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Sleep spindles – where they come from, what they do

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Sleep spindles –

Where they come from, what they do

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Abstract

Sleep spindles are extensively studied electroencephalographical rhythms that recur periodically during non-rapid-eye-movement sleep and that are associated with rhythmic discharges of neurons throughout the thalamocortical system. Their occurrence thus constrains many aspects of the communication between thalamus and cortex, ranging from sensory transmission, to cortical plasticity and learning, to development and disease. I review these functional aspects in conjunction with novel findings on the cellular and molecular make-up of spindle-pacemaking circuits. A highlight in the search of roles for sleep spindles is the repeated finding that spindles correlate with memory consolidation in humans and animals. By illustrating that spindles are at the forefront understanding on how the brain might benefit from sleep rhythms, I hope to stimulate further experimentation.

A What are sleep spindle waves?

Sleep spindles are brief oscillatory events that appear in the human electroencephalogram (EEG) during periods of drowsiness and sleep. These brain-generated electrical rhythms are prominent EEG hallmarks of non-rapid-eye-movement (NREM) sleep, which makes up for ~80% of a normal night's sleep. Per night, 4-5 epochs of ~90 min are spent in NREM sleep. Stage N1 of NREM sleep refers to drowsiness, stage N2 to light sleep, and stage N3 to deep and restorative sleep. The remaining 20% consist of rapid-eye-movement (REM) sleep that is well-known for the rapid movements of the eyes and for vivid dreaming periods.

During NREM sleep, the brain generates electrical rhythms that are synchronized throughout large cortical areas. The NREM sleep EEG shows a continuous power spectrum of

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2
3 frequencies, from 0.75 Hz up to tens of Hz, with a broad peak centered \sim 0.5-4 Hz, indicating
4
5 a dominance of low-frequency rhythms. Three rhythms have a distinct graphical signature on
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7 a background of on-going oscillations and serve as EEG hallmarks of NREM sleep: the K-
8
9 complexes (0.5-1 Hz), delta (δ) rhythms (1-4 Hz) and the sleep spindles, also referred to as
10
11 the sleep sigma (σ) band (10-15 Hz). A single sleep spindle lasts \sim 0.5-3 s and is recognized
12
13 based on \sim 5-20 successive deflections of the human EEG signal (Fig. 1A). These deflections
14
15 reach a maximum at the middle of the spindle event, gradually increasing before (“waxing”)
16
17 and decreasing thereafter (“waning”), thence the name “spindles” (Fig. 1A). Within the
18
19 consolidated NREM sleep epochs lasting \sim 90 min in humans, spindles are but brief oscillatory
20
21 events that recur maximally a few times per minute.
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26
27 The neural mechanisms of spindle generation have been studied for decades in
28
29 different mammalian species, initially via electrophysiological and computational methods,
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31 later in combination with molecular and imaging approaches. A surge of interest in spindles
32
33 sparked in the past years in the context of sleep’s implication in learning and memory
34
35 formation (Fogel and Smith 2011; Rasch and Born 2013). In humans, spindles are now
36
37 divided into two types that have different frequencies, topographic distributions and
38
39 putative functional roles, as indicated by non-invasive scalp EEG recordings and functional
40
41 imaging techniques (Fogel and Smith 2011; Rasch and Born 2013).
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47

48 **B Where do spindles come from?**

49
50 The earliest reports on spindles go along with the very first attempts to monitor brain
51
52 electricity across the skull using galvanometers (Box 1). Since then, the thalamus has moved
53
54 to center stage as the site of origin of spindle wave generation. The electrical events
55
56 underlying spindle rhythmicity, and their spread throughout the thalamocortical (TC) system,
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1
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3 are now documented at the level of EEG and of local field potential recordings in the
4
5 anesthetized and sleeping brain, from rodent, to carnivore, to primate, to human (Fig. 1A, B).
6
7 Moreover, spindle-related rhythms can be reproduced in brain slices from ferrets and
8
9 rodents and have been followed from multiunit activity, to single cell discharge, to the flux of
10
11 specific ions across the membrane (Fig. 1C-E).
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13

14
15 There are three successive phases of spindles that are comparable between species
16
17 and that I review sequentially here: 1) the initiation of spindle generation, 2) spindle
18
19 pacemaking and synchronization, and 3) spindle termination. Many important mechanistic
20
21 aspects of spindle generation have been previously reviewed in detail (Beenhakker and
22
23 Huguenard 2009; McCormick and Bal 1997; Timofeev and others 2012). I will present well-
24
25 established knowledge briefly referencing key review articles, while concentrating on recent
26
27 insights in more detail. I will highlight in particular that spindles occur in temporal
28
29 coordination with other sleep rhythms, and are increasingly understood as just one element
30
31 in what appears to be a large-scale grouping of brain rhythms throughout the TC and the
32
33 hippocampal system.
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40 *B1. The thalamic reticular nucleus*

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43 The first electrophysiological recordings of TC neurons, the principal excitatory
44
45 neurons of thalamic nuclei projecting to cortex, indicated that rhythmic inhibitory synaptic
46
47 potentials always occurred in phase with spindle wave generation (Purpura 1968). Andersen
48
49 and Andersson (Andersen and Andersson 1968) postulated a set of widely disseminated
50
51 inhibitory distributor neurons in thalamus to explain this coordinated inhibition. Based on
52
53 lesion experiments, Steriade and colleagues realized that, rather than a diffusely distributed
54
55 circuit, a well-defined nucleus encircling the thalamus, the thalamic reticular nucleus (TRN),
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3 generates this inhibition and thereby acts as a spindle pacemaker (reviewed in (Fuentelba
4 and Steriade 2005)). The TRN forms a thin envelope, ~1 mm in diameter in humans, around
5
6 most of the principal thalamic nuclei and covers these like an umbrella along their frontal-
7
8 caudal extent. TRN cells throughout mammalian species appear uniform in that they all
9
10 express the neurotransmitter γ -aminobutyric acid (GABA), they possess long and thin
11
12 dendrites running in parallel to the TRN borders, and most of them express the Ca^{2+} -binding
13
14 protein parvalbumin; nevertheless, cells in TRN probably form functionally heterogeneous
15
16 classes that go along with variable soma size, discharge properties, dendritic appendages
17
18 and expression of other Ca^{2+} -binding proteins (Fig. 2)(Pinault 2004; Scheibel and Scheibel
19
20 1966). The TRN is subdivided into several, partially overlapping sensory sectors that receive
21
22 topographically organized sensory information from visual, auditory, somatosensory,
23
24 gustatory, visceral, motor and limbic circuits (Pinault 2004; Zikopoulos and Barbas 2007). The
25
26 TRN does not project to cortex, whereas it is strongly innervated by descending cortical
27
28 input arising in deep layer 6 from corresponding first-order sensory areas, and, at least in
29
30 monkey, from prefrontal cortex that may overlap several sensory domains. The TRN cells
31
32 target most principal thalamic nuclei in all species and synapse onto excitatory TC cells
33
34 (reviewed in (Fuentelba and Steriade 2005; Pinault 2004)). Axonal projections arborize
35
36 extensively and penetrate deeply into principal thalamus, crossing several nuclei in
37
38 horizontal dorsal-caudal projections (Scheibel and Scheibel 1966) and innervating numerous
39
40 TC neurons through multiple, closely spaced ($< 10 \mu\text{m}$) presynaptic boutons (Wanaverbecq
41
42 and others 2008). By providing GABAergic inhibitory feedback to specific and non-specific
43
44 thalamus, the TRN controls communication between thalamic nuclei and across TC loops. By
45
46 being highly responsive to cortical feedback from sensory and higher cortical areas, the TRN
47
48 shapes multiple aspects of sensory transmission, ranging from receptive field organization
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3 up to anticipation and attentional modulation of sensory perception (reviewed in (Pinault
4
5 2004; Vukadinovic 2011)).
6

