



Slow wave oscillations in Schizophrenia First-Degree Relatives: A confirmatory analysis and feasibility study on slow wave traveling

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ABSTRACT

Abnormal sleep oscillations have recently been proposed as endophenotypes of schizophrenia. However, optimization of methodological approaches is still necessary to standardize analyses of their microstructural characteristics. Additionally, some relevant features of these oscillations remain unexplored in pathological conditions. Among others, slow wave traveling is a promising proxy for diurnal processes of brain connectivity and excitability. The study of slow oscillations propagation appears particularly relevant when schizophrenia is conceptualized as a dys-connectivity syndrome. Given the rising knowledge on the neurobiological mechanisms underlying slow wave traveling, this measure might offer substantial advantages over other approaches in investigating brain connectivity. Herein we: 1) confirm the stability of our previous findings on slow waves and sleep spindles in FDRs using different automated algorithms, and 2) report the dynamics of slow wave traveling in FDRs of Schizophrenia patients. A 256-channel, high-density EEG system was employed to record a whole night of sleep of 16 FDRs and 16 age- and gender-matched control subjects. A recently developed, open source toolbox was used for slow wave visualization and detection. Slow waves were confirmed to be significantly smaller in FDRs compared to the control group. Additionally, several traveling parameters were analyzed. Traveled distances were found to be significantly reduced in FDRs, whereas origins showed a different topographical pattern of distribution from control subjects. In contrast, local speed did not differ between groups. Overall, these results suggest that slow wave traveling might be a viable method to study pathological conditions interfering with brain connectivity.

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1. Introduction

At the turn of the 20th Century, Eugen Bleuler coined the term schizophrenia (SCZ) from the greek *σχίζω* (*schizo*, divided) and *φρήν* (*phren*, brain/mind), suggesting the presence of a dis-integration of fun-

damental brain-mind functions in affected patients. Over the past 20 years, a growing number of authors returned to this original conceptualization and described SCZ as a network disorder (Tononi and Edelman, 2000) for which neuroimaging findings are currently laying a biological foundation (Giraldo-Chica and Woodward, 2017; Kambeitz et al., 2016).

Non-Rapid Eye Movement (NREM) sleep brain oscillations, sleep spindles and sleep slow waves, are thought to reflect the anatomical and functional integrity of the thalamocortical system (Steriade, 2003) and have been increasingly associated with neuronal plasticity mechanisms (Diekelmann and Born, 2010). These sleep oscillations may represent a preferential window of observation for dynamic EEG brain connectivity, due to the absence of fluctuating levels of attention

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and interfering symptoms that are known to influence experimental outcomes during wakefulness.

Sleep spindles typically appear on EEG recordings at the onset of stage 2 NREM sleep (N2) as phasic, waxing-and-waning “spindle”-shaped 12–16 Hz oscillations. These oscillations originate in the Reticular Thalamic Nuclei but are synchronized by a complex excitatory-inhibitory interplay between the thalami and the cortex (von Krosigk et al., 1993; Fuentealba and Steriade, 2005; Timofeev et al., 2000; Bonjean et al., 2011; Piantoni et al., 2016).

Slow waves, the hallmark of NREM stage 3 (N3), are high voltage 1–4 Hz waves arising from the synchronous alternation between active (up) and quiescent (down) firing states of large neuronal ensembles (Steriade, 2003). Slow wave generation has typically been attributed to the cortex (Steriade et al., 1993), although growing literature suggests a role for the thalamus in their full expression (Lemieux et al., 2014; Crunelli et al., 2015; Gent et al., 2018a). Slow waves propagate across the scalp in highly reproducible patterns, typically along the antero-posterior axis (Massimini et al., 2004). These oscillations and their traveling have been linked to the integrity of white matter tracts (Buchmann et al., 2011; Piantoni et al., 2013; Kurth et al., 2017; Schoch et al., 2018) and increasing evidence suggests they might be a fingerprint of brain connectivity (Kurth et al., 2017).

Sleep oscillations have been extensively explored in SCZ, and impaired spindle density has been the most consistent finding (Castelnovo et al., 2016, 2018; Zhang et al., 2019; Kaskie and Ferrarelli, 2019). However, results are not unanimous, especially among the few papers addressing early-course psychosis. The literature on slow waves is less conspicuous and findings lack consistency, perhaps due to pharmacological and/or methodological confounding effects (see Castelnovo et al., 2018 for a discussion on this topic). One study of five unmedicated SCZ patients reported reduced slow wave density and amplitude which was most prominent in the first cycle, in the context of a loss of physiological homeostatic decrease across cycles (Hiatt et al., 1985). Reduced delta power, slow wave number and density (only in the first cycle) were confirmed in a larger sample including 19 drug-naïve patients (Keshavan et al., 1998). A trend towards reduced delta sleep was also reported in another small sample of drug-naïve patients diagnosed with Schizophreniform Disorder (Poulin et al., 2008). A clear slow wave sleep (SWS) deficit was found in 15 unmedicated, chronic SCZ patients with profound disturbances of sleep continuity and architecture (Yang and Winkelman, 2006). Reduced delta power was also reported in a sample of early-course psychosis patients but it did not significantly differentiate SCZ from other psychotic disorders (Manoach et al., 2014). Furthermore, some authors attempted to clarify the relationship between slow waves and cognitive processing in SCZ. Reduced SWS was found to correlate with visuospatial memory impairment in SCZ patients (Göder et al., 2004); the same group also reported a reduction of delta power in the same population, restricted to temporal and occipital channels (Göder et al., 2006). More recently, preserved slow wave densities and amplitudes were reported in chronic, medicated patients who did, however, lack learning-dependent coordination of slow wave activity across the cortex (Bartsch et al., 2019). Notably, a reduced slow wave density in channels overlying a vast pre-frontal area has been recently reported using high-density electroencephalography (hdEEG) in early-course psychosis (Kaskie et al., 2019).

