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Hippocampal ripples mediate motor learning during brief rest breaks in humans

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Abstract

Although research on the hippocampus has largely focused on its role in active learning, critical aspects of learning and memory happen offline, during both wake and sleep. When healthy young people learn a motor sequence task, most of their performance improvement happens not while typing, but offline, during interleaved rest breaks. Although patients with dense amnesia due to hippocampal damage show a normal amount of motor sequence learning, they show a different pattern. They actually lose speed over the breaks and compensate while typing. This indicates that an intact hippocampus is necessary for offline motor learning during wake but does not specify its mechanism. Here, we studied epilepsy patients (n=20) undergoing direct intracranial EEG monitoring of the hippocampus as they learned the same motor sequence task. Like healthy young people, they showed greater speed gains across rest breaks than while typing. They also showed a higher ripple rate during the breaks that predicted offline gains in speed. This suggests that motor learning during brief rest breaks during wake is mediated by hippocampal ripples. These findings complement rodent studies showing memory replay during hippocampal ripples in the wakeful rest that follows learning. Disrupting these ripples impairs memory, consistent with a causal role. The findings also provide a mechanistic explanation of human neuroimaging reports of increased hippocampal activation and sequential motor memory replay during rest breaks that predict performance improvement. Finally, they expand our understanding of the role of hippocampal ripples beyond declarative memory to include enhancing motor procedural memory.

Significance Statement

In patients with epilepsy undergoing direct EEG monitoring of the hippocampus, we found a higher rate of ripples during the brief rest breaks of a motor learning task than during task execution. Furthermore, the ripple rate during these rest breaks predicted the amount of offline motor learning. We conclude that the hippocampus contributes to motor learning during brief rest breaks, and propose that this offline learning is mediated by ripples.

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Introduction

Hippocampal ripples, brief bursts of ~70-150 Hz activity, reflect neuronal firing and contribute to the consolidation of hippocampally dependent memories. In rodents, hippocampal firing during spatial navigation represents ongoing experience. During the wakeful rest and sleep that follows, the hippocampus replays these patterns of firing during sharp-wave ripples.[1, 2] Disrupting these ripples during either offline state impairs the memories, suggesting that ripple-related memory replay is a common mechanism of memory consolidation during both wake and sleep.[3-5]

Recent studies of humans also tie offline learning during wake to hippocampal function, even for tasks not generally considered to be hippocampally dependent. When healthy young participants learn a procedural motor task (i.e., the finger tapping Motor Sequence Task, MST), most of the improvement in performance happens offline, during brief (10-30 s) rest periods between typing trials, and not during the actual typing. This phenomenon, labeled micro-offline gains, to distinguish it from the more macro-scale of offline learning occurring over hours of sleep,[6] is associated with increased hippocampal activation and sequential memory replay during rest breaks that predict the level of offline improvement.[7, 8] In contrast, patients with dense amnesia due to hippocampal damage, despite intact overall learning of the MST, actually show negative micro-offline gains (i.e., losses), whereas their healthy, age-matched peers retain their learning over breaks.[9] Collectively, these findings suggest that the hippocampus is required to either improve (in young adults) or maintain (in older adults) motor memory over brief periods of wakeful rest. Here, we test the hypothesis that offline improvement of motor memory during these brief periods of wakeful rest depends specifically on hippocampal ripples. To do so, we studied inpatients with pharmacologically intractable epilepsy undergoing invasive monitoring with hippocampal electrodes as part of a pre-surgical work-up. We divided the MST into its online (during typing) and offline (during interleaved rest breaks) components and examined ripples

during each period and their relations with performance improvement (i.e., micro-online and -offline gains in speed).

