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2 **Impaired sleep-dependent memory consolidation predicted by 3 reduced sleep spindles in Rolandic epilepsy**

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25 **Abstract**

26 **Background and Objectives:** Sleep spindles are prominent thalamocortical brain oscillations during sleep that
27 have been mechanistically linked to sleep-dependent memory consolidation in animal models and healthy controls.
28 Sleep spindles are decreased in Rolandic epilepsy and related sleep-activated epileptic encephalopathies. We
29 investigate the relationship between sleep spindle deficits and deficient sleep dependent memory consolidation in
30 children with Rolandic epilepsy.

31 **Methods:** In this prospective case-control study, children were trained and tested on a validated probe of memory
32 consolidation, the motor sequence task (MST). Sleep spindles were measured from high-density EEG during a 90-
33 minute nap opportunity between MST training and testing using a validated automated detector.

34 **Results:** Twenty-three children with Rolandic epilepsy (14 with resolved disease), and 19 age- and sex-matched
35 controls were enrolled. Children with active Rolandic epilepsy had decreased memory consolidation compared to
36 control children ($p=0.001$, mean percentage reduction: 25.7%, 95% CI [10.3, 41.2]%) and compared to children
37 with resolved Rolandic epilepsy ($p=0.007$, mean percentage reduction: 21.9%, 95% CI [6.2, 37.6]%). Children with
38 active Rolandic epilepsy had decreased sleep spindle rates in the centrot temporal region compared to controls
39 ($p=0.008$, mean decrease 2.5 spindles/min, 95% CI [0.7, 4.4] spindles/min). Spindle rate positively predicted sleep-
40 dependent memory consolidation ($p=0.004$, mean MST improvement of 3.9%, 95% CI [1.3, 6.4]%, for each unit
41 increase in spindles per minute).

42 **Discussion:** Children with Rolandic epilepsy have a sleep spindle deficit during the active period of disease which
43 predicts deficits in sleep dependent memory consolidation. This finding provides a mechanism and noninvasive
44 biomarker to aid diagnosis and therapeutic discovery for cognitive dysfunction in Rolandic epilepsy and related
45 sleep activated epilepsy syndromes.

46 **Introduction**

47 Rolandic epilepsy (RE, also called self-limited epilepsy with centrotemporal spikes, SeLECTS; previously called
48 benign Rolandic epilepsy; childhood epilepsy with centrotemporal spikes; or benign epilepsy with centrotemporal
49 spikes) is a common focal developmental epilepsy that accounts for 8-23% of childhood epilepsy^{1,2}. RE is
50 characterized by a transient period of sleep-potentiated seizures and epileptiform discharges best localized to the
51 inferior Rolandic cortex during childhood. Seizures in RE usually present before 11 years old, with a peak at 5-8
52 years¹, and always remit by late adolescence, though epileptiform activity can persist for years after seizure
53 resolution³. In addition to seizures, children with RE exhibit cognitive deficits during school-age years⁴ that also
54 resolve by a decade after seizure resolution¹. The severity of cognitive symptoms varies, but approximately 7% of
55 children with RE have severe cognitive deficits consistent with a severe epileptic encephalopathy⁵.

56 The mechanism of cognitive dysfunction in RE is an area of active research. We recently discovered that
57 epileptiform spikes interfere with sleep spindles, prominent bursts of 9-15 Hz oscillations mechanistically linked to
58 memory consolidation during stage 2 sleep^{6,7}, in RE and severe sleep activated epileptic encephalopathies⁸⁻¹⁰. In
59 contrast to measures of spike rate, sleep spindle rate predicts IQ, processing speed, and sensorimotor coordination
60 in RE⁸, and changes in spindle rate predict cognitive response to high-dose benzodiazepine treatment in severe
61 epileptic encephalopathies⁹. Similar findings have subsequently been reported in other epilepsy populations^{11,12},
62 suggesting that sleep spindle deficits may provide a robust, generalizable biomarker for several cognitive symptoms
63 observed in epilepsy.

64 Sleep spindles have been most strongly linked to the cognitive process of sleep-dependent memory
65 consolidation¹³⁻²¹. Whether spindle deficits relate specifically to deficits in sleep-dependent memory consolidation
66 in epilepsy remains unknown. To evaluate for evidence of deficits in sleep-dependent memory consolidation in
67 children with Rolandic epilepsy and investigate the link between this memory function and sleep spindles, we
68 performed a prospective trial in children with RE and typically developing controls. We hypothesized that memory
69 consolidation would be lower in children with active RE and that sleep spindle rate would predict the degree of
70 memory consolidation over the period of sleep recorded. Identifying this cognitive deficit and demonstrating a

71 relationship with sleep spindles provides both a mechanism and noninvasive biomarker for cognitive dysfunction
72 in RE.

73

74 **Methods**

75 ***Subjects***

76 We performed a prospective, case-control study in children with RE and age- and sex-matched controls. Children
77 with RE were required to have a history of at least one focal motor or generalized seizure and an EEG with sleep-
78 activated centrotemporal spikes. Children with RE were classified as having active epilepsy (seizure within 12
79 months) or resolved epilepsy (seizure-free for at least 12 months). We chose this classification because most children
80 with RE who are seizure-free for 1 year have entered sustained remission from epilepsy¹. Control children were
81 required to have no history of seizures and no known neurological disorders. Children with attention disorders and
82 mild learning difficulties were included, as these profiles are consistent with known RE comorbidities⁴. Eligible
83 children were identified from the community and Massachusetts General Hospital (MGH) pediatric neurology and
84 general pediatrics clinics, the EEG lab, and through posted advertisements. Informed consent was obtained from all
85 participants and this study was approved by the Massachusetts General Hospital Institutional Review Board.

