

Neural Correlates of human cognitive abilities during sleep

Fang, Zhuo¹, Ray, Laura B.^{1,4}, Owen, Adrian M.^{1,2}, & Fogel, Stuart M.^{1-5*}.

1. Brain & Mind Institute, Western University, London, Canada, 2. Department of Psychology, Western University, London, Canada, 3. School of Psychology, University of Ottawa, Ottawa, Canada, 4. University of Ottawa Institute for Mental Health Research, Ottawa, Canada, 5. University of Ottawa Brain and Mind Research Institute, Ottawa, Canada.

Corresponding author:

Dr. Stuart M. Fogel

Assistant Professor

School of Psychology

Director, Sleep Neuroscience

University of Ottawa Institute for Mental Health Research

University of Ottawa

Ottawa, Ontario, Canada

(613) 562-5800 x4295

sfogel@uottawa.ca

socialsciences.uottawa.ca/sleep-lab/

ABSTRACT

1 Inter-individual differences in sleep spindles are highly correlated with “Reasoning” abilities
2 (problem solving skills; i.e., the ability to employ logic, identify complex patterns), but not Short
3 Term Memory or Verbal abilities. Simultaneous electroencephalography and functional
4 magnetic resonance imaging (EEG-fMRI) have revealed brain activations time-locked to
5 spindles (e.g., thalamic, paralimbic, and motor cortical areas)—yet the functional significance of
6 inter-individual differences in spindle-related brain activation remains to be investigated. Using
7 EEG-fMRI during sleep, we identified, for the first time, the neural activation patterns time-
8 locked to spindles that are correlated with cognitive abilities. Similar to previous studies,
9 activations time-locked to spindles were observed in thalamocortical circuitry and basal ganglia
10 regions. Importantly, spindle-related activation in a subset of these regions were specifically
11 related to inter-individual differences in Reasoning, but not STM or Verbal abilities. These
12 results may help elucidate the physiological mechanisms which support the function of sleep
13 for the capacity for reasoning.

14 **Keywords:** sleep, spindles, cognitive abilities, simultaneous EEG-fMRI

15 INTRODUCTION

16 The sleep spindle is the only known spontaneous neural oscillation that has been identified
17 as an electrophysiological marker of cognitive abilities and aptitudes, that are typically assessed
18 by intelligence quotient (**IQ**) tests (for review, see Fogel & Smith, 2011). As one of the defining
19 features of Stage 2 non-rapid eye movement (**NREM**) sleep, spindles are traditionally defined
20 as neural oscillations between 11 and 16 Hz (Iber et al., 2007), lasting up to ~3 sec in duration
21 (Rechtschaffen & Kales 1968). Spindles are remarkably stable from night-to-night, but vary
22 considerably from one individual to another, and have even been suggested to be an
23 “electrophysiological fingerprint” (De Gennaro et al., 2005) because of the trait-like nature of
24 spindles (Silverstein & Michael Levy, 1976). Previous studies have revealed that interindividual
25 differences in spindle characteristics are related to the capacity for reasoning (i.e., the ability to
26 identify complex patterns and relationships, the use of logic, existing knowledge, skills, and
27 experience to solve novel problems (Fogel & Smith, 2007; Fogel & Smith, 2006; Nader & Smith,
28 2001, 2003). Moreover, the relationship between spindles and cognitive abilities is specific to
29 the capacity for Reasoning, over-and-above Verbal abilities and short-term memory (Fang et al.,
30 2017; Fogel et al., 2007). These studies have provided insight into the electrophysiological
31 correlates of Reasoning abilities, insofar as to suggest that efficient functioning of the neural
32 substrates that support spindle generation (e.g., thalamocortical circuitry) may be related to the
33 capacity for these cognitive skills. Interestingly, spindle production is reduced with age (Carrier
34 et al., 2001; Fogel et al., 2014; Fogel et al., 2017), and abnormal in developmental disorders,
35 such as Autism (Limoges et al., 2005), learning disabilities (Shibagaki et al., 1982) and in
36 schizophrenia (Wamsley et al., 2012). Thus, a better understanding of the neural basis of the
37 relationship between spindles and cognitive abilities may ultimately help to better understand
38 the significance to a variety of normal and abnormal cognitive functioning in healthy individuals

39 and in neurological conditions. This may eventually lead to novel interventions to precisely
40 target cases where spindle production is abnormal or non-optimal. However, it is necessary to
41 first understand the physiological correlates of the relationship between spindles and
42 Reasoning abilities in healthy individuals, which is the principle aim of the current study.

43 The association between sleep spindles and individual differences in cognitive abilities has
44 been well documented. For example, Nader and Smith (Fogel & Smith, 2006; Nader & Smith,
45 2001, 2003) found that both the number of sleep spindles and sigma power (12–14 Hz) uniquely
46 correlated with Performance IQ scores, over-and-above Verbal IQ (Fogel et al., 2007).
47 Consistently, Bodizs and colleagues (Bódizs et al., 2005) found that spindle density was
48 correlated with Reasoning abilities (i.e., “fluid intelligence”) measured by the Raven’s
49 Progressive Matrices (Raven, Court, and Raven 1976). Similar studies identified a positive
50 correlation between right-parietal fast spindles and visuospatial abilities assessed by the Rey–
51 Osterrieth Complex Figure test (Bódizs et al., 2008), and a positive correlation between
52 spindles and the intellectual abilities measured by the Cattell Culture Fair Intelligence Test,
53 specifically in woman but not in men (Ujma et al., 2014). Although, a relationship in men was
54 subsequently identified by the same group in daytime sleep (Ujma et al., 2015). Most recently,
55 Fang and colleagues (Fang et al., 2017) used the Cambridge Brain Sciences (**CBS**) test battery
56 (Hampshire et al., 2012) to explore if the relationship between sleep spindles and intellectual
57 ability was a direct relationship, or whether this could be partially (or fully explained) by other
58 spindle-related factors such as sleep quality or circadian chronotype. They found that, indeed,
59 the relationship between spindles and Reasoning abilities was independent of sleep quality and
60 circadian chronotype. Taken together, these studies support the notion that sleep spindles are
61 an electrophysiological marker of cognitive abilities, and specifically, the ability to solve

62 problems using logic and reasoning. However, the brain regions supporting the relationship
63 between the sleep spindles and cognitive abilities are still unknown.

64 Only a small number of studies have employed simultaneous electroencephalography and
65 functional magnetic resonance imaging (**EEG-fMRI**) to explore brain activations time-locked to
66 spindles (Andrade et al., 2011; Caporro et al., 2012; Laufs et al., 2007; Schabus et al., 2007;
67 Tyvaert et al., 2008). Spindle-related activations have been consistently found in the thalamus
68 and the temporal lobe, for both fast spindles and slow spindles (Andrade et al., 2011; Caporro
69 et al., 2012; Laufs et al., 2007; Schabus et al., 2007; Tyvaert et al., 2008), and activation of the
70 cingulate cortex and motor areas have been reported to be associated with sleep spindles
71 during NREM sleep (Andrade et al., 2011; Caporro et al., 2012). Interestingly, activation of the
72 putamen has also been found to be correlated with spindle events (Caporro et al., 2012; Tyvaert
73 et al., 2008) and Andrade et al. (2011) found a strong interaction between sleep spindle
74 occurrence and hippocampal formation functional connectivity. In addition, by directly
75 comparing fast spindles vs. slow spindles, Schabus et al. (2007) observed that slow spindles
76 increase activations in the superior temporal gyrus while fast spindles recruit activations in the
77 sensorimotor area, mesial frontal cortex, hippocampus, and cerebellum. Not surprisingly, given
78 the methodological complexities and limitations of EEG-fMRI recordings during sleep, most of
79 these studies used relatively small sample sizes ($n < 15$), suggesting that additional studies
80 investigating the neural correlates of sleep spindles in a larger sample is warranted.
81 Nonetheless, taken together, the extant literature intriguingly suggest that brain activations
82 associated with the action of sleep spindles involve well-known spindle-generating regions (e.g.,
83 thalamic and cortical regions), as well as regions which subserve cognitive functioning and
84 memory (e.g., hippocampal, striatal, prefrontal, motor cortical and cerebellar regions).

