Using Sleep as a Window into Early Brain Recovery from Alcoholism

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IT IS NOW well-known that sleep disturbances are highly prevalent during alcohol abuse and dependence. These sleep disturbances persist well into the period of abstinence and may be associated with relapse (for review, see Brower, 2015). Over at least the last 4 decades (Wagman and Allen, 1975), researchers have been exploring how withdrawal from alcohol affects sleep by examining electrophysiological characteristics of the sleeping brain. Polysomnographically (PSG) defined sleep stages (macroarchitecture) and specific waveforms (microarchitecture) from the sleep electroencephalogram provide a window into the neurochemical changes of the brain induced by alcohol (Brower, 2015; Colrain et al., 2014; Conroy et al., 2010).

The report by Willoughby and colleagues (2015) adds to this literature by examining a major component of the event related potential response in sleep, the K-complex (KC). In their manuscript, "Partial K-complex recovery following short-term abstinence in individuals with alcohol use disorder" the authors find that recently abstinent individuals (n = 16) with alcohol use disorder (AUD) had lower KC amplitude and incidence compared with gender-and age-matched controls (n = 13) (Willoughby et al., 2015). Moreover, the KC amplitude in AUD participants increased significantly from baseline to the follow-up 1 month later, but did not change from month 1 to 3. The age of the sample was in the early 40s, and the genders were fairly split between males and females. This study is one of only a few to examine changes in sleep over time in recovering alcoholics (see Table 1).

THE SIGNIFICANCE OF THE K-COMPLEX

While the exact function of the KC is still unknown, the KC represents a single delta wave (a high amplitude wave) that is considered to have a protective mechanism from external perturbations of sleep (Colrain, 2005; De Gennaro et al., 2000). The generation of a KC typically requires a large number of healthy neurons to fire in synchrony. Therefore, the characteristics of these waves may provide information about the state of brain health.

Understanding how delta sleep (also referred to as slow wave sleep or N3 sleep) is affected by alcohol is important because slow wave sleep is thought to be an output measure of the key regulating factor of sleep, sleep homeostasis. Sleep homeostasis (process S) along with the circadian process (process C) make up the 2 major regulating processes of sleep (Borbély, 1982). Changes in the characteristics of KCs in sleep may provide valuable insight into the way the brain recovers from alcohol use.

USING SENSITIVE MEASURES TO ASSESS CHANGING PHYSIOLOGY IN SLEEP DURING EARLY ABSTINENCE

It has been proposed that the incidence and the amplitude of specific components of the KC, for example P2, N550, and P900, are sensitive markers of brain recovery from the effects of alcoholism and aging (Colrain et al., 2009; Nicholas et al., 2002). This is particularly true of the N550 component of the KC, as it is thought to be related to "brain integrity" (Colrain et al., 2009, 2010). In the current study, the amplitude of the N550 was lower than controls at baseline and increased from baseline to the 1 month follow-up. Although the amplitude did not continue to increase between month 1 to 3, a previous study found that the N550 and P900 amplitudes were higher after an additional 12 months of abstinence (Colrain et al., 2012). Participants in that study had been abstinent between 54 and 405 days, whereas the participants in the current study had only been abstinent 17 days. This provides a glimpse into changes in KC activity at a time even earlier in the abstinence period than previously examined.

Other methodologies have been used to evaluate autonomic nervous system (ANS) changes in sleep during early recovery from alcohol dependence. For example, cardiovascular measurements such as heart rate variability (HRV) and high frequency power (HF), an index reflecting cardiac vagal modulation, provide information about ANS functioning during early abstinence. HRV is important because HF-HRV reactivity to alcohol has been related to relapse in some patients (Garland et al., 2012). In a 1 night polysomnogram

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Table 1. Changes During Sleep in Early Abstinence in Alcoholics; Studies with Multiple Time Points

Author (year)	*N* Baseline Time 2 Time 3	Gender[a] (F)	Age, years (SD)	Length of alcohol dependence, years (SD)	Time since last drink (days) *M* (SD)	Estimated lifetime alcohol consumption, kg (SD)	Measure	Duration of study (months)	Finding
Colrain and colleagues (2012)	B: 42 12 months: 15	B: 27 12 months: 3	52.1 (7.2)	29.3 (6.7)	165.3 (107.7)	1,283 (814)	Evoked KCs P200, N550 P900	12	KC amplitude higher at 12 months
de Zambotti and colleagues (2015)	B: 15 2 months: 13 4 months: 9	B: 7[a]	42.3 (8.2)	16.4 (9.0)	23.7 (6.2)	1,532 (1,323)	HRV, HR, TP, HF_a, HF_{prop}, HF_{pf}	4	Recovery in HR, HF_a and TP from B to 4 months
Willoughby and colleagues (2015)	B: 16 1 month: 14 2 months: 9	B: 7[a]	41.6 (8.3)	15.4 (8.73)	17.1 (6.75)	1,436 (1,268)	Evoked KCs P200, N550 P900	3	KC amplitude increased from B to 1 month; no change 1 to 2 months