86

87 ***Experimental overview***

88 The experimental timeline is outlined in **Figure 1**. Briefly, the subjects arrived at the Athinoula A. Martinos Center
89 for Biomedical Imaging at approximately 10:00 AM and completed training on the finger tapping motor sequence
90 typing task (MST) on each hand using separate sequences. This was followed by EEG placement and a nap
91 opportunity of approximately 90 minutes. At approximately 3:00 PM, the nap opportunity ended, and the subjects
92 were tested on the MST sequences on each hand. The subjects then underwent a brain MRI in an adjacent imaging
93 suite after a small meal. Data were processed and analyzed as described below.

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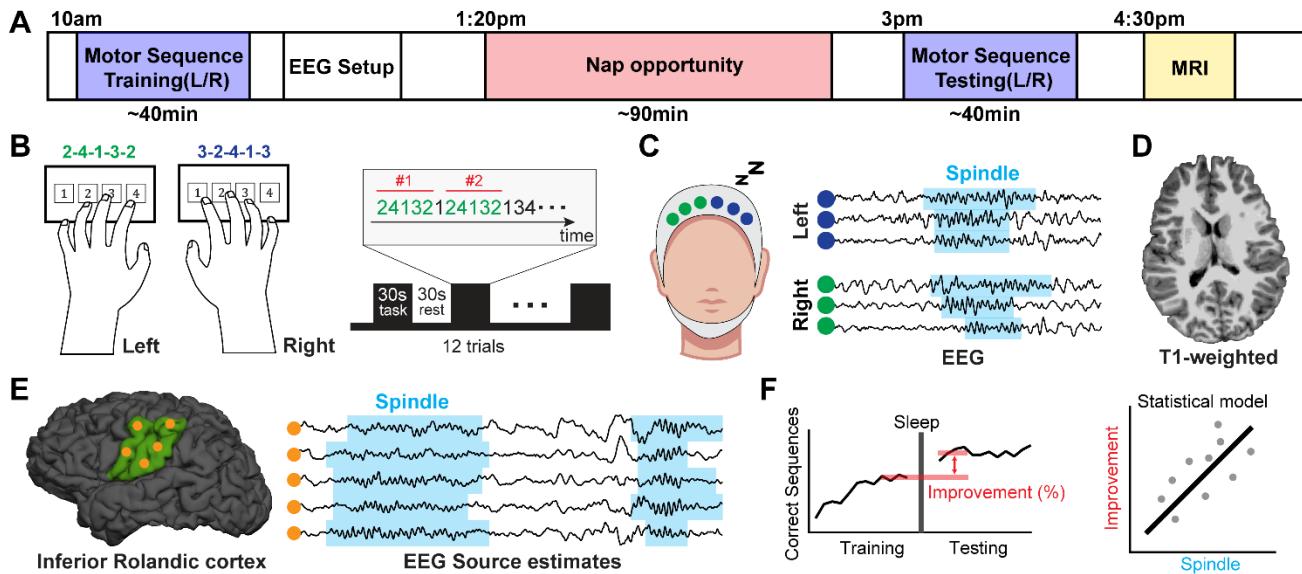


Figure 1. Illustration of the study design. **A)** Overview of the experiment. **B)** Subjects were trained on the motor sequence typing task (MST) with the left and right hands before the nap opportunity and tested after the nap opportunity. **C)** During the nap opportunity, high density EEG were recorded from which sleep spindles were subsequently detected. **D)** After the MST testing, an MRI was obtained. **E)** Sleep spindles were also detected in the inferior Rolandic cortex using electrical source imaging. **F)** Memory consolidation was measured from the MST task and compared to spindle rate during the nap opportunity.

95 Finger tapping motor sequence task

96 For our memory task, we used a well-validated probe of sleep dependent memory consolidation, the finger tapping
97 motor sequence task (MST). This task has been validated to capture sleep-dependent memory consolidation in
98 healthy adults, where performance improves after sleep compared to an equal period of wakefulness²².

99 Subjects were asked to place their fingers on four numerically labeled keys on a standard number pad. They
100 were then instructed to repeatedly type a 5-digit sequence (e.g., 4-1-3-2-4) as quickly and accurately as possible
101 during twelve 30 second trials separated by 30 second rest periods (Figure 1B)²². To minimize the involvement of
102 working memory, the sequence was displayed on a monitor during the typing trials. Subjects were trained on
103 separate sequences with their left and right hands before sleep, with a 10-minute break between left- and right-hand
104 training sessions. Following sleep, subjects were tested on the same sequences on the left and right hand respectively
105 with an intervening 10-minute break.

106 To exclude performance outliers across trials, for each subject and each hand, we fit an exponential model

107 to the learning curve during training, and included a constant offset to the exponential model during the post-sleep
108 testing, as in ²³. If performance on a trial was less than expected (defined as more than two standard deviations
109 below the model fit), it was excluded as an outlier. The causes of outliers include inattention, task interruption, or
110 misplacement of the fingers on the keys, for example.

111 To quantify sleep-dependent memory consolidation, for each hand, we calculated the percentage difference
112 between the mean of the last three correct sequences in the training session and the mean of the first three correct
113 sequences in the testing session, following previously published procedures²².