85 Interestingly, some of the regions activated during spindle events, are thought to support
86 human cognitive abilities. For example, the thalamocortical circuitry, one of the most important
87 neural substrates related to spindle generation (Steriade, Contreras et al.,1993; Steriade,
88 McCormick, & Sejnowski, 1993), has been observed to be involved in reasoning abilities
89 assessed by Raven’s Progressive Matrices test (Gray et al., 2003), the Wechsler Adult Scale
90 of Intelligence (WAIS-III) (Wechsler, 1997), and other reasoning ability-related tasks, especially
91 with regard to the prefrontal cortex and the thalamus (Bugg et al., 2006; Kroger, 2002; Melrose,
92 Poulin, & Stern, 2007; Waltz et al., 1999). In addition, the basal ganglia region, especially the
93 striatal areas (i.e. caudate and putamen), which are recruited during spindle events (Caporro
94 et al., 2012; Tyvaert et al., 2008), have also been found to be related to cognitive functions,
95 including reward-based learning (O’Doherty, 2004), planning (Elsinger et al., 2006), motor
96 execution (Monchi et al., 2006), and reasoning (Melrose et al., 2007; Rodriguez-Moreno &
97 Hirsch, 2009). Recently, Hampshire et al. (2012) employed the Cambridge Brain Sciences
98 cognitive test battery to identify and distinguish the brain networks that support distinct cognitive
99 abilities (e.g., Reasoning, Verbal, and Short Term Memory). It was found that the inferior frontal
100 sulcus, the inferior parietal cortex, and the dorsal portion of the anterior cingulate /
101 supplementary motor area activations related to Reasoning abilities and were disassociated
102 from brain regions that related to Verbal abilities and Short Term Memory. While it is intriguing
103 that a subset of regions which support Reasoning abilities are also regions activated with the
104 occurrence of sleep spindles, it remains to be investigated whether spindle-related activations
105 in these areas are correlated with interindividual differences in Reasoning abilities.

106 Thus, it is clear that spindle characteristics are linked to Reasoning abilities, however, the
107 neural correlates of this relationship remain unknown. Therefore, here, using a large sample of
108 simultaneous EEG-fMRI recordings during sleep, we sought to identify, for the first time, the

109 neuroanatomical function correlates of the relationship between sleep spindles and Reasoning
110 abilities. We hypothesized that the neural activation patterns, time-locked to spindles would be
111 related to distinct cognitive abilities whereby consistent with previous cognitive and
112 electrophysiological studies, spindle-related brain activations would be correlated with
113 Reasoning but not STM or Verbal abilities. This will provide insight into the neural basis of the
114 functional correlates of sleep spindles.

115 **RESULTS**

116 **Cognitive abilities: Cambridge Brain Sciences Trials**

117 Based on previous literature (Hampshire et al., 2012), the raw scores from each of the
118 12 subtests were Z-score normalized using the mean and standard deviation of each subtest
119 from a large population (N = 44,600). Each test item was then weighted according to the factor
120 loadings from Hampshire et al. (Hampshire et al., 2012) and then the respective sub-tests were
121 averaged to create the Reasoning, STM and Verbal sub-scores and transformed to a mean of
122 100 and a SD of 15, so that test scores were readily comparable to results from similar studies
123 that employed test batteries tapping into Reasoning and Verbal abilities, such as the
124 Multidimensional Aptitude Battery - II (Fogel et al., 2007; Fogel & Smith, 2006) and other
125 commonly used batteries of cognitive abilities (e.g., Wechsler Adult Intelligence Scale). The
126 descriptive statistics of each subtest are shown in **Table 1**.

Table 1. Descriptive statistics of the 3 CBS Trials subscales (Reasoning, Short-term memory (STM) and Verbal abilities).

IQ Measures	Range	Mean \pm SD	Median
Reasoning	78.84 - 108.17	95.65 \pm 7.20	96.46
STM	84.38 - 115.33	101.60 \pm 6.77	102.30
Verbal	88.51 - 110.92	99.62 \pm 5.12	99.52

127

128 **Sleep Architecture:**

129 Participants slept, on average, a total of 44.20 (SD=23.84) minutes in the scanner during
130 the experimental sleep session (**Table 2**). All N=29 participants experienced NREM2 sleep,
131 N=20 had SWS sleep, and N=8 had rapid eye movement (REM) sleep. Given the focus of the
132 current investigation, we did not analyze REM data. Participants had on average, a total of
133 334.74 (SD=212.29) total bandwidth sleep spindles at Cz during NREM sleep. Spindle
134 parameters for all spindles at Cz (11-16 Hz), slow spindles at Fz (11-13.5 Hz) and fast spindles
135 at Pz (13.5-16 Hz) during NREM sleep are shown in the **Table 2**.

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Table 2. Sleep architecture and sleep spindle parameters for spindles at Fz, Cz and Pz during NREM sleep from EEG-fMRI recording sessions.

	M	SD
Sleep Architecture		
Wake (min)	26.87	20.25
NREM1 (min)	5.84	4.38
NREM2 (min)	23.87	14.50
SWS (min)	14.77	17.17
NREM (min)	39.29	19.33
REM	17.80	10.76
Total Sleep	44.20	23.84
Total bandwidth (11-16 Hz) spindles at Cz		
Number	334.74	212.29
Duration (sec)	0.49	0.05
Amplitude (μV)	27.21	6.43
Density	8.22	2.34
Slow spindles (11-13.5 Hz) at Fz		
Number	249.41	179.40
Duration (sec)	0.38	0.06
Amplitude (μV)	42.71	9.44
Density	6.00	2.20
Fast (13.5-16 Hz) spindles at Pz		
Number	92.48	69.66
Duration (sec)	0.38	0.08
Amplitude (μV)	21.53	6.01
Density	2.50	1.80

Abbreviations: non-rapid eye movement sleep (NREM); stage 1 sleep (NREM1); stage 2 sleep (NREM2); slow wave sleep (SWS); rapid eye movement sleep.

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145 **Relationship between sleep spindles and cognitive abilities**

146 Standard multiple linear regression revealed that, taken together, Reasoning, Short Term
147 Memory and Verbal abilities significantly accounted for variability in spindle amplitude ($F(3, 25)$
148 $= 4.884$, $r^2 = 0.370$, $p = 0.008$), but not duration ($F(3, 25) = 0.531$, $r^2 = 0.060$, $p = 0.665$) or
149 density ($F(3, 25) = 2.522$, $r^2 = 0.232$, $p = 0.081$) at Cz during NREM sleep (**Table 3**). Similar to
150 previous studies (Fang et al., 2017; Fogel et al., 2007), inspection of the semipartial coefficients
151 revealed that Reasoning ability ($t(25) = 2.191$, $r = 0.401$, $p = 0.038$; **Figure 1**) uniquely
152 accounted for variability in spindle amplitude over and above STM ($t(25) = 0.314$, $r = 0.063$, p
153 $= 0.756$) and Verbal ($t(25) = 0.972$, $r = 0.191$, $p = 0.341$) abilities. The same regression analyses
154 were conducted for slow spindles at Fz and fast spindles at Pz, however, we did not observe
155 any significant relationship between spindles and cognitive abilities.