Results

Twenty-three epilepsy inpatients with intracranial hippocampal recordings enrolled in the study. Three patients were excluded after failing a motor screening test. After completing a warm-up task to familiarize them with the structure of the task, 20 patients trained on the MST. The MST involves repeatedly typing a five-digit sequence (e.g., 4-1-3-2-4) "as quickly and accurately as possible" on a keypad for 12 30-s trials separated by 30-s rest periods (Fig. 1A). Participants typed with the hand contralateral to the hippocampus with implanted electrodes. If both hippocampi were implanted, they typed with the hand contralateral to the presumed healthier hippocampus based on medical records and hippocampal electrophysiology. After excluding two participants with too few usable trials, 18 participants (age: 32+/-13; range: 17-56; 5M,13F) were included in the analyses (Table S1). Typing speed was quantified as the inverse of the average interval between adjacent key presses within each correctly typed sequence (i.e., key presses/s).[6] Micro-online gains were defined as the difference in typing speed between the first and the last correct sequence of each 30-s trial. Micro-offline gains were defined as the difference in typing speed between the last correct sequence of one trial and the first correct sequence of the next. Total gains are the sum of micro-offline and micro-online gains. The micro-online gain from the last (12th) typing trial was excluded from analyses as it is not followed by a corresponding rest period. Family-wise error rate corrected probability levels are reported to control for multiple comparisons.

Participants showed significant learning over the course of MST training (Total gains: 0.5±0.094; t_{17}=2.35, p=.025) and most of this improvement happened offline (Fig. 1). They showed significant micro-offline gains (2.43±3.64; t_{17}=2.84, p=.004) and a trend to lose speed online, while typing (-1.91±4.23; t_{17}=-1.92, p=.088). Across participants, total micro-offline gains were significantly greater than micro-online gains (4.35±7.84; t_{17}=3.35, p=.009; Fig. 1A, right), and

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they were also numerically greater than online gains on every trial (Fig. 1B). The finding of greater learning during offline (rest) than online (typing) periods is consistent with previous studies of healthy young adults.[6, 7]

We identified hippocampal ripples (70-150 Hz) during MST training using an automated ripple detector adapted from previous studies.[10-12] Ripples were detected in intracranial EEG recordings targeting the hippocampus contralateral to the hand that performed the MST. Detected ripples showed the characteristic sharp-wave and oscillatory ripple band activity in the wideband filtered signal (0.3-250 Hz) during both online and offline periods (Fig. 2).[13] We calculated the ripple rate (ripples/s), averaged over hippocampal electrodes for each participant during each online and offline period. Across participants and trials, the mean ripple rate was significantly higher during offline than online periods (Fig. 3A; 0.23±0.09 vs. 0.16±0.07; t_{17}=3.21, p=.018). Ripple rate was also numerically higher during offline than online periods on every trial.

Participants with more ripples during the rest breaks showed correspondingly greater offline gains (Fig. 3B right; r=.50, p= .033), consistent with our hypothesis that offline memory consolidation during wake depends on hippocampal ripples. In contrast, the number of ripples during typing did not significantly correlate with total online gains (Fig. 3B left; r=.23, p=.56). We then investigated whether ripple rate predicted gains on a trial-by-trial basis (see data in 1B and 3A). Ripple rate significantly predicted individual trial gains (est.=1.66; 95% CI: : 0.43-2.88; p=.01) and this relation differed for online vs. offline periods (est.= -3.18; 95% CI: -4.90-1.47; p<.001). Post-hoc tests found a significant effect of offline ripple rate on offline gains (est.=1.6; 95% CI: 0.12-3.07; p=.037) but no effect of online ripple rate on online gains (est.=-0.14; 95% CI: : -2.23-1.25; p=.89; Fig. 3C).

Discussion

Our primary findings are that *i)* there are more hippocampal ripples during brief, 30-s breaks while learning a motor procedural task than during actual task performance and *ii)* ripple rates during these offline periods predict task improvement, both on a subject-by-subject and a

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trial-by-trial basis. These findings are consistent with rodent studies showing ripple-related memory replay during the wakeful rest that follows spatial navigation.[14, 15] Disrupting these ripples impairs memory, suggesting that they play a causal role.[3, 4] They also complement neuroimaging findings in humans of hippocampal activation and sequential memory replay during MST rest breaks that predict the level of offline improvement.[7, 8] The absence of offline learning during both wake[9] and sleep[16] in patients with dense amnesia due to hippocampal damage, together with the present findings, suggests that the hippocampus is necessary for offline learning and that this learning depends on ripples. These findings support ripple-related memory replay as a common mechanism of memory consolidation during wake and sleep in humans.