114

115 ***EEG recordings***

116 EEG recordings were acquired with a 70-channel cap (Easycap, Vectorview, Elekta-Neuromag, Helsinki, Finland)
117 at a sampling rate of 2035 Hz or 2000 Hz, and the data were subsequently downsampled to 407 Hz or 400 Hz for
118 analysis. In each case, impedances were maintained below 10 kΩ. Electrode locations were digitized using a 3D
119 digitizer (Fastrak, Polhemus Inc., Colchester, VA). All recordings were manually inspected and sleep-staged by a
120 board-certified neurophysiologist following standard procedures. To target sleep spindles, N2 was selected for
121 analysis, as done previously. Channels with continuous artifact were excluded. The remaining data were re-
122 referenced to an average signal for subsequent analysis.

123

124 ***MRI recordings***

125 Following the MST testing, all subjects underwent a same-day brain MRI. MRI data were collected on a 3T
126 Magnetom Prisma Siemens MRI scanner with a 64-channel head coil at the Martinos Center for Biomedical
127 Imaging with the following parameters: Multiecho MEMPRAGE (TE = 1.74 milliseconds, TR = 2530 milliseconds,
128 flip angle = 7°, voxel size = 1 × 1 × 1 mm³), T2 FLAIR (TE = 3 milliseconds, TR = 5000 milliseconds, flip angle =
129 7°, voxel size = 0.9x0.9x0.9 mm³). ESI analysis was performed with the MNE-C software package
130 (<https://mne.tools/stable/index.html/>). Cortical brain surfaces were reconstructed using FreeSurfer 7.1.1
131 (<https://surfer.nmr.mgh.harvard.edu/>) from MEMPRAGE and T2 FLAIR data.

132

133 ***Electrical Source Imaging (ESI)***

134 Digitized electrode coordinates were aligned to the MEMPRAGE data using the nasion and auricular points as
135 fiducial markers, and multiple points collected along the facial surface. A three-compartment boundary element
136 model was generated for the forward model using the watershed algorithm in FreeSurfer²⁴. EEG source activity was
137 estimated using the dSPM algorithm in the MNE software package²⁵. To do so, source estimates of EEG activity
138 were generated for 10,242 vertices per hemisphere. Then, source activity was averaged across 162 vertices per
139 hemisphere by averaging across circles with 1 cm radius using a full-width half-max smoothing kernel in MNE.

140 Because epileptiform spikes in RE have been well-localized to the inferior Rolandic cortex, and we have
141 previously reported a spindle deficit in this region in a separate cohort²⁶, this cortical region was selected as our
142 Region of Interest (ROI) for source analysis. To define this ROI, for each subject, a sphere from the most superior
143 vertex in the Rolandic cortex with a radius equal to half of the distance between the most superior and inferior
144 vertices in Rolandic cortex was labeled and excluded from the precentral and postcentral gyrus labels in Freesurfer,
145 following procedures described previously^{26,27}.

146

147 ***Sleep spindle detector***

148 To measure sleep spindles, we applied an automated spindle detector that we developed specifically to perform well
149 in the setting of sharp events, which are common features in the EEG recordings from patients with epilepsy and
150 young children⁸. To build a spindle detector robust to both healthy and disease states, the detector was trained and
151 validated on manual spindle markings from healthy children, children with continuous spike and wave sleep with
152 encephalopathy, and children with Rolandic epilepsy, resulting in 19,625 manually marked spindles from 115
153 unique pediatric subjects²⁸ not included in this project.

154 To apply the spindle detector, for each EEG channel or source space time series of interest, we evaluated
155 0.5 s intervals of data and computed three features: theta band power (4-8 Hz), sigma band power (9-15 Hz), and
156 the Fano factor of the oscillation intervals, which is a measure of cycle regularity⁸. We chose 0.5 s intervals, which
157 are the typical minimum duration accepted for sleep spindles²⁹, to maintain a 2 Hz frequency resolution, allowing
158 reliable estimation of the theta band power. Spindle detections separated by less than 1 s were concatenated⁸.

159 For EEG data, spindle rate was averaged across electrodes in each brain region (Central, Temporal, Frontal,
160 Parietal and Occipital) as in ⁸. For ESI data, the spindle rate across all vertices within the inferior Rolandic cortex
161 were averaged to create a single spindle rate for this ROI per hemisphere, as in ²⁶.

162

163 ***Statistical analyses***

164 To test for differences in spindle rate between groups (control, resolved RE, and active RE), we applied a mixed-
165 effects linear model with spindle rate as the dependent variable, group and age as predictors, and a random subject-
166 specific intercept to account for two observations per subject (left and right hemispheres for each subject). For our
167 primary hypothesis that spindle rate is decreased in the epileptogenic region in Rolandic epilepsy, this model was
168 estimated from spindle rates recorded in the centrot temporal scalp and inferior Rolandic cortex. To confirm the
169 spatial specificity of this result, this model was also applied to other brain regions.

170 To test for evidence of sleep-dependent memory consolidation using the MST, we applied a mixed-effects
171 linear model with sleep-dependent memory consolidation (see ***Data analysis***) as the dependent variable; age, and
172 whether the subject slept or remained awake during the rest opportunity as predictors; and a subject-specific
173 intercept to account for two observations per subject (improvement from the left and right hands for each subject).
174 We estimated the model separately for each patient group.

175 To test for differences in sleep-dependent memory improvement between groups for subjects who slept
176 during the rest opportunity, we estimated a mixed-effects linear model with sleep-dependent memory consolidation
177 as the dependent variable, group and age as predictors, and a subject-specific intercept to account for two
178 observations per subject (improvement from the left and right hands for each subject).

