Published in final edited form as:

Am J Psychiatry. 2010 November ; 167(11): 1339–1348. doi:10.1176/appi.ajp.2010.09121731.

Thalamic Dysfunction in Schizophrenia Suggested by Whole-Night Deficits in Slow and Fast Spindles

Fabio Ferrarelli, M.D., Ph.D.¹, Michael J. Peterson, M.D., Ph.D.¹, Simone Sarasso, Ph.D.¹, Brady A. Riedner, B.A.¹, Michael J. Murphy, B.S.¹, Ruth M. Benca, M.D., Ph.D.¹, Pietro Bria, M.D.², Ned H. Kalin, M.D.¹, and Giulio Tononi, M.D., Ph.D.¹

¹ University of Wisconsin, School of Medicine and Public Health. Department of Psychiatry. 6001 Research Park Blvd., Madison, WI 53719

² Catholic University of the Sacred Heart. Department of Psychiatry. Largo F. Vito #1, 00168 Rome, Italy

Abstract

Slow waves and sleep spindles are the two main oscillations occurring during NREM sleep. While slow oscillations are primarily generated and modulated by the cortex, sleep spindles are initiated by the thalamic reticular nucleus (TRN), and regulated by thalamo-reticular and thalamo-cortical circuits. In a recent high-density electroencephalographic (hd-EEG) study we found that 18 medicated schizophrenics had reduced sleep spindles compared to healthy and depressed subjects during the first NREM episode. Here we investigated whether spindle deficits were: a) present in a larger sample of schizophrenic patients; b) consistent across the night; c) related to antipsychotic medications; d) suggestive of impairments in specific neuronal circuits. Whole night hd-EEG recordings were performed in 49 schizophrenics, 20 non-schizophrenic patients on antipsychotics and 44 healthy subjects. In addition to sleep spindles, several parameters of slow waves were assessed. Schizophrenics had whole-night deficits in spindle power (12–16 Hz) and in slow (12–14 Hz) and fast (14–16 Hz) spindle amplitude, duration, number and integrated spindle activity (ISA) in prefrontal, centroparietal and temporal regions. ISA and spindle number had the largest effect sizes ($ES \geq 2.21$). By contrast, no slow wave deficits were found in schizophrenics. These results indicate that spindle deficits i) can be reliably established in schizophrenics, ii) are stable across the night, iii) are unlikely to be due to antipsychotic medications, and iv) point to deficits in TRN and thalamo-reticular circuits.

Introduction

Schizophrenia is a disabling, chronic illness, which has marked socio-economic impacts on the patients and the entire community (1). Despite considerable efforts, the neurobiology of schizophrenia remains elusive (2), and its diagnosis is based exclusively on descriptive symptomatology. To date, a symptom-based approach has not increased our understanding of schizophrenia. This is because clinical symptoms vary across the course of the illness, thus complicating the identification of underlying neurobiological mechanisms (3).

Correspondence to: Giulio Tononi.

Parts of this research were presented at the American Psychiatric Association Annual Meeting, San Diego, CA. May 2007, and the Society of Biological Psychiatry Annual Meeting, San Diego, CA. May 2007.

All work was performed at the University of Wisconsin, School of Medicine and Public Health. Department of Psychiatry. 6001 Research Park Blvd., Madison, WI 53719.

Drs. Ferrarelli, Sarasso, and Bria, and Mr. Riedner and Mr. Murphy report no competing interests.

An alternative approach employed in schizophrenia research involves measuring cognitive/neurophysiological parameters in healthy and schizophrenic subjects (4). Deficits in these parameters can reveal dysfunctions in neuronal mechanisms which are stable over time, and largely symptom-independent in schizophrenics (5). Moreover, these dysfunctions likely implicate specific brain circuits, which may help identifying better genetic/molecular targets for the diagnosis and treatment of schizophrenia (6).

Sleep offers important advantages for investigating possible dysfunctions in brain circuits in schizophrenics. Sleep recordings minimize waking-related confounding factors, including fluctuation in attention, reduced cognitive ability, and presence of active symptoms. Additionally, the two main NREM sleep rhythms, slow waves and spindles, reflect the activity of complementary thalamocortical circuits. Slow waves are 1 Hz oscillations characterized by large amplitude, positive-negative deflections, which are generated by cortical neurons, and propagated by intracortical and cortico-thalamocortical circuits (7). Sleep spindles are waxing/waning 12–16 Hz oscillations, which are initiated by the TRN and regulated by thalamo-thalamic and thalamo-cortical circuits (8). Thus, the identification of reduced slow wave and/or spindle parameters may help identifying deficits in specific brain circuitries in schizophrenia.

We previously found that sleep spindles were reduced in the first NREM episode of eighteen medicated schizophrenics (9). Schizophrenics showed deficits in spindle amplitude, duration and number compared to healthy and depressed subjects. Furthermore, ISA, which was calculated integrating the amplitude of each spindle over time, was reduced in sixteen of eighteen schizophrenics (9).

Here we extended these results by performing whole-night hd-EEG recordings in forty-nine schizophrenics. To assess medication effects on spindles, we investigated spindle activity in non-schizophrenic patients taking antipsychotics. Additionally, to establish whether spindle deficits primarily reflect impairments of TRN and intra-thalamic circuits we analyzed several sleep slow wave parameters.