HF_a, high frequency power, an index of cardiac vagal modulation; HF_{pf}, HF peak frequency, an index reflecting respiration rate; HF_{prop}, proportion of total power, sympathovagal balance; HR, heart rate; HRV, heart rate variability; KC, K-complex; TP, total power, an index of total HRV.
[a]Number of females reported at baseline available only.

study with concomitant HRV measures, de Zambotti and colleagues (2014) found that ANS functioning (including elevated heart rate, low total HRV, and low HF during the night) was disrupted in recently abstinent (mean 20 days) alcoholics. In follow-up study, de Zambotti and colleagues (2015) evaluated HRV during sleep at 3 time points: baseline, 2 month follow-up, and 4 month follow-up. Their follow-up study showed that HRV improved across 4 months, even in those with long-term alcohol dependence.

Another methodology called a sleep delay protocol has been used to assess homeostatic regulation in AUD participants. In this protocol, participants stay awake 3 hours later than their typical bedtime on the night of their PSG. Slow wave activity (SWA) during the first part of the night is analyzed to determine the response of the homeostatic sleep drive to the sleep delay. Recently sober (at least 3 weeks into abstinence) AUD participants showed a lower accumulation of SWA in the first part of the night and a slower dissipation of SWA across the night compared to healthy controls (Armitage et al., 2012) and to age-matched depressed participants (Brower et al., 2011). These protocols included a single night of study and it is not yet known whether repeat testing would show a more robust S response to a sleep challenge at a second time point further into abstinence.

DO IMPROVEMENTS IN MEASURES OF SLEEP AND AUTONOMIC FUNCTIONING DURING EARLY ABSTINENCE INDICATE SIGNS OF RECOVERY?

The current study concludes that impairments in KC generation in alcohol dependent individuals improve with abstinence. Whether the current findings reflect a global sign of "recovery of sleep" in early abstinence may be a larger question requiring additional research. In earlier work, the authors cautioned against the interpretation that these findings reflect recovery of sleep (Colrain et al., 2012) given that individuals with AUD continue to experience sleep problems well into abstinence. It has been estimated that approximately one-quarter of AUD patients will have persistent insomnia despite continued abstinence (Brower, 2015). Future studies are poised to explore which neurophysiological or ANS markers distinguish the AUD patients that continue to experience insomnia versus those that do not. For this to occur, information on subjective sleep complaints and sleep schedules prior to the testing night are important adjunctive assessments. A previous study found that AUD participants may not perceive the degree to which their sleep is objectively disturbed (Conroy et al., 2006). Future studies may reveal more information about the relationship between objective and subjective changes in sleep in early abstinence.

KC IN RECOVERY AND RELAPSE

Risk of relapse is often highlighted as one of the major concerns for sleep disturbance in early abstinence. The authors of the current study note in the study limitations that

they were unable to determine whether KC recovery predicted relapse rate (Willoughby et al., 2015). Of the total current sample, $n = 3$ (21%) relapsed to alcohol within the first month and $n = 5$ (55%) relapsed between the 1 and 3 month follow-up sessions. It is interesting to note that while the numbers are small, fewer individuals relapsed during the first month when KC amplitude was improving and incidence was increasing compared to the second month when neither the KC amplitude nor incidence changed. Future studies might examine the relationship between KC incidences over time and relapse. Greater retention of participants is needed. As shown in Table 1, participant retention rate has been a challenge; no more than 15 participants have been studied over 1 year. Moreover, additional information on male/female ratio at follow-up is needed. In summary, additional data on how many individuals return to drinking over time may expand this line of research.

SUMMARY AND SIGNIFICANCE

In summary, Willoughby and colleagues (2015) provide further evidence of how highly sensitive markers of the effects of alcohol begin to recover in sleep, particularly in the first month after drinking cessation. While the current study did not show significant improvement between the 1 and 3 month visits, there is evidence to suggest that continued recovery of KCs does occur after 1 year of prolonged abstinence (Colrain et al., 2012).

One of the strengths of the study was the use of a unique method to evoke brain characteristics at a time early in abstinence. This method, and respiratory occlusions (Colrain et al., 1999) to evoke KCs during sleep, have been used previously (Bellesi et al., 2014; Colrain et al., 1999, 2012) to assess sleep integrity following alcohol use as well as across aging (Crowley et al., 2002). Whether delivering the tones through earphones (Colrain et al., 1999, 2012; Willoughby et al., 2015) versus speakers (Tasali et al., 2008) is associated with different safety or efficacy profiles may be an area of additional inquiry. A study limitation was the possible influence of other comorbidities present in the AUD sample; 35% of the sample was using other drugs of abuse. No information is known to date about how substances of abuse affect KC incidence or amplitude. This may be an area for further research. Finally, the aforementioned studies provide further insight into the mechanisms of sleep regulation and recovery across early to prolonged abstinence. This may have treatment implications. While a number of randomized placebo-controlled trials have explored how various medications affect PSG characteristics during abstinence (Brower, 2015), additional studies are needed to evaluate whether treatments targeting sleep mechanisms might further hasten biochemical recovery in the brain in individuals with AUD.