179 To test for a possible confounding relationship between MST performance during training and sleep-
180 dependent memory consolidation, we estimated a linear mixed-effects model with sleep-dependent memory
181 consolidation as the dependent variable, the mean number of correct sequences in the last three training trials and
182 age as predictors, and a subject-specific intercept (improvement from the left and right hands for each subject).

183 To test for a relationship between spindle rate and sleep-dependent memory improvement in the
184 centrot temporal region and inferior Rolandic cortex, we estimated a linear mixed-effects model with sleep-dependent

185 memory consolidation as the dependent variable, spindle rate and age as predictors, and a subject-specific intercept.
186 In doing so, we assumed that spindle rate in the left hemisphere was linked to memory improvement with the right
187 hand, and spindle rate in the right hemisphere was separately linked to memory improvement with the left hand³⁰.

188

189 ***Data availability***

190 Raw data were generated at Massachusetts General Hospital and the Athinoula A. Martinos Center for Biomedical
191 Imaging. Derived data supporting the findings of this study are available from the corresponding author upon
192 reasonable request. The code for spindle detection is available at <https://github.com/Mark-Kramer/Spindle->
193 [Detector-Method](#)

194

195 **Results**

196 ***Subject characteristics***

197 Between January 2020 and December 2023, 23 children with RE (9 with active disease, 5F, age 6.0-12.8 years), 14
198 children with resolved disease (8F, age 8.8-17.8 years), and 19 control children (8F, age 6.9-18.7 years) were
199 enrolled in this prospective study. Among children who slept, the average duration of N2 sleep per EEG recording
200 was 22.6 min (range: 9.6-49.7 min) in active RE, 27.1 min (range: 4.1-71.3 min) in resolved RE, and 21.3 min
201 (range: 1.8-43.7 min) in controls. We

202 detected no significant differences in
203 the average duration of N2 sleep
204 between groups (one-way ANOVA,
205 p=0.7). Subject characteristics are

Table 1. Subject characteristics

	Active (n=9)	Resolved (n=14)	Control (n=19)	One-way ANOVA / Chi-square test (p)
Age (years)	10.3 (6.0-12.8)	12.0 (8.8-17.8)	13.1 (6.9-18.7)	0.11
Female sex (%)	55.6	57.1	42.1	0.65
Right handedness (%)	100.0	92.9	94.7	0.73
Sleep opportunity (min)	96.1 (90.0-145.0)	93.9 (90.0-110.0)	92.5 (90.0-108.0)	0.66

206 provided in **Table 1**.

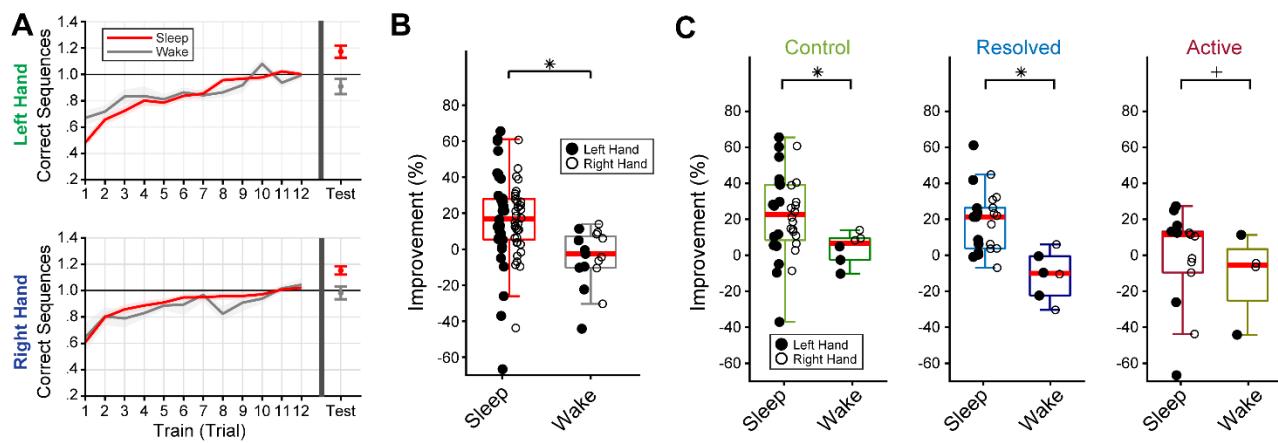
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208 ***The motor sequence task captures sleep dependent memory consolidation in children***

209 During the nap opportunity provided, 34 children slept (7 active RE, 11 resolved RE, and 16 controls) and eight

210 children remained awake for the duration of the opportunity (2 active RE, 3 resolved RE, and 3 controls). The
211 duration of the nap opportunity was similar between groups ($p=0.7$, one-way ANOVA, **Table 1**). Among children
212 who slept, the duration of N2 sleep was similar between groups ($p=0.7$, one-way ANOVA, **Table 1**).

213 Children who slept had a greater improvement in their performance of the MST during testing (mean 16.5%,
214 range [-66.7, 65.6]%) than children who did not sleep (mean -5.5%, range [-44.2, 14.0]%; mean improvement
215 between groups of 20.8%, 95% CI [7.0, 34.7]%, $p=0.004$; **Figure 2A-B**). This finding was qualitatively consistent
216 in each patient group (**Figure 2C**; controls, mean improvement between groups of 23.5% (95% CI [1.5, 45.5]%,
217 $p=0.037$); resolved RE, mean improvement of 34.2% (95% CI [18.3, 50.0]%, $p=0.0002$), active RE, mean
218 improvement between groups of 21.5% (95% CI [-4.1, 47.2]%, $p=0.094$).