7
8 What is the current understanding of how the TRN network acts as a pacemaker for
9
10 spindles? Since the first unit recordings from TRN cells in sleeping cats, it became clear that
11
12 the TRN is a very active brain nucleus that discharges at typically at least ~20 Hz throughout
13
14 all vigilance states, but the exact temporal pattern of discharge varies (Mukhametov and
15
16 others 1970). Thalamic neurons, and TRN cells in particular, undergo substantial changes in
17
18 resting membrane potentials according to the state of vigilance of the brain (reviewed in (Bal
19
20 and McCormick 1997)). When the activity in wake-promoting structures ceases, as is the
21
22 case at sleep onset (Saper and others 2010), depolarizing effects of monoaminergic
23
24 neurotransmitters on TRN are withdrawn and the resting membrane potentials falls by 10-12
25
26 mV from levels ~-50 mV to <-60 mV. Whereas regularly timed action potential discharge is
27
28 elicited from depolarized resting membrane potentials (>-55 mV), TRN cells switch to a
29
30 drastically different discharge mode once they are resting at ~-65 mV or at more
31
32 hyperpolarized levels. This is because membrane hyperpolarization overlaps with the
33
34 activation range of a voltage-gated Ca^{2+} channel, also called low-threshold Ca^{2+} channel or T-
35
36 channel (Huguenard 1996). T-channels are encoded by a family of 3 genes, *Ca_v3.1*, *Ca_v3.2*
37
38 and *Ca_v3.3*, of which the latter two are expressed in TRN (Astori and others 2011). As their
39
40 name says, these channels possess a low activation threshold (~-60 mV) and provoke
41
42 triangular-shaped Ca^{2+} spikes that rapidly, yet transiently, depolarize the neuron to
43
44 threshold for Na^+ action potentials (Huguenard 1996). Action potentials riding on top of
45
46 these Ca^{2+} spikes are then grouped in high-frequency bursts of several hundred Hz that are
47
48 key to TRN's capacities to pacemake spindles.
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B2. The initiation of sleep spindles

Cells in TRN undoubtedly belong to the most dedicated burst-generating neurons in the brain, as exemplified by the combination of powerful cellular and synaptic specifications (Fig. 2). The most prevalent T-channel subtype of the TRN cells is the $Ca_v3.3$ channel that is expressed at high densities along TRN dendrites and that makes up for ~70% of somatically recorded current, with the remaining current being generated by $Ca_v3.2$ channels (Astori and others 2011). T-channel expression occurs in a gradient that increases with increasing somatodendritic distance and that reaches maximum levels ~100 μm from the soma, as indicated through Ca^{2+} imaging (Crandall and others 2010). At more distal sites (>125 μm), the large amount of T-channels boosts the burst propensity of these dendritic compartments. A burst generated therein propagates to the soma and ensures a massive depolarizing drive, explaining the robust Ca^{2+} spike generated in TRN somas that initiates bursts of action potential discharge in TRN axons (Destexhe and others 1996). Voltage-gated Ca^{2+} channels of the R-type (Zaman and others 2011) and rapid K^+ channels of the K_v3 gene family (Espinosa and others 2008) further sustain the rhythmic burst discharge mechanism.

What are the synaptic mechanisms triggering burst discharge? Low-threshold spikes are easily initiated in distal dendritic compartments through glutamatergic stimuli, independently of the somatic membrane polarization (Crandall and others 2010). At these sites, corticothalamic projections predominate and provide one of the most important initial triggers for TRN bursting through the generation of excitatory postsynaptic potentials (EPSPs) (Fig. 3A)(reviewed in (Fuentelba and Steriade 2005)). Cortico-TRN synapses are the most abundant excitatory afferents onto TRN cells; these synapses have high levels of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type ionotropic glutamate receptors at their postsynaptic sites and the pronounced frequency facilitation of the

1
2
3 synapses imposes a powerful excitatory drive (reviewed in (Fuentelba and Steriade 2005)).
4
5 The dominant role of cortico-TRN projections in triggering burst discharge is important for
6
7 the temporal coordination of spindles with other sleep rhythms (see also Chapter B6).
8
9 Additionally, several modulatory synaptic afferents arising in wake-promoting brain stem
10
11 impinge onto TRN cells that could regulate spindle occurrence at periods of NREM sleep
12
13 termination (Fig. 2)(see e.g. (Sun and others 2013)).
14
15

16
17 Recently, light-induced activation of channelrhodopsin-2 expressed in mouse TRN cells
18
19 was used to induce putative burst discharge, and such stimuli were occasionally followed by
20
21 spindle-like rhythms in the EEG during NREM sleep states (Halassa and others 2011; Kim and
22
23 others 2012). This shows directly that TRN bursts can drive EEG sleep spindles.
24
25

26
27 TRN cells provide a strong inhibitory output to TC cells via the generation of burst
28
29 inhibitory postsynaptic potentials (burst IPSPs, Fig. 3B) that involve synaptic GABA_A receptors
30
31 (reviewed in (Beenhakker and Huguenard 2009; McCormick and Bal 1997)) and, through
32
33 spillover of GABA, extrasynaptically located GABA_A receptors (Fig. 3B)((Rovó and others,
34
35 FENS Abstract 2012). Additionally, extrasynaptic GABA_B receptors activated during bursts
36
37 contribute a sizeable, slow component of the burst-mediated hyperpolarization (reviewed in
38
39 (Beenhakker and Huguenard 2009)). Widely used sedative-hypnotic agents for insomnia
40
41 allosterically strengthen GABA_A receptor function and typically boost σ power in the NREM
42
43 sleep EEG, consistent with the important role of these receptors in spindle-generating
44
45 networks (reviewed in (Winsky-Sommerer 2009)).
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52 *B3. The pacemaking and synchronization of spindles*

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55 Through their divergent projections, single TRN cells inhibit multiple TC cells, thereby
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57 driving these to rebound burst discharge (Fig. 3B). In return, excitatory postsynaptic
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3 potentials (EPSPs) generated at TC-TRN synapses re-excite TRN cells. In a back-and-forth
4
5 excitation and inhibition cycle, TRN and TC neuron pools interact like two ping-pong players
6
7 and increasingly recruit cells into the synchronized discharge (reviewed in (Beenhakker and
8
9 Huguenard 2009; McCormick and Bal 1997)).