Methods

Participants

Forty-nine schizophrenics, forty-four healthy subjects, and twenty non-schizophrenic patients taking antipsychotics were recruited. All subjects were between 18 and 55 years of age. Exclusion criteria were: substance abuse/dependence within the last 6 months, identifiable neurological disorders, or diagnosed sleep disorders. Healthy subjects with first-degree relatives with psychiatric diagnoses were also excluded. Demographic and clinical variables were similar across groups except for gender, body mass index, and medication doses (Supp. Tab.1). A psychiatrist interviewed all participants and administered the Structured Clinical Interview for DSM-IV to confirm, or exclude, psychiatric diagnoses, and further evaluated schizophrenics with Positive and Negative Syndrome Scales (PANSS). Schizophrenics were diagnosed as paranoid (N=35), undifferentiated (N=5), disorganized (N=5) or residual subtypes (N=4). They were receiving second-generation (N=35), first- and second-generation (N=10), or first-generation (N=4) antipsychotics. They were also receiving benzodiazepines (N=10), antidepressants (N=22), and mood stabilizers (N=11). Schizophrenics were outpatients with mean duration of illness of 15 years (SD=8), and mean total PANSS scores of 88.5 (SD=12.7).

Non-schizophrenic patients had various psychiatric diagnoses: major depression (N=4), bipolar affective disorder (N=10), post-traumatic stress disorder (N=2), panic disorder (N=2), and generalized anxiety disorder (N=2). Seventeen were receiving second-generation

antipsychotics, three first-generation antipsychotics. Additionally, five were receiving benzodiazepines, seven antidepressants, and three mood stabilizers.

EEG Recordings

Whole-night hd-EEGs were performed with 256-electrode nets designed to improve electrodes contact with the scalp, thereby enabling long-duration recordings (EGI, Eugene, OR). EEGs were performed at the Wisconsin Psychiatric Institute and Clinic (WISPIC). The study was approved by the University of Wisconsin's institutional review board. After a complete description of the study, written informed consent was obtained. The participants were then placed in a sleep suite and allowed to sleep at their self-reported bedtime until morning.

EEG analysis

EEG signals were band-passed (0.5–50 Hz) and digitized at 500 Hz. After excluding electrodes located on the neck/face region and channels with impedances >150 KOhms, 175–185 channels per subject were retained. Sleep stages were scored on C3A2 and C4A1 derivations by two authors blind to subjects' identity using AASM criteria (10). Inter-rater reliability was >90%. Artifacts were visually excluded during scoring. Additional artifacts were removed rejecting 20-second epochs which exceeded thresholds based on mean power for each channel in 0.75–4.5 and 20–30 Hz bands. Signals were then re-referenced to the average from all included channels. This montage was used for computing power spectra of non-REM epochs (9).

Spindle analysis

NREM epochs were filtered between 11 and 16 Hz, and rectified filtered signals were used as time series for each channel. Because signal amplitude varied considerably across channels, thresholds relative to the mean amplitude of each channel were used. For each spindle the amplitude was the maximum above an upper threshold, the beginning and end the points preceding or following this maximum (≥ 0.25 sec.) when amplitude dropped below a lower threshold. The lower threshold was set at two times the mean amplitude of the channel signal. The upper threshold was set at the lesser of either 8 times the mean amplitude, or the average between this value and an average upper threshold value calculated for each channel in a group (N=12) of healthy subjects. For each spindle the duration, amplitude, number, and ISA were measured (9). To characterize spindles in slow (12–14 Hz) and fast (14–16 Hz) ranges, spindle parameters were calculated from NREM data filtered in these two frequency bands. Slow and fast spindles have different topography, and likely involve different thalamocortical modules. By exploring both ranges we investigated whether spindle deficits were generalized or rather restricted to specific thalamocortical modules.

Slow wave analysis

To detect slow waves, we employed a recently developed procedure (11). Briefly, each EEG signal was referenced to the average of the 2 earlobes and band-pass filtered at 0.5–4.0 Hz. Then, waves were detected as negative deflections between two zero crossings. The zero crossing detection was chosen because of the high degree of variability in positive deflections, compared to the stability of negative deflections. Only waves with 0.25 to 1.0 second consecutive zero crossings detected in artifact-free NREM epochs were considered slow waves. Total incidence of waves, negative peak amplitude, and average slopes for each wave were determined. Average slopes were defined as the negative peak amplitude divided by the time from the previous zero crossing (down-slopes), or until the next zero crossing (up-slopes).

Statistical analyses

To compare demographics, sleep architecture and EEG power between groups one-way ANOVAs, followed by post-hoc unpaired t-tests, were performed. Group differences in spindle

amplitude, duration, number and ISA or in slow wave incidence, amplitude, down- and up-slope, were assessed with statistical nonparametric mapping (SnPM) (12). For spindle parameters we also calculated Cohen's *d* (13). Finally, we performed correlation analyses between spindles and several clinical parameters of schizophrenics, including PANSS scores.

Results

Sleep architecture

The three groups did not differ in sleep architecture (one-way ANOVA: $F \leq 2.92$, $df = (2, 110)$, $p > 0.05$) (Tab. 1), except for sleep latency (one-way ANOVA: $F = 4.8$, $df = (2, 110)$, $p = 0.01$). Specifically, post-hoc *t*-tests showed increased sleep latency in schizophrenics relative to healthy controls ($p < 0.01$). No difference was found between schizophrenics and non-schizophrenic patients taking antipsychotics, or between them and healthy subjects ($p \geq 0.1$).

