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Using sleep as a window into early brain recovery from alcoholism

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Abstract

Chronic alcohol abuse and dependence can affect many of the neurotransmitters involved in sleep –wake regulation. Polysomnography (PSG) and electrophysiology (EEG) are useful tools to measure indirectly how the brain is affected by, and recovers from, acute and chronic alcohol use. A specific EEG marker sensitive to these changes is the K-complex (KC), a characteristic of stage 2 sleep, thought to have a protective mechanism from external perturbations of sleep. In their manuscript in the current issue, Willoughby et al found that recently abstinent individuals (mean of 17 days of abstinence) with alcohol use disorder (AUD) had lower KC amplitude and incidence compared with sex- and age-matched controls.

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26 Moreover, the KC amplitude in AUD participants increased significantly from baseline to follow
27 up one month later, but did not change from month 1 to 3. Willoughby et al is one of only a few
28 studies to examine changes in sleep characteristics over time in recovering alcoholics. This
29 commentary reviews the recent work of Willoughby et al in the context of related research and
30 discusses future targets for research.

31

32 ***Introduction***

33 It is now well known that sleep disturbances are highly prevalent during alcohol abuse
34 and dependence. These sleep disturbances persist well into the period of abstinence and may be
35 associated with relapse, for review see Brower (2015). Over at least the last four decades
36 (Wagman and Allen, 1975), researchers have been exploring how withdrawal from alcohol
37 affects sleep by examining electrophysiological characteristics of the sleeping brain.
38 Polysomnographically (PSG) defined sleep stages (macroarchitecture) and specific waveforms
39 (microarchitecture) from the sleep electroencephalogram (EEG) provide a window into the
40 neurochemical changes of the brain induced by alcohol (Brower, 2015, Colrain et al., 2014,
41 Conroy et al., 2010).

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

52 ***The significance of the K Complex***

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

58 Understanding how delta sleep (also referred to as slow wave sleep or N3 sleep) is
59 affected by alcohol is important because slow wave sleep is thought to be an output measure of
60 the key regulating factor of sleep, sleep homeostasis. Sleep homeostasis (process S) along with
61 the circadian process (process C) make up the two major regulating processes of sleep (Borbély,
62 1982). Changes in the characteristics of KCs in sleep may provide valuable insight into the way
63 the brain recovers from alcohol use.

64 *Using sensitive measures to assess changing physiology in sleep during early abstinence*

65 It has been proposed that the incidence and the amplitude of specific components of the
66 KC, e.g. P2, N550 and P900, are sensitive markers of brain recovery from the effects of
67 alcoholism and ageing (Colrain et al., 2009, Nicholas et al., 2002). This is particularly true of
68 the N550 component of the KC, as it is thought to be related to “brain integrity” (Colrain et al.,
69 2009, Colrain et al., 2010). In the current study, the amplitude of the N550 was lower than
70 controls at baseline and increased from baseline to the one month follow up. Although the
71 amplitude did not continue to increase between month 1 to 3, a previous study found that the
72 N550 and P900 amplitudes were higher after an additional 12 months of abstinence (Colrain et
73 al., 2012). Participants in that study had been abstinent between 54 and 405 days, whereas the
74 participants in the current study had only been abstinent 17 days. This provides a glimpse into
75 changes in KC activity at a time even earlier in the abstinence period than previously examined.

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

82 polysomnogram study with concomitant HRV measures, deZambotti et al found that ANS
83 functioning (including elevated heart rate, low total HRV, and low HF during the night) was
84 disrupted in recently abstinent (mean 20 days) alcoholics (de Zambotti et al., 2014). In follow
85 up study, deZambotti and colleagues evaluated HRV during sleep at three time points: baseline,
86 2 month follow up and 4 month follow up (deZambotti et al., 2015). Their follow up study
87 showed that HRV improved across four months, even in those with long-term alcohol
88 dependence.