Although procedural memory is classically thought to rely on the striatum,[17, 18] the hippocampus is engaged while learning procedural motor tasks,[19, 20] and more so during rest than typing periods on the MST.[7, 8] But neuroimaging cannot answer the questions of whether the hippocampus is simply engaged during offline motor learning or contributes to that learning, and if the latter, by what mechanism? In patients with amnesia due to hippocampal damage, we demonstrated that the hippocampus is necessary for the offline consolidation of motor procedural learning over both wake[9] and sleep.[16] Specifically, despite intact total learning of the MST across training, unlike their healthy peers, patients with amnesia showed offline losses with compensation during typing. They also failed to show overnight performance improvement. The present findings suggest a lack of ripple-related memory replay as a culprit in these losses of offline learning. Collectively, these findings support a critical role for the hippocampus in the offline consolidation of motor procedural learning during both wake and sleep.

There were significantly fewer ripples during typing than rest periods, and no correlation between ripple rates and online gains. This likely reflects differences in hippocampal activity during active vs. offline learning as seen in rodent studies.[21] During spatial navigation, hippocampal place cells exhibit location-specific firing, primarily in the theta band, to provide a map of the environment (a similar phenomenon is seen in humans[22]). During the wakeful rest that

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follows, hippocampal neurons repeatedly reactivate recent experiences via the firing of place cells on a much faster time scale during ripples.[14, 15] This ripple-related replay correlates with memory improvement[23] and disrupting these ripples consistently impairs memory, consistent with a causal role.[3, 4]

In the present study, as in previous studies of young adults, participants showed online losses of speed followed by marked offline improvements.[6] This pattern could reflect motor fatigue accumulating during typing and its dissipation during the rest break that follows.[24] If this were the case, any learning acquired during the previous typing period could only be fully expressed after rest. Alternatively, this pattern could reflect an enhancement of learning during rest as a result of ripple-related memory replay. These explanations are not mutually exclusive, though our correlations of micro-offline gains with hippocampal ripples, both across and within participants, argues for ripple-related replay as an important driver of offline learning.

In conclusion, the hippocampus is necessary for the offline consolidation of motor learning during both wake and sleep and this offline learning during wake appears to be mediated by ripples.

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METHODS

Participants: Inpatients with epilepsy undergoing continuous intracranial EEG monitoring of the hippocampus as part of their clinical care were evaluated for participation. Twenty-three participants who met the following inclusion criteria enrolled in the study: ≥12 years old; no prior cortical or subcortical resection; no prior neurosurgical procedure that was expected to interfere with sleep oscillations; estimated IQ ≥70 based on neuropsychological assessment and/or the single word reading subtest of the Wide Range Achievement Test-4 (WRAT-4[25]); no history of marked developmental delay or marked motor impairment. Participation for three participants was discontinued after they failed to pass a motor screening test requiring them to correctly type the sequence "1,2,3,4" a total of 24 times during two 30 s trials separated by a 30 s rest period. Of the 20 remaining participants, two were excluded because invalid trials on the Motor Sequence Task (MST) affected the calculation of gains in ≥7 of the 22 online and offline periods (see Excluded MST Data below). The final sample was comprised of 18 participants (age: 32+/-12; range: 17-56; 5M,13F; See Table S1). All participants provided informed consent in accordance with the Partners Institutional Review Board and the Declaration of Helsinki.

Motor Sequence Task (MST)

MST Hand Selection: Participants performed the MST with the hand contralateral to the hippocampus with implanted electrodes (n=9). If participants had bilateral hippocampal implants, they used the hand contralateral to the presumed healthier hippocampus (n=9) based on review of medical records, MRI, and hippocampal electrophysiology by a board certified epileptologist and neurophysiologist (CJC).

MST Warmup: To acclimate participants to the structure of the MST, they were administered a 'warmup' task prior to MST training. Participants rested the index and middle fingers of the hand that they were not using for the MST on the keypad buttons labeled 3 and 4. They were instructed

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to repeatedly type the sequence 3-4 “as quickly and accurately as possible” for three 10 s typing periods separated by 10 s rest breaks. The sequence remained on the screen for the duration of the task. During the typing periods the screen remained green and a dot appeared in a horizontal line on the screen with each key press. After the line reached the right border, the dots disappeared one at a time, from right to left, with each additional key press. After 10 s, the screen turned red, and participants rested for 10 s. A countdown of the number of seconds until the screen turned green was displayed as spelled out numbers. The last three numbers were replaced with tones to alert the participants to get ready to resume typing when the screen turned green again.