Sleep abnormalities have also been investigated in SCZ First-Degree Relatives (FDRs) (D'Agostino et al., 2018; Schilling et al., 2016; Manoach et al., 2014; Sarkar et al., 2010; Keshavan et al., 2004), who exhibit neuroanatomical (Capizzano et al., 2011), neurofunctional (Giraldo-Chica and Woodward, 2017; Kambeitz et al., 2016; Whitfield-Gabrieli et al., 2009), neurophysiological (Earls et al., 2016) and neurocognitive (Sitskoorn et al., 2004; Snitz et al., 2005) profiles similarly to their affected relatives. We

previously reported subtle abnormalities of sleep oscillations in this population that may represent a marker of susceptibility to SCZ (D'Agostino et al., 2018).

Despite a generally positive progression, the field of sleep oscillations in the SCZ spectrum remains largely open to debate due to partially inconsistent results. As with several other biomarkers, this might be related to the intrinsic heterogeneity of the selected samples in terms of clinical stage and presentation, genetic load and medication regimens. Moreover, the majority of available studies employed different analysis methods that somewhat limit the possibility of comparing data (Castelnovo et al., 2018).

To address this methodological issue, here we aimed to confirm our previous findings on sleep oscillation abnormalities in FDRs through a standardized and easily reproducible approach which employs a novel and accessible tool for the detection of sleep oscillations. We also aimed to explore the feasibility of adopting slow wave traveling as an effective measure of brain dysconnectivity in SCZ by evaluating its use in FDRs.

2. Materials and method

2.1. Participants

Sixteen adult healthy FDRs of patients diagnosed with SCZ (50% males, age 48.5 ± 14.2) and sixteen age- and gender-matched control subjects (50% males, age 49.8 ± 12.7) with no personal or family history of psychiatric disorders were included in the analyses. History of developmental, neurologic, psychiatric and sleep disorders and use of any drug interfering with CNS functioning were excluded. The same population was used in our previous publication on sleep spindles and slow waves (D'Agostino et al., 2018), where further details on cognition, perceptual experiences and general medical status are available. The study was approved by the San Paolo Hospital ethics committee and by the University of Wisconsin Health Sciences Institutional Review Board.

2.2. Sleep EEG data acquisition

All-night sleep recordings were acquired with a hd-EEG system (Electrical Geodesic Sensor Net for long-term monitoring, 256 channels). Lights-out was within one hour of the participants' reported bedtime, and subjects were allowed to sleep ad libitum. EEG recordings were scored according to AASM criteria (Iber et al., 2007) and reviewed by a sleep expert (AC). All EEG signals were collected at 500 Hz and high-pass filtered at 0.1 Hz. Recording procedures and pre-processing routines used to remove bad channels and artifacts were detailed elsewhere (D'Agostino et al., 2018).

2.3. NREM sleep oscillations analysis

Microstructural sleep oscillatory activity was analyzed with an open-source, Matlab-based user-friendly toolbox that offers the possibility to standardize the detection procedure (Mensen et al., 2016). The toolbox allows us to specify a large number of parameters for the detection of slow waves (e.g. the amplitude threshold, the minimum slow wave length or the minimum traveled distance to classify an EEG oscillation as a slow wave). Thanks to the optimization of its Matlab code, it also offers the possibility to rapidly compare outputs. Results were consistent across methods as assessed by an exploratory preliminary analysis (see Fig. 1). Findings on mastoid-referenced data obtained using parameters proposed as “default” by the toolbox will be presented here. The algorithm and the parameters employed to detect slow waves is detailed extensively elsewhere (Mensen et al., 2016) and will be briefly summarized here.