219
220 **Figure 2. The motor sequence typing task captures sleep dependent memory consolidation. A)** All children
221 showed normal learning of the task during the 12 training trials (left), but children who stayed awake had
222 decreased improvement after the nap opportunity compared to those who slept. **B)** Memory improvement of the
223 nap opportunity is plotted for each subject, each hand. **C)** Memory improvement in children who slept compared
224 to those who stayed awake in resolved, active RE, and control groups. * $p<0.05$, + $p<0.1$

219
220 **Children with active RE have impaired sleep-dependent memory consolidation**

221 To evaluate for deficits in sleep-dependent memory consolidation in children with active RE, we compared the MST
222 improvement between groups. All children demonstrated learning of the task during the training trials, with initial
223 improvement and subsequent plateau in performance (**Figure 3A-D**). Across all groups, 4.5% of trials were

224 excluded as outliers; there was no difference in the percentage of excluded trials between groups (controls: 4.7%;
 225 resolved RE: 4.6%; active RE: 3.9%; $p=0.5$, one-way ANOVA). We detected no relationship between the final
 226 performance of the task during training and the degree of sleep-dependent memory consolidation ($p=0.6$, linear
 227 mixed effects model). Children with active RE have decreased memory consolidation compared to control children
 228 ($p=0.001$, mean percentage reduction: 25.7%, 95% CI [10.3, 41.2]%) and compared to children with resolved RE
 229 ($p=0.007$, mean percentage reduction: 21.9%, 95% CI [6.2, 37.6]%; **Figure 3D-E**). Consistent results were observed
 230 for each hand and in all groups. Thus, children with RE have a transient deficit in sleep-dependent memory
 231 consolidation during the active phase of their disease.

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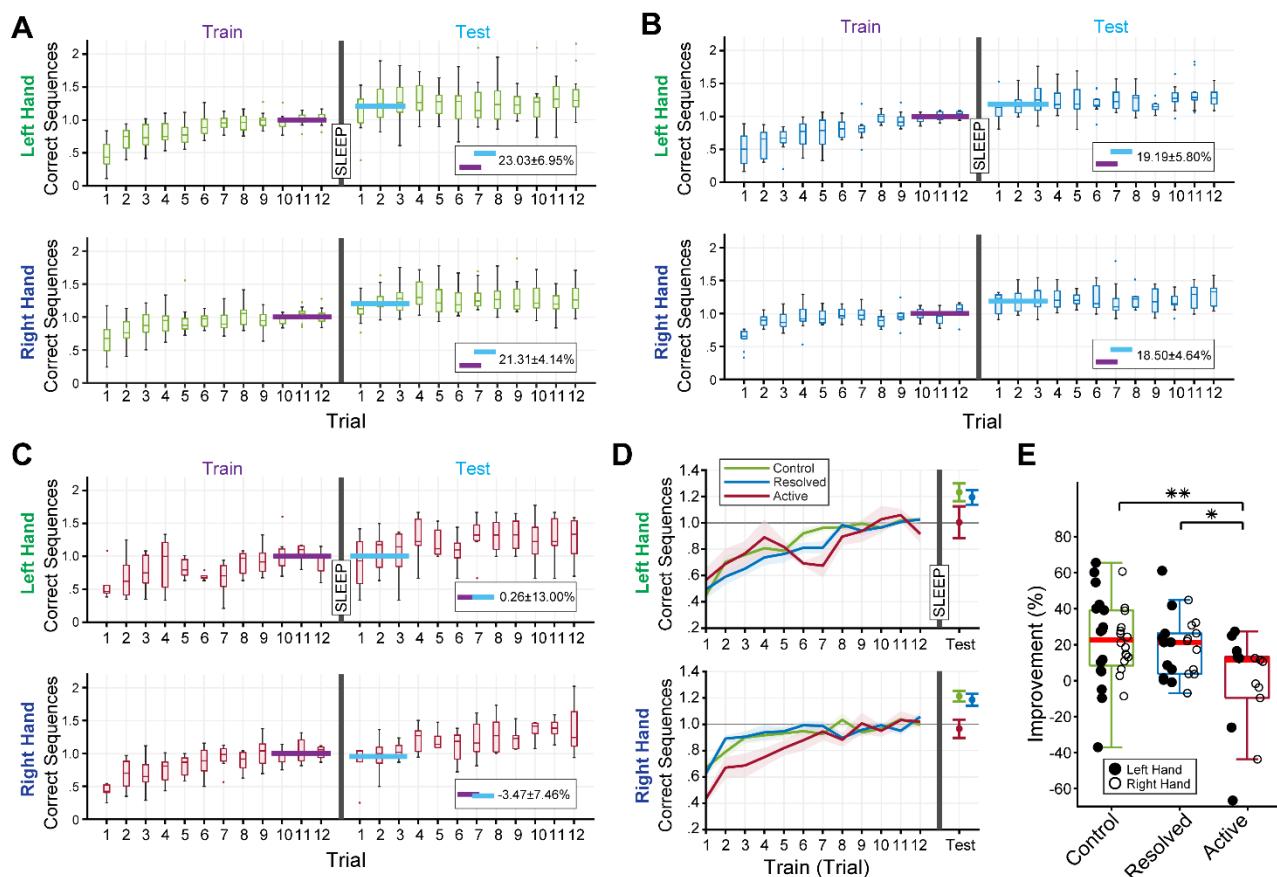