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

99 ***Do improvements in measures of sleep and autonomic functioning during early abstinence***
100 ***indicate signs of recovery?***

101 The current study concludes that impairments in KC generation in alcohol dependent
102 individuals improve with abstinence. Whether the current findings reflect a global sign of
103 “recovery of sleep” in early abstinence may be a larger question requiring additional research.
104 In earlier work, the authors cautioned against the interpretation that these findings reflect
105 recovery of sleep (Colrain et al., 2012) given that individuals with AUD continue to experience
106 sleep problems well into abstinence. It has been estimated that approximately one quarter of
107 AUD patients will have persistent insomnia despite continued abstinence (Brower, 2015) .
108 Future studies are poised to explore which neurophysiological or ANS markers distinguish the
109 AUD patients that continue to experience insomnia versus those that do not. For this to occur,
110 information on subjective sleep complaints and sleep schedules prior to the testing night are
111 important adjunctive assessments. A previous study found that AUD participants may not

112 perceive the degree to which their sleep is objectively disturbed (Conroy et al., 2006). Future
113 studies may reveal more information about the relationship between objective and subjective
114 changes in sleep in early abstinence.

115 *KC in recovery and relapse*

116 Risk of relapse is often highlighted as one of the major concerns for sleep disturbance in
117 early abstinence. The authors of the current study note in the study limitations that they were
118 unable to determine whether KC recovery predicted relapse rate. Of the total current sample,
119 n=3 (21%) relapsed to alcohol within the first month and n=5 (55%) relapsed between the 1
120 month and 3 month follow up sessions. It is interesting to note that while the numbers are small,
121 fewer individuals relapsed during the first month when KC amplitude was improving and
122 incidence was increasing compared to the second month when neither the KC amplitude nor
123 incidence changed. Future studies are might examine the relationship between KC incidences
124 over time and relapse. Greater retention of participants is needed. As shown in Table 1,
125 participant retention rate has been a challenge; no more than 15 participants have been studied
126 over one year. Moreover, additional information on male/ female ratio at follow up is needed. In
127 summary, additional data on how many individuals return to drinking over time may expand this
128 line of research.

129 *Summary and significance*

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

135 One of the strengths of the study was the use of a unique method to evoke brain
136 characteristics at a time early in abstinence. This method, and respiratory occlusions (Colrain et
137 al., 1999) to evoke KCs during sleep, have been used previously (Bellesi et al., 2014, Colrain et
138 al., 1999, Colrain et al., 2012) to assess sleep integrity following alcohol use as well as across
139 aging (Crowley et al., 2002). Whether delivering the tones through earphones (Colrain et al.,
140 2012, Colrain et al., 1999, Willoughby et al., 2015) versus speakers (Tasali et al., 2008) is

141 associated with different safety or efficacy profiles may be an area of additional inquiry. A study
142 limitation was the possible influence of other comorbidities present in the AUD sample; 35% of
143 the sample was using other drugs of abuse. No information is known to date about how
144 substances of abuse affect KC incidence or amplitude. This may be an area for further research.
145 Finally, the aforementioned studies provide further insight into the mechanisms of sleep
146 regulation and recovery across early to prolonged abstinence. This may have treatment
147 implications. While a number of randomized placebo-controlled trials have explored how various
148 medications affect PSG characteristics during abstinence (Brower, 2015), additional studies are
149 needed to evaluate whether treatments targeting sleep mechanisms might further hasten
150 biochemical recovery in the brain in individuals with AUD.

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

156

157 Conflict of Interest

158 The author has no conflicts of interest to declare.

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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	Sex ^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 et al 2012	B: 42 12 Mo:15	B: 27 12 Mo: 3	52.1 (7.2)	29.3 (6.7)	165.3 (107.7)	1283 (814)	Evoked KCs P200, N550 P900	12	KC amplitude higher at 12 months
Zambotti et al 2015	B: 15 2 Mo: 13 4 Mo: 9	B: 7 ^a	42.3 (8.2)	16.4 (9.0)	23.7 (6.2)	1532 (1323)	HRV, HR, TP, HF _a , HF _{prop} , HF _{pf}	4	Recovery in HR, HF _a and TP from B to 4 months.
Willoughby et al 2015	B: 16 1 Mo: 14 2 Mo: 9	B: 7 ^a	41.6 (8.3)	15.4 (8.73)	17.1 (6.75)	1436 (1268)	Evoked KCs P200, N