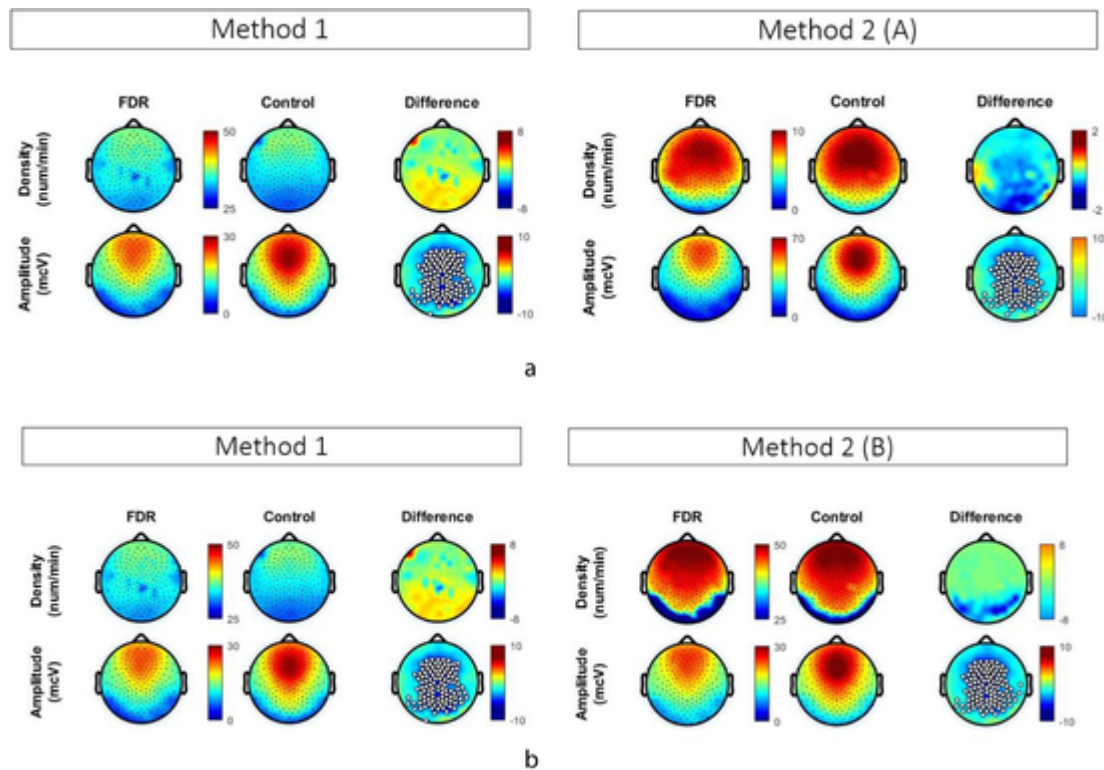


Fig. 1. A comparison of two slow wave detection methods. Method 1 is based on the slow wave detection algorithm described by Riedner et al., 2007 (Riedner et al., 2007), which was used in our previous work (D'Agostino et al., 2018). Method 2 is the output obtained with the novel toolbox (<https://github.com/Mensen/swa-matlab>) using default parameters described in Methods section (A) and a set of parameters chosen to reproduce previous analysis as closer as possible to Method 1 (B). Intergroup-comparison results were comparable between the 2 methods. FDR: first degree relatives; Control: age and gender matched control group. Density: number of sleep slow waves over time (minutes). Amplitude: negative peak amplitude in mcV.

The canonical wave was derived from the calculation of the negative envelope — i.e. the mean activity of the most negative 2.5% of channels at each sample independently in the time series. Individual slow waves in the canonical wave were detected starting from its local minima, that were also used as initial points to inspect further wave properties. Data-driven, dynamic amplitude thresholds were applied (5 standards deviations of the median amplitude). Defaults for the minimum and maximum wavelength for the canonical wave were 250 ms and 1250 ms, respectively. A correlation method was used for the detection of slow waves at each individual channel, i.e. slow waves at the single-channel level were detected by cross-correlating the negative portion of the canonical wave with the individual channels over a specified time window.

Traveling properties of each slow wave were derived from a delay map obtained interpolating individual delays over the scalp (across “active” channels) on a 40 × 40-unit grid. Although delay maps already offer meaningful information about traveling, average delay maps might be influenced by a number of factors, as the direction of traveling and traveled distance. Therefore, we decided to investigate three other traveling parameters: origins, traveled distance and local speed.

All potential streamlines for each traveling wave were calculated using each channel's coordinates as a seed to examine the optimal streamlines to and from the channel. Only 3 streamlines are retained by the toolbox: (1) the one with the longest linear displacement (the distance between the starting and ending points of the wave), (2) the one with the longest distance traveled (the cumulative sum of all coordinates of the line) if different from the longest displacement, and (3) the stream of most angular deviation from the longest displacement. Given the current lack of a standardized method or theoretical background to choose a streamline over others, we used the first one (1) in line with other authors that previously published on this topic (Massimini et

al., 2004; Kurth et al., 2017). All potential waves that traveled for less than a minimum traveling time (set at 40 ms, i.e. approximately 0.8 cm considering a traveling speed of 2 m/s from previous studies) were discarded.

Origins were calculated as the first point of each streamline. As streamlines were calculated on a 40 × 40 grid, in order to plot them we then recalculated the number of origins at each electrode as the sum of the origins in the grid falling within a radius equal to the distance between each neighboring electrode (stable in the system of coordinates adopted for Electrical Geodesic Sensor Net).

To calculate the local speed (i.e. the speed of a wave at each particular electrode), the highest possible number of streamlines was needed to cover the entire scalp. Therefore, we implemented the toolbox saving all streamlines in the final output along with the three described above. Local speed was estimated from the 40 × 40 grid delay map, calculating the space unit grid divided by the time gradient, i.e. the difference between two consecutive tiles of the grid, on the x and y axes. We then calculated the local speed vector in units/s for each tile as the vector sum of the x and y speed vectors.

Of note, we focused our analysis on whole-night stage 3 sleep and repeated an exploratory analysis for sleep stage 3 in first cycle, because this latter sleep period was comparable between the two groups in terms of sleep architecture (see Supplementary Figs. 1 and 2).

Although the main focus of the study was on sleep slow waves, we also performed a confirmatory analysis on sleep spindles (see Supplementary Fig. 3). The toolbox allows to detect sleep spindles by implementing a published Wavelet-based algorithm that has been found to outperform other 4 (published) automated spindles detectors, including the one reported in our previous study (Warby et al., 2014).