Figure 3. Decreased sleep-dependent memory consolidation in active RE. Box plots of correct sequences normalized by the last three trainings trials in A) control group, B) resolved RE group, and C) active RE group. D-E) Children with active RE showed normal learning of the task during the 12 training trials, but decreased sleep-dependent improvement compared to children with resolved RE and controls. $**p\leq 0.005$, $*p\leq 0.01$

233 **Children with active RE have decreased sleep spindles in the epileptic zone**

234 Based on our prior findings⁸, we hypothesized that children with active RE would have decreased sleep spindles in
235 the centrot temporal region compared to controls. Indeed, we found that children with active RE had decreased
236 spindle rates in the central (p=0.01, mean decrease 2.4 spindles/min, 95% CI [0.6, 4.1] spindles/min) and temporal
237 electrodes (p=0.01, mean decrease 2.8 spindles/min, 95% CI [0.7, 5.0] spindles/min) compared to the control
238 children (**Figure 4**). Combining central and temporal channels, children with active RE had a reduced spindle rate
239 in the centrot temporal region compared to control children (p=0.008, mean decrease 2.5 spindles/min, 95% CI [0.7,

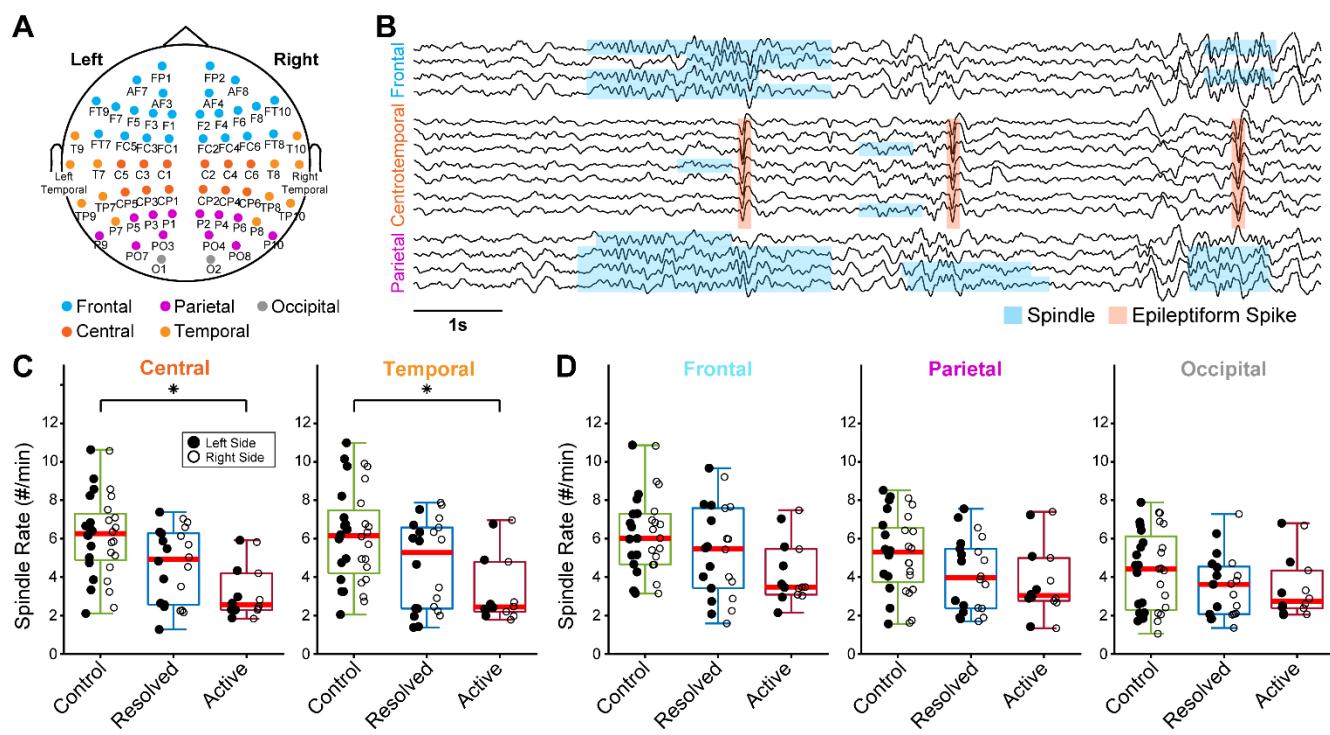


Figure 4. Focal sleep spindle deficit in the epileptic cortex in active RE. **A)** Illustration of electrode groups corresponding to frontal (blue), parietal (purple), occipital (gray), central (red), and temporal (orange). **B)** Example visualization showing the absence of sleep spindles (blue) in a cortical region impacted by epileptiform spikes (red). **C)** Spindle rate is decreased in the central and temporal regions in children with active RE compared to controls, *p<0.05. **D)** There is a trend toward a decrease in spindle rate in the frontal region (p=0.06) in the active RE group compared to the control group. There is no evidence of a difference in spindle rate between active RE and control groups in parietal (p=0.2) or occipital (p=0.3) regions. In each boxplot, the red line indicates the median, and the box indicate the 25th and 75th percentiles. The whiskers extend to the most extreme data points.

240 4.4] spindles/min)⁸. We found no evidence of a difference in spindle rate between groups in any other brain region.
241 This finding replicates our prior work⁸ in a second cohort, and we conclude that spindle rate is transiently and
242 focally decreased in the cortical epileptic zone in children with active RE.