MST Administration: The MST had the same structure as the warmup with the following exceptions: the participant used four fingers on the keypad (index, middle, ring, pinkie) to type a 5-digit sequence (e.g., 4-1-3-2-4) and there were twelve 30 s typing trials separated by 30 s rest periods. If a participant did not follow task instructions (e.g., typed an incorrect sequence or misplaced their fingers on the keys), they were corrected in real time by the experimenter and the trial was flagged as invalid.

MST outcome measures: The primary outcome measures were total gains, micro-online gains, and micro-offline gains in typing speed. Typing speed for each correctly typed sequence was quantified as the inverse of the interval between the first and last keypress of the sequence (i.e., key presses/s). Micro-online gains are defined as the difference in typing speed between the first and the last correct sequence of each typing trial.[6] Micro-offline gains are defined as the difference in typing speed between the last correct sequence of a trial and the first correct sequence of the next trial. Total gains are the sum of micro-offline and micro-online gains per trial and are equal to the difference in typing speed between the first correct sequence of one trial and the first correct sequence of the next. The micro-online gain from the last (12th) typing trial was not included in the calculations as there is no subsequent rest period, leaving a total of 11 online and 11 offline gains per participant.

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Excluded MST data: It is not possible to calculate online gains on trials with no correctly typed sequences, nor is it possible to calculate offline gains for the rest period before and after it. The same is true for trials that were rendered invalid for other reasons, including interruptions by clinical staff or a participant's failure to follow task instructions (e.g., using the same finger on more than one number key). The data from the two participants were excluded from analysis because invalid trials affected the calculation of gains for ≥7 of the 22 online and offline periods. In included participants, the gains of an average of <1 period per participant could not be scored (4% of the periods).

Hippocampal Ripple Measurement

Intracranial recordings: All participants had intracranial recordings targeting the hippocampus. In three participants, foramen ovale electrodes were used. In four participants, a single stereotactically placed electroencephalography (SEEG) electrode was placed that targeted the hippocampal body, and this electrode was used for analysis. In the remaining 13 participants, an SEEG electrode targeting the hippocampal head was used for analysis. In each SEEG case, the three deepest contacts were bipolar referenced, creating two channels per subject for ripple analysis.

Data acquisition: Data were acquired at 1024 or 2048 Hz with a Natus Quantum or EMU40 clinical system (Natus Medical Inc., Middleton, WI, USA). Data recorded at 2048 Hz were downsampled to 1024 Hz.

Signal preprocessing: Data were high pass filtered above 0.1 Hz using a two-pass Finite Impulse Response (FIR) filter in Matlab using the Fieldtrip toolbox.[26] Sixty Hz line noise and its first harmonic were removed using a two-pass bandstop Butterworth filter.

Automated Ripple Detection: Ripples were detected in offline and online periods separately given the different levels of baseline activity. Hippocampal electrodes were bipolar referenced to adjacent electrodes on the same lead. The bipolar signal was bandpass filtered (70-150 Hz). The

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envelope of the bandpass signal was calculated using the Hilbert transform. The root-mean-squared amplitude of the ripple band envelope was calculated for each electrode and the threshold for ripple detection was set to the upper 95th percentile, in the range of other studies.[11, 12] Each detected ripple was required to exceed this threshold for >6 ms; have at least 6 peaks, indicating 3 full cycles, in both the raw and the bandpass filtered signal to exclude epileptic spikes;[27] and have a ripple-band envelope >3 SDs above the mean during the 200 ms window around the ripple peak.

Statistical Analyses

To determine whether online, offline, and total gains differed from zero, we used one sample t-tests. Paired t-tests were used to compare offline and online gains. To determine whether those participants with higher ripple rates also had greater offline gains, we used Pearson correlations. These analyses were corrected for multiple comparisons (family-wise error rate) using non-parametric permutation testing.[28] For each permutation, we randomly swapped half the pair labels (t-tests) or randomly shuffled the values of one variable (correlations). The null distribution for each test category was based on 10,000 permutations. In each permutation we extracted the maximum absolute test statistic within each category. A two-tailed significance threshold of $p<.05$ was set at the 95th percentile of each resulting distribution (absolute value thresholds: paired t-tests: $t=1.77$; unpaired t-tests: $t=2.12$; correlation coefficients: $r=.47$). Corrected p-values were estimated from these distributions.