For topographical analysis, we applied statistical nonparametric mapping and a suprathreshold cluster analysis to control for multiple

comparisons (Nichols and Holmes, 2002) using an appropriate threshold t -value ($t = 2.042$, corresponding to $\alpha = 0.05$ for the given degrees of freedom) with fixed number of combinations ($n = 50,000$).

3. Results

Slow wave density during whole-night NREM sleep was comparable between FDRs and the control group, whereas slow wave amplitude was reduced in FDRs with both slow wave detection algorithms (see Fig. 1), validating our previous results. Findings on density (absence of significant differences in absolute and normalized values) and amplitude (a large cluster of 85 channels showing reduced absolute values, $p = 0.0152$) were stable during sleep stage 3 (see Fig. 2). Likewise, we were able to confirm the lack of spindle density deficits in FDRs compared to control subjects, and the reduction of spindle power (see Supplementary Fig. 1 for details) we previously found in the same sample using a completely different algorithm.

Findings related to slow wave traveling during stage N3 are summarized in Fig. 2. FDRs showed increased mean delay values over the midline from central to posterior regions and increased values over frontal regions. However, when looking at absolute topographical maps these findings only showed a trend towards significance (18 channels, $p = 0.0907$ after multiple-comparison correction). Normalized values (z-scores obtained subtracting the mean and dividing for the standard deviation) reached significance over the midline cluster (25 channels, $p = 0.0099$, after multiple comparison correction). No correlation was observed between mean delay and amplitude values.

The topographical map of origins, expressed as a percentage of the sum of values across channels (a measure of normalization), showed a significant increase over frontal regions ($n = 13$, $p = 0.001$) and a strong decrease over midline central and posterior regions (9 channels, $p = 0.012$ and 8 channels, $p = 0.021$, respectively). These results paralleled the distribution of the delay maps, that showed much shorter

