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The Impact of Sleep on Neurocognition and Functioning in Schizophrenia—Is It Time to Wake-Up?

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Abstract

People with schizophrenia (SZ) display substantial neurocognitive deficits that have been implicated as major contributors to poor daily functioning and disability. Previous reports have identified a number of predictors of poor neurocognition in SZ including demographics, symptoms, and treatment adherence, as well as body mass index, aerobic fitness, and exercise activity. However, the putative impact of sleep has received relatively limited consideration, despite sleep disturbances, which are pervasive in this population, resulting in symptoms that are strikingly similar to the neurocognitive deficits commonly observed in SZ. Here we argue for the consideration of the impact of sleep on neurocognition in people with SZ and propose recommendations for future research to elucidate the links between sleep parameters, neurocognition and daily functioning.

Keywords

sleep; neurocognition; schizophrenia; slow wave sleep; spindles; functioning; psychosis

INTRODUCTION

People with schizophrenia (SZ) display substantial neurocognitive deficits across multiple domains [1,2]. These deficits have been identified as major predictors of poor functioning and disability [2-5], thus representing a serious public health concern and an important target for interventions [6,7]. Studies examining predictors of neurocognitive functioning in SZ have centered on a number of variables including demographics (e.g., age, education, parental education, income, socioeconomic status) [8-11], symptoms (e.g., depression,

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CONFLICTS OF INTEREST

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negative symptoms) [10,12,13], and treatment adherence [12], as well as body mass index (BMI), aerobic fitness, and exercise activity [14-17]. However, as sleep disturbance (SD) symptoms are strikingly similar to the cognitive deficits observed in SZ [18], here we argue for the consideration of the impact of SD on neurocognition and functioning in this population.

EVIDENCE FOR THE IMPACT OF SLEEP ON NEUROCOGNITION

Extensive preclinical and clinical research literatures converge in highlighting the critical role SD plays in degrading memory and other neurocognitive abilities, pointing to deterioration in multiple cognitive domains [19-22]. Attention and working memory appear to be particularly susceptible to the impact of poor sleep, as evident by a large meta-analysis (70 studies, $N=1458$) indicating moderate-to-large effect sizes [23]. Previous reports have implicated a number of sleep-related processes as relevant to neurocognitive sequelae. Slow Wave Sleep (SWS), often referred to as “deep sleep”, consists of Stage 3 of non-rapid eye movement (NREM) sleep and is characterized by 0.5–4 Hz high amplitude oscillatory EEG activity [24]. SWS has been associated with both declarative and spatial navigational memory [25-27], with augmentation using transcranial current oscillating at a frequency mimicking SWS during sleep resulting in enhanced declarative memory retention [28]. Similarly, spindle activity has also been implicated in neurocognitive functioning. Spindles are generated by the interplay of the thalamic reticular nucleus, thalamic relay nuclei, and cortex during NREM sleep [29-31] and are characterized by waxing/waning bursts of 10–16 Hz activity. Findings suggests spindles facilitate synaptic plasticity and memory consolidation [24,30,32-36], specifically declarative memory [37], the integration of new information into existing knowledge [38], as well as directed remembering and forgetting [39]. Altogether, these findings point to SWS and spindle activity as promising targets for investigating the neural activity underlying the links between SD and neurocognitive functioning.

SLEEP IN PEOPLE WITH SCHIZOPHRENIA—CHARACTERISTICS AND IMPACT ON NEUROCOGNITION

Germane to SZ, reports indicate SD are highly prevalent in this population, with nearly 4 out of 5 individuals with SZ endorsing sleep problems [40]. These findings appear to be unrelated to onset and/or chronicity of psychosis, with substantial SD have been documented among individuals at clinical high risk for psychosis [41,42]. Likewise, nearly half of early psychosis patients reported experiences of insomnia and nearly 80% were diagnosed with at least one sleep disorder [43]. A burgeoning research literature supports the link between sleep and neurocognition in SZ [18,44-51], although the findings are not universal, potentially due to diversity of sleep parameters and cognitive domains investigated, as well as a lack of replication [52]. Specifically, results suggest significant associations between SWS and impaired neurocognitive performance in medication-naïve [53], medicated [54-56], and unmedicated individuals with SZ [57,58], with multiple domains being negatively impacted including processing speed and inhibition [49], attention [53,58], procedural learning [56,59], visuospatial memory [55,60], and declarative memory

[55,60]. Conversely, extended SWS was found to be correlated with quicker problem solving [61] and enhanced attention [62]. Likewise, reduction of sleep spindle activity has been linked with impaired neurocognition in individuals with SZ [50,63-65] including impaired memory consolidation [64], inattention [53,66], and verbal cognition [67]. Augmenting spindles in isolation did not improve sleep-dependent memory processes in SZ [68], speaking to the need for their precise temporal coordination with slow oscillations during SWS [69].