To assess the relation of gains with ripples on a trial-by-trial basis within participants, we employed linear mixed effects models with Subject as a random effect to account for repeated measures. We used Ripple Rate, Period (Online, Offline) and their interaction as fixed effects to predict Gains, while allowing the Intercept and Ripple Rate to vary randomly within Subject (Subject Gains ~ Ripple Rate * Period + (1 + Ripple Rate | Subject)). To test our main hypothesis that offline ripples predict gains during offline periods, we investigated online and

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offline periods in separate linear models (e.g., Offline Gains ~ Offline Ripple Rate + (1 + Offline Ripple Rate | Subject)). P-values for the mixed effect model estimates were calculated using the Kenward-Roger method.[29] Confidence intervals of the estimates were calculated using a semiparametric bootstrap approach (5,000 iterations) implemented in R using the lmeresampler package.[30] All models and statistical inference methods were implemented in R using the lme4,[31] sjPlot[32] packages.

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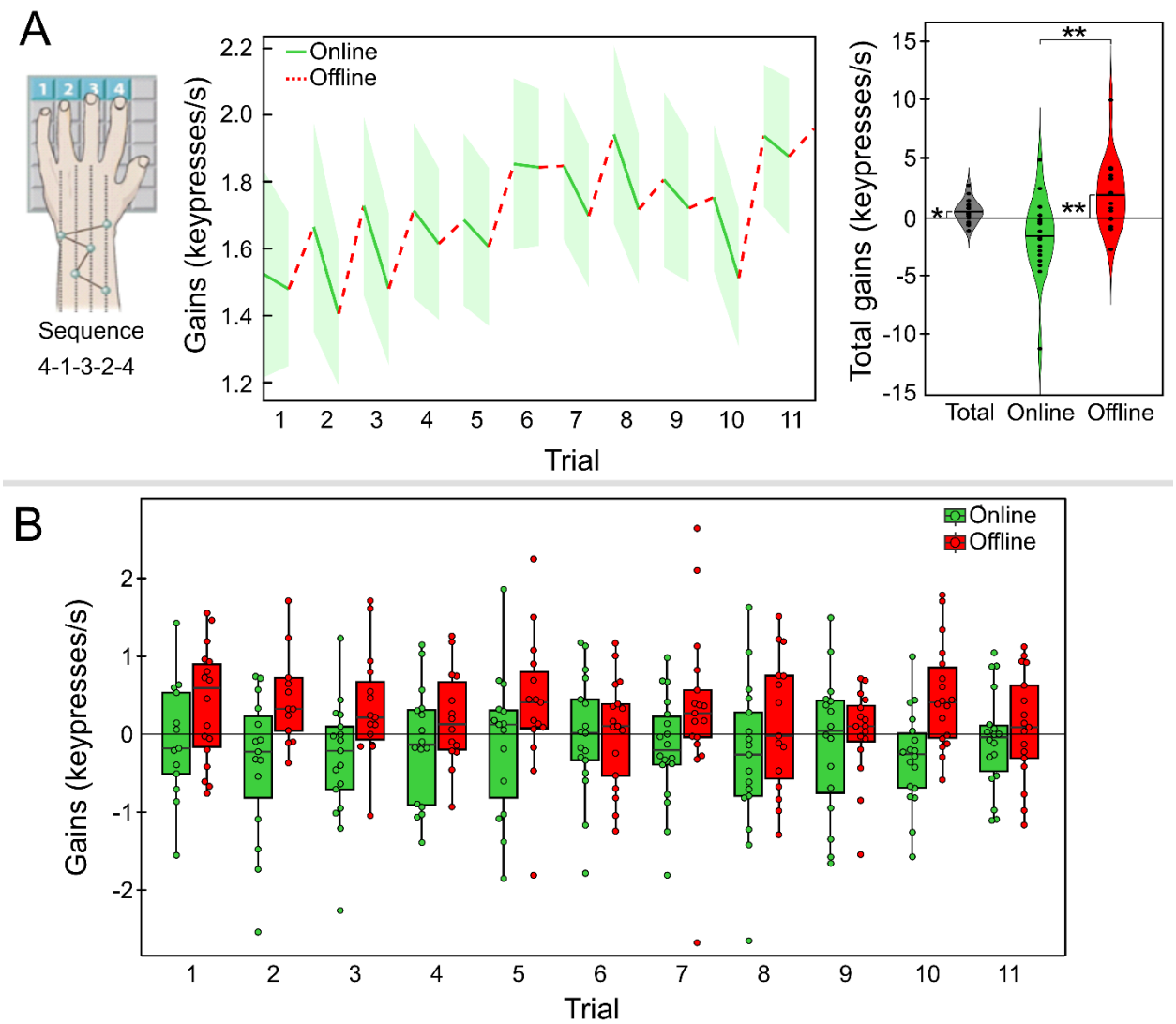