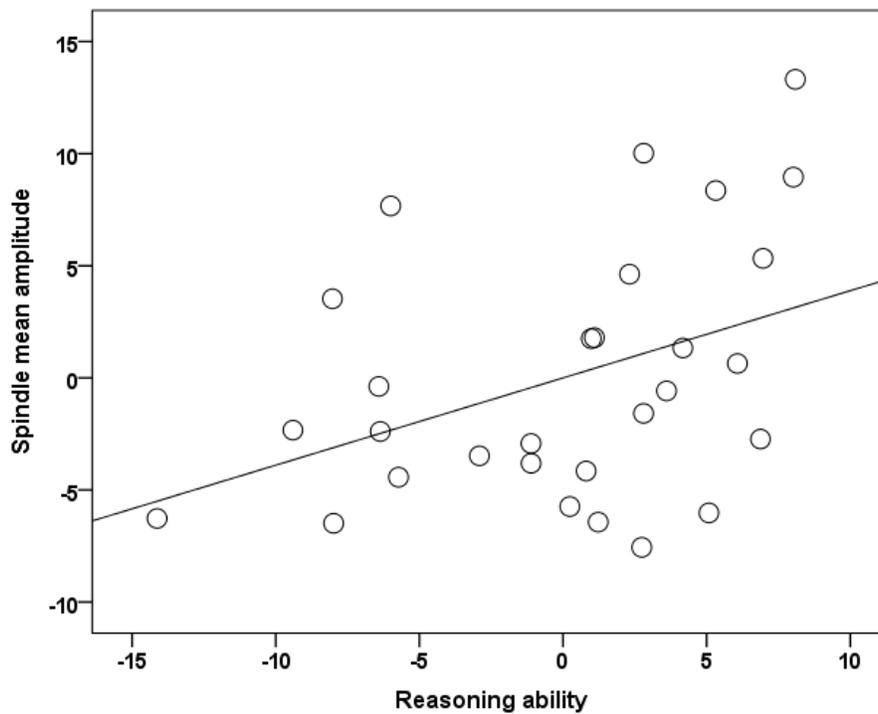
Table 3. Multiple regression analyses of the relationship between Cambridge Brain Sciences Trials and 11-16Hz spindles at Cz during NREM sleep. See **Figure 1**.

Overall regression effect			
Sleep Spindle parameter	r^2	$F(3,25)$	p
Amplitude	0.37	4.884	0.008*
Duration	0.060	0.531	0.665
Density	0.232	2.522	0.081
Post-hoc effects analyses			
CBS measures	Semipartial r	$t(25)$	p
Reasoning	0.401	2.191	0.038*
Verbal	0.191	0.972	0.341
STM	0.063	0.314	0.756

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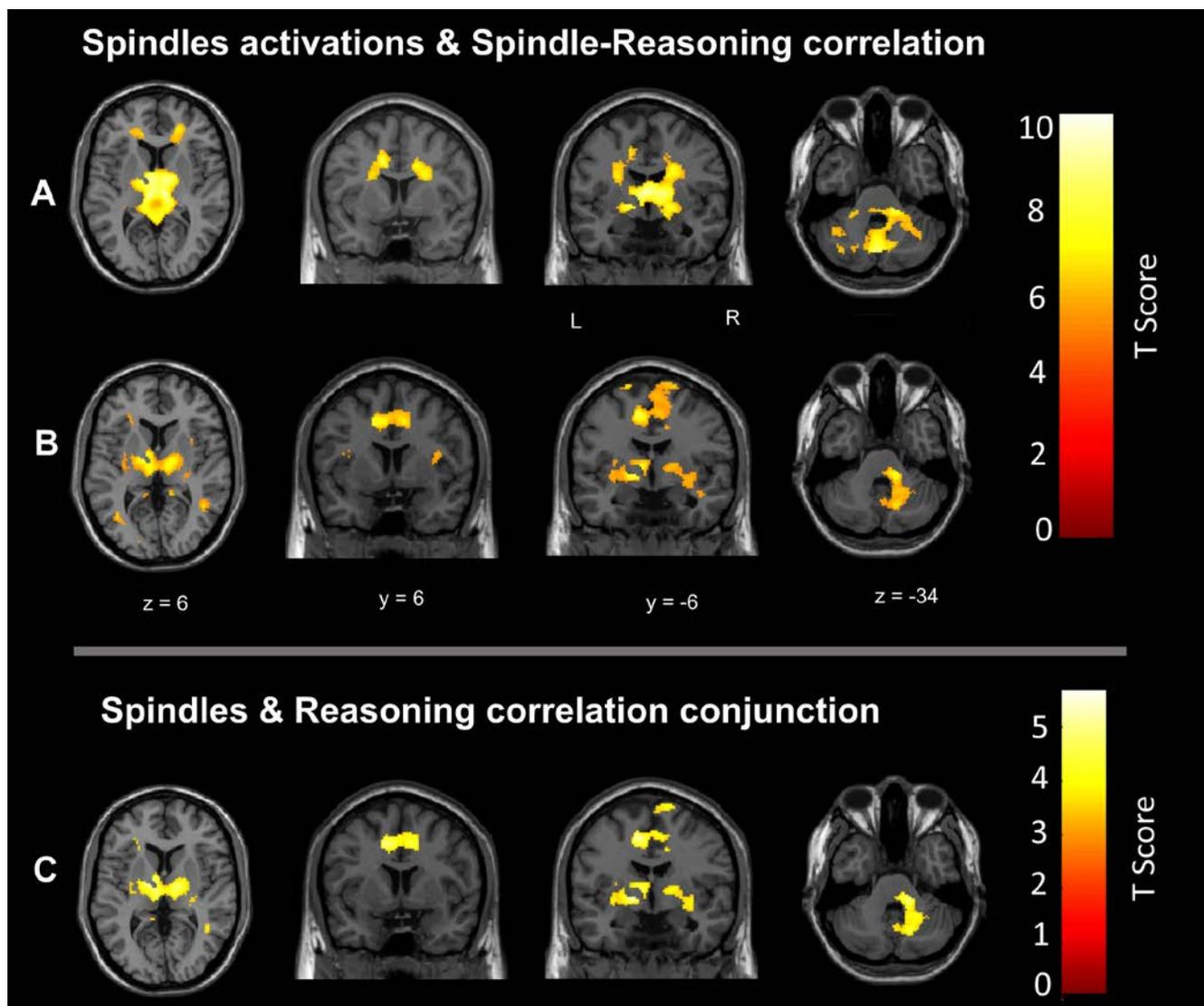
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160 **Figure 1.** The unique relationship (i.e., semipartial correlation, $r(29) = 0.401$, $p = 0.038$) between
161 Reasoning ability, over-and-above STM and Verbal abilities with spindle amplitude during NREM2.

162

163 **Activation of brain regions time-locked to spindles during NREM sleep**

164 As shown in **Figure 2A**, activations time-locked to all spindles (11-16 Hz) at Cz during
165 NREM sleep, were observed in the thalamus/midbrain, the bilateral striatum (putamen/globus
166 pallidum and caudate), the medial frontal cortex, cerebellum, and the brain stem (cluster-level
167 FWE corrected $p < 0.05$, **Table 4**). These results were statistically robust, as it is worth noting
168 that even when a conservative whole-brain voxel-wise FWE statistical threshold correction (p
169 < 0.05) was used, activations remained statistically significant in the thalamus/midbrain, the
170 brainstem, the cerebellum, and the right putamen.



171

172 **Figure 2. Cerebral activation time-locked to sleep spindles and correlation between spindle-related**
173 **activation and Reasoning abilities. A.** Activations time-locked to sleep spindles per se during NREM sleep. **B.**
174 Spatial correlation maps between activations time-locked to sleep spindles and Reasoning abilities. **C.** Conjunction
175 between A and B.

176

177 Given the two physiologically distinct spindles types (fast and slow), we also explored
178 the brain activations time-locked to fast (13.5-16 Hz) spindles and slow (11-13.5 Hz) spindles
179 during NREM sleep. As shown in **Figure S1**, activations time-locked to fast spindles at Pz
180 (**Figure S1A**) and slow spindles at Fz (**Figure S1B**) were very similar in most brain regions,
181 including the thalamus, the precuneus, and the cerebellum. There were no significant
182 differences between fast spindle and slow spindle-related activations.

Table 4. Statistically significant activations time-locked to 11-16Hz sleep spindles at Cz during NREM sleep (see **Figure 2A**).

Hemisphere	Region	MNI Coordinate			Peak z score	FWE corrected p-value
		X	Y	Z		
Right	thalamus	10	-22	12	6.47	< 0.001
Left	thalamus	-12	-26	16	6.00	<0.001
Left	caudate	-14	12	12	6.07	<0.001
Left	putamen/pallidum	-18	-2	-4	4.22	0.001
Right	putamen/pallidum	18	-4	-4	5.32	<0.05
Bilateral	cerebellum	2	-62	-10	5.88	<0.001
Left	anterior cingulate	-16	32	18	5.16	0.001
Right	anterior cingulate	12	22	28	3.94	0.001
Middle	middle cingulate	0	24	32	4.53	0.001

Note: Significant brain responses after Family Wise Error (FWE) correction $p < 0.05$ at the cluster-level.