In conclusion, future studies will benefit from greater participant recruitment and retention, a larger representation of female participants, excluding participants who are using substances other than alcohol, the addition of subjective sleep reports, and data on concomitant habitual sleep-wake patterns. Considering sleep as a window into the brain's recovery from chronic alcohol use is a novel and rapidly expanding area with many opportunities for growth.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare.

REFERENCES

Armitage R, Hoffmann R, Conroy DA, Arnedt JT, Brower KJ (2012) Effects of a 3-hour sleep delay on sleep homeostasis in alcohol dependent adults. Sleep 35:273–278.

Bellesi M, Riedner B, Garcia-Molina G, Cirelli C, Tononi G (2014) Enhancement of sleep slow waves: underlying mechanisms and practical consequences. Front Syst Neurosci 8:208.

Borbély AA (1982) A two process model of sleep regulation. Hum Neurobiol 1:195–204.

Brower K (2015) Assessment and treatment of insomnia in adult patients with alcohol use disorders. Alcohol 49:417–427.

Brower K, Hoffmann R, Conroy D, Arnedt J, Armitage R (2011) Sleep homeostasis in alcohol-dependent, depressed and healthy control men. Eur Arch Psychiatry Clin Neurosci 261:559–566.

Colrain I (2005) The K-complex: a seven-decade history. Sleep 28:255–273.

Colrain I, Crowley K, Nicholas C, Afifi L, Baker F, Padilla M, Turlington S, Trinder J (2010) Sleep evoked delta frequency responses show a linear decline in amplitude across the adult lifespan. Neurobiol Aging 31:874–883.

Colrain I, Crowley K, Nicholas C, Padilla M, Baker F (2009) The impact of alcoholism on sleep evoked Delta frequency responses. Biol Psychiatry 66:177–184.

Colrain I, Nicholas C, Baker F (2014) Alcohol and the sleeping brain, in *Handbook of Clinical Neurology*, Vol. 125 (Sullivan EV, Pfefferbaum A eds), pp 415–431. Elsevier B.V., Amsterdam, Netherlands.

Colrain I, Padilla M, Baker F (2012) Partial recovery of alcohol dependence-related deficits in sleep evoked potentials following 12 months of abstinence. Front Neurol 3:13.

Colrain I, Webster K, Hirst G (1999) The N550 component of the evoked K-complex: a modality non-specific response? J Sleep Res 8:273–280.

Conroy D, Arnedt J, Brower K, Strobbe S, Consens F, Hoffmann R, Armitage R (2006) Perception of sleep in recovering alcohol dependent patients with insomnia: relationship with future drinking. Alcohol Clin Exp Res 30:1986–1999.

Conroy D, Arnedt J, Brower K, Zucker R (2010) Sleep and substance use and abuse, in *Sleep and Mental Illness* (Pandi-Perumal S, Kramer M eds), pp 341–351. Cambridge University Press, New York, NY.

Crowley K, Trinder J, Colrain I (2002) An examination of evoked K-complex amplitude and frequency of occurrences in the elderly. J Sleep Res 11:129–140.

De Gennaro L, Ferrara M, Bertini M (2000) The spontaneous K-complex during stage 2 sleep: is it the 'forerunner' of delta waves? Neurosci Lett 291:41–43.

Garland E, Franken I, Howard M (2012) Cue-elicited heart rate variability and attentional bias predict alcohol relapse following treatment. Psychopharmacology 222:17–26.

Nicholas C, Sullivan E, Pfefferbaum A, Trinder J, Colrain I (2002) The effects of alcoholism on auditory evoked potentials during sleep. J Sleep Res 11:247–253.

Tasali E, Leproult R, Ehrmann D, Van Cauter E (2008) Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci USA 22:1044–1049.

Wagman A, Allen R (1975) Effects of alcohol ingestion and abstinence on slow wave sleep of alcoholics. Adv Exp Med Biol 59:453–466.

Willoughby A, de Zambotti M, Baker F, Colrain I (2015) Partial K-complex recovery following short-term abstinence in individuals with alcohol use disorder. Alcohol Clin Exp Res 39:1417–1424.

de Zambotti M, Baker F, Sugarbaker D, Nicholas C, Trinder J, Colrain I (2014) Poor autonomic nervous system functioning during sleep in recently detoxified alcohol-dependent men and women. Alcohol Clin Exp Res 38:1373–1380.

de Zambotti M, Willoughby A, Baker F, Sugarbaker D, Colrain I (2015) Cardiac autonomic function during sleep: effects of alcohol dependence and evidence of partial recovery with abstinence. Alcohol 49:409–415.