10
11
12 In TRN dendrites, T-channels are integrated in cooperative ionic assemblies that render
13
14 burst generation repetitive. T-channel activation causes a rapid and homogeneous
15
16 accumulation of Ca^{2+} in the interior of TRN dendrites to levels of at least a few micromolar
17
18 (Fig. 1E)(Crandall and others 2010; Cueni and others 2008). These Ca^{2+} levels are high
19
20 enough to activate Ca^{2+} -dependent small-conductance type 2 (SK2) K^+ channels that are
21
22 found throughout large portions of proximal TRN dendrites. Low-threshold Ca^{2+} spikes are
23
24 thus invariably followed by SK2-channel-mediated afterhyperpolarizations (Fig. 3B)(Cueni
25
26 and others 2008). Through T-channel - SK2 channel interplay, TRN cells generate rhythmic
27
28 sequences of bursts (Fig. 3B), further sustaining rhythmic inhibition of TC cells.
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34 When portions of the cortex are lesioned, the occurrence and synchrony of spindles in
35
36 thalamus is greatly reduced in the remaining areas (reviewed in (Steriade 2006)). To
37
38 conceptualize this cortical control of spindles, it is important to remember that once excited,
39
40 TRN cells will produce widespread recruitment of TC cells not only in the topographically
41
42 corresponding section, but also in non-specific thalamic areas. As also demonstrated in
43
44 computational models (Bonjean and others 2011), these will in turn excite broad cortical
45
46 areas.
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51 Very important for the controlled build-up of spindle synchronization are the
52
53 reciprocal inhibitory interactions between TRN cells that are mediated through slowly
54
55 deactivating GABA_A receptors. These limit the participation of neighboring TRN cells in
56
57 synchronized discharge through shunting and burst inhibition (reviewed in (Beenhakker and
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1
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3 Huguenard 2009)). Additionally, TRN cells are assembled in clusters with juxtaposed cell
4
5 bodies that are connected through electrical synapses built by connexin36-containing gap
6
7 junctions (reviewed in (Cruikshank and others 2005)). Their low-pass filter characteristics
8
9 allow the low-threshold spikes to spread well and augment synchronized burst propensity in
10
11 coupled cells.
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14 15 16 17 *B4. The propagation of spindles to cortical areas*

18
19 EEG spindle waves are scalp reflections of synaptic currents generated by cortical
20
21 neurons. How do intrathalamic network reverberations produce EEG spindle waves?
22
23 Thalamocortical cell axons from specific and non-specific nuclei propagate to cortical
24
25 recipient areas, making the majority of their synapses in layer 4 and 5 of sensory cortices,
26
27 respectively, with additional projections to supra- and infragranular layers (Meyer and
28
29 others 2010). When many TC cells burst simultaneously, strong and rhythmic feedforward
30
31 excitatory volleys are observed in both sensory and prefrontal cortices that entrain ~30% of
32
33 pyramidal and ~80% of fast-spiking interneurons into rhythmic discharges (Peyrache and
34
35 others 2011). Surprisingly, rhythmic activity is seen with only millisecond-delays in upper
36
37 cortical layers, indicating that intracortical circuitry is entrained, and further amplifies, the
38
39 thalamically imposed rhythm (Kandel and Buzsáki 1997). The initial waxing phase of EEG
40
41 spindles is likely related to this accruing participation of larger cortical cell populations into
42
43 the rhythms.
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50 51 52 *B5. The termination of spindles*

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55 Several intrinsic and synaptic mechanisms exist in TRN cells that dampen rhythmic
56
57 burst discharge. Great importance has been attributed to lateral inhibition between TRN
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3 cells that is mediated by GABAergic inhibition, but probably also by peptidergic modulation,
4
5 which ensure that bursting TRN cells limit the participation of their neighbors in
6
7 synchronized discharge. Inhibitory inputs also arise from basal ganglia, substantia nigra and
8
9 pretectal areas (reviewed in (Zikopoulos and Barbas 2007)). Dendrites of TRN cells intertwine
10
11 into small bundles and form dendrodendritic synapses that are thought to act as a brake,
12
13 inhibiting neighboring neurons and destabilizing network synchrony (Pinault 2004). Other
14
15 mechanisms of termination are found in intrinsic ionic mechanisms that reduce burst
16
17 propensity in both TRN and TC cells as a result of repetitive burst discharge and accumulated
18
19 Ca^{2+} entry through T-channels (Fig. 3C). In TC cells, Ca^{2+} -sensitive adenylate cyclases activate
20
21 gradually once repetitive rebound spikes occur, leading to the synthesis of cAMP and the
22
23 activation of the hyperpolarization-activated cation-nonspecific (HCN) channels (Lüthi and
24
25 McCormick 1999). This depolarization reduces the excitability of TC neurons, contributing to
26
27 the breakdown of TC-TRN reverberations. In TRN cells, Ca^{2+} -induced Ca^{2+} release and
28
29 associated cation channel activation at somatic levels, and sarco/endoplasmic reticulum
30
31 Ca^{2+} -ATPase (SERCA)-mediated sequestration of Ca^{2+} (Cueni and others 2008) and
32
33 recruitment of Na^+ -dependent K^+ channels (reviewed in (Coulon and others 2012)) in
34
35 dendrites, attenuate TRN burst firing. Finally, asynchronous cortical synaptic activity also
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37 contributes to spindle termination (Bonjean and others 2011).
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48 *B6. The temporal organization of spindles*

49
50 Spindles appear during NREM sleep in temporal coherence with several sleep rhythms
51
52 that emerge from distinct brain areas (reviewed in (Steriade 2006)). A dominant role in the
53
54 temporal organization of sleep spindles is played by the cortical “slow waves” that underlie
55
56 the low-frequency power (<1 Hz) of the NREM sleep EEG. Slow waves arise from substantial
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3 (>10 mV), rapid and highly synchronized fluctuations of the membrane potential of cortical
4
5 neurons between two states, a depolarized “up” state (>-60 mV) and a hyperpolarized
6
7 “down” (<-70 mV) state (reviewed in (Steriade 2006; Timofeev and others 2012)). The “up”
8
9 state is accompanied by wake-like repetitive action potential firing in cortical neurons across
10
11 all layers and cell types, creating a strong excitatory feedback via cortico-TRN synapses
12
13 (Sanchez-Vives and McCormick 2000). Cortical waves thus impose periodically recurring
14
15 excitation onto TRN and TC cells, thereby triggering intrathalamic network reverberations.
16
17 Through prolonged excitation during “up” states, slow rhythms matching those of cortex are
18
19 also induced in TC and TRN neurons (Crunelli and Hughes 2010). The strong feedback
20
21 control, combined with widespread TC projections, ensures spatially coherent spreading of
22
23 spindling over cortical territories (reviewed in (Steriade 2006)). The cortical control of
24
25 spindles explains their link to EEG slow waves, resulting in spike-like waveforms called K-
26
27 complexes in humans (Fig. 1A). However, spindles also occur independently of slow rhythms,
28
29 occasionally in localized cortical regions (Nir and others 2011). In rodents, spindle waves
30
31 appear throughout NREM sleep (Fig. 1B)(Vyazovskiy and others 2004), predominantly at
32
33 periods of NREM sleep termination when low-frequency δ power weakens. Well-
34
35 documented is the surge of σ power (10-15 Hz) ~30 s before NREM-REM sleep transitions
36
37 that depends on burst discharge in TRN (Astori and others 2011; Wimmer and others 2012).