Fig. 1: Micro-online and -offline gains across MST trials.

A : *Left*: Participants rested four fingers on a key pad with keys labeled 1, 2, 3, 4. They were instructed to repeatedly type a five digit sequence (e.g., 4-1-3-2-4) "as quickly and accurately as possible." During the 30 s typing trials, the screen was green and the sequence was displayed on top. After 30 s, the screen turned red and participants rested for 30 s. Training consisted of 12 typing trials and 11 rest breaks. *Middle*: Plot of mean online (green solid line) and offline (dotted red line) gains over the 30 s of each typing and rest period across participants (x-axis). *Right*: Violin plots showing distribution of the sum of total gains, micro-online gains and micro-offline gains for 11 trials across participants. The black dots represent individual data points and

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horizontal lines represent means. Significant differences are indicated with asterisks (***** = p<.05, ****** = p<.005).

B *:* Boxplots of micro-online and -offline gains by trial. Each circle is the gain for a participant in a given trial. Boxes extend to the median and 25th and 75th percentile of gains. Whisker lines extend to the maximum/minimum non-outlier values (less than 1.5 of the interquartile range from the upper or lower quartile (Wickham 2016)). Horizontal lines represent trial medians.

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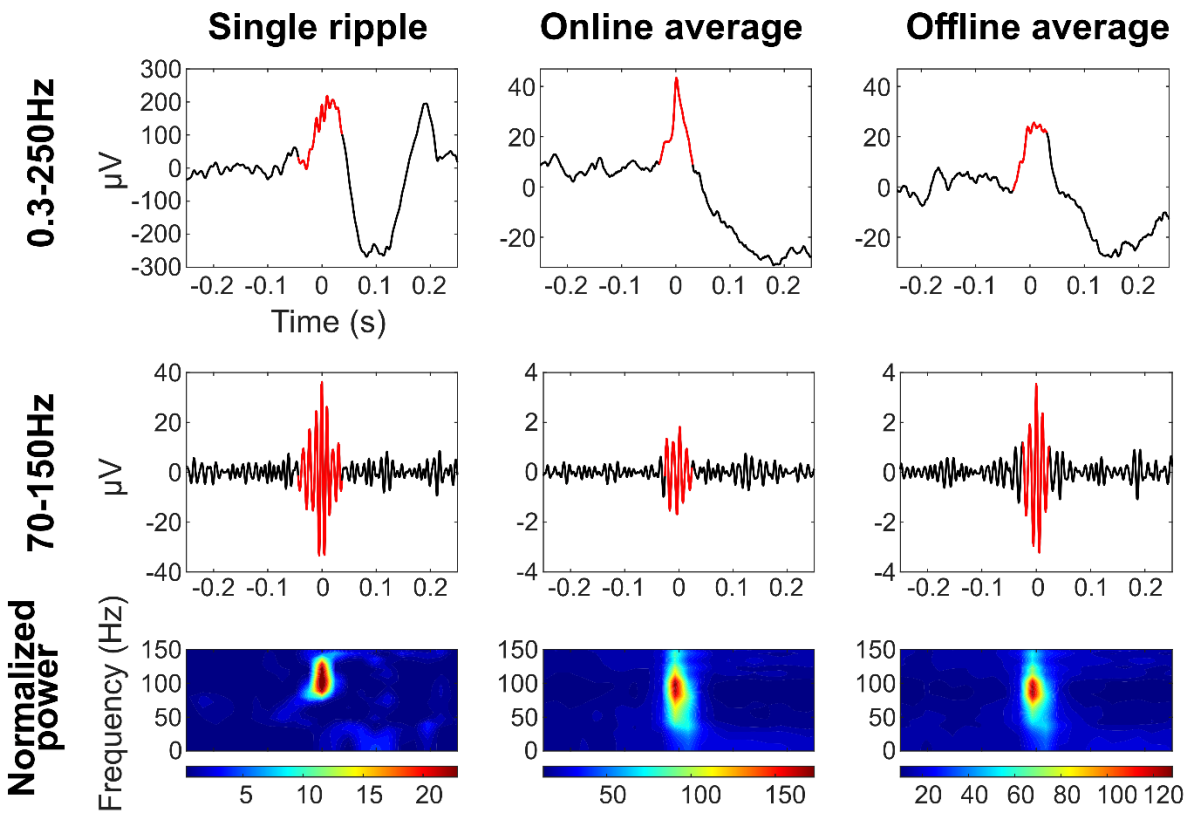