183

184 **Correlation between cognitive abilities and brain activations time-locked to spindles**

185 To examine the neural correlates of the relationship between sleep spindles and cognitive
 186 abilities, we conducted whole-brain spatial correlation analyses between brain activation maps
 187 time-locked to all spindles at Cz and the scores on the three cognitive factors (Reasoning, STM,
 188 and Verbal abilities) assessed by the Cambridge Brain Sciences tests. As shown in **Figure 2B**,
 189 Reasoning ability was significantly correlated with spindle-related activation maps in the
 190 thalamus, bilateral putamen, brainstem/pons anterior cingulate cortex, the middle cingulate
 191 cortex, the paracentral lobe, the posterior cingulate cortex, the precuneus, and bilateral
 192 temporal lobe (see **Table 5**).

193

194

Table 5. Whole brain correlations between Reasoning ability and 11-16Hz spindle-related activations at Cz during NREM sleep. (see **Figure 2B**)

Hemisphere	Region	MNI Coordinate			Peak z	FWE corrected
		X	Y	Z	score	p-value
Left	paracentral lobe	-12	-32	58	5.01	<0.001
Middle	anterior cingulate	-6	12	26	4.44	<0.001
Middle	middle cingulate	-8	10	40	4.07	<0.001
Left	Precuneus	-14	-58	32	5.12	<0.001
Left	putamen/pallidum	-16	-6	-2	4.39	<0.001
Right	putamen	32	-6	-8	3.38	<0.001
Left	thalamus	-12	-10	6	4.18	< 0.001
Right	thalamus	16	-10	8	4.03	< 0.001
Right	cerebellum	14	-64	-34	3.80	< 0.001
Left	temporal lobe	-42	-58	-2	4.30	<0.05
Right	temporal lobe	48	-52	-4	4.24	<0.05

Note: Significant brain responses after Family Wise Error (FWE) correction $p < 0.05$ at the cluster-level.

195

196 Since Reasoning ability was highly inter-correlated with Verbal ability ($r = 0.596$, $p =$
197 0.001), and marginally correlated with STM ability ($r = 0.357$, $p = 0.058$), to ensure that the
198 relationship between Reasoning ability and the spindle-related activations was not accounted
199 for by Verbal or STM abilities, we also examined the correlations between spindle-related
200 activations and Short Term Memory, and also Verbal abilities, respectively. However, no
201 significantly correlated activations were observed between Short Term Memory or Verbal
202 abilities and the spindle-related activations. This demonstrates that a subset of spindle-related
203 activations was specifically related to Reasoning abilities, but not to Short Term Memory or
204 Verbal abilities. This is consistent with, and provides physiological support for the current and
205 previous studies (Bódizs et al., 2005; Fang et al., 2017; Fogel et al., 2007; Schabus et al., 2006;
206 Ujma et al., 2014, 2015), demonstrating that Reasoning abilities are uniquely correlated to sleep

207 spindles. The same whole-brain spatial correlation analyses were conducted for fast spindle
208 and slow spindle activation maps, however, we did not observe significant correlations between
209 any cognitive ability and the activation maps for each individual spindle type.

210 From **Figure 2**, we can see that there were several overlapping regions between the
211 spindle activation maps (**Figure 2A**) and the maps that show activations time-locked to spindles
212 that were correlated with Reasoning abilities (**Figure 2B**). The conjunction (at $p < 0.001$ using
213 the conjunction null) between the spindle activation maps and the Reasoning-related spindle
214 correlation maps (**Figure 2C**), show several regions were consistently high and jointly activated
215 in both the spindle and Reasoning-spindle correlation maps, including the thalamus, medial
216 frontal cortex, bilateral putamen, and the cerebellum (**Table 6**).

Table 6. Conjunction between the spindle-related activation maps and the spindle-related activations correlated with reasoning abilities maps. (see **Figure 2C**)

Hemisphere	Region	MNI Coordinate			Peak z score	FWE corrected p-value
		X	Y	Z		
Middle	anterior cingulate	-8	12	26	4.10	<0.001
Middle	middle cingulate	-14	5	42	4.17	<0.001
Left	putamen/pallidum	-16	-6	-2	4.39	<0.001
Left	putamen	-32	-10	-4	3.75	<0.001
Left	thalamus	-12	-10	6	4.18	< 0.001
Right	thalamus	12	-10	8	4.00	< 0.001
Right	cerebellum	14	-64	-34	3.80	< 0.001

Note: Significant brain responses after Family Wise Error (FWE) correction $p < 0.05$ at the cluster-level.

217

218 Finally, to ensure that activations time-locked to spindles were specific to spindles per se,
219 and not to some general epiphenomena of NREM sleep, a separate analysis investigated
220 activations time-locked to the same number of randomly distributed onsets during NREM sleep,

221 instead of onsets aligned to spindles events. The results revealed only a small single cluster at
222 the left frontal lobe (peak coordinate: -28, -2, 68; uncorrected $p < 0.005$), which did not overlap
223 with the activations time-locked to spindles (**Figure S2**), and did not survive correction for
224 multiple comparisons, suggesting that this activation is non-specific to NREM sleep, and likely
225 spurious. No correlation was observed between Reasoning ability and the uncorrected random
226 onsets map. This suggests that the reactivations reported here, are specifically related to
227 spindle events, and not simply to NREM sleep in general.

228

229 **DISCUSSION**

230 Sleep supports normal human cognitive performance, such as attention, language,
231 reasoning, decision making, learning and memory (for review, see Alhola & Polo-Kantola 2007;
232 Diekelmann 2014; Diekelmann & Born 2010; Goel et al. 2009; Harrison & Horne 2000).
233 Previous EEG studies have identified sleep spindles as a biological marker of cognitive abilities,
234 and in particular, reasoning abilities (Bódizs et al., 2005; Fang et al., 2017; Fogel et al., 2007;
235 Fogel & Smith, 2011; Schabus et al., 2006; Ujma et al., 2014, 2015). Only a few EEG-fMRI
236 studies have explored the brain activations correlated with sleep spindles (Andrade et al., 2011;
237 Caporro et al., 2012; Laufs et al., 2007; Schabus et al., 2007; Tyvaert et al., 2008). Interestingly,
238 some of these regions are also known to support reasoning abilities. However, the
239 neuroanatomical functional correlates of the relationship between spindles and Reasoning
240 abilities are unknown. Here, we identified the neural activation patterns time-locked to spindles
241 that are correlated to cognitive abilities. Using a large sample of simultaneous EEG-fMRI sleep
242 recordings, the results of the present study support three main findings: (1) similar to previous
243 studies (Fang et al., 2017; Fogel et al., 2007), spindles detected at Cz (11-16Hz) during NREM
244 sleep were related to Reasoning but not Short Term Memory or Verbal abilities, (2) similar to

245 previous studies (Andrade et al., 2011; Caporro et al., 2012; Laufs et al., 2007; Schabus et al.,
246 2007; Tyvaert et al., 2008), activations time-locked to spindles were observed in the thalamus,
247 bilateral striatum, middle cingulate cortex, and cerebellum, and (3) Reasoning abilities were
248 correlated with spindle-related activations in a subset of these regions including the thalamus,
249 bilateral striatum, medial frontal gyrus, middle cingulate cortex, and precuneus. These results
250 are specific to spindles *per se*, and cannot be attributed to some epiphenomena during NREM
251 sleep; given that these results were not observed when random onsets during NREM sleep
252 were used instead of onsets time-locked to spindle events. Altogether, our results identified for
253 the first time, the neural correlates of the relationship between spindles and Reasoning abilities.