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45 Interestingly, spindles are also temporally associated with hippocampal activity. High-
46
47 frequency (100-400 Hz) sharp-wave ripples (SPWRs) are found in hippocampus during quiet
48
49 wakefulness and NREM sleep and represent a re-activation of firing patterns found during
50
51 exploration, probably contributing to the formation of memory traces (reviewed in
52
53 (Girardeau and Zugaro 2011)). Close temporal associations exist between hippocampal
54
55 SPWRs and cortical spindles mostly in prefrontal, but also in sensory areas in rats and
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3 humans (reviewed in (Rasch and Born 2013)). Such observations point to a widely
4
5 coordinated synchronization of major brain memory systems and TC rhythms, and embed
6
7 spindles in the transfer of newly acquired hippocampal memory traces to cortex for long-
8
9 term storage.
10

11 12 13 14 *B7. Human sleep spindles*

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16
17 Two different types of spindles were already reported in early stages of EEG recordings
18
19 from humans (reviewed in (Rasch and Born 2013)). The slower spindle with a frequency ~12
20
21 Hz predominates in frontal cortical areas, whereas the faster ones ~14 Hz is found in parietal
22
23 zones. Presurgical depth EEG recordings from epileptic patients suggest a sharp border
24
25 between slow and fast spindles in the supplementary motor area (Andrillon and others
26
27 2011), while other experimenters observed more gradual frequency changes along the
28
29 rostral-caudal axis (Peter-Derex and others 2012). The origin of fast and slow spindles is not
30
31 clarified, but is relevant as fast and slow spindles differentially engaged in learning-related
32
33 brain activity (Möller and others 2011). Functional magnetic resonance imaging (fMRI)
34
35 showed that both spindle types largely, but not completely, shared the thalamic areas
36
37 activated (Schabus and others 2007). There were also common activation patterns in cortex,
38
39 including cingulate cortex, anterior insula and superior temporal gyrus. However, fast
40
41 spindles overall showed a broader cortical activation pattern, covering also supplementary
42
43 motor areas and, notably, a greater recruitment of hippocampal areas. Interestingly, spindle
44
45 activity during stage N2 of NREM sleep correlated with neuronal activation in hippocampus,
46
47 suggesting that TC oscillations drive hippocampus (Andrade and others 2011; Peter-Derex
48
49 and others 2012).
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C What do spindles do?

C1. Sensory transmission

The definition of sleep states involves a reduced responsiveness to sensory inputs. As the TC system is the major recipient of sensory afferents, changes in its electrical activity will affect the throughput of sensory stimuli. Early *in vivo* studies, some of which carried out by the Nobel Prize winner David Hubel, demonstrated that the fidelity of retinogeniculate information transfer varied with the state of arousal, and is in particular degraded during periods of drowsiness and sleep (Livingstone and Hubel 1981), when TC neurons are hyperpolarized and preferentially discharge in bursts rather than in linearly coding tonic trains of action potentials (reviewed in (Bal and McCormick 1997)).

Spindles are particularly efficient in vetoing sensory activation of the cortex and are key elements in the reduced sensory responsiveness during sleep. For example, it is harder to wake-up somebody while his brain generates spindles than when it does not do so (Yamadori 1971). Event-related potentials, which are EEG deflections in response to sensory stimuli, are altered in shape during NREM sleep, but do so more extensively when elicited during a spindle (Cote and others 2000). A recent imaging study looking at auditory cortex activation during sounds showed that activation was essentially nil during spindles, but remained substantial during spindle-free NREM sleep (Fig. 4) (Dang-Vu and others 2011; Schabus and others 2012). The dominant recruitment of inhibition throughout cortical layers plausibly contributes to the lack of cortical response (Peyrache and others 2011). A protective role of sleep spindles was directly demonstrated in mice in which spindle power at periods of exit from NREM sleep was intensified through genetic modification of TRN bursting (Wimmer and others 2012). These animals showed a higher acoustic arousal

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2
3 threshold when exposed to incremental white noise, suggesting that sleep spindles retard
4
5 the transition from NREM sleep to waking.
6

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8 Why would the brain use short spindle events to protect itself from arousal? Sensory
9
10 disconnection during sleep varies constantly, with recurring periods of strong sensory
11
12 decline and of weakened, but still significant responsiveness closer to the waking state. It
13
14 seems that NREM sleep repeatedly opens time windows for sensory stimuli to penetrate into
15
16 cortex. Considering that spindles often occur during cortical up states, it is possible that they
17
18 represent cortically triggered efforts to enhance sensory shut-down after a brief period of
19
20 heightened responsiveness. Conversely, properly timed auditory stimuli can enhance slow
21
22 fluctuations in the cortex as they probably boost cortical activity during up states (Ngo and
23
24 others 2013).
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31 *C2. Synaptic plasticity and memory*

32
33 Via the excitation imposed by TC afferents onto cortex, spindles induce coordinated
34
35 firing in cortical circuits. Across cortical layers, single action potentials occur time-locked to
36
37 the spindle rhythm, as monitored in local field potential recordings (Contreras and others
38
39 1997), priming connected neurons for spike-timing-dependent forms of plasticity.
40
41 Additionally, groups of action potentials discharge at >100 Hz in cortical neurons may modify
42
43 synaptic strength in a non-Hebbian form of plasticity, i.e. independently of the temporal
44
45 correlation between pre- and postsynaptic activity. For example, burst-like discharge in
46
47 cortical layer 5 neurons induces a long-term depression of excitatory synapses formed by
48
49 supragranular afferents and a strengthening of somatic inhibitory inputs (Birtoli and Ulrich
50
51 2004; Kurotani and others 2008).
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3 Spindle-related spike trains recorded in anesthetized cat were applied in cellular
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5 studies in rat cortical brain slices to mimic temporally correlated pre- and postsynaptic
6
7 activity thought to occur during spindles (Rosanova and Ulrich 2005). As a result, a long-term
8
9 potentiation (LTP) at excitatory connections between layer 2/3 and layer 5 was observed
10
11 (Fig. 5A). Interestingly, the detailed sequence of interspike interval in the spindle train
12
13 mattered, as a random shuffling of these or using mean frequency rates (30 Hz) were inferior
14
15 in inducing LTP. Aside from cortex, recent studies have unraveled that rhythmic bursting in
16
17 TRN cells induces LTP at TC-TRN synapses (Astori and Lüthi 2013). Spindle rhythms thus drive
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19 cortical synchronized discharge and associated long-term synaptic strengthening and
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21 override a global downregulation of synapses during low-frequency rhythms in cortex.
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26 The synaptic potentiation observed by spindles links to repeated observations that
27
28 spindle correlate with memory formation and learning capacity in humans. Declarative
29
30 memory tasks involving cued recall of word pairs went along with increased spindle density
31
32 (in number of events per 30 s) during the first period of N2 NREM sleep, without any
33
34 changes in sleep structure or other frequency bands (Gais and others 2002; Schabus and
35
36 others 2004). Spindle density increased locally within brain areas implicated in learning, as
37
38 documented in other training tasks (Fig. 5B) (Johnson and others 2012). The increase in
39
40 spindle density correlated linearly with the performance improvement. Spindle density also
41
42 correlates positively with learning capacity and intelligence measures (Fig. 5C). Links
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44 between spindles and memory formation are now documented for rodents exposed to
45
46 associative learning (Eschenko and others 2006; Mölle and others 2009) and for more
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48 sophisticated aspects of the learning process in humans (reviewed in (Rasch and Born
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50 2013)).
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3 How could changes in spindle parameters, such as their intensity/amplitude or their
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5 frequency/occurrence, facilitate learning? A combined EEG and fMRI study on associative
6
7 visual memory found that, during post-learning sleep, the amplitude of individual spindles
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9 correlated with neuronal activation in both hippocampus and in higher visual areas selective
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11 for the visual objects (Bergmann and others 2012). This finding is consistent with
12
13 observations on enhanced temporal coupling between cortical slow oscillations, spindles
14
15 and hippocampal ripples after learning (Mölle and others 2009). However, in naturally
16
17 sleeping rats, prefrontal cortex responded more weakly to hippocampal SPWRs during
18
19 spindle epochs than during spindle-free periods (Peyrache and others 2011), leaving open
20
21 whether spindle-related proplastic effects are related to spindle-ripple coupling. It is also
22
23 important to note that not only spindles, but slow wave intensity also correlates with
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25 declarative learning (Rasch and Born 2013), indicating that sleep-related learning is a multi-
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27 component process with several sleep rhythms involved.
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36 *C3. Neuronal development*