EEG power analysis

Whole-night NREM EEG power was calculated between 0.5 and 40 Hz for the three groups (Fig. 1A). One-way ANOVA revealed group differences in the spindle range (12–16 Hz, $F \geq 3.5$, $df = 2, 110$, $p \leq 0.03$). Post-hoc *t*-tests showed power reductions in schizophrenics compared to healthy subjects (12–16 Hz, $p \leq 0.03$) and non-schizophrenic patients taking antipsychotics (12–16 Hz, $p \leq 0.02$), but no difference between non-schizophrenic patients and healthy subjects ($p \geq 0.3$, Fig. 1B). Power deficits were present in each sleep cycle, and were restricted to spindle range.

Spindle analysis

An initial analysis was performed for spindle amplitude, duration, number, and ISA in 12–16 Hz, the frequency range decreased in schizophrenics. The topography of each parameter was similar across groups, with peaks in prefrontal and centroparietal areas. Spindle parameters in these regions were markedly reduced in schizophrenics (Fig. 1C). Spindle amplitude was decreased in schizophrenics vs. healthy and medicated psychiatric comparison subjects ($p < 0.0004$, SnPM) in centroparietal areas (Fig. 1C), while spindle duration was decreased in schizophrenics vs. healthy and medicated psychiatric comparison subjects ($p < 0.0002$, SnPM) in prefrontal regions (Fig. 1C). Schizophrenics also showed deficits in spindle number and ISA vs. healthy ($p < 0.0001$, SnPM) and medicated psychiatric comparison subjects ($p < 0.0001$, SnPM) in prefrontal and centroparietal regions. No difference was found between healthy and medicated psychiatric comparison subjects for any spindle parameter (Fig. 1C).

Additional analyses were performed for slow (12–14 Hz) and fast (14–16 Hz) spindles. Schizophrenics showed deficits in slow spindle duration, number and ISA compared to both healthy and medicated psychiatric comparison subjects in prefrontal regions (SnPM, $p \leq 0.001$, Figure 2, left panel). We found no difference in slow spindle amplitude across the three groups, or between healthy and medicated psychiatric controls in other slow spindle parameters. Deficits in fast spindle duration (prefrontal), amplitude (centroparietal), number and ISA (prefrontal and centroparietal) were found in schizophrenics vs. both healthy and medicated psychiatric comparison subjects (SnPM, $p \leq 0.001$, Figure 2, right panel). Additionally, schizophrenics had reduced fast spindle number and ISA in the left temporal cortex (SnPM, $p \leq 0.0004$). No difference was observed in fast spindle parameters between healthy and medicated psychiatric comparison subjects.

To determine the magnitude of spindle deficits in schizophrenics Cohen's *d*, which measures effect size (ES), was calculated for spindle parameters. Cohen's *d* analysis showed that prefrontal (for spindle duration), centroparietal (for spindle amplitude, number and ISA), and left temporal (for spindle number and ISA) areas were the most affected in schizophrenics.

Moreover, Cohen's d values ranged from $ES=1.4$, for spindle amplitude to $ES\geq 2.21$ for spindle number and ISA.

Slow wave analysis

In addition to slow wave activity (SWA, 1–4.5 Hz) we computed slow wave incidence, negative peak amplitude, down-slope, and up-slope. In previous work we demonstrated that each of these parameters represent different aspects of cortical synchronization during slow waves (11). The topography of these parameters showed similar antero-posterior gradients across groups, with clear peaks in prefrontal areas, where SWA is usually maximal, and lowest values in posterior parietal and occipital areas (Figure 3B). No significant difference for any slow wave parameter was found across groups (SnPM, $p\geq 0.2$).

Cognitive ability and spindles

To establish possible correlations between general cognitive ability and spindles schizophrenics ($N=20$), healthy subjects ($N=19$) and non-schizophrenic patients taking antipsychotics ($N=12$) were administered a computerized version of the Ravens progressive matrices (RPM) test (14), which is widely used in research/clinical settings to measure intelligence (15). We found that schizophrenics (mean=36, $SD=9$) and medicated comparison subjects (mean=37.5, $SD=13$) had similar RPM scores ($p=0.94$), but both had lower scores relative to healthy subjects (mean=44, $SD=9$). Moreover, RPM scores of schizophrenics did not correlate with ISA ($r=0.18$, $p=0.42$) or spindle number ($r=0.17$, $p=0.48$).

Clinical and spindle parameters in schizophrenics

We also performed multiple regression/correlation analyses between clinical characteristics and spindle parameters in schizophrenics (Tab.2). Spindle number was inversely related to age ($r=-.33$; $p=.021$) and stereotyped thinking of PANSS negative symptoms ($n7$, $r=-.32$; $p=.028$). Moreover, both ISA and spindle number were inversely related to positive symptoms of PANSS (ISA: $r=-.40$; $p=.005$; spindle number: $r=-.37$; $p=.01$). Specifically, spindle number was correlated only with conceptual disorganization ($p2$, $r=-0.34$, $p=0.03$), and hallucinations ($p3$, $r=-0.4$, $p=0.01$), while ISA was correlated exclusively with hallucinations ($r=-0.48$, $p=0.002$).