243

244 ***Spindle rate predicts contralateral sleep-dependent memory improvement***

245 Based on the proposed mechanistic relationship between sleep spindles and sleep-dependent memory consolidation⁶,
246 we hypothesized that spindle rate would predict sleep-dependent memory consolidation in children as measured by
247 performance in the contralateral hand³⁰. As hypothesized, we found a positive correlation between spindle rate in
248 the centrot temporal region and sleep-dependent memory consolidation across children ($p=0.004$, mean MST
249 improvement of 3.9%, 95% CI [1.3, 6.4]%, for each unit increase in spindle rate; **Figure 5**). We found no evidence
250 that age predicted memory consolidation ($p=0.8$). From these findings, we conclude that centrot temporal spindle
251 rate predicts sleep-dependent memory consolidation in children. This finding is consistent with the proposed
252 mechanistic relationship between sleep spindles and sleep-dependent memory consolidation.

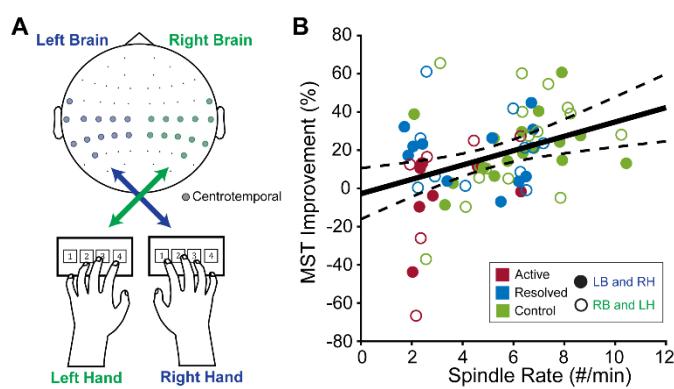


Figure 5. Spindle rate correlates with sleep-dependent memory improvement in the centrot temporal region. A) MST improvements with left and right hand are linked with the spindle rate in the contralateral hemisphere. B) Sleep spindle rate in the centrot temporal region positively correlates with the degree of sleep-dependent memory consolidation. Black (dashed) curves indicate estimated model fit (95% confidence interval). LB: left brain; RH: right hand; RB: right brain; LH: left hand.

253 ***Spindle rate in the inferior Rolandic cortex is decreased in active RE and predicts sleep-dependent memory***
254 ***consolidation***

255 To focus our analysis specifically on the irritative zone in RE, we performed electrical source imaging, targeting
256 the inferior Rolandic cortex as our region of interest (see Materials and Methods). We then estimated spindle rate

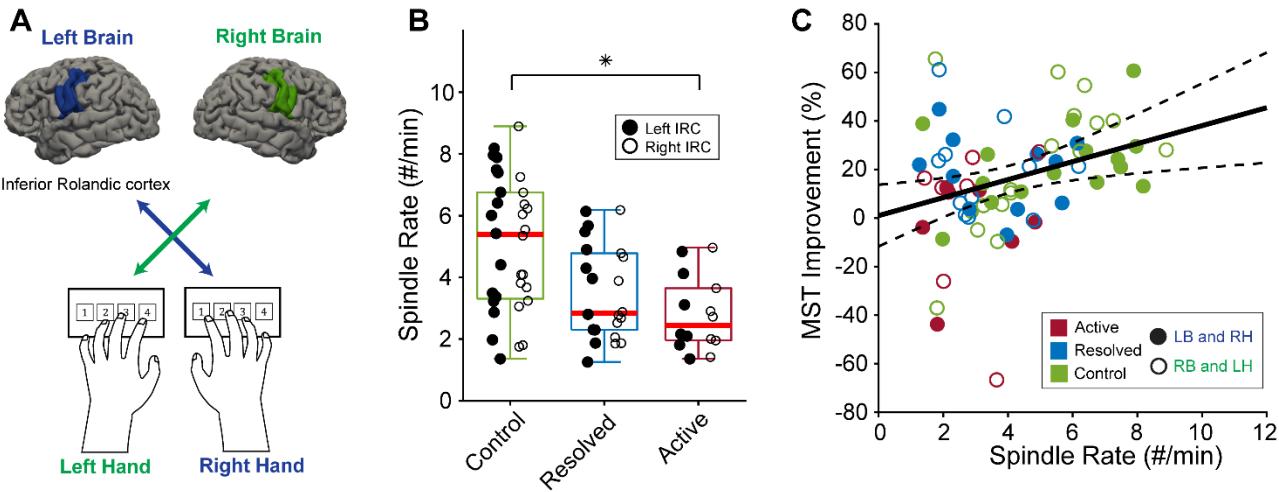


Figure 6. Spindle rate correlates with sleep-dependent memory improvement in inferior Rolandic cortex. A) MST improvements with left and right hand are linked with the spindle rate in the contralateral inferior Rolandic cortex. **B)** Children with active RE showed a reduced spindle rate, * $p < 0.05$. **C)** Sleep spindle rate in inferior Rolandic cortex positively correlates with the degree of sleep-dependent memory consolidation. Black (dashed) curves indicate estimated model fit (95% confidence interval). IRC: Inferior Rolandic cortex). LB: left brain; RH: right hand; RB: right brain; LH: left hand.