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38 Spindles are accompanied by rhythmic fluctuations of intracellular signaling systems. In
39
40 TRN cells, Ca^{2+} increases during every burst discharge in large portions of dendrites and is
41
42 sequestered through SERCAS into the endoplasmic reticulum (ER) (Fig. 1E, Fig. 3C). Luminal
43
44 Ca^{2+} levels regulate major ER functions in cell physiology, including gene transcription and
45
46 protein synthesis. T-channel-mediated Ca^{2+} accumulation in the ER may hence drive
47
48 transcriptional activity specifically during spindle rhythmicity. Furthermore, in TC cells,
49
50 rhythmic low-threshold bursts lead to waves of cAMP synthesis through activation of Ca^{2+} -
51
52 sensitive adenylate cyclases (Fig. 3C)(Lüthi and McCormick 1999), known to be important for
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54 synapse specification (Gorbunova and Spitzer 2002). Interestingly, first signs of organized
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3 electrical activity in the developing brain of rodents and humans occur as spindle-like, 10 Hz-
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5 rhythms in association with spontaneous muscle twitches in limbs (reviewed in (Hanganu-
6
7 Opatz 2010)). It is proposed that these early brain rhythms act as a template for cortical map
8
9 organization, but whether spindle-associated Ca^{2+} and cAMP signals are relevant for sensory
10
11 circuit formation remains open. Spindle-mediated fluctuations in intracellular signaling
12
13 perhaps play a role throughout adulthood by maintaining and shaping TC connectivity in the
14
15 mature brain in response to on-going sensory activity and learning.
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22 **D Conclusions and Perspectives**

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24
25 Spindles were the first EEG rhythm reported and the first network oscillation for which
26
27 a cellular mechanism was elucidated. These oscillations continue to exemplify the neuronal
28
29 structure and significance of rhythms for the brain, as indicated by the make-up of
30
31 oscillatory units, the design of circuits engaging in successive synchronization and
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33 desynchronization and their conditioned recruitment by other brain areas. Spindle
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35 rhythmogenesis is based on an elaborated cooperation between ionic and synaptic
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37 mechanisms in the pacemaker circuits. Knowledge about these is relevant in the continued
38
39 search of specific drug targets that could improve treatment of sleep disorders. Spindles
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41 separate sleep into distinct phases of sensory accessibility, enabling periods of almost
42
43 complete annihilation of sensory throughput with periods in which sensory information does
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45 reach the cortex. At the same time, spindles enable epochs of heightened plasticity that fall
46
47 together with the emergence of hippocampal rhythms. Therefore, do spindles promote
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49 sensory protection to ensure the internal processing of information? Do spindles facilitate
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51 the association between hippocampal and cortical activity that allows the purported transfer
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53 from short-term to long-term memory sites? How does such a function correlate with the
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3 dominant recruitment of inhibition in cortex by spindles? From all we can see today, spindles
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5 seem designed to unify the brain's diverse structures into a single major processing center,
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7 yet more analysis is required to link their impact on cortical units and on hippocampal-
8
9 cortical coordination.

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12 First efforts to modify spindles specifically are underway. Chronic manipulations, such
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14 as those possible with genetic interference (Astori and others 2011; Wimmer and others
15
16 2012), will determine their role in sleep architecture and TC connectivity. Acute modification
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18 (Halassa and others 2011) could be envisaged as a way to test their implication in learning
19
20 processes, for example by combining associative learning in rodents with optogenetic
21
22 manipulation of spindle occurrence during post-learning sleep. These possibilities currently
23
24 remain overflown with questions to be resolved experimentally: Do optogenetic stimuli
25
26 come close to cortically mediated initiation of thalamic pacemakers? How should
27
28 optogenetically elicited spindles be timed relative to the occurrence of other rhythms? Is it
29
30 sufficient to modify spindle occurrence independently of other rhythms to induce learning?
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36 What will be the impact of global vs. modality-specific TRN stimulation?
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39 Decreased spindle activity has been presented as a hallmark in schizophrenia
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41 (Ferrarelli and others 2010), and developmental models of schizophrenia in rat revealed
42
43 aberrant timing of spindles relative to cortical and hippocampal rhythms (Phillips and others
44
45 2012). Such sleep disturbances fit well with the idea that abnormal perceptions in
46
47 schizophrenia are due to impaired corticothalamic communication (Vukadinovic 2011). Such
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49 novel links between spindles and neurological disease may ultimately prompt therapeutic
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51 approaches involving directed manipulation of sleep rhythms.
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Box 1.

The historical origins of sleep spindle research. The German medical doctor Hans Berger (1873-1941), working as a psychiatrist in Jena, was driven to identify measurable parameters about the brain's psychical energy and about mental telepathy. He initially experimented on human patients with skull defects to measure brain volume, pulsations of intracranial blood flow and intracranial temperature. Around 1900, he turned to his first recording to record the electrical activity of the brain, but then suspended these efforts due to the poor data quality, clinical and academic obligations, and medical service during the First World War. He picked up his scientific work in the 1920's, and, through a decade-long painstaking improvement of galvanometric recordings from the human brain, he came up with the first clear recordings of rhythmic brain activities. He noted in particular the rhythmic appearance of brief oscillatory events in the 10 Hz range, which he called alpha waves, and which he thought were representing some form of mental activity, while the faster beta waves (15-20 Hz) represented the brain's metabolic state (Berger 1933). In the last decade of his life, great skepticism was brought against his work and the significance of Berger's "Elektrenphalogram" was not recognized until researchers such as Sir Adrian, Jaspers and Bremer reproduced his findings and further developed techniques and animal preparations to record brain electrical activity. Their studies sparked discussions about the electrical signals generating and the cellular mechanisms underlying the observed rhythms. Spindle waves soon became the focus of these discussions when Adrian noted that rhythmic activity observed in cortex during anesthesia could be recorded in the white matter, from the cut end of fibers from thalamus to cortex (Adrian 1941). The 50's and 60's brought landmark developments within the field of thalamic function. Moruzzi and Magoun identified the brainstem reticular activating system as a main wake-promoting structure (Moruzzi and

