detailed in Methods), (2) number of correct image-pairs recalled in evening test; Evening test: (3) number of falsely recalled image-pairs; (4) number of correctly recognized images; (5) number of falsely recognized lures in evening test; (6-9) Same assessments for morning test; (10) Recogntion memory accuracy (Methods) at evening test; (11) Recogntion memory accuracy (Methods) at morning test; (12) difference between recognition memory accuracy between morning and evening. Rightmost column is the difference between the differences measured over intervention night and undisturbed night.

| Participant id | Session id | Start of session time of day | N stimulation blocks | Total session length (minutes) | Stimulation type (b = bipolar, u = unipolar) | Stimulation site* | RTCL input (probe) site* | Number of iEEG electrodes | Intervention type (S = sync-stim, M = mixed phase) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | 12:15 AM | 5 | 86 | b | RPF | mixture of RMH and LMH | 10 | M |
| 2 | 2 | 12:09 AM | 7 | 94 | b | LPF | LEC | 10 | S |
| 3 | 3 | 11:30 PM | 10 | 96 | b | RPF | RAH | 8 | S |
| 4 | 4 | 2:00 AM | 8 | 118 | b | LPF | LPHG | 12 | S |
| 5 | 5 | 12:05 AM | 8 | 55 | b | RT | RAH | 9 | S |
| 6 | 6 | 2:09 AM | 8 | 87 | u | RT | RAH | 10 | S |
| 7 | 7 | 11:35 PM | 10 | 100 | u | RTO | RMH | 9 | S |
| 8 | 8 | 10:50 PM | 13 | 55 | u | RPF | RMH | 10 | M |
| 9 | 9 | 11:00 PM | 11 | 90 | u | LPF | LAH | 10 | S |
| 10 | 10 | 12:25 AM | 10 | 55 | u | LPF | LMH | 10 | M |
| 11 | 11 | 1:50 AM | 6 | 163 | u | LPF | RAH | 12 | M |
| 12 | 12 | 11:30 PM | 6 | 45 | u | RPF | RAH | 13 | M |
| 12 | 13 | 2:15 AM | 8 | 132 | u | RPF | RAH | 13 | M |
| 13 | 14 | 2:35 AM | 6 | 112 | u | RPF | RAH | 10 | S |
| 14 | 15 | 3:45 AM | 5 | 59 | u | RPF | RMH | 9 | S |
| 15 | 16 | 12:05 PM | 4 | 59 | u | RT | RT | 11 | S |
| 16 | 17 | 12:15 AM | 5 | 57 | u | LPF | LMH | 14 | S |
| 17 | 18 | 2:00 AM | 6 | 35 | u | RPF | RMH | 13 | S |
| 18 | 19 | 12:05 AM | 6 | 55 | u | RPF | REC | 14 | S |

**Supplementary Table 4. Real-time closed-loop intervention night information**

Shaded rows are intervention sessions with full cognitive testing that are also reported in Supplementary Table 2, Fig. 1f,g. Shading color corresponds to stimulation type listed in the rightmost column, sync stimulation in the orbitofrontal cortex (red) or other areas (brown), and mixed-phase stimulation (gray), white background sessions are included in neurophysiology analysis but not cognitive testing. Columns (left to right): (1) Participant ID (Participant #12 participated in two intervention nights); (2) Intervention session number; (3) Number of stimulation blocks per session (4) Total length of session (first stim-block till the end of the last stim-block) (min); (5) Stimulation type – unipolar/bipolar; (6) Stimulation site - hemisphere and approximate location (exact MR scans provided in Extended Data Fig. 2); (7) Location of probe used as input to RTCL system: hemisphere and approximate location in MTL (exact MR scans are provided in Extended Data Fig. 2); (8) Number of iEEG electrodes recorded in session (note that there are 6-8 iEEG contacts per electrode); (9) RTCL mode – sync-stim (red – stimulation site in the prefrontal cortex, brown – in other anatomical areas) /mixed-phase stim (gray). *Abbreviations: R = right hemisphere, L = Left hemisphere; PF = prefrontal cortex, T = temporal cortex, TO = Temporal-occipital cortex, AH=Anterior Hippocampus, MH = Middle Hippocampus, EC = Entorhinal cortex, PHG = Parahippocampal gyrus.