257 from this region across groups. Replicating our prior results²⁶ in this new cohort, we found reduced spindle rate in
258 the inferior Rolandic cortex in children with active RE compared to control children ($p=0.027$, mean decrease 1.85
259 spindles/min, 95% CI [0.21, 3.49], **Figure 6**). We also found that spindle rate in the inferior Rolandic cortex
260 predicted sleep dependent memory consolidation as measured in the contralateral hand across children ($p=0.014$,
261 mean MST improvement of 3.7%, 95% CI [0.8, 6.7]%, for each unit increase in spindle rate). We again found no
262 evidence that age predicted memory consolidation ($p=0.3$). Consistent with results estimated from the scalp EEG,
263 these findings support the proposed mechanistic relationship between sleep spindles and sleep-dependent memory
264 consolidation.

265

266 4. Discussion

267 Sleep spindles are prominent thalamocortical brain oscillations in the sleep EEG that have been mechanistically
268 linked to essential sleep-dependent cognitive processes in animal models^{7,31,32} and healthy controls^{13,19,22,33}. Here we

269 identify a deficit in sleep-dependent memory consolidation in Rolandic Epilepsy, the most common focal
270 developmental epilepsy in childhood. We find that a transient, focal deficit in sleep spindle rate correlates with a
271 transient deficit in sleep-dependent memory consolidation. Further, that sleep spindle rate positive predicts sleep
272 dependent memory consolidation in RE and control children.

273 Increasing evidence suggests that sleep spindles are a key oscillatory mechanism required for off-line
274 memory consolidation during N2 sleep³⁴. Sleep spindles are generated by GABAergic neurons in the thalamic
275 reticular nucleus and coordinated by well-delineated thalamocortical circuits. Spindle rate is higher in cortical
276 regions that are linked to prior learning experiences¹⁵, and spindles accompany the cortical reactivation patterns of
277 memory replay during sleep²⁰. In rodent models, calcium recordings during sleep suggest that sleep spindles gate
278 dendritic calcium shifts required for synaptic plasticity. Spindle oscillations also coordinate hippocampal sharp
279 wave ripple oscillations that reflect neuronal replay in rodents^{7,31,35} and in humans³⁶. In healthy adults, the
280 relationship between sleep spindles and sleep-dependent memory consolidation is well-established for both
281 procedural^{13,14,22,30,33} and declarative^{15,16,21} tasks. In healthy children, sleep spindle rate, not sleep duration³⁷, predicts
282 general cognitive abilities^{18,38} and sleep-dependent memory consolidation for declarative^{18,19} and procedural³⁹ tasks.
283 Sleep spindle rate has been reported to be decreased in autism, developmental delay, and attention deficit
284 hyperactivity disorder^{40,41} and correlate with cognitive abilities in children with dyslexia⁴² and epilepsy⁸. Critically,
285 several studies have found that medications and interventions that increase sleep spindles improve memory
286 consolidation, and medications that disrupt spindles impair memory consolidation^{9,43-45}, suggesting a mechanistic
287 link between sleep spindles and memory performance. Further supporting sleep spindles as generalizable biomarker
288 for sleep-dependent memory processes across ages and conditions, we find that focal spindle rate predicts sleep
289 dependent memory consolidation on a motor procedural task in healthy children and children with focal epilepsy.

290 The motor sequence typing task involves learning and typing a 5-digit sequence as quickly and accurately
291 as possible during a training period, and again during a testing period, separated by wakefulness or sleep. This task
292 has been validated to capture sleep-dependent memory consolidation in healthy adults²², adults with schizophrenia
293 and adults with epilepsy⁴⁶. In healthy children, one study found robust sleep-dependent improvements in the motor
294 sequence task in 9-11 years old children while two studies in 6-11 years old children failed to detect sleep-dependent

295 improvements^{37,47}. In this study, we analyzed children 6-18 years old from three groups – children with active RE,
296 in remission, and control subjects – and found greater improvements in the performance of the motor sequence task
297 in children who slept compared to those who did not, and a positive relationship between the degree of consolidation
298 and sleep spindle rate. In our cohort, we did not find a relationship between the degree of consolidation and age.
299 Our use of a short nap opportunity, where the state of consciousness was observed continuously by EEG, may have
300 afforded a more sensitive detection of sleep than self-report used in prior studies. These findings support the motor
301 sequence task as a sensitive measure of sleep-dependent memory consolidation in school-age children.

302 Although our sample size was relatively small, our findings of a focal spindle deficit in RE replicate results
303 from a prior study⁸, increasing the rigor of this finding. Here, we also used short naps instead of a full night of sleep,
304 as prior work has demonstrated that nocturnal spindle rate can be reliably estimated from daytime naps in adults⁴⁸
305 and predict several measures of cognitive ability in children^{8,49}. However, a full night could capture further sleep
306 dynamics, such as alterations in sleep homeostasis⁵⁰, which were not evaluated here.

307 In conclusion, children with active RE have deficits in sleep-dependent memory consolidation that can be
308 predicted by non-invasive measures of sleep spindle rate. This work supports sleep spindles as a mechanistic
309 biomarker for memory consolidation in children with RE and controls, and implicates disruption of this rhythm in
310 the cognitive symptoms observed in RE.

311

312 **Author Contribution:**

313 H.K and C.J.C planned the study, analyzed the data; H.K. wrote the first draft of the manuscript; H.K, D.M.C,
314 E.A.K, S.K.G, J.F.H, E.D.B, K.G.W, W.S and C.J.C collected data, wrote the manuscript; M.A.K, D.S.M
315 contributed to developing analysis methods and provided feedback; C.J.C supervised the study.

316

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319

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