254 **Spindle-related activation of thalamocortical circuitry**

255 Consistent with previous EEG-fMRI studies of spindle-related activations (Andrade et al.,
256 2011; Caporro et al., 2012; Laufs et al., 2007; Schabus et al., 2007; Tyvaert et al., 2008), our
257 results identified and confirmed the brain regions associated with spindle events during NREM
258 sleep in both cortical (including the media prefrontal, anterior cingulate cortex, and middle
259 cingulate cortex), and subcortical areas (including the thalamus and bilateral caudate, putamen,
260 and pallidum), indicating the role of cortico-thalamic-basal ganglia circuitry in spindle generation.
261 In addition, positron emission tomography (PET) studies have shown changes in regional
262 cerebral blood flow in the thalamus related to sleep spindles (Hofle et al., 1997). These human
263 neuroimaging findings are supported by a large body of animal studies, which at the cellular
264 level, suggest that spindles reflect oscillatory activity in widespread thalamocortical circuits, and
265 involve complex interactions between reticular, thalamocortical and pyramidal cells (Steriade,
266 2005). Classically, spindle generation was shown to be maintained by synchronized firing in the
267 reticular-thalamocortical-reticular circuit (Steriade, Nunez, & Amzica, 1993; von Krosigk et al.,
268 1993). More recent evidence (Bonjean et al., 2011) however, suggests that corticothalamic

269 input initiates spindles by triggering spike bursts in the reticular nucleus and are terminated by
270 desynchronization of thalamic and cortical neuronal firing. Thus, taken together, animal and
271 recent human neuroimaging studies, including the current study, supports the involvement of
272 thalamocortical circuitry in spindle generation.

273 The results of the current study identified a correlation between Reasoning, but not Short
274 Term Memory or Verbal abilities with spindle-related brain activations in thalamocortical
275 circuitry, especially the thalamus and the prefrontal cortex (PFC) region, which are thought to
276 be implicated in modulation of cognitive performance (Blair, 2006; Ferguson & Gao, 2015;
277 Mitchell & Chakraborty, 2013). Spindles and the thalamus have been shown to be related to
278 human intellectual abilities (Fangmeier et al., 2006; Melrose et al., 2007). The thalamus,
279 especially the mediodorsal thalamus has been reported to be related to the fluid intelligence
280 (Van der Werf et al., 2003; Van Der Werf et al., 2000) particularly for the extrapolation
281 component process of inductive reasoning (Jia et al., 2011; Liang et al., 2014) and other higher-
282 level cognition (e.g., problem solving, working memory, goal direct seeking) (Karatekin et al.,
283 2000; Mitchell & Chakraborty, 2013; Schiff et al., 2002; Shirvalkar et al., 2006). Lesions studies
284 in both humans (De Witte et al., 2011; Kubat-Silman et al., 2002; Little et al., 2010) and non-
285 human primates (for review, see Mitchell & Chakraborty 2013) have revealed that thalamic
286 damage impairs various broadly defined aspects of cognitive performance, including
287 discrimination, memory, learning, attention and other neuropsychological behaviors. Other
288 neuroanatomical studies (Bohlken et al., 2014) found that only thalamic volume was
289 significantly correlated with general intellectual functioning. In addition, at least one study
290 identified structural and functional abnormalities in the thalamus in adults with reduced
291 intellectual functioning who experienced prenatal exposure to alcohol (Clark et al., 2000). Thus,

292 suggesting that integrity and functioning of the neural circuitry involved in spindle generation
293 support intellectual abilities, and in particular Reasoning abilities.

294 The prefrontal cortex has been defined as the projection area of the mediodorsal thalamus
295 (Behrens et al., 2003), and the prefrontal-thalamic loop plays a critical role in various higher-
296 order cognitive processes, especially executive function (for reviews see Baxter 2013;
297 Ferguson & Gao 2015; Funahashi 2013; Mitchell & Chakraborty 2013; Watanabe & Funahashi
298 2012). A large body of literature has identified the role of the prefrontal cortex area in fluid
299 intelligence and Reasoning (Coricelli & Nagel, 2009; Duncan, 2000; Gray et al., 2003; Melrose
300 et al., 2007; Sandman et al., 2014; Waltz et al., 1999). For example, patients with damage to
301 the prefrontal cortex exhibited a selective and catastrophic deficit for both deductive and
302 inductive reasoning tasks (Waltz et al., 1999). In addition, Gray et al., (2003) found that
303 individuals with higher fluid intelligence have greater activations in the prefrontal cortex.
304 Coricelli and Nagel (2009) have shown that reasoning abilities correlate with neural activity in
305 the medial prefrontal cortex. Additionally, at least one neuroanatomical MRI study employing
306 voxel-based morphometry has revealed a positive correlation between gray matter intensity in
307 the medial prefrontal cortex and reasoning abilities assessed by Cattell's Culture Fair
308 Intelligence Test, and also the WAIS-R (Gong et al., 2005). Taken together, these findings
309 suggest that the thalamus and prefrontal cortex region supports Reasoning abilities.

310 **Spindle-related activation of the basal ganglia**

311 Consistent with previous results (Caporro et al., 2012; Tyvaert et al., 2008), the present
312 study shows that the basal ganglia, including striatal areas (caudate and putamen) and the
313 globus pallidus were recruited during spindle events. The basal ganglia are primarily known for
314 playing a role in cognitive functions (for reviews see Burgaleta et al. 2014; Chakravarthy et al.
315 2010; Leisman et al. 2014; Doyon et al. 2009) such as action selection, reward-based learning,

316 motor sequence learning, planning (Elsinger et al., 2006) and motor execution (Monchi et al.,
317 2006). In addition, several studies have observed robust activations in the basal ganglia for
318 reasoning-related tasks compared to other cognitive tasks, including the caudate nucleus,
319 putamen and globus pallidus (Ferguson & Gao, 2015; Melrose et al., 2007; Rodriguez-Moreno
320 & Hirsch, 2009). Taken together, these findings complement the results of the current study
321 whereby activation of the putamen time-locked spindles was correlated with Reasoning abilities.
322 The Reasoning subtests of the Cambridge Brain Sciences Trials, consists of tasks requiring
323 planning (Shallice, 1982), spatial rotation (Silverman et al., 2000), and visuomotor ability
324 (Folstein et al., 1975). Sandman et al., (2014) has reported that the morphometry of the
325 putamen was associated with performance on reasoning-related subtests of the WAIS including
326 block design, matrix reasoning and perceptual index in preadolescent children. These findings
327 suggest that the function and structure of the basal ganglia are related to Reasoning abilities.
328 The current study suggests that interindividual differences in spindle-related activation of these
329 regions are related to Reasoning ability.

330 **Spindle-related activation of the cerebellum**

331 Similar to previous studies (Schabus et al., 2007), here, we also observed spindle-related
332 activation of the cerebellum which was also correlated with Reasoning abilities. Many studies
333 overlook cognition-related activity in the cerebellum, although this area is responsible for
334 modulating thalamic activity through direct cerebello-thalamic projections, which may be related
335 to spindle generation (Calzavara et al., 2005; Shouse & Serman, 1979). In addition, it has
336 been suggested that the cerebellum supports cognitive functions (for reviews, see Gordon 2007;
337 Rapoport et al. 2000; Stoodley 2012) such as response reassignment during a complex task
338 (Bischoff-Grethe et al., 2002), decision making (Blackwood et al., 2004), associative learning
339 (Logan & Grafton, 1995), adaptation (Krakauer & Mazzoni, 2011), and executive function

340 (Bellebaum & Daum, 2007; Tomasi et al., 2007). Importantly, the cerebellum is activated during
341 the deductive reasoning processing (Goel et al., 2000; Goel & Dolan, 2004) supporting our
342 finding that reasoning-related functions supported by the cerebellum is reflected during sleep,
343 time-locked to spindles.

344 Unlike previous studies, we did not observe spindle-related activation of the medial
345 temporal lobe (Andrade et al., 2011; Caporro et al., 2012; Laufs et al., 2007; Schabus et al.,
346 2007; Tyvaert et al., 2008). In addition, Schabus et al., (2007) and Andrade et al. (2011)
347 reported brain activation differences between fast spindles and slow spindles, particularly in
348 hippocampal regions. However, here, we observed similar activation patterns for both spindle
349 types and no significant differences between spindle types. However, we did find medial frontal
350 activation for slow, but not fast spindle events. Despite having a large proportion of participants
351 who slept for an adequate amount of NREM sleep, there may not have been an adequate
352 number of each spindle type when categorized orthogonally for sufficient power, or perhaps not
353 enough intersubject variability to detect any relationship to cognitive abilities. Moreover, sleep
354 was recorded only from the first couple of hours of the night, where the relationship between
355 Reasoning abilities and spindles has been found to be much less robust than the later part of
356 the night (Fogel et al., 2007). This might also help explain that when separated into fast spindles
357 and slow spindles, we did not observe significant relationship with Reasoning abilities in each
358 spindle subtype. Lastly, due to the limited duration, and high intersubject variability of sleep in
359 the scanner, we did not have sufficient SWS to test whether a different pattern of results was
360 observed during SWS.