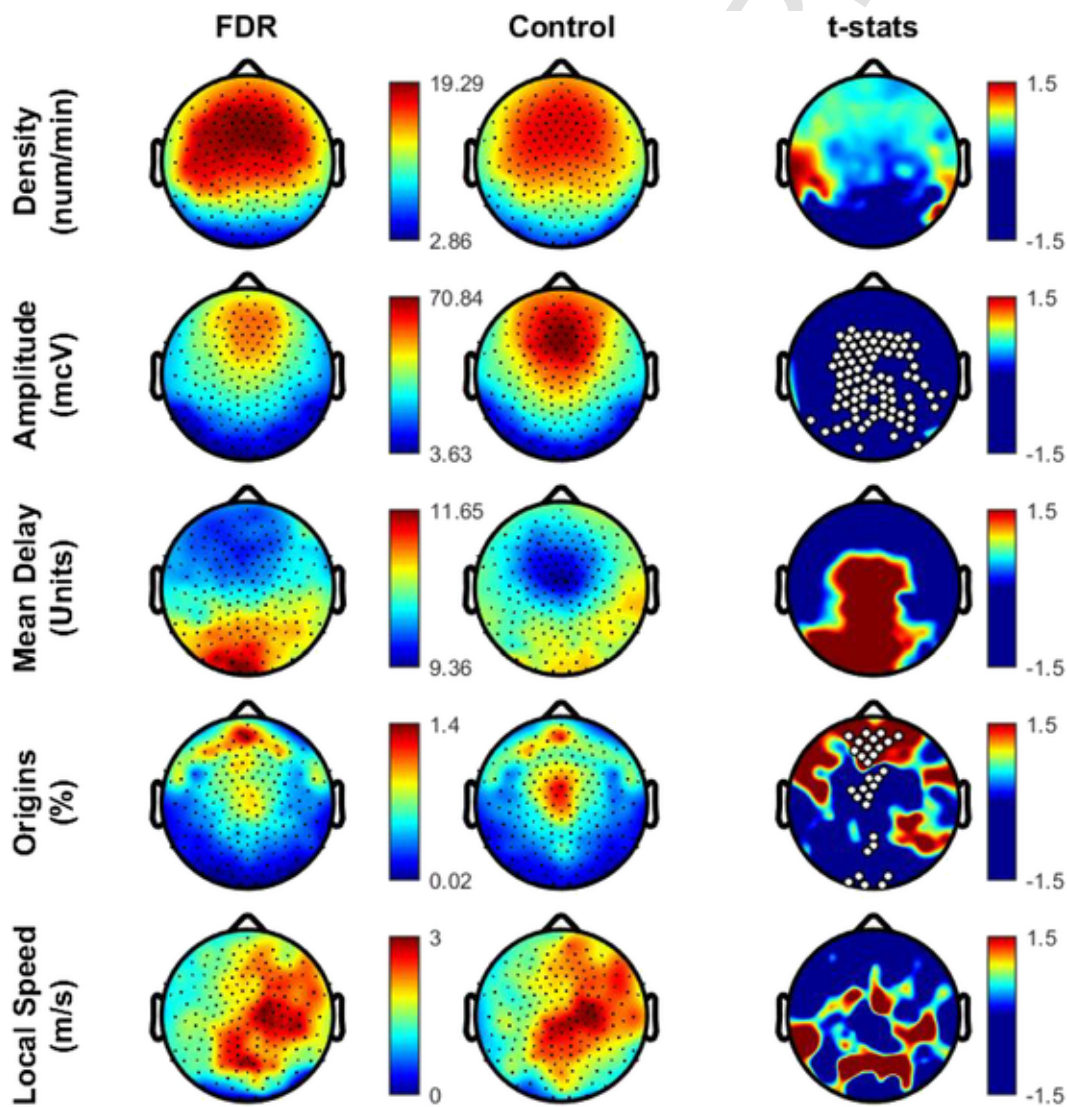


Fig. 2]. Topographical maps of slow wave parameters during whole night sleep stage N3. FDR: schizophrenia first degree relatives. Control: age and gender matched control group. t -Stats: map showing the individual electrode t -value (two-tailed, unpaired) maps for the comparison between FDR and control subjects in terms of absolute values. First row: slow wave density (number per hour of N3 sleep) at each channel. Second row: slow wave mean amplitude (average of negative peaks values for each channel). Third to six rows: topographical maps of slow wave traveling parameters. Third row: slow wave average delays (delays at individual channels obtained correlating the canonical wave to individual channel slow waves). Fourth row: slow wave origins (expressed as density, i.e. number of slow waves per minute). Fifth row: local speed (the speed of a wave at each particular electrode). Blue: FDR < control. RED: FDR > control. White dots: significance ($p < 0.05$) at the cluster level (after multi-comparison correction). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

delays in the front compared to the back. In contrast, local speed was no different between groups.

As shown in Fig. 3, traveled distance differed significantly between FDRs and control subjects (2-tailed unpaired t -test, $p = 0.043$). As amplitude and traveled distance are known to be modulated by across-night dynamics, we performed the same analyses during the first NREM sleep cycle, where N3 activity is maximal. We were able to confirm similar findings when N3 sleep of the first NREM sleep cycle was analyzed (see Supplementary Figs. 1 and 2).

4. Discussion

A significant reduction in slow wave amplitude combined with an unaltered slow wave density confirmed our previous slow wave report in SCZ FDRs (D'Agostino et al., 2018). We previously noticed that, unlike the consistency of findings reported across SCZ samples for sleep spindles, slow wave data remain controversial, possibly due to the diverse methodological approaches employed by different groups (Castelnovo et al., 2018). Conducting replication studies is critical to establish credible scientific evidence, even when converging lines of evidence and solid theoretical hypotheses support original data (Nicker-son, 2018).

We also observed a reduction of slow wave traveled distances in the FDR sample compared to healthy individuals with a negative familiar history. Shorter propagation distances likely reflect dysfunctional long-range connectivity among distributed cortical regions. Evidence suggest that slow wave propagation parameters are linked to white matter microstructure (Kurth et al., 2017), whereas new research has begun to unveil a role for the thalamus in the coordination of sleep oscillations (Gent et al., 2018a). Specifically, recent optogenetic research revealed that burst activation of centro-medial thalamic neurons mimics Up-states in the cingulate cortex and enhances diffuse synchronization of cortical slow waves during sleep through a relay in the antero-dorsal thalamus (Gent et al., 2018b).

We previously hypothesized that disrupted cortical synchronization might increase the risk of developing SCZ, although thalamic dysfunction reflected by the well-established impairment of sleep spindle generation may be necessary for the disease onset. Current results do not contradict this interpretation as it seems plausible that both cortico-cortical and thalamocortical connectivity regulate slow wave traveling. Although further research is needed, a larger impairment in slow wave

traveling associated with major abnormalities in sleep spindle density is expected in patients with SCZ.

We also reported abnormality of slow wave origins in FDRs, with an increase over frontal regions and a strong decrease over midline central and posterior regions compared to control subjects. Should these properties of slow wave traveling be confirmed in SCZ patients, they might reflect the connectivity impairment that has extensively been shown during wakefulness. Although several hypotheses remain to be tested and these preliminary results only support a speculative discussion, we suggest that the increased number of slow wave frontal origins in FDRs might be a compensatory mechanism for the relative lack of central and posterior activity and the global reduction of speed and traveled distance. Further studies exploring slow wave traveling and its origins in SCZ patients are necessary to confirm this hypothesis.

Finally, SWS is crucial for the consolidation of memories (Stickgold, 2005) and has been specifically associated with the consolidation of declarative memories (Marshall et al., 2006). Although sleep-dependent consolidation was not tested in our sample, other studies have shown FDRs share similar deficits with patients during a word-pairs association task (Denis et al., 2018) and in declarative memory (Whyte et al., 2005). Future studies should assess whether reduced amplitude and propagation dynamics of slow waves in FDRs also reflect the specific abnormalities of memory processing observed in this population.

The present study has some limitations. First, the sample size was relatively small ($N = 16$ in each group), albeit in line with available studies including whole-night sleep data in FDRs, which range from 13 to 19 (Sarkar et al., 2010; Manoach et al., 2014; Schilling et al., 2016). Furthermore, this has been considered adequate to detect large effect sizes, while desensitizing inference to small effect sizes, for classical inference based on α (Friston, 2012). Another potential limitation was that the sleep macrostructure was found to differ between the two groups. Altered parameters such as duration of stages N2 and N4, reduced TST and low sleep quality have previously been reported in FDRs compared to healthy control populations (Sarkar et al., 2010; Manoach et al., 2014; Schilling et al., 2016). However, we have previously shown that differences in architecture are unlikely to affect slow-wave analysis due to the lack of difference observed between the two samples in terms of density (D'Agostino et al., 2018). In order to control for this potential bias, similar results have been replicated for the first cycle, within which sleep architecture parameters were comparable between groups (see Supplementary Figs. 2 and 3). Finally, although our analysis should be considered confirmatory, we acknowledge that other results might be obtained with different samples even if the same methods are applied. This limitation reflects the intrinsic variability of the population studied, which putatively differs in terms of genetic susceptibility to SCZ across samples.