Discussion

Schizophrenics had whole-night deficits in spindle amplitude, duration, number and ISA. Spindle number and ISA were the most affected ($ES\geq 2.21$), and were inversely correlated with clinical symptoms. No spindle abnormalities were found in non-schizophrenic patients taking antipsychotics, suggesting that medications are unlikely to be responsible for spindle deficits. In sharp contrast to changes in spindles, schizophrenics were no different from controls in several slow wave parameters.

Slow wave findings in schizophrenia

Slow waves are EEG manifestations of periods of synchronous firing and silence of cortical neurons at 1–4 Hz. Slow waves are cortically generated by intrinsic conductances and cortico-cortical connections, although thalamocortical neurons also contribute to the synchronous onset of cortical firing. Slow waves are prominent in NREM N3, also known as slow wave sleep (SWS) (10). While sleep architecture, including time spent in SWS, has been extensively explored in schizophrenia (25), SWA, the integrated EEG power at 1–4 Hz, has been scantily investigated, with conflicting reports. Two studies reported negative findings (9,26); three studies found reduced SWA in schizophrenics, associated with marked SWS decrease (16, 27,28). SWS deficits have not been consistently found in schizophrenics (29), occur more often

in institutionalized patients with profound cognitive impairment (30), and have been established in other psychiatric groups (31). We found no SWS or SWA reduction in our schizophrenia group, which consisted of outpatient subjects with moderate cognitive deficits. Additionally, none of the other slow wave parameters measured, including incidence, amplitude, up-slopes and down-slopes, each reflecting different aspects of cortical synchronization, differed between schizophrenic and control subjects. These findings confirm previous reports that slow wave deficits may involve just a subgroup of schizophrenics (29). The absence of slow wave impairments in schizophrenics also suggests that spindles deficits may not merely reflect reduced daytime experience, since slow waves are a highly reliable measure of daytime plastic changes. Specifically, a recent study in rats showed that more exploratory behavior during wakefulness determined increased SWA during subsequent sleep, and that SWA correlated with levels of BDNF, a molecular marker of plasticity (32). Moreover, numerous studies in humans reported that learning specific tasks increase SWA in task-related cortical areas, while reducing inputs to specific cortical areas determine reduced SWA in these areas (33).

Spindle findings in schizophrenia

In the present and prior hd-EEG investigations we found deficits in the spindle activity of schizophrenics. Only a handful of studies, based on a few EEG channels, and a limited number of subjects, have previously investigated spindles in schizophrenics. One study reported higher spindle counts during the first NREM episode in five schizophrenics compared to healthy controls (16). Schizophrenics also had a significant increase in stage 2 sleep, when spindles mostly occur, which is the likely explanation for their increased spindles incidence. Two other studies, in nine (17) and eleven (18) schizophrenics and healthy subjects found no difference in spindles, but this may be a consequence of the limited number of channels (C3 and C4), and of the spindle range (slow=12–14 Hz) analyzed. Indeed, in our previous hd-EEG study we found that spindle deficits were localized medial to C3 and C4 (9), while here we established that slow spindle deficits were restricted to prefrontal regions.

Spindle deficits are present throughout the night

We previously reported reduced sleep spindles in schizophrenics during the first NREM episode (9). Here we established that spindle deficits were present throughout the night, and did not reflect differences in the time course of spindle activity between schizophrenics and healthy subjects (19).

Spindle deficits are unlikely due to antipsychotics

Since studying large numbers of unmedicated schizophrenics presents ethical/logistical challenges, we recruited non-schizophrenic patients to evaluate the effects of antipsychotics on spindles. These patients showed no difference in spindle activity compared to healthy controls, thus suggesting that antipsychotics are unlikely to explain the spindle deficits of schizophrenics. Few studies investigated the effects of antipsychotics on sleep EEG in healthy and schizophrenic subjects. In healthy subjects one study reported no difference in sleep EEG power after single doses of olanzapine (20); another study found that single doses of haloperidol or risperidone had no effects on sleep EEG, while olanzapine led to decreased high frequency (>10 Hz) power during the second and fourth sleep episodes (21). One study, where schizophrenics were randomized to placebo or single dose olanzapine, found that the olanzapine group showed reduced spindle density compared to baseline nights (22). Another study investigating long-term effects of olanzapine on sleep EEG in schizophrenics reported no difference in their spindle power after four weeks of treatment (23). Altogether, these results suggest that olanzapine maybe the antipsychotic medication that affects spindle activity in acute, but not chronic doses. In this study only three schizophrenics were taking olanzapine,

and schizophrenics showed no correlation between duration/dosage of antipsychotics and spindle parameters.

Spindle deficits are unrelated to reduced general cognitive ability

We also investigated possible correlations between spindles and general cognitive ability assessed with RPM, a test employed in research/clinical settings to measure intelligence. Both schizophrenics and antipsychotic-medicated psychiatric controls showed lower RPM scores than healthy subjects, yet only schizophrenics had spindle deficits. Moreover, RPM's scores of schizophrenics did not correlate with spindle parameters. These results suggest that spindle deficits in schizophrenics are unrelated to reduced general cognitive ability. However, these findings do not exclude possible correlations between spindle reduction and deficits in specific neurocognitive paradigms in schizophrenia. Certain neurocognitive paradigms of attention and memory have been examined as putative endophenotypes for schizophrenia (4). Similarly, some studies showed that spindles are associated with these cognitive functions (24). Thus, future investigations exploring the relationship between spindle deficits and specific neurocognitive deficits in schizophrenia may provide further insight into the neural circuits underlying such impairments.