361 The clinical significance and applications of the relationship between spindles and
362 cognitive abilities is yet to be realized. Deficient or dysfunctional spindle generation may be
363 associated with compromised intellectual functioning. More specifically, it has been suggested

364 that deficient gating mechanisms of thalamocortical circuitry (Bixler,1968) may explain
365 abnormal spindle production in children with mental disability (Gibbs & Gibbs, 1962; Shibagaki
366 & Kiyono, 1983) . Moreover, the present study is an important first step which may lead to the
367 development of novel interventions utilizing spindle-enhancing neuromodulatory techniques
368 (e.g., neurofeedback, transcranial direct current stimulation, pharmacological) to improve
369 daytime cognitive performance and explore the physiological mechanisms which support the
370 function of sleep for memory and cognitive performance. Such an approach could target
371 cognitive deficits, in cases where spindle production is abnormal such as in learning disabilities
372 (Gibbs & Gibbs, 1962; Shibagaki & Kiyono, 1983), below normal cognitive functioning (Fogel &
373 Smith, 2011) , normal, healthy aging (Carrier et al., 2001; Fogel et al., 2014; Fogel et al., 2017),
374 developmental disorders (Limoges et al., 2005) and in schizophrenia (Wamsley et al., 2012).

375 Here, we investigated what neural substrates support cognitive strengths and
376 weaknesses. There are considerable interindividual differences in sleep spindles, which are
377 very trait-like(Gaillard & Blois, 1981; Silverstein & Michael Levy, 1976). While the neural
378 circuitry and generating mechanisms of spindles are well-understood, the neurophysiological
379 basis of the relationship between spindles and cognitive abilities remain to be fully elucidated.
380 In summary, our results show for the first time the neuroanatomical functional correlates of the
381 relationship between sleep spindles and intellectual abilities. In particular, our study found
382 that the extent of the activation of the prefrontal cortex, basal ganglia, cerebellum and the
383 thalamus time-locked to sleep spindles was correlated with interindividual differences in
384 Reasoning, but not Verbal or STM abilities. Thus, spindles may serve as an electrophysiological
385 marker of brain activations in regions which support the ability to employ reasoning to solve
386 problems and apply logic in novel situations.

387

388 **METHODS**

389 **Participants**

390 A total of 35 healthy right-handed adults (20 female) between 20-35 years old ($M = 25.6$,
391 $SD = 3.6$), were recruited to participate in this study. All participants were non-shift workers and
392 medication-free, had no history of head injury or seizures, had a normal body mass index (<25),
393 and did not consume excessive caffeine, nicotine or alcohol. To be included, interested
394 participants had to score <10 on the Beck Depression (Beck et al., 1974) and the Beck Anxiety
395 (Beck et al., 1988) inventories and have no history or signs of sleep disorders indicated by the
396 Sleep Disorders Questionnaire (Douglass et al., 1994). All participants were required to keep a
397 regular sleep-wake cycle (bed-time between 22h00-24h00, wake-time between 07h00-09h00)
398 and to abstain from taking daytime naps at least 7 days prior to and throughout participation in
399 the study. Compliance with this schedule was assessed using both sleep diaries and wrist
400 actigraphy (Actiwatch 2, Philips Respironics, Andover, MA, USA) worn on the non-dominant
401 wrist. All participants met the MRI safety screening criteria. In addition, participants were given
402 a letter of information, provided informed written consent before participation, and were
403 financially compensated for their participation. This research was approved by the Western
404 University Health Science research ethics board.

405 Sample sizes were determined a-priori based on previous studies, and power calculated,
406 where possible using G*Power for Mac version 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009;
407 Faul, Erdfelder, Lang, & Buchner, 2007). Based on the most comparable simultaneous EEG-
408 fMRI studies (Andrade et al., 2011; Caporro et al., 2012; Laufs et al., 2007; Schabus et al.,
409 2007; Tyvaert et al., 2008), previous studies have employed sample sizes $N < 15$. A recent study
410 by our group using the same cognitive tests as the current study (Fang et al., 2017) found
411 robust associations between spindles and cognitive abilities in a sample size of $N = 24$,

412 replicating previous findings in smaller samples (e.g., $N < 12$: Fogel et al., 2007; Fogel & Smith,
413 2006). Based on power calculation for correlation with $p(2\text{-tailed}) = 0.05$ ($b = 0.20$, effect size =
414 0.56) from (Fang et al., 2017), an $N = 22$ was required. Thus, $N = 29$ subjects included in this
415 study was considered to provide adequate statistical power for the main effects of interest.

416 **Experimental procedure**

417 Each participant underwent a screening/orientation session one week prior to the
418 experimental sleep session. All participants completed the CBS test battery online at least 3
419 days prior to the experimental session. The experimental sleep session took place between
420 21h00 and 23h00, during which time simultaneous EEG-fMRI was recorded while participants
421 slept in the scanner. To be included in the analyses, participants were required to sleep for a
422 period of at least 5 minutes of uninterrupted NREM sleep during the sleep session. This was
423 considered to be the minimum amount of data necessary for EEG and fMRI data analysis
424 purposes, and to ensure a minimum duration, quality and continuity of sleep. It should be noted
425 that all subjects had at least 14.67 minutes of sleep, with at least 63 total bandwidth spindles
426 (11-16 Hz) at Cz. Importantly, the average duration of NREM sleep was 39.29 minutes, with an
427 average of 334.74 total bandwidth spindles (11-16 Hz) at Cz. Following the sleep session,
428 participants were allowed to sleep in the nearby sleep laboratory for the remainder of the night.

429 Of the 35 participants who met the inclusion criteria, only 5 participants did not meet the
430 5-minute consolidated NREM sleep criteria for the sleep session. As well, one participant did
431 not complete the Cambridge Brain Sciences Trials test battery. In total, 29 participants (M age
432 = 23.97, SD = 3.83, 17 female) were included in the final data analyses.

433 **Cognitive ability test**

434 The Cambridge Brain Sciences test battery (Hampshire et al., 2012) was used to assess
435 participants' cognitive abilities. Cambridge Brain Sciences is a web-based battery of 12
436 cognitive tests that assesses a broad range of cognitive abilities including reasoning, problem
437 solving, planning, attention, and memory. A recent study, based on scores from a population-
438 sized pool of 44,600 participants, revealed three factors that govern performance across the
439 Cambridge Brain Sciences subtests. These factors have been described as "Reasoning",
440 "Short Term Memory" and "Verbal" ability (Hampshire et al., 2012). The descriptive statistics of
441 each subtest score are shown in **Table 1**.