IMPLICATIONS FOR FUTURE RESEARCH

Despite their high prevalence and clinical significance, at present there are limited data on the impact of SD on neurocognition in SZ and there are no data quantifying their influence on daily functioning. The extant studies have been limited by small samples, reliance of cross-sectional designs, as well as evaluations of a narrow range of sleep parameters and neurocognitive domains. Additionally, the common use of retrospective self-reports, which are susceptible to various cognitive biases in individuals with SZ [70], is also problematic. Most notably, there have been no experimental studies examining the impact of SD on neurocognition and functioning in people with SZ, limiting the ability to determine whether SD are a cause or an effect of clinical phenomena. Altogether, the available data indicates that despite their chronic and ubiquitous nature, SD remain poorly understood and modeled in SZ, their impact is rarely considered in clinical trials targeting neurocognitive deficits, and they remain largely unaddressed by clinicians.

Addressing this critical gap in knowledge would require employment of a multi-pronged approach. Specifically, here we propose recommendations for investigators to employ in future studies examining the links between sleep and poor neurocognition in SZ:

1. A greater emphasis should be placed on employment of experimental studies over correlational and/or cross-sectional designs. Such a strategy could clarify and confirm the causal links between neurobiological, physiological, and subjective characteristics of sleep and neurocognition. Recent reports have recommended the use of controlled sleep deprivation as an experimental model of SZ [71]. Likewise, pharmacological approaches (e.g., Ketamine) have been used to model sleep in SZ [72-74].
2. Consistent with the National Institute of Mental Health (NIMH)'s Research Domain Criteria (RDoC) framework, studies would benefit from concurrent assessments of multiple domains using complementary methodologies (e.g., polysomnography, electroencephalogram (EEG), behavioral, subjective, ambulatory assessments, as well as imaging).
3. Studies should aim to identify sleep parameters impacting poor neurocognition, as well as explore whether any specific neurocognitive domains may be more susceptible for deterioration due to poor sleep.
4. The scope of outcomes should be expanded beyond traditional neurocognitive test batteries to include measures of daily functioning, social cognition, and quality of life.

5. Studies should aim to ascertain the impact of sleep on biomarkers associated with poor neurocognition in SZ (e.g., neurotrophins, inflammation markers).
6. Finally, it is imperative future studies examine putatively relevant biological variables (e.g., sex, age, BMI, menstrual cycle a menopause) to ascertain their potential impact on the link between sleep and neurocognition in SZ.

Our group is currently undertaking such a study aiming to address these very questions (PI: Kimhy; “*Neurocognition After Perturbed Sleep (NAPS)*”; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT05032963) Identifier: [NCT05032963](https://clinicaltrials.gov/ct2/show/study/NCT05032963)).