Altered spindles suggest thalamic/TRN dysfunctions in schizophrenia

Animal studies have shown conclusively that the neuronal substrates of spindles involve a cortex-TRN-thalamus circuit. Specifically, it is well established that the TRN is the spindle pacemaker, and that TRN/thalamus circuits can generate spindles in isolation, although cortical inputs may contribute to initiate/amplify spindle oscillations (8). Thus, spindle deficits in schizophrenics may result from impairments in either TRN/thalamus circuits or in corticothalamic afferents to these intra-thalamic circuits. Of all spindle parameters, the number, which likely reflects the pacemaker activity of TRN/thalamus circuits, was the most reduced in schizophrenics, and correlated with both positive and negative symptoms. Moreover our cohort of schizophrenics had no deficits in slow waves, cortically generated oscillations which are synchronized and propagated by cortico-thalamic connections. Altogether, these findings suggest that a dysfunction within TRN/thalamus circuits may be primarily responsible for spindle deficits in schizophrenia. Cortico-thalamic afferents, however, may also play a role, as suggested by neuroimaging (36), electrophysiological (37), and post-mortem (38) studies reporting corticothalamic connectivity deficits in schizophrenia.

The TRN is uniquely placed between the thalamus and the cortex, as it receives excitatory afferents from both cortical and thalamic neurons and sends GABA-ergic inhibitory projections to all thalamic nuclei. Cortical afferents to the TRN far outweigh thalamic projections, and recent findings revealed diffuse prefrontal projections to frontal as well as sensory TRN sectors, which may regulate the ability to perform tasks in an environment with competing sensory inputs (39). These data, together with evidence showing an involvement of the thalamus in cortico-cortical communication (40), suggest that TRN-thalamus circuits may play a critical role in cognitive functions, including working memory, language, and sensorimotor integration, which require a high degree of cortico-cortical coordination/synchronization and are defective in schizophrenia (15). The TRN is also a strategic hub where peripheral stimuli can be blocked, or selectively enhanced on their way to the cortex. Recent evidence has shown directly that the TRN is implicated in sensory gating and attentional modulation. Intracranial recordings in primates showed that visual attention involves both increased activity in lateral geniculate nucleus (LGN) and reduced firing of TRN, which send inhibitory efferents to LGN (41). Furthermore, pharmacologically-induced reductions in TRN activity, established with intracellular recordings, induce P50 auditory gating deficits, reflected in increased test/conditioning auditory response ratios (42). Importantly, sensory gating and attention deficits occur in several groups of schizophrenics, including first-break and medication-naïve patients

(43,44), and a recent fMRI study showed an increased homodynamic response in the thalamus, which was correlated with higher P50 response ratios, in schizophrenics compared to healthy controls (45).

Given the limited research available, we can only speculate about the molecular mechanisms mediating TRN deficits in schizophrenia. Recent electrophysiological recordings in rats showed that during development GABA currents induce depolarization in TRN neurons, which is responsible for the bursting activity observed during spindles (46). These findings suggest that GABA currents/receptors in the TRN play a critical role in the development of spindles, and are consistent with the involvement of GABA deficits in the neurobiology of schizophrenia (47). TRN has also a high number of alpha7 nicotinic receptors (48), which are associated with P50 deficits, learning disabilities, and hallucinations (34). Based on these findings, it would be important to measure spindle activity and P50 in the same schizophrenia group, to assess a possible common neurobiological basis for these deficits in schizophrenia.

Future studies will be needed to establish whether spindle deficits are present in other schizophrenia populations, including medication-naïve and first-break patients. Such studies would help confirm spindle deficits at illness onset, and in absence of medication confounds. It will also be critical to employ compounds which selectively block/activate nicotinic, GABA, or NMDA receptors, which are localized on TRN neurons and are thought to be defective in schizophrenia. These studies could establish which drugs may ameliorate both symptoms and spindle activity in schizophrenics, thus providing further insight into which neurotransmitters - and neuronal pathways- are impaired in schizophrenia. Finally, TMS in combination with hd-EEG and fMRI will be needed to evaluate the functioning of cortico-TRN-thalamic-cortical loops in schizophrenia (37).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures and Acknowledgements:

Funding sources: Supported by the schizophrenia program of the HealthEmotions Research Institute and a National Institutes of Health – National Institute of Mental Health Conte Center grant 1P20MH077967-01A1 (Dr. Tononi); and a European Union Marie Curie International Reintegration Grant FP7-PEOPLE-2007-5-4-3-IRG-N^o208779 (Dr. Ferrarelli).

Dr. Peterson has research grant support from Sanofi-aventis.

Dr. Benca has served as a consultant/advisory board member and received speaking honoraria from Sanofi-aventis, Sepracor, Takeda Pharmaceuticals and Wyeth Pharmaceuticals. She has been a consultant/advisory board member for GlaxoSmithKline, Eli Lilly, Neurocrine Biosciences and Pfizer Pharmaceuticals.