442 **Polysomnographic Recording and Analysis**

443 **Recording Parameters.** EEG was recorded using a 64-channel magnetic resonance (MR)-
444 compatible EEG cap which included one electrocardiogram (ECG) lead (Braincap MR, Easycap,
445 Herrsching, Germany) and two MR-compatible 32-channel amplifiers (Brainamp MR plus, Brain
446 Products GmbH, Gilching, Germany). EEG caps included scalp electrodes referenced to FCz.
447 Two bipolar electrocardiogram (ECG) recordings were taken from V2-V5 and V3-V6 using an
448 MR-compatible 16-channel bipolar amplifier (Brainamp ExG MR, Brain Products GmbH,
449 Gilching, Germany). Using high-chloride abrasive electrode paste (Abralyt 2000 HiCL; Easycap,
450 Herrsching, Germany), electrode-skin impedance was reduced to < 5 KOhm. To reduce
451 movement-related EEG artifacts, participants' heads were immobilized in the MRI head-coil
452 using foam cushions. EEG was digitized at 5000 samples per second with a 500-nV resolution.
453 Data were analog filtered by a band-limiter low pass filter at 500 Hz and a high pass filter with
454 a 10-sec time constant corresponding to a high pass frequency of 0.0159 Hz. Data were
455 transferred via fiber optic cable to a personal computer where Brain Products Recorder
456 Software, Version 1.x (Brain Products, Gilching, Germany) was synchronized to the scanner
457 clock. EEG was monitored online with Brain Products RecView software using online artifact

458 correction. Sleep stages were scored in accordance with
459 standard criteria (Iber et al., 2007) using the “VisEd Marks” toolbox (<https://github.com/jade>
460 [sjardins/vised_marks](https://github.com/sjardins/vised_marks)) for eeglab (Delorme & Makeig, 2004). Automatic spindle detection was
461 carried out using a previously published (Fogel et al., 2014; Fogel et al., 2015) and validated
462 (Ray et al., 2015) method employing EEGLab-compatible (Delorme & Makeig, 2004) software
463 (github.com/stuartfogel/detect_spindles) written for MATLAB R2014a (The MathWorks Inc.,
464 Natick, MA). The detailed processing steps and procedures are reported elsewhere (Ray et al.,
465 2015) and are thus presented only briefly here. The EEG data were initially downsampled to
466 250 Hz. The detection was performed at Fz, Cz and Pz derivations. The spindle data were
467 extracted from movement artifact-free, NREM stage 2 sleep epochs. The detection method
468 (Ray et al., 2015) used a complex demodulation transformation of the EEG signal with a
469 bandwidth of 5 Hz centered about a carrier frequency of 13.5 Hz (i.e., 11–16 Hz) (Iber et al.,
470 2007). To utilize a fixed amplitude detection threshold, but still account for individual differences
471 in spindles, each data point was transformed into a z-score using the mean and standard
472 deviation derived from a 60-sec sliding window. Events (spindle onsets, peaks, and offsets)
473 were then detected on the transformed signal with a z-score threshold of $z = 2.33$,
474 corresponding to the 99th percentile. The dependent variables of interest extracted from this
475 method include spindle amplitude, spindle duration, and spindle density (number of spindles
476 per minute of NREM sleep) for each participant and at each derivation (Fz, Cz and Pz). Spindles
477 were categorized so that they were orthogonal (non-overlapping detections) at the scalp
478 locations where they predominate topographically (Jobert et al., 1992; Werth et al., 1997;
479 Zeitlhofer et al., 1997) as slow spindles (11–13.5 Hz) at Fz, total bandwidth spindles (11-16 Hz)
480 at Cz, and fast spindles (13.5–16 Hz) at Pz (**Table 2**). Despite having no minimum detection

481 criteria, the detection method employed here did not detect spindles lower than 0.2 sec, as
482 found in a previous validation study (Ray et al., 2015).

483 **MRI Imaging Acquisition and Analysis**

484 **Recording Parameters.** Brain images were acquired using a 3.0T TIM TRIO magnetic
485 resonance imaging system (Siemens, Erlangen, Germany) and a 64-channel head coil. In all
486 participants, a structural T1-weighted MRI image was acquired using a 3D MPRAGE sequence
487 (TR = 2300 ms, TE = 2.98 ms, TI = 900 ms, FA = 9°, 176 slices, FoV = 256×256 mm², matrix
488 size = 256×256×176, voxel size = 1×1×1 mm³). Multislice T2*-weighted fMRI images were
489 acquired during the sleep session with a gradient echo-planar sequence using axial slice
490 orientation (TR = 2160 ms, TE = 30 ms, FA = 90°, 40 transverse slices, 3 mm slice thickness,
491 10% inter-slice gap, FoV = 220×220 mm², matrix size = 64×64×40, voxel size = 3.44×3.44×3
492 mm³). Importantly, the sequence parameters were chosen so that the gradient artifact would
493 be time stable, and the lowest harmonic of the gradient artifact (18.52 Hz) would occur outside
494 the spindle band (11-16 Hz). This was achieved by setting the MR scan repetition time to 2160
495 ms, such that it matched a common multiple of the EEG sample time (0.2 ms), the product of
496 the scanner clock precision (0.1 μs) and the number of slices (40 slices) used (Mulert & Lemieux,
497 2009) .

498 **Image Preprocessing**

499 Functional images were preprocessed and analyzed using SPM8
500 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>; Welcome Department of Imaging
501 Neuroscience, London, UK) implemented in MATLAB (ver. 8.5 R2015a) for Windows (Microsoft,
502 Inc. Redmond, WA). Functional scans of each session were realigned using rigid body
503 transformations, iteratively optimized to minimize the residual sum of squares between the first

504 and each subsequent image separately for each session. A mean realigned image was then
505 created from the resulting images. The structural T1-image was coregistered to this mean
506 functional image using a rigid body transformation optimized to maximize the normalized mutual
507 information between the two images. Coregistration parameters were then applied to the
508 realigned blood-oxygen-level dependent (BOLD) time series. The coregistered structural
509 images were segmented into grey matter, white matter and cerebrospinal fluid. An average
510 subject-based template was created using DARTEL in SPM8. All functional and anatomical
511 images were spatially normalized using the resulting template, which was generated from the
512 structural scans. Finally, spatial smoothing was applied on all functional images (Gaussian
513 kernel, 8 mm full-width at half-maximum (FWHM)).

514 **Sleep sessions**

515 For data acquired during the simultaneous EEG-fMRI sleep recordings, within-session
516 series of consecutive fMRI volumes sleep stage scored as NREM stage 2 sleep according to
517 standard criteria (Iber et al., 2007) by an expert, registered polysomnographic technologist were
518 selected from the complete fMRI time series of sleep session. To be included in the fMRI
519 analysis, the EEG had to be visibly movement artifact-free and be a segment of uninterrupted
520 sleep longer in duration than 55 volumes (i.e., ~120 seconds or longer; corresponding to the
521 minimum amount of sleep that was needed to perform the automated spindle detection),
522 resulting in the inclusion of 36% of the total recorded data (i.e., 11,466 of 31,852 MRI volumes
523 during NREM stage 2 sleep). Each time series corresponding to NREM stage 2 sleep that met
524 these criteria, were entered into the general linear model (GLM) as a separate session so that
525 no gaps existed in the design matrix. For each participant, brain responses were estimated in
526 an event-related design using a fixed-effects GLM including responses time-locked to spindle
527 events (11-16 Hz) detected at Cz, slow spindles (11-13.5 Hz) detected at Fz, and fast spindle

528 events (13.5-16 Hz) detected at Pz. Consistent with similar previous studies (Andrade et al.,
529 2011; Bergmann et al., 2011; Dang-Vu et al., 2008; Schabus et al., 2007), the vectors, including
530 spindle events, were convolved with the canonical hemodynamic response function (HRF), as
531 well as with its temporal and dispersion derivatives. Nuisance variables in the model included:
532 the movement parameters estimated during realignment (translations in x, y, and z directions
533 and rotations around x, y, and z axes), the squared value of the movement parameter, the first
534 derivative of each movement parameter, and the square of the first derivative of each
535 movement parameter, as well as, to the mean white matter intensity and the mean cerebral
536 spinal fluid intensity for each participant. Slow wave activity is a defining characteristic of NREM
537 sleep (Iber et al., 2007), but is related to spindle generation (Mölle et al., 2011; Siapas & Wilson,
538 1998). This activity was accounted for by including spectral power (μV^2) in the delta band (0.5-
539 4 Hz) for each TR window (2160 ms) as a variable of no interest, convolved with the
540 hemodynamic response function. Slow drifts were removed from the time series using a high
541 pass filter with a cut-off period of 128 seconds. Serial correlations in the fMRI signal were
542 estimated using an autoregressive (order 1) plus white noise model and a restricted maximum
543 likelihood (ReML) algorithm. These analyses generated statistical parametric t maps [(SPM(T))].
544 The resulting contrast images were then smoothed (FWHM 6 mm Gaussian Kernel) and
545 entered into a second-level analysis.