Despite these limitations, the use of standardized and open source methods for the analysis of sleep oscillations is critical to boost reproducibility of results and comparability across studies. Overall, the results of the current analysis on slow wave traveling are encouraging and could unfold a novel path for future research in patients with SCZ and related disorders. Although functional MRI measures have clearly begun to dissect abnormal connectivity in SCZ, the slow temporal resolution of hemodynamic responses is known to limit this technique (Houck et al., 2017). EEG-based measures can complement imaging findings to capture the full extent of functional connectivity abnormalities in SCZ. In addition to the exquisite temporal resolution of all EEG measures, sleep parameters reflect the spontaneous activity of a brain detached from its environment, which reaches its peak of autonomous “offline” processing during slow waves sleep. Along with several other groups, we encourage access to this privileged window of enquiry to further unravel the neural circuitry underlying SCZ. Emerging findings will eventually allow us to design novel pharmacological and non-phar-

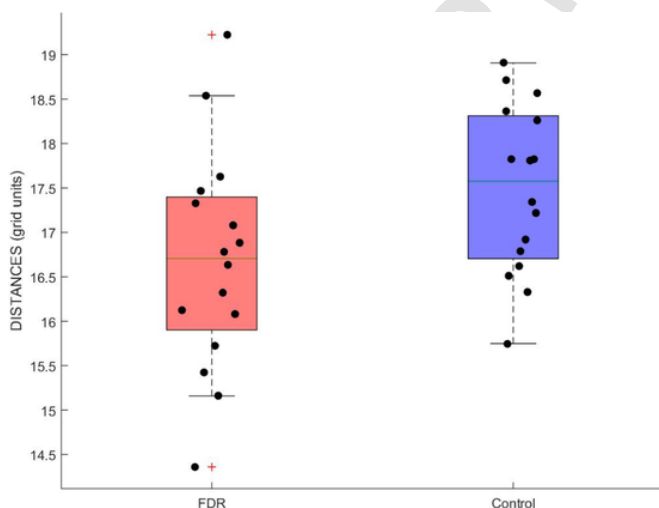


Fig. 3. Traveled slow wave distance during whole night sleep stage N3. Distance was calculated as the line of longest displacement. Units of measurement are referred to a grid of 40×40 tiles. FDR: schizophrenia first degree relatives. Control: age and gender matched control group.

macological strategies to alleviate symptoms by targeting sleep abnormalities (Zhang et al., 2019; Kaskie et al., 2019).

5. Conclusions

The study of slow wave traveling is rapidly evolving into a successful, noninvasive analysis method of brain connectivity that might enhance the understanding of neurodevelopmentally abnormal trajectories (Kurth et al., 2017). This pattern has never been studied in disorders typically associated with disrupted brain connectivity such as SCZ.

The refined spatiotemporal resolution of hd-EEG signal coupled with the lack of wake-related confounds during sleep make traveling slow wave oscillations a highly promising candidate marker for SCZ. Future studies will need to confirm the stability of our findings in larger samples of FDR, as well as to assess slow wave traveling deficits in SCZ patients, which may lead to the discovery of pathogenetic and prognostic biomarkers for SCZ and related psychotic disorders.

Contributions

AC and ADA designed the study, wrote the protocol and drafted the manuscript. AC conducted EEG analyses, aided by MZ and BAR. CC, CZ and FD recruited participants and performed sleep EEG recordings. MC guaranteed all sleep recording procedures at her site. BAR and GT provided the EEG equipment across both experimental sites and, together with FF, were responsible of data collected at their location. FF and SS supervised experimental procedures and contributed critical advice on the discussion of findings. All authors critically reviewed the manuscript.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2020.03.025>.

References

Bartsch, U, Simpkin, A J, Demanuele, C, Wamsley, E, Marston, H M, Jones, M W, 2019. Distributed slow-wave dynamics during sleep predict memory consolidation and its impairment in schizophrenia. *NPJ Schizophr.* 5 (18).
 Bonjean, M, Baker, T, Lemieux, M, Timofeev, I, Sejnowski, T, Bazhenov, M, 2011. Corticothalamic feedback controls sleep spindle duration in vivo. *J. Neurosci.* 31 (25), 9124–9134. doi:10.1523/JNEUROSCI.0077-11.2011.
 Buchmann, A, Kurth, S, Ringli, M, Geiger, A, Jenni, O G, Huber, R, 2011. Anatomical markers of sleep slow wave activity derived from structural magnetic resonance images. *J. Sleep Res.* 20 (4), 506–513. doi:10.1111/j.1365-2869.2011.00916.x.
 Capizzano, A A, Toscano, J L N, Ho, B C, 2011. Magnetic resonance spectroscopy of limbic structures displays metabolite differences in young unaffected relatives of schizophrenia probands. *Schizophr Res* 131 (1), 4–10.
 Castelnovo, A, D'Agostino, A, Casetta, C, Sarasso, S, Ferrarelli, F, 2016. Sleep spindle deficit in schizophrenia: contextualization of recent findings. *Curr Psychiatry Re* 18 (8), 72. doi:10.1007/s11920-016-0713-2.