Dr. Kalin has served as a consultant/advisory board member to Amgen, Inc., AstraZeneca, Bristol-Myers-Squibb, CeNeRx BioPharma, Inc., Corcept Therapeutics, Cyberonics Inc., Cypress Biosci, Eli Lilly and Company, Forest Laboratories, General Electric Corp (GE Healthcare), GlaxoSmithKline, Janssen Pharmaceuticals, Jazz Pharmaceutical, Neurocrine Biosciences, Inc., Neuronetics, Novartis, Otsuka American Pharmaceuticals, Pfizer Pharmaceuticals, Sanofi-Syntholabs, Sommerset Pharmaceuticals, Inc., Takeda International, Tularik, and Wyeth Pharmaceutical. He is a shareholder with Corcept and CeNeRx; an editor for Elsevier; and he is the owner of Promoter Neurosciences, LLC. Dr. Kalin holds patents for the promoter sequences for corticotropin-releasing factor CRF2alpha and method of identifying agents that alter the activity of the promoter sequences; promoter sequences for urocortin II and the use thereof; and promoter sequences for corticotropin-releasing factor binding protein and use thereof.

Dr. Tononi has served as a consultant for Tikvah Therapeutics and Respireonics. He has received speaking honoraria from Sanofi-aventis and Respireonics. He has research support from Sanofiaventis, and pending support from Respireonics.

References

1. Jenkins JH, Schumacher JG. Family burden of schizophrenia and depressive illness. Specifying the effects of ethnicity, gender and social ecology. *Br J Psychiatry* 1999;174:31–8. [PubMed: 10211148]
2. Egan MF, Weinberger DR. Neurobiology of schizophrenia. *Curr Opin Neurobiol* 1997;7(5):701–7. [PubMed: 9384552]
3. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005;10(1):40–68. image 5. [PubMed: 15263907]
4. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. *Schizophr Bull* 2007;33(1):49–68. [PubMed: 17101692]
5. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr Bull* 2000;26(1):119–36. [PubMed: 10755673]
6. Thaker GK. Schizophrenia endophenotypes as treatment targets. *Expert Opin Ther Targets* 2007;11(9):1189–206. [PubMed: 17845145]
7. Steriade M. Grouping of brain rhythms in corticothalamic systems. *Neuroscience* 2006;137(4):1087–106. [PubMed: 16343791]
8. Fuentealba P, Steriade M. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. *Prog Neurobiol* 2005;75(2):125–41. [PubMed: 15784303]
9. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, Watson A, Bria P, Tononi G. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry* 2007;164(3):483–92. [PubMed: 17329474]
10. Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger MM, Hirshkowitz M, Kapen S, Keenan SA, Kryger MH, Penzel T, Pressman MR, Iber C. The visual scoring of sleep in adults. *J Clin Sleep Med* 2007;3(2):121–31. [PubMed: 17557422]
11. Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, Tononi G. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep* 2007;30(12):1643–57. [PubMed: 18246974]
12. Nichols TE, Holmes AP. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* 2002;15(1):1–25. [PubMed: 11747097]
13. Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Erlbaum; 1988.
14. Raven J. The Raven's progressive matrices: change and stability over culture and time. *Cogn Psychol* 2000;41(1):1–48. [PubMed: 10945921]
15. Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, Gur RE. Computerized neurocognitive scanning: II. The profile of schizophrenia. *Neuropsychopharmacology* 2001;25(5):777–88. [PubMed: 11682261]
16. Hiatt JF, Floyd TC, Katz PH, Feinberg I. Further evidence of abnormal non-rapid-eyemovement sleep in schizophrenia. *Arch Gen Psychiatry* 1985;42(8):797–802. [PubMed: 4015324]
17. Van Cauter ELP, Kerkhofs M, Hubain P, L' Hermite-Baleriaux M, Leclercq R, Brasseur M, Copinschi G, Mendlewicz J. Circadian and Sleep-related Endocrine Rhythms in Schizophrenia. *Arch Gen Psychiatry* 1991;48:348–56. [PubMed: 1848971]
18. Poulin J, Daoust AM, Forest G, Stip E, Godbout R. Sleep architecture and its clinical correlates in first episode and neuroleptic-naïve patients with schizophrenia. *Schizophr Res* 2003;62(1–2):147–53. [PubMed: 12765755]
19. De Gennaro L, Ferrara M. Sleep spindles: an overview. *Sleep Med Rev* 2003;7(5):423–40. [PubMed: 14573378]
20. Lindberg N, Virkkunen M, Tani P, Appelberg B, Virkkala J, Rimón R, Porkka-Heiskanen T. Effect of a single-dose of olanzapine on sleep in healthy females and males. *Int Clin Psychopharmacol* 2002;17(4):177–84. [PubMed: 12131601]
21. Gimenez S, Clos S, Romero S, Grasa E, Morte A, Barbanoj MJ. Effects of olanzapine, risperidone and haloperidol on sleep after a single oral morning dose in healthy volunteers. *Psychopharmacology (Berl)* 2007;190(4):507–16. [PubMed: 17205319]