546 The resulting group-level analysis consisted of one sample t-tests for each contrast of
547 interest (i.e., all spindle events, fast spindle events, and slow spindle events). To investigate
548 the relationship between the magnitude of the spindle-dependent activation and the cognitive
549 abilities assessed by the CBS Trials, cognitive test scores for each subtest (i.e., Reasoning,
550 Verbal, and Short Term Memory) were entered as covariates of interest in the described GLM.
551 These activation maps constituted maps of the t-statistic [SPM(t)] testing for the main effect for

552 each contrast of interest. Statistical inferences were performed at a threshold of $p < 0.05$, family
553 wise error (FWE) corrected at the cluster level.

554 **Overlap between spindle-related maps and reasoning-spindle correlation maps**

555 To illustrate the overlap of activations between the spindle-related activation maps and
556 reasoning-spindle correlation maps, the conjunction was taken as the minimum t-statistic using
557 the conjunction hypothesis (Friston et al., 2005; Nichols et al., 2005) over: (1) a t-map testing
558 for the main effect of the spindle events during the sleep session, and (2) a t-map testing for
559 the main effect of the correlation between the Reasoning ability and spindle events. These two
560 statistical maps were thresholded at $p < 0.05$, FWE corrected at the cluster level.

561 Finally, to confirm that activations time-locked to spindles and correlated with Reasoning
562 abilities were not simply an epiphenomenon of NREM sleep, we generated the same number
563 of random events as sleep spindles in each segment of NREM sleep for all participants during
564 the sleep session. These random onsets did not overlap with any spindle events. We conducted
565 the exact same GLM as for actual spindle onsets, with the only difference being that the
566 randomly generated onsets were included in the model, as opposed to the spindle onsets.

567

568

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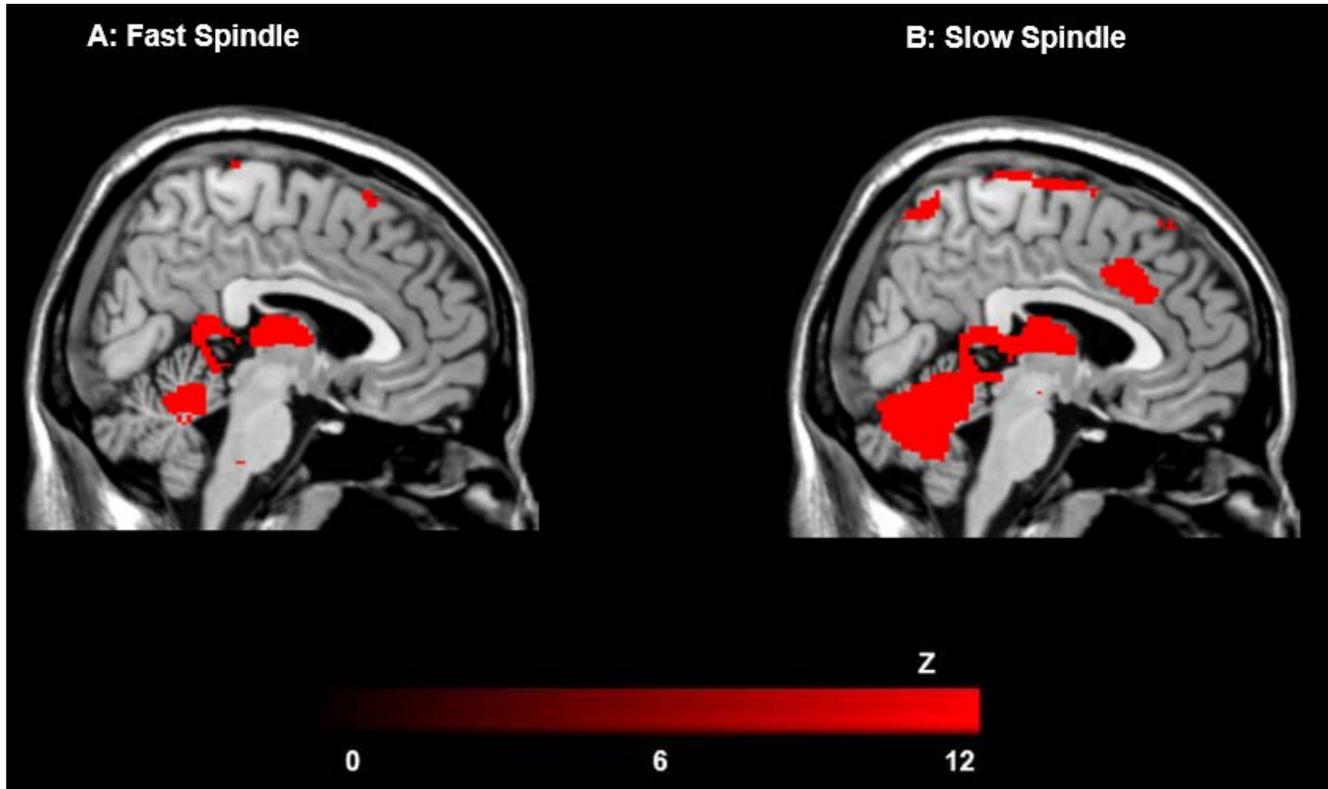
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935 **SUPPLEMENTARY FIGURES**

936 **Figure S1. Cerebral activation of fast and slow spindles.** Activations time-locked to fast spindles (13.5-16 Hz)
937 at Pz (**A**) and slow spindles (11-13.5 Hz) at Fz (**B**) were similar in all brain areas, but visibly to a greater extent in
938 fast spindles (with the exception of medial frontal activation in slow but not fast spindles). However, there were no
939 significant difference between fast spindles vs. slow spindle-related activations.



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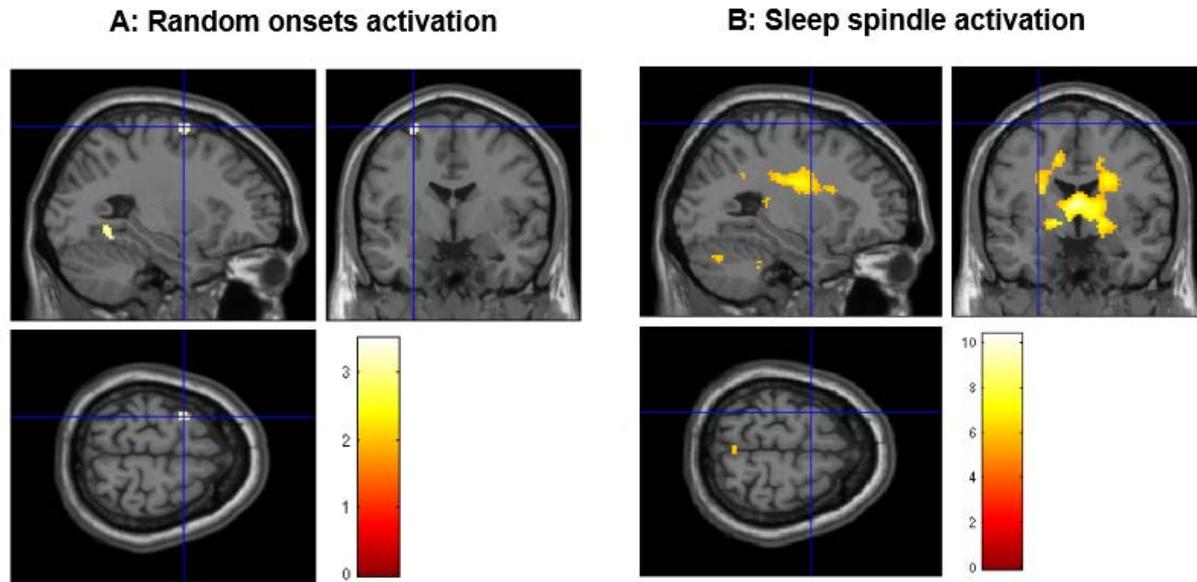
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948 **Figure S2. Cerebral activations time-locked to random onsets in NREM stage sleep.** The results revealed a
949 small single cluster at left frontal lobe which did not survive FWE correction (peak coordinate: -28, -2, 68;
950 uncorrected $p < 0.005$) (A), and did not overlap with activations time-locked to spindles (B).