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2
3 Magoun 1949). Moreover, intracellular recordings from thalamic neurons revealed that
4
5 these neurons experience prolonged rhythmic inhibitory synaptic events in phase with the
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7 oscillatory periods (Purpura 1968), originating from an intrathalamic source (Andersen and
8
9 Andersson 1968). The leading researcher at the end of 1900's was Mircea Steriade, who,
10
11 from the 1980s on, demonstrated that TRN was the pacemaker for sleep spindles and
12
13 responsible for generating rhythmic inhibitory synaptic potentials throughout principal
14
15 thalamic nuclei (reviewed in (Fuentelba and Steriade 2005)). His work on the intact brain
16
17 found even greater acclaim when spindle rhythms could be reproduced in brain slice
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19 preparations containing the TRN, further confirming that they arose from a localized
20
21 pacemaker element within the brain (reviewed in (Steriade and others 1993)).
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10 11 **Figure legends**

12
13 **Figure 1. Sleep spindles and spindle-like rhythms are documented at multiple levels of**
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15 **neuronal circuitry analysis. A**, EEG recording of spindles from a sleeping human subject from
16
17 two corresponding sites on primary somatosensory cortex (C3-A2, C4-A1). Note the regular
18
19 appearance of sleep spindles, evident as grouped EEG deflections occurring at higher
20
21 frequencies than background (*). K-complexes intertwined with sleep spindles are marked
22
23 by #. The spindle labeled with ** is expanded on the right to illustrate the waxing and
24
25 waning waveform. Traces were kindly provided by Dr. R. Heinzer, Cantonal Hospital of the
26
27 University of Lausanne, Switzerland. **B**, Local field potential recordings from layer 5 of
28
29 primary somatosensory (S1) and auditory (A1) areas in an adult C57Bl/6J mouse during
30
31 NREM sleep. Same labeling for *,** and # as in A. Spindles were detected based on band-
32
33 pass filtering of the traces between 10-15 Hz (bottom trace on the right). Traces were kindly
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35 provided by Dr. L. Fernandez, University of Lausanne, Switzerland. **C**, Spontaneous rhythmic
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37 multiunit discharges in a mouse brain slice containing TRN and adjacent ventrobasal
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39 thalamic complex. Waxing and waning waveform of each grouped discharge is apparent.
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41 Expanded portion is taken from the area labeled with a small black bar and shown to the
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43 right. **D**, Intracellular recording of a TC neuron engaged in spindle-like rhythms in a ferret
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45 slice containing the dorsal lateral geniculate nucleus of the thalamus and the adjacent
46
47 perigeniculate nucleus, a carnivore equivalent of the visual TRN (for further information, see
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49 Steriade and others, 1993). Note rhythmic occurrence of inhibitory postsynaptic potentials
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3 that are occasionally eliciting rebound burst discharge. Black bar illustrates portion of the
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5 trace that is expanded to the right. Time scale in D also applies for A-C. E, Ca^{2+} imaging of
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7 proximal dendrites of a TRN cell as it generates repeated burst discharge elicited through
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9 somatic current injection. Images were acquired at the time of discharge indicated by
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11 vertical lines. Imaging was carried out as described in Cueni and others (2008). Note the
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13 marked increase in Ca^{2+} levels throughout the imaged dendritic portion and its almost
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15 complete decay during the interburst phase.
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22 **Figure 2. Morphological, ionic and synaptic properties of TRN cells that contribute to**
23 **vigorous burst discharge.** Reconstructed rat TRN cell labeled with neurobiotin during a
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25 juxtacellular recording (for details, see Pinault, 2004 and references therein). Note the
26
27 multiple thin dendrites emerging from the soma, some of which branch extensively and form
28
29 hairy appendages. The subcellular distribution is indicated for T-channels (orange-brown
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31 gradient, with darker colors indicating greater expression levels) and for SK2 channels
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33 (green). SK2 channel expression was demonstrated up to $\sim 100 \mu\text{m}$ from the soma. Single
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35 dendrites were chosen to illustrate T- and SK2 channel distribution in color code.
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37 Mechanisms of burst control involving high-voltage-activated Ca^{2+} channels, Ca^{2+} -induced
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39 Ca^{2+} release and Ca^{2+} -activated cation channels were described at the somatic level. The
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41 axon, emerging from a primary dendrite, expresses high levels of Na^+ channels (red).
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43 Synaptic afferents for which their subcellular distribution is known are positioned
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45 accordingly. Excitatory afferents are labeled with a circle, inhibitory afferents with a line.
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47 Cholinergic afferents mediate both excitation and inhibition. Insets show a single burst and
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49 repetitive burst discharge (for details, see Pinault, 2004 and references therein). CT,
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3 corticothalamic; ACh, acetylcholine. Reconstructed cell and electrophysiological traces were
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5 kindly provided by Dr. D. Pinault, INSERM, University of Strasbourg, France.
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10 **Figure 3. T-channel-dependent mechanisms of spindle initiation, synchronization and**
11 **termination. A-C**, Schematic drawings of membrane portions from TRN and TC cells with
12 color-coded Ca_v3 channels (yellow), SK2 channels (green), HCN channels (blue) and cation
13 channels (violet) and associated mechanisms of Ca^{2+} signaling. Na^+ channels are not
14 represented. Colored circles and associated color clouds indicate ion flow through channels.
15 Yellow, Ca^{2+} ; Green K^+ ; Blue Na^+ . Membrane voltage traces indicate the electrophysiological
16 events associated to these schemes. Traces are from recordings in mouse thalamic slices and
17 were kindly provided by Dr. S. Astori, University of Lausanne, Switzerland. **A**, Initiation of
18 spindles occurs through recruitment of burst discharge via cortical EPSPs. **B**, Spindle
19 synchronization is mediated via reciprocal synaptic interactions between TRN and TC cells
20 through burst IPSPs, rebound burst generation in TC cells, and TC-TRN EPSPs. Repetitive
21 burst discharge in TRN cells occurs through Ca_v3 -SK2 channel interplay. **C**, Termination of
22 spindles occurs through multiple mechanisms involving Ca^{2+} -mediated alterations of TRN
23 and TC cell excitability. *Top*, TRN cells undergo a dampening of burst discharge through (*left*)
24 somatic activation of cation channels (via activation of Ca^{2+} channels and Ca^{2+} -induced Ca^{2+}
25 release (CICR) through ryanodine receptors) and through (*right*) dendritic sequestration of
26 Ca^{2+} via SERCAs, limiting SK2 channel activation. *Bottom*, TC cells generate a membrane
27 afterdepolarization (arrow) through repetitive burst IPSPs, Ca^{2+} -mediated activation of
28 adenylate cyclases and consequent upregulation of HCN channels.
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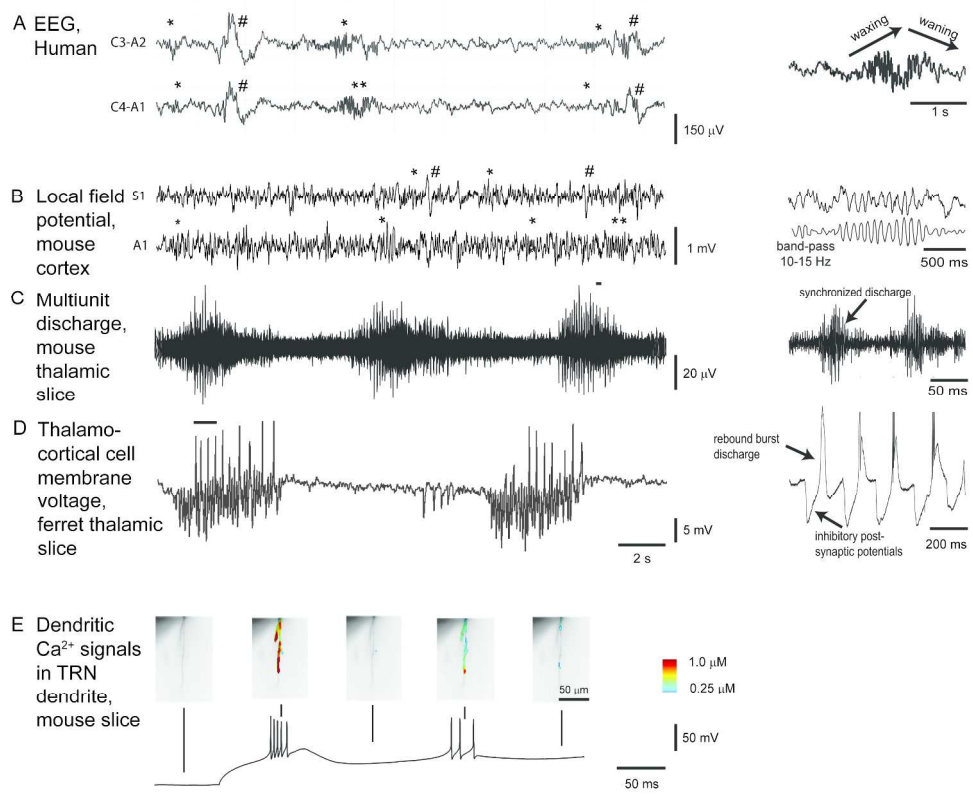
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3 **Figure 4. Annihilation of auditory cortex activation during spindle-containing, but not**
4 **during spindle-free epochs of NREM sleep. A,** Schematic of experimental design. Human
5 EEG trace of NREM sleep with spindle-free and spindle-containing episodes. Brief auditory
6 stimuli (300 ms, 400 Hz) were applied at time points indicated by blue squares. EEG trace
7 was provided by Dr. R. Heinzer, Cantonal University Hospital of Lausanne, Switzerland. **B,**
8 Functional magnetic resonance imaging of responses to auditory stimuli during three EEG-
9 defined states (indicated above the images). Yellow voxels indicate brain areas activated in
10 response to the stimulus. During waking, clear responses are evoked in auditory cortex (top)
11 and in brainstem and collicular areas (bottom) involved in sound detection. During spindle-
12 free NREM sleep, similar brain areas are activated; see Dang-Vu and others (2011) for
13 explanations as to the difference in activation patterns between waking and spindle-free
14 NREM sleep. During spindle-containing NREM sleep epochs, no fMRI signals are detectable
15 in cortex and brainstem. Red arrows highlight small activation of inferior collicular areas
16 (enlarged in inset). X and y refer to brain coordinates used for fMRI. Picture adapted, with
17 permission, from Dang-Vu and others (2011).
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41 **Figure 5. Sleep spindles and their relation to synaptic plasticity, memory and intelligence.**