22. Goder R, Fritzer G, Gottwald B, Lippmann B, Seeck-Hirschner M, Serafin I, Aldenhoff JB. Effects of olanzapine on slow wave sleep, sleep spindles and sleep-related memory consolidation in schizophrenia. *Pharmacopsychiatry* 2008;41(3):92–9. [PubMed: 18484550]
23. Muller MJ, Rossbach W, Mann K, Roschke J, Muller-Siecheneder F, Blumler M, Wetzel H, Russ H, Dittmann RW, Benkert O. Subchronic effects of olanzapine on sleep EEG in schizophrenic patients with predominantly negative symptoms. *Pharmacopsychiatry* 2004;37(4):157–62. [PubMed: 15467971]
24. Fogel SM, Nader R, Cote KA, Smith CT. Sleep spindles and learning potential. *Behav Neurosci* 2007;121(1):1–10. [PubMed: 17324046]
25. Monti JM, Monti D. Sleep disturbance in schizophrenia. *Int Rev Psychiatry* 2005;17(4):247–53. [PubMed: 16194796]
26. Tekell JL, Hoffmann R, Hendrickse W, Greene RW, Rush AJ, Armitage R. High frequency EEG activity during sleep: characteristics in schizophrenia and depression. *Clin EEG Neurosci* 2005;36(1):25–35. [PubMed: 15683195]
27. Goder R, Aldenhoff JB, Boigs M, Braun S, Koch J, Fritzer G. Delta power in sleep in relation to neuropsychological performance in healthy subjects and schizophrenia patients. *J Neuropsychiatry Clin Neurosci* 2006;18(4):529–35. [PubMed: 17135379]
28. Keshavan MS, Reynolds CF 3rd, Miewald MJ, Montrose DM, Sweeney JA, Vasko RC Jr, Kupfer DJ. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. *Arch Gen Psychiatry* 1998;55(5):443–8. [PubMed: 9596047]
29. Manoach DS, Stickgold R. Does abnormal sleep impair memory consolidation in schizophrenia? *Front Hum Neurosci* 2009;3:21. [PubMed: 19750201]
30. Yang C, Winkelman JW. Clinical significance of sleep EEG abnormalities in chronic schizophrenia. *Schizophr Res* 2006;82(2–3):251–60. [PubMed: 16377158]
31. Peterson MJ, Benca RM. Sleep in mood disorders. *Psychiatr Clin North Am* 2006;29(4):1009–32. [PubMed: 17118279]
32. Huber R, Tononi G, Cirelli C. Exploratory behavior, cortical BDNF expression, and sleep homeostasis. *Sleep* 2007;30(2):129–39. [PubMed: 17326538]
33. Massimini M, Tononi G, Huber R. Slow waves, synaptic plasticity and information processing: insights from transcranial magnetic stimulation and high-density EEG experiments. *Eur J Neurosci* 2009;29(9):1761–70. [PubMed: 19473231]
34. Court J, Spurden D, Lloyd S, McKeith I, Ballard C, Cairns N, Kerwin R, Perry R, Perry E. Neuronal nicotinic receptors in dementia with Lewy bodies and schizophrenia: alfabungarotoxin and nicotine binding in the thalamus. *J Neurochem* 1999;73(4):1590–7. [PubMed: 10501205]
35. Freedman R, Ross R, Leonard S, Myles-Worsley M, Adams CE, Waldo M, Tregellas J, Martin L, Olincy A, Tanabe J, Kisley MA, Hunter S, Stevens KE. Early biomarkers of psychosis. *Dialogues Clin Neurosci* 2005;7(1):17–29. [PubMed: 16060593]
36. Camchong J, Dyckman KA, Chapman CE, Yanasak NE, McDowell JE. Basal ganglia-thalamocortical circuitry disruptions in schizophrenia during delayed response tasks. *Biol Psychiatry* 2006;60(3):235–41. [PubMed: 16458267]
37. Ferrarelli F, Massimini M, Peterson MJ, Riedner BA, Lazar M, Murphy MJ, Huber R, Rosanova M, Alexander AL, Kalin N, Tononi G. Reduced evoked gamma oscillations in the frontal cortex in schizophrenia patients: a TMS/EEG study. *Am J Psychiatry* 2008;165(8):996–1005. [PubMed: 18483133]
38. Akbarian S, Kim JJ, Potkin SG, Hetrick WP, Bunney WE Jr, Jones EG. Maldistribution of interstitial neurons in prefrontal white matter of the brains of schizophrenic patients. *Arch Gen Psychiatry* 1996;53(5):425–36. [PubMed: 8624186]
39. Zikopoulos B, Barbas H. Circuits formultisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Rev Neurosci* 2007;18(6):417–38. [PubMed: 18330211]
40. Sherman SM. Thalamic relays and cortical functioning. *Prog Brain Res* 2005;149:107–26. [PubMed: 16226580]
41. McAlonan K, Cavanaugh J, Wurtz RH. Guarding the gateway to cortex with attention in visual thalamus. *Nature* 2008;456(7220):391–4. [PubMed: 18849967]

42. Krause M, Hoffmann WE, Hajos M. Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. *Biol Psychiatry* 2003;53(3):244–53. [PubMed: 12559658]
43. Freedman R, Olincy A, Ross RG, Waldo MC, Stevens KE, Adler LE, Leonard S. The genetics of sensory gating deficits in schizophrenia. *Curr Psychiatry Rep* 2003;5(2):155–61. [PubMed: 12685995]
44. Luck SJ, Gold JM. The construct of attention in schizophrenia. *Biol Psychiatry* 2008;64(1):34–9. [PubMed: 18374901]
45. Tregellas JR, Davalos DB, Rojas DC, Waldo MC, Gibson L, Wylie K, Du YP, Freedman R. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. *Schizophr Res* 2007;92(1–3):262–272. [PubMed: 17336502]
46. Pangratz-Fuehrer S, Rudolph U, Huguenard JR. Giant spontaneous depolarizing potentials in the developing thalamic reticular nucleus. *J Neurophysiol* 2007;97(3):2364–72. [PubMed: 17251370]
47. Reynolds GP, Harte MK. The neuronal pathology of schizophrenia: molecules and mechanisms. *Biochem Soc Trans* 2007;35(Pt 2):433–6. [PubMed: 17371293]
48. Martin LF, Kem WR, Freedman R. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology (Berl)* 2004;174(1):54–64. [PubMed: 15205879]