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REFERENCES

1. Green MF, Nuechterlein KH. The MATRICS initiative: Developing a consensus cognitive battery for clinical trials. *Schizophr Res.* 2004;72(1):1–3. [PubMed: 15531401]
2. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, et al. The MATRICS consensus cognitive battery, part 1: Test selection, reliability, and validity. *Am J Psychiatry.* 2008 Feb;165(2):203–13. [PubMed: 18172019]
3. Kern RS, Gold JM, Dickinson D, Green MF, Nuechterlein KH, Baade LE, et al. The MCCB impairment profile for schizophrenia outpatients: Results from the MATRICS psychometric and standardization study. *Schizophr Res.* 2011 Mar;126(1-3):124–31. [PubMed: 21159492]
4. Keefe RS. Cognitive deficits in patients with schizophrenia: effects and treatment. *J Clin Psychiatry.* 2006;68(14):8–13.
5. Green MF, Nuechterlein KH, Kern RS, Baade LE, Fenton WS, Gold JM, et al. Functional co-primary measures for clinical trials in schizophrenia: Results from the MATRICS Psychometric and Standardization Study. *Am J Psychiatry.* 2008 Feb;165(2):221–8. [PubMed: 18172017]
6. Green M Cognition, Drug Treatment, and Functional Outcome in Schizophrenia: A Tale of Two Transitions. *Am J Psychiatry.* 2007 Jul;164(7):992–4. [PubMed: 17606645]
7. Green MF. Stimulating the development of drug treatments to improve cognition in schizophrenia. *Annu Rev Clin Psychol.* 2007;3:159–80. [PubMed: 17716052]
8. Czepielewski LS, Alliende LM, Castañeda CP, Castro M, Guinjoan SM, Massuda R, et al. Effects of socioeconomic status in cognition of people with schizophrenia: Results from a Latin American collaboration network with 1175 subjects. *Psychol Med.* 2021 Jun 23;1–12.
9. Weinberg D, Lenroot R, Jacomb I, Allen K, Bruggemann J, Wells R, et al. Cognitive subtypes of schizophrenia characterized by differential brain volumetric reductions and cognitive decline. *JAMA Psychiatry.* 2016 Dec 1;73(12):1251–9. [PubMed: 27829096]
10. Wells R, Swaminathan V, Sundram S, Weinberg D, Bruggemann J, Jacomb I, et al. The impact of premorbid and current intellect in schizophrenia: Cognitive, symptom, and functional outcomes. *NPJ Schizophr.* 2015 Nov 4;1:15043. [PubMed: 27336046]
11. Gilbert E, Mérette C, Jomphe V, Émond C, Rouleau N, Bouchard RH, et al. Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms of outcome and response to treatment. *Eur Arch Psychiatry Clin Neurosci.* 2014 Jun;264(4):333–43. [PubMed: 24173295]
12. Rangel A, Muñoz C, Ocampo MV, Quintero C, Escobar M, Botero S, et al. Neurocognitive subtypes of schizophrenia. *Actas Esp Psiquiatr.* 2015 May-Jun;43(3):80–90. [PubMed: 25999155]
13. Green MF, Horan WP, Mathis KI, Wynn JK. Neurocognition and functional outcome in schizophrenia: filling in the gaps. *Eur Psychiatry.* 2019 Feb;56:60–8. [PubMed: 30500572]

14. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. Aerobic fitness and body mass index in individuals with schizophrenia: Implications for neurocognition and daily functioning. *Psychiatry Res.* 2014;220(3):784–91. [PubMed: 25219618]
15. Kimhy D, Vakhrusheva J, Bartels MN, Armstrong HF, Ballon JS, Khan S, et al. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: A single-blind, randomized clinical trial. *Schizophr Bull.* 2015 Jul;41(4):859–68. [PubMed: 25805886]
16. Kimhy D, Lauriola V, Bartels MN, Armstrong HF, Vakhrusheva J, Ballon JS, et al. Aerobic exercise for cognitive deficits in schizophrenia - The impact of frequency, duration, and fidelity with target training intensity. *Schizophr Res.* 2016 Apr;172(1-3):213–5. [PubMed: 26852401]
17. Vakhrusheva J, Marino B, Stroup TS, Kimhy D. Aerobic Exercise in People with Schizophrenia: Neural and Neurocognitive Benefits. *Curr Behav Neurosci Rep.* 2016 Jun;3(2):165–75. [PubMed: 27766192]
18. Pocivavsek A, Rowland LM. Basic Neuroscience Illuminates Causal Relationship between Sleep and Memory: Translating to Schizophrenia. *Schizophr Bull.* 2018 Jan 13;44(1):7–14. [PubMed: 29136236]
19. Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol.* 2005 Mar;25(1):117–29. [PubMed: 15798944]
20. Killgore WDS. Effects of sleep deprivation on cognition. *Prog Brain Res.* 2010;185:105–29. [PubMed: 21075236]
21. Miller MA, Wright H, Hough J, Cappuccio FP. Sleep and Cognition. In: *Sleep and its Disorders Affect Society.* London (UK): IntechOpen; 2014.
22. Ahuja S, Chen RK, Kam K, Pettibone WD, Osorio RS, Varga AW. Role of normal sleep and sleep apnea in human memory processing. *Nat Sci Sleep.* 2018 Sep 4;10:255–69. [PubMed: 30214331]
23. Lim J, Dinges DF. A Meta-Analysis of the Impact of Short-Term Sleep Deprivation on Cognitive Variables. *Psychol Bull.* 2010 May;136(3):375–89. [PubMed: 20438143]
24. Zhang Y, Gruber R. Can slow-wave sleep enhancement improve memory? A review of current approaches and cognitive outcomes. *Yale J Biol Med.* 2019 Mar 25;92(1):63–80. [PubMed: 30923474]
25. Peigneux P, Laureys S, Fuchs S, Collette F, Perrin F, Reggers J, et al. Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron.* 2004;44(3):535–45. [PubMed: 15504332]
26. Mander BA, Rao V, Lu B, Saletin JM, Lindquist JR, Ancoli-Israel S, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci.* 2013;16(3):357–64. [PubMed: 23354332]
27. Varga AW, Ducca EL, Kishi A, Fischer E, Parekh A, Koushyk V, et al. Effects of aging on slow-wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol Aging.* 2016;42:142–9. [PubMed: 27143431]
28. Westerberg CE, Florczak SM, Weintraub S, Mesulam MM, Marshall L, Zee PC, et al. Memory improvement via slow-oscillatory stimulation during sleep in older adults. *Neurobiol Aging.* 2015 Sep;36(9):2577–86. [PubMed: 26116933]
29. Berry RB, Wagner MH. *Sleep Medicine Pearls.* Philadelphia (US): Saunders; 2014.
30. Cox R, Hofman WF, Talamini LM. Involvement of spindles in memory consolidation is slow wave sleep-specific. *Learn Mem.* 2012 Jun 14;19(7):264–7. [PubMed: 22700468]
31. De Gennaro L, Ferrara M. Sleep spindles: An overview. *Sleep Med Rev.* 2003 Oct;7(5):423–40. [PubMed: 14573378]
32. Ramanathan DS, Gulati T, Ganguly K. Sleep-Dependent Reactivation of Ensembles in Motor Cortex Promotes Skill Consolidation. *PLoS Biol.* 2015 Sep 18;13(9):e1002263. [PubMed: 26382320]
33. Durkin J, Suresh AK, Colbath J, Broussard C, Wu J, Zochowski M, et al. Cortically coordinated NREM thalamocortical oscillations play an essential, instructive role in visual system plasticity. *Proc Natl Acad Sci U S A.* 2017 Sep 26;114(39):10485–90. [PubMed: 28893999]