42 **A,** Application of spindle-like rhythmic action potential trains in rat somatosensory cortical
43 brain slices induces long-term potentiation. *Left,* Stimulation train applied to presynaptic
44 afferents (Pre, upper electrode) and to postsynaptic cells (Post, lower electrode) to induce
45 joint pre- and postsynaptic activity. The stimulation protocol was repeated 30 times at 0.6
46 Hz. *Right,* sample EPSPs before (dotted line) and > 30 min after (solid line) conditioning
47 protocols. Adapted, with permission, from Rosanova and Ulrich 2005. **B,** High-resolution EEG
48 monitoring of post-training spindle rates in human subjects exposed to a brain-computer
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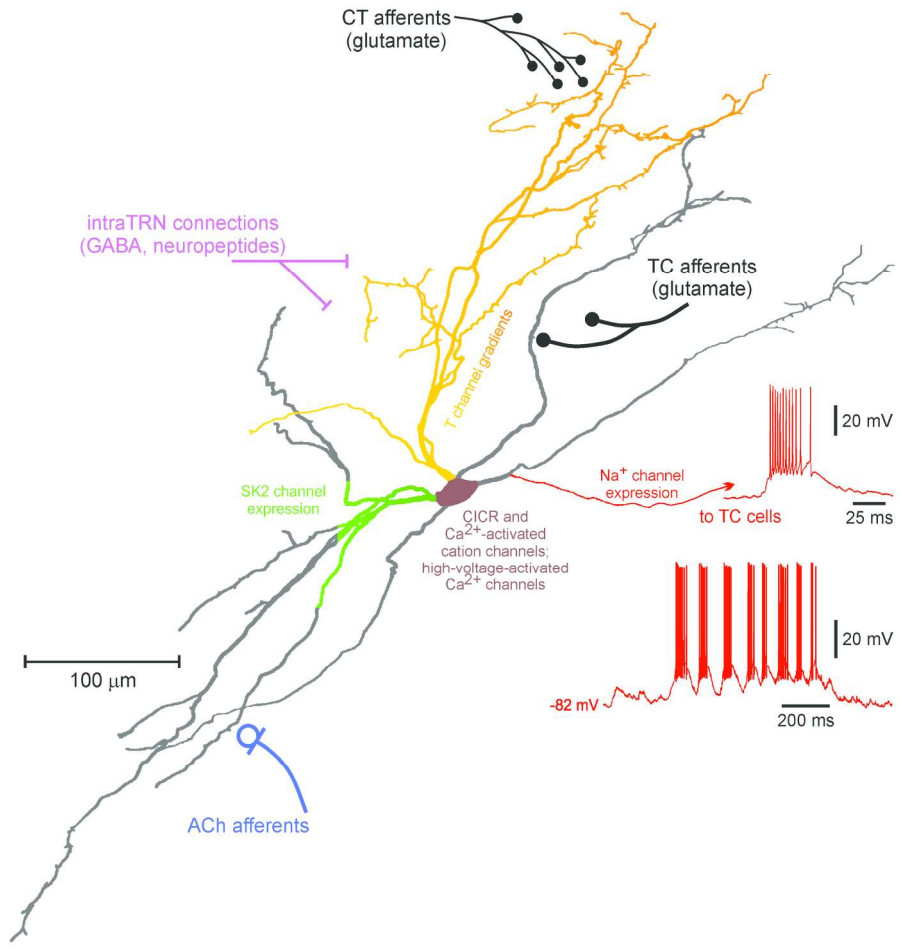
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3 interface task. Warm and cold colors indicate percentage increases and decreases in spindle
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5 rates, respectively, relative to the day preceding training. White circle indicates the position
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7 of the task electrode used for brain-computer interfacing. Note local increases in spindle
8
9 density consistent with the site of learning. Grey colors indicate no change. Adapted from
10
11 (Johnson and others 2012). **C**, Linear correlation between total number of spindles measured
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13 at sites C3 and C4. Spindles were included in the count if the intraspindle frequency was 12.0
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15 –16.0 Hz, if the duration was > 0.5 s, and the amplitude reached 10 mV. Every data point
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17 represents one participant. Correlation coefficient was 0.75. Adapted from Fogel and others
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19 ((Fogel and others 2007)).
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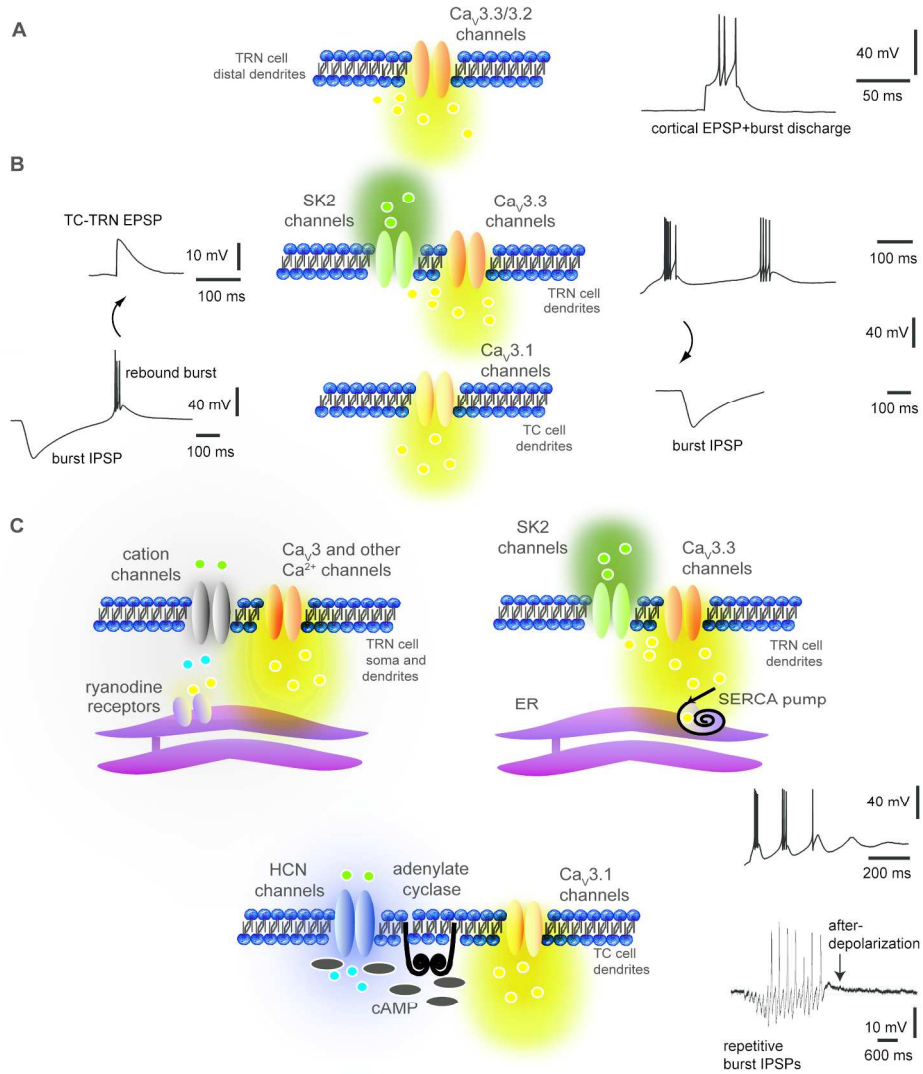