Castelnovo, A, Graziano, B, Ferrarelli, F, D'Agostino, A, 2018. Sleep spindles and slow waves in schizophrenia and related disorders: main findings, challenges, and future perspectives. *Eur. J. Neurosci.* 1–21. doi:10.1111/ejn.13815.
 Crunelli, V, David, F, Lőrincz, M L, Hughes, S W, 2015. The thalamocortical network as a single slow wave-generating unit. *Curr. Opin. Neurobiol.* 31, 72–80. doi:10.1016/j.conb.2014.09.001.
 D'Agostino, A, Castelnovo, A, Cavallotti, S, Casetta, C, Marcatili, M, Gambini, O, et al., 2018. Sleep endophenotypes of schizophrenia: slow waves and sleep spindles in unaffected first-degree relatives. *NPJ Schizophr.* 4 (1), 2. doi:10.1038/s41537-018-0045-9.
 Denis, D, Sato, E, Larson, O, Kohnke, E J, Parr, E, King, J, et al., 2018. Sleep dependent memory consolidation in early course schizophrenia patients and familial high-risk relatives. *Sleep* 41 (S1), A369–A370.
 Diekelmann, S, Born, J, 2010. The memory function of sleep. *Nat. Rev. Neurosci.* 11 (2), 114–126. doi:10.1038/nrn2762.
 Earls, H A, Curran, T, Mittal, V, 2016. A meta-analytic review of auditory event-related potential components as endophenotypes for schizophrenia: perspectives from first-degree relatives. *Schizophr. Bull.* 42 (6), 1504–1516.
 Friston, K, 2012. Ten ironic rules for non-statistical reviewers. *Neuroimage* 61 (4), 1300–1310.
 Fuentealba, P, Steriade, M, 2005. The reticular nucleus revisited: intrinsic and network properties of a thalamic pacemaker. *Prog. Neurobiol.* 75 (2), 125–141.
 Gent, T C, Basseti, C, Adamantidis, A R, 2018. Sleep-wake control and the thalamus. *Curr. Opin. Neurobiol.* 52, 188–197. doi:10.1016/j.conb.2018.08.002.
 Gent, T C, Bandarabadi, M, Herrera, C G, Adamantidis, A R, 2018. Thalamic dual control of sleep and wakefulness. *Nat. Neurosci.* 21 (7), 974–984.
 Giraldo-Chica, M, Woodward, N D, 2017. Review of thalamocortical resting-state fMRI studies in schizophrenia. *Schizophr. Res.* 180, 58–63. doi:10.1016/j.schres.2016.08.005.
 Göder, R, Boigs, M, Braun, S, Friege, L, Fritzer, G, Aldenhoff, J B, Hinze-Selch, D, 2004. Impairment of visuospatial memory is associated with decreased slow wave sleep in schizophrenia. *J. Psychiatr. Res.* 38 (6), 591–599.
 Göder, R, Aldenhoff, J B, Boigs, M, Braun, S, Koch, J, Fritzer, G, 2006. Delta power in sleep in relation to neuropsychological performance in healthy subjects and schizophrenia patients. *J. Neuropsychiatry Clin Neurosci* 18 (4), 529–535.
 Houck, J M, Çetin, M S, Mayer, A R, Bustillo, J R, Stephen, J, Aine, C, Cañive, J, Perrone-Bizzozero, N, Thoma, R J, Brookes, M J, Calhoun, V D, 2017. Magnetoencephalographic and functional MRI connectomics in schizophrenia via intra- and inter-network connectivity. *Neuroimage* 145, 96–106 Pt A.
 Iber, C, Ancoli-Israel, S, Chesson, A, Quan, S, 2007. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. First edition American Academy of Sleep Medicine, Westchester, IL.
 Kambeitz, J, Kambeitz-Ilanovic, L, Cabral, C, Dwyer, D B, Calhoun, V D, van den Heuvel, M P, et al., 2016. Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. *Schizophr. Bull.* 42 (S1), S13–S21. doi:10.1093/schbul/sbv174.
 Kaskie, R E, Ferrarelli, F, 2019. Sleep disturbances in schizophrenia: what we know, what still needs to be done. *Curr. Opin. Psychol.* 34, 68–71. doi:10.1016/j.copsyc.2019.09.011.
 Kaskie, R E, Gill, K M, Ferrarelli, F, 2019. Reduced frontal slow wave density during sleep in first-episode psychosis. *Schizophr. Res.* 206, 318–324. doi:10.1016/j.schres.2018.10.024.
 Keshavan, M S, Diwadkar, V A, Montrose, D M, Stanley, J A, Pettegrew, J W, 2004. Premorbid characterization in schizophrenia: the Pittsburgh high risk study. *World Psychiatry* 3, 163–168.
 von Krosigk, M, Bal, T, McCormick, D A, 1993. Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261 (5119), 361–364.
 Keshavan, M S, Reynolds, C F 3rd, Miewald, M J, Montrose, D M, Sweeney, J A, Vasko, R C Jr, et al., 1998. Delta sleep deficits in schizophrenia: evidence from automated analyses of sleep data. *Arch. Gen. Psychiatry.* 55 (5), 443–448. doi:10.1001/archpsyc.55.5.443.
 Kurth, S, Riedner, B A, Dean, D C, O'Muircheartaigh, J, Huber, R, Jenni, O G, et al., 2017. Traveling slow oscillations during sleep: a marker of brain connectivity in childhood. *Sleep* 40 (9). doi:10.1093/sleep/zsx121.
 Lemieux, A, Chen, J Y, Lonjers, P, Bazhenov, M, Timofeev, I, 2014. The impact of cortical deafferentation on the neocortical slow oscillation. *J. Neurosci.* 34, 5689–5703.
 Manoach, D S, Demanuele, C, Wamsley, E J, Vangel, M, Montrose, D M, Miewald, J, et al., 2014. Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. *Front. Hum. Neurosci.* 8 (762).
 Marshall, L, Helgadottir, H, Mölle, M, Born, J, 2006. Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613.
 Massimini, M, Huber, R, Ferrarelli, F, Hill, S, Tononi, G, 2004. The sleep slow oscillation as a traveling wave. *J. Neurosci.* 24 (31), 6862–6870.
 Mensen, A, Riedner, B, Tononi, G, 2016. Optimizing detection and analysis of slow waves in sleep EEG. *J. Neurosci. Methods* 274, 1–12. doi:10.1016/j.jneumeth.2016.09.006.
 Nichols, T E, Holmes, A P, 2002. Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum. Brain Mapp.* 15 (1), 1–25.
 Nickerson, L D, 2018. Replication of resting state-task network correspondence and novel findings on brain network activation during task fMRI in the human connectome project study. *Scient. Report.* 8 (17534).
 Piantoni, G, Poil, S S, Linkenkaer-Hansen, K, Verweij, I M, Ramautaur, J R, Van Someren, E J, Van Der Werf, Y D, 2013. Individual differences in white matter diffusion affect sleep oscillations. *J. Neurosci.* 33 (1), 227–233. doi:10.1523/JNEUROSCI.2030-12.2013.