34. Miyamoto D, Hirai D, Fung CCA, Inutsuka A, Odagawa M, Suzuki T, et al. Top-down cortical input during NREM sleep consolidates perceptual memory. *Science*. 2016 Jun 10;352(6291):1315–8. [PubMed: 27229145]
35. Wei Y, Krishnan GP, Komarov M, Bazhenov M. Differential roles of sleep spindles and sleep slow oscillations in memory consolidation. *PLoS Comput Biol*. 2018 Jul 9;14(7):e1006322. [PubMed: 29985966]
36. Kam K, Parekh A, Sharma RA, Andrade A, Lewin M, Castillo B, et al. Sleep oscillation-specific associations with Alzheimer's disease CSF biomarkers: Novel roles for sleep spindles and tau. *Mol Neurodegener*. 2019 Feb 21;14(1):10. [PubMed: 30791922]
37. Holz J, Piosczyk H, Feige B, Spiegelhalter K, Baglioni C, Riemann D, et al. EEG sigma and slow-wave activity during NREM sleep correlate with overnight declarative and procedural memory consolidation. *J Sleep Res*. 2012 Dec;21(6):612–9. [PubMed: 22591117]
38. Tamminen J, Payne JD, Stickgold R, Wamsley EJ, Gaskell MG. Sleep spindle activity is associated with the integration of new memories and existing knowledge. *J Neurosci*. 2010 Oct 27;30(43):14356–60. [PubMed: 20980591]
39. Saletin JM, Goldstein AN, Walker MP. The role of sleep in directed forgetting and remembering of human memories. *Cereb Cortex*. 2011 Nov;21(11):2534–41. [PubMed: 21459838]
40. Klingaman EA, Palmer-Bacon J, Bennett ME, Rowland LM. Sleep Disorders Among People With Schizophrenia: Emerging Research. *Curr Psychiatry Rep*. 2015 Oct;17(10):79. [PubMed: 26279058]
41. Lunsford-Avery JR, Mittal VA. Sleep dysfunction prior to the onset of schizophrenia: A review and neurodevelopmental diathesis-stress conceptualization. *Clin Psychol Sci Pract*. 2013;20(3):291–320.
42. Zanini M, Castro J, Coelho FM, Bittencourt L, Bressan RA, Tufik S, et al. Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations? *Neurosci Biobehav Rev*. 2013 Dec;37(10 Pt 2):2631–7. [PubMed: 24096189]
43. Reeve S, Sheaves B, Freeman D. Excessive sleepiness in patients with psychosis: An initial investigation. *PLoS One*. 2021 Jan 15;16(1):e0245301. [PubMed: 33449971]
44. Wulff K, Joyce E. Circadian rhythms and cognition in schizophrenia. *Br J Psychiatry*. 2011 Apr;198(4):250–2. [PubMed: 21972273]
45. Chan MS, Chung KF, Yung KP, Yeung WF. Sleep in schizophrenia: A systematic review and meta-analysis of polysomnographic findings in case-control studies. *Sleep Med Rev*. 2017 Apr;32:69–84. [PubMed: 27061476]
46. Manoach DS, Stickgold R. Abnormal Sleep Spindles, Memory Consolidation, and Schizophrenia. *Annu Rev Clin Psychol*. 2019 May 7;15:451–79. [PubMed: 30786245]
47. Pritchett D, Wulff K, Oliver PL, Bannerman DM, Davies KE, Harrison PJ, et al. Evaluating the links between schizophrenia and sleep and circadian rhythm disruption. *J Neural Transm*. 2012 Oct;119(10):1061–75. [PubMed: 22569850]
48. Davies G, Haddock G, Yung AR, Mulligan LD, Kyle SD. A systematic review of the nature and correlates of sleep disturbance in early psychosis. *Sleep Med Rev*. 2017 Feb;31:25–38. [PubMed: 26920092]
49. Laskemoen JF, Büchmann C, Barrett EA, Collier-Høegh M, Haatveit B, Vedal TJ, et al. Do sleep disturbances contribute to cognitive impairments in schizophrenia spectrum and bipolar disorders? *Eur Arch Psychiatry Clin Neurosci*. 2020 Sep;270(6):749–59. [PubMed: 31587109]
50. Bartsch U, Simpkin AJ, Demanuele C, Wamsley E, Marston HM, Jones MW. (2019). Distributed slow-wave dynamics during sleep predict memory consolidation and its impairment in schizophrenia. *NPJ Schizophr*. 2019 Nov 4;5(1):18. [PubMed: 31685816]
51. Schilling C, Schlipf M, Spietzack S, Rausch F, Eisenacher S, Englisch S, et al. 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*. 2017 Apr;267(3):213–24. [PubMed: 27565806]