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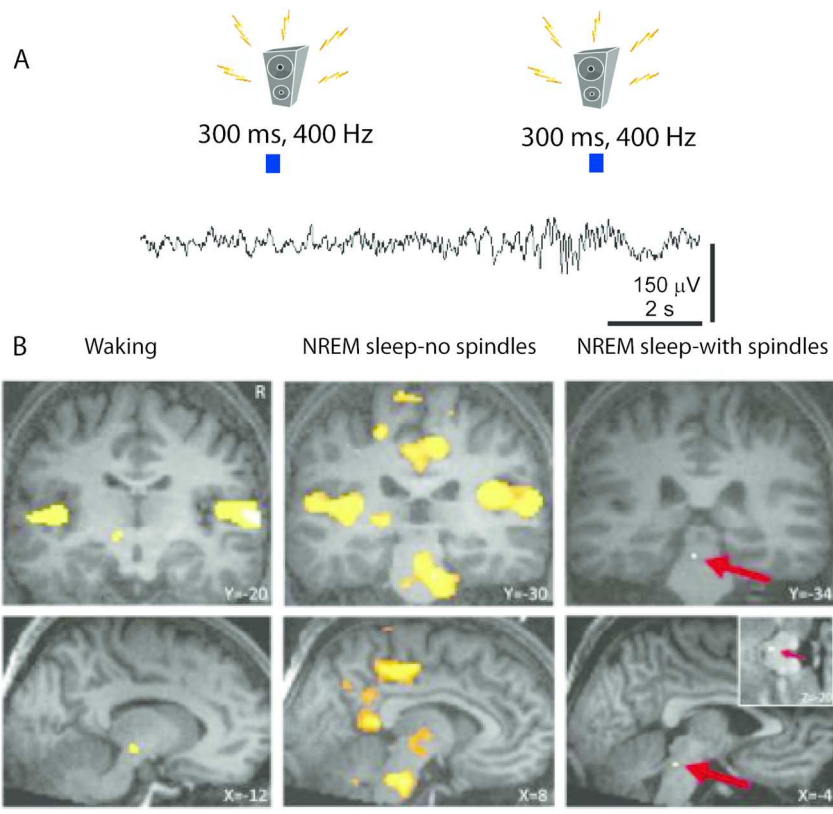


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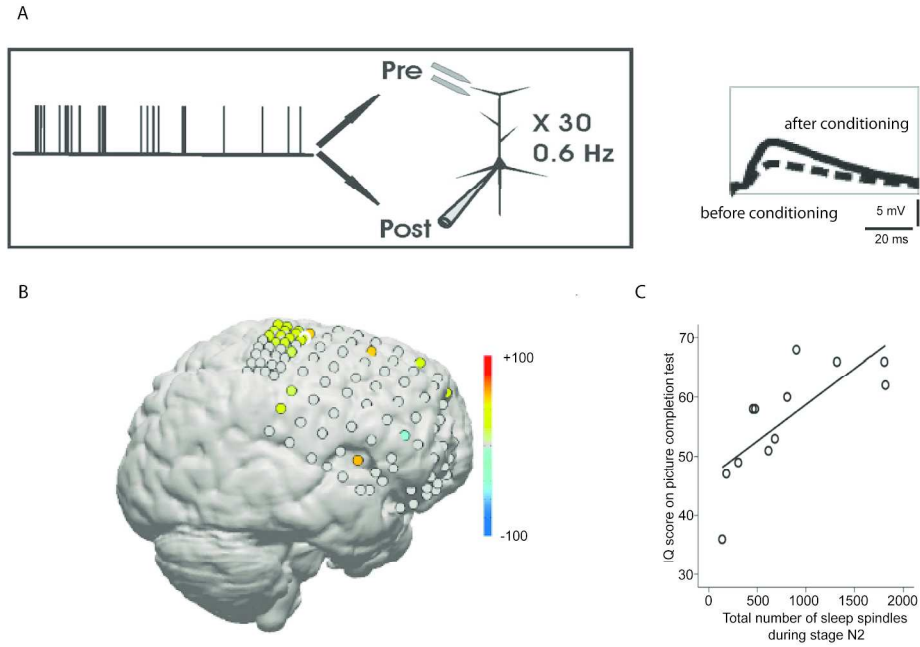
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