Fig. 2: Oscillatory and spectral characteristics of detected ripples

The first column shows an example of a single detected ripple, the second and third columns show the average of ripples detected during online (typing) and offline (rest) periods (red indicates ripples). The top row shows wide-band filtered data, the middle row shows data filtered from 70-150 Hz, and the bottom row shows time frequency spectrograms. Each plot is centered on the maximum in the 70-150 Hz filtered signal at the time of a detected ripple. For the online and offline averages, the ripples are also shifted to align the peak of the oscillations.

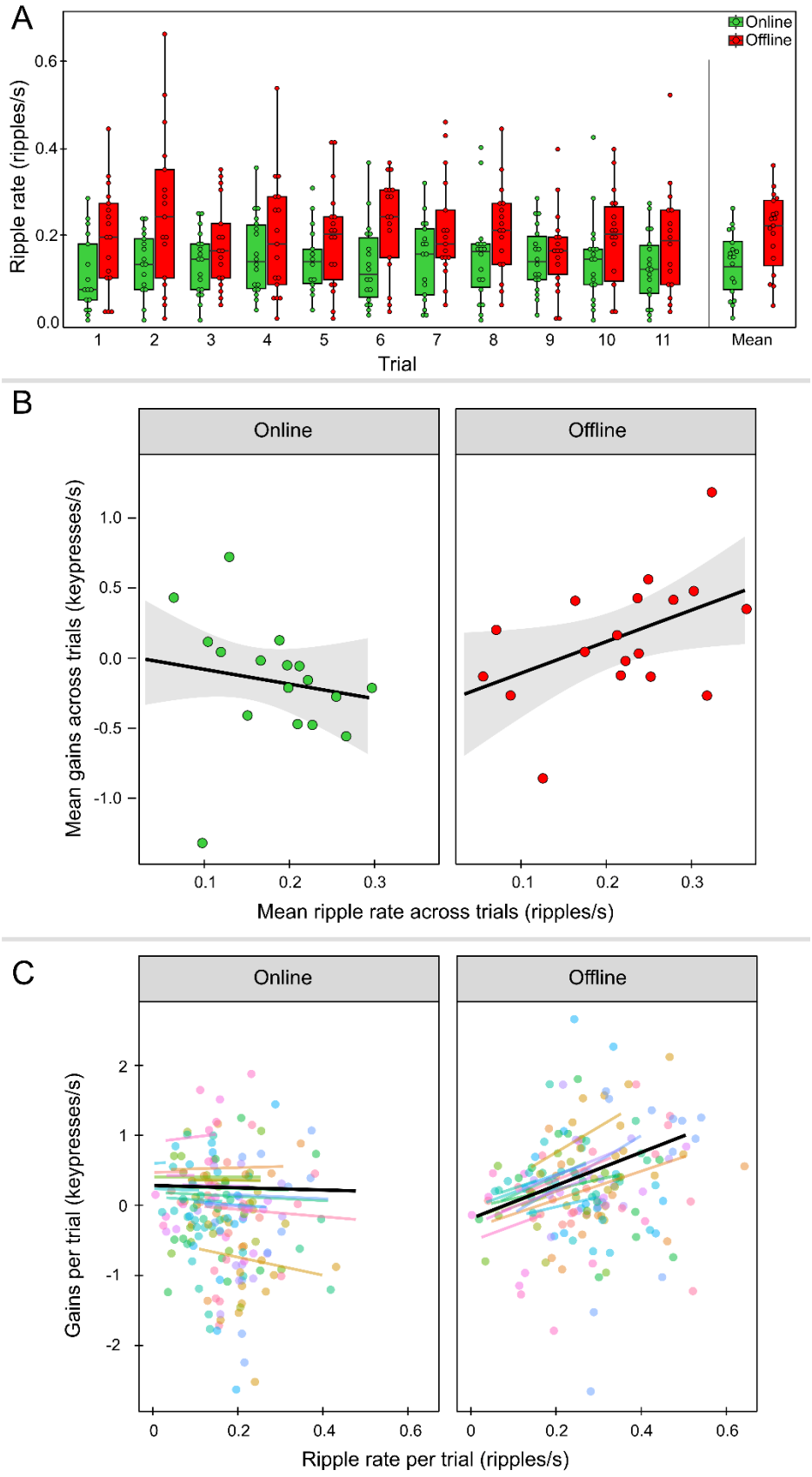
A
Online
Offline
Ripple rate (ripples/s)
0.0
0.2
0.4
0.6
1
2
3
4
5
6
7
8
9
10
11
Mean
Trial
B
Online
Offline
Mean gains across trials (keypresses/s)
1.0
0.5
0.0
-0.5
-1.0
0.1
0.2
0.3
Mean ripple rate across trials (ripples/s)
C
Online
Offline
Gains per trial (keypresses/s)
2
1
0
-1
-2
0
0.2
0.4
0.6
Ripple rate per trial (ripples/s)