52. Carruthers SP, Brunetti G, Rossell SL. Sleep disturbances and cognitive impairment in schizophrenia spectrum disorders: a systematic review and narrative synthesis. *Sleep Med.* 2021 Aug;84:8–19. [PubMed: 34090012]
53. Forest G, Poulin J, Daoust AM, Lussier I, Stip E, Godbout R. Attention and non-REM sleep in neuroleptic-naïve persons with schizophrenia and control participants. *Psychiatry Res.* 2007 Jan 15;149(1-3):33–40. [PubMed: 17141330]
54. Bromundt V, Köster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, Stoppe G, et al. Sleep - Wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry.* 2011 Apr;198(4):269–76. [PubMed: 21263013]
55. Göder R, Fritzer G, Gottwald B, Lippmann B, Seeck-Hirschner M, Serafin I, et al. Effects of olanzapine on slow wave sleep, sleep spindles and sleep-related memory consolidation in schizophrenia. *Pharmacopsychiatry.* 2008 May;41(3):92–9. [PubMed: 18484550]
56. Manoach DS, Cain MS, Vangel MG, Khurana A, Goff DC, Stickgold R. A failure of sleep-dependent procedural learning in chronic, medicated schizophrenia. *Biol Psychiatry.* 2004 Dec 15;56(12):951–6. [PubMed: 15601605]
57. Yang C, Winkelman JW. Clinical significance of sleep EEG abnormalities in chronic schizophrenia. *Schizophr Res.* 2006 Feb 28;82(2-3):251–60. [PubMed: 16377158]
58. Chang YS, Hsu CY, Tang SH, Lin CY, Chen MC. Correlation of attention deficit, rapid eye movement latency and slow wave sleep in schizophrenia patients. *Psychiatry Clin Neurosci.* 2009 Apr;63(2):176–9. [PubMed: 19335387]
59. Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, et al. Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. *J Psychiatr Res.* 2010 Jan;44(2):112–20. [PubMed: 19665729]
60. Göder R, Boigs M, Braun S, Friege L, Fritzer G, Aldenhoff JB, et al. Impairment of visuospatial memory is associated with decreased slow wave sleep in schizophrenia. *J Psychiatr Res.* Nov-Dec 2004;38(6):591–9. [PubMed: 15458855]
61. Ramakrishnan M, Sartory G, Van Beekum A, Lohrmann T, Pietrowsky R. Sleep-related cognitive function and the K-complex in schizophrenia. *Behav Brain Res.* 2012 Oct 1;234(2):161–6. [PubMed: 22743003]
62. Göder 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.* Fall 2006;18(4):529–35. [PubMed: 17135379]
63. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry.* 2007 Mar;164(3):483–92. [PubMed: 17329474]
64. Manoach DS, Pan JQ, Purcell SM, Stickgold R. Reduced Sleep Spindles in Schizophrenia: A Treatable Endophenotype That Links Risk Genes to Impaired Cognition? *Biol Psychiatry.* 2016 Oct 15;80(8):599–608. [PubMed: 26602589]
65. Wamsley EJ, Tucker MA, Shinn AK, Ono KE, McKinley SK, Ely AV, et al. Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? *Biol Psychiatry.* 2012 Jan 15;71(2):154–61. [PubMed: 21967958]
66. Keshavan MS, Montrose DM, Miewald JM, Jindal RD. Sleep correlates of cognition in early course psychotic disorders. *Schizophr Res.* 2011 Sep;131(1-3):231–4. [PubMed: 21724373]
67. Manoach DS, Demanuele C, Wamsley EJ, Wamsley EJ, Montrose DM, Miewald J, et al. Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. *Front Hum Neurosci.* 2014 Oct 7;8:762. [PubMed: 25339881]
68. Wamsley EJ, Shinn AK, Tucker MA, Ono KE, McKinley SK, Ely AV, et al. The Effects of Eszopiclone on Sleep Spindles and Memory Consolidation in Schizophrenia: A Randomized Placebo-Controlled Trial. *Sleep.* 2013 Sep 1;36(9):1369–76. [PubMed: 23997371]
69. Demanuele C, Bartsch U, Baran B, Khan S, Vangel MG, Cox R, et al. Coordination of slow waves with sleep spindles predicts sleep-dependent memory consolidation in schizophrenia. *Sleep.* 2017 Jan 1;40(1):zsw013.

70. Blum LH, Vakhrusheva J, Saperstein A, Khan S, Chang RW, Hansen MC, et al. Depressed mood in individuals with schizophrenia: A comparison of retrospective and real-time measures. *Psychiatry Res.* 2015 Jun 30;227(2-3):318–23. [PubMed: 25895490]
71. Kumari V, Ettinger U. Controlled sleep deprivation as an experimental medicine model of schizophrenia: An update. *Schizophr Res.* 2020 Jul;221:4–11. [PubMed: 32402603]
72. Ketamine Ferrarelli F, NMDA hypofunction, and sleep oscillatory abnormalities in schizophrenia. *Schizophr Res.* 2020;222:1–2. [PubMed: 32565154]
73. Castro-Zaballa S, Cavelli ML, Gonzalez J, Nardi AE, Machado S, Scorza C, Torterolo P. EEG 40 Hz Coherence Decreases in REM Sleep and Ketamine Model of Psychosis. *Front Psychiatry.* 2019 Jan 17;9:766. [PubMed: 30705645]
74. Mahdavi A, Qin Y, Aubry AS, Cornec D, Kulikova S, Pinault D. A single psychotomimetic dose of ketamine decreases thalamocortical spindles and delta oscillations in the sedated rat. *Schizophr Res.* 2020 Aug;222:362–74. [PubMed: 32507548]