- Piantoni, G, Halgre, E, Cash, S S, 2016. The contribution of thalamocortical core and matrix pathways to sleep spindles. *Neural Plasticity* 3024342.
- Poulin, Julie, Stip, Emmanuel, Godbout, Roger, 2008. REM sleep EEG spectral analysis in patients with first-episode schizophrenia. *JOURNAL OF PSYCHIATRIC RESEARCH* 42, 1086–1093.
- Riedner, B A, Vyazovskiy, V V, Huber, R, Massimini, M, Esser, S, Murphy, M, Tononi, G, 2007. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. *Sleep* 30 (12), 1643–1657.
- Sarkar, S, Katshu, M Z, Nizamie, S H, Praharaj, S K, 2010. Slow wave sleep deficits as a trait marker in patients with schizophrenia. *Schizophr. Res.* 124, 127–133.
- Schilling, C, Schlipf, M, Spietzack, S, Rausch, F, Eisenacher, S, Englisch, S, et al., 2016. Fast sleep spindle reduction in schizophrenia and healthy first-degree relatives: association with impaired cognitive function and potential intermediate phenotype. *Eur. Arch. Psychiatry Clin. Neurosci.* 267 (3), 213–224. doi:10.1007/s00406-016-0725-2.
- Schoch, S F, Riedner, B A, Deoni, S C, Huber, R, LeBourgeois, M K, Kurth, S, 2018. Across-night dynamics in traveling sleep slow waves throughout childhood. *Sleep* 41 (11). doi:10.1093/sleep/zsy165.
- Sitskoon, M M, Aleman, A, Ebisch, S J, Appels, M C, Kahn, R S, 2004. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr. Res.* 71 (2), 285–295.
- Snitz, B.E., MacDonald III, A.W., Carter, C.S., 2005. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes.
- Steriade, M, 2003. The corticothalamic system in sleep. *Front. Biosci.* 8, d878–d899.
- Steriade, M, Nunez, A, Amzica, F, 1993. A novel slow (<1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci.* 13, 3252–3265.
- Stickgold, R, 2005. Sleep-dependent memory consolidation. *Nature* 437, 1272–1278.
- Timofeev, I, Grenier, F, Bazhenov, M, Sejnowski, T J, Steriade, M, 2000. Origin of slow cortical oscillations in deafferented cortical slabs. *Cereb. Cortex* 10, 1185–1199.
- Tononi, G, Edelman, G M, 2000. Schizophrenia and the mechanisms of conscious integration. *Brain Res. Brain Res. Rev.* 31 (2–3), 391–400.
- Warby, S C, Wendt, S L, Welinder, P, Munk, M G S, Carrillo, O, Sorensen, H B D, Jennum, P, Peppard, P E, Perona, P, Mignot, M, 2014. Sleep spindle detection: crowdsourcing and evaluating performance of experts, non-experts, and automated methods. *Nat. Methods* 11 (4), 385–392.
- Whitfield-Gabrieli, S, Thermenos, H W, Milanovic, S, Tsuang, M T, Faraone, S V, McCarley, R W, et al., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc. Natl. Acad. Sci.* 106 (4), 1279–1284.
- Whyte, M C, McIntosh, A M, Johnstone, E C, Lawrie, S M, 2005. Declarative memory in unaffected adult relatives of patients with schizophrenia: a systematic review and meta-analysis. *Schizophr. Res.* 78, 13–26. doi:10.1016/j.schres.2005.05.018.
- Yang, C, Winkelman, J W, 2006. Clinical significance of sleep EEG abnormalities in chronic schizophrenia. *Schizophr. Res.* 82, 251–260.
- Zhang, Y, Quiñones, G M, Ferrarelli, F, 2019. Sleep spindle and slow wave abnormalities in schizophrenia and other psychotic disorders: recent findings and future directions. *Schizophr. Res.* pii S0920-9964 (19), 30500–30506. doi:10.1016/j.schres.2019.11.002.