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Fig. 3: Hippocampal ripple rates during online and offline periods and their relations to micro-online and -offline gains.

A : Boxplots of hippocampal ripples during online and offline periods for each trial. Each circle is an individual data point. Boxes extend to the median and 25th and 75th percentile of ripple rate across participants. Whisker lines extend to the maximum/minimum non-outlier values (less than 1.5 of the interquartile range from the upper or lower quartile (Wickham 2016)). Horizontal lines within the boxes represent medians. Mean online and offline ripple rates per participant (across trials) are shown on the far right.

B : Scatter plots of number of ripples and gains summed across trials. Each participant is a circle. The shading represents the standard error of the regression line.

C : Scatter plots of ripples and gains per trial for each participant for online and offline periods. The color of the dots and the corresponding regression line represents individual participants.

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Supplementary materials

Table S1: Participant information

MST hand	HPC implant(s)	Etiology	Antiseizure medications
L	B	Multiple cavernous malformations	Clobazam
L	B	Non-lesional	None
R	B	Non-lesional	Cannabidiol, Clorazepate, Oxcarbazepine
R	B	Non-lesional	Lamotrigine
L	B	traumatic brain injury	Lacosamide
L	R	Non-lesional	Gabapentin, Lamotrigine, Oxcarbazepine
R	L	Left mesial temporal sclerosis	Clobazam, Zonisamide, Lamotrigine
L	R	Right mesial temporal sclerosis	Lamotrigine
L	R	Perinatal stroke	Lacosamide, Oxcarbazepine, Clobazam
L	R	Right mesial temporal sclerosis	None
R	L	Left mesial temporal sclerosis	None
R	L	Non-lesional	Lacosamide, Divalproex
L	R	Focal cortical dysplasia	Lamotrigine, Cannabidiol, Lacosamide
R	L	Non-lesional	Lamotrigine
R	B	Right mesial temporal sclerosis	Clobazam, Cannabidiol
L*	B	Periventricular nodular heterotopia	Levetiracetam, Cannabidiol, Lacosamide
L*	B	Bilateral mesial temporal sclerosis	Clobazam, Lamotrigine
L*	B	Suspected neonatal hypoxic ischemic injury	Brivaracetam, Gabapentin, Carbamazepine

MST Hand: The hand used for the MST. ***HPC Implant(s)***: Hemisphere with hippocampal implants: L=left, R=right, B=bilateral

***** denotes participants with Foramen Ovale leads.