Figure 1. Schizophrenics had deficits in spindle range (12–16 Hz) power and other spindle parameters

(A) Mean EEG power spectra in 0.25 Hz resolution of whole-night NREM sleep of schizophrenics, healthy and medicated controls. One-way ANOVA revealed significant differences between the three groups, from 12 to 16 Hz ($F > 3.61$, $df = 2, 106$, $p < 0.05$). (B) Post-hoc t-tests showed statistically significant differences between schizophrenics and healthy controls from 12.5 to 15.75 Hz and between schizophrenics and medicated controls from 12 to 16 Hz. (black bars). (C) Color plots: Topography of several spindle parameters (amplitude, duration, number, and ISA) in schizophrenics ($N = 49$), healthy ($N = 44$), and medicated ($N = 20$) control subjects. White plots: Topographic distribution of the electrodes showing a significant reduction (gray area; Statistical non-Parametric Mapping, SnPM) in spindle parameters in schizophrenic vs, healthy, schizophrenic vs. medicated, and healthy vs. medicated subjects.

Figure 2. Topography of slow (12–14 Hz) and fast (14–16 Hz) spindle deficits in schizophrenia (Left panel) Deficits in slow (12–14 Hz) sleep spindle duration, number and integrated spindle activity (ISA) in schizophrenics vs. both healthy and medicated psychiatric controls were established in a prefrontal region (Statistical non Parametric Mapping, SnPM, $p \leq 0.001$). No significant reduction in slow spindle amplitude across the three groups as well as between healthy and medicated psychiatric controls in the other slow spindle parameters was found. (Right panel) Deficits in fast (14–16 Hz) sleep spindle duration (prefrontal), amplitude (centroparietal), as well as number and ISA (both prefrontal and centroparietal) were assessed in schizophrenics vs. both healthy and medicated psychiatric controls (SnPM, $p \leq 0.001$). Additionally, for fast spindle number and ISA a significant reduction in the left temporal cortex was established (SnPM, $p \leq 0.001$). No significant reduction in any fast spindle parameter between healthy and medicated psychiatric controls was found.

Figure 3. Slow wave parameters are not defective in schizophrenia

(A) Slow waves occurring during whole night NREM sleep were detected using an automated algorithm, and several slow wave parameters, including incidence, amplitude, down- and up-slope were measured. (B) No significant difference in the topography of each of these slow wave parameters was found across the three groups.

Table 1

Sleep architecture variables of subject groups.

Sleep Variables	Healthy Control (n=44)		Schizophrenics (n=49)		Medicated Control (n=20)	
	Mean ± S.D.		Mean ± S.D.		Mean ± S.D.	
Total sleep time (min)	447.6 ± 62.0		472.5 ± 91.0		465.8 ± 75.8	n.s.
Sleep onset latency ^d (min)	14.1 ± 1.5		26.7 ± 3.6		20.5 ± 4.3	<0.01
Sleep maintenance ^e (%)	90.8 ± 9.0		91.2 ± 10.5		92.8 ± 9.6	n.s.
NREM N1 (%)	6.3 ± 1.3		5.7 ± 1.3		7.9 ± 1.9	n.s.
NREM N2 (%)	51.6 ± 4.4		55.5 ± 5.6		52.5 ± 6.3	n.s.
NREM N3 (%)	21.5 ± 3.6		19.9 ± 5.3		19.6 ± 5.0	n.s.
REM (%)	20.6 ± 2.5		18.9 ± 2.65		20.0 ± 2.8	n.s.

^aOne-way ANOVA followed by post-hoc two-tailed unpaired t-test between schizophrenics and healthy control groups

^bOne-way ANOVA followed by post-hoc two-tailed unpaired t-test between schizophrenics and medicated control groups

^cOne-way ANOVA followed by post-hoc two-tailed unpaired t-test between medicated and healthy control groups

^dSleep onset latency is defined as the time from the beginning of the recording until the first stage 2 NREM sleep epoch.

^eSleep maintenance is the total sleep time divided by total recording time minus sleep onset latency

Table 2
Correlations between clinical and spindle parameters in schizophrenia patients.

Spindle parameter	Spindle Number	ISA
Duration of illness	$r = -.25$; $p = .09$	$r = -.15$; $p = .31$
Number of hospitalizations	$r = .09$; $p = .53$	$r = .18$; $p = .21$
Age	$r = -.33$; $p = .02$	$r = -.09$; $p = .51$
Medication dose	$r = -.18$; $p = .20$	$r = -.13$; $p = .38$
Positive symptoms	$r = -.40$; $p = .005$	$r = -.37$; $p = .01$
Negative symptoms	$r = -.32$; $p = .02$	$r = -.28$; $p = .06$
General symptoms	$r = -.20$; $p = .17$	$r = -.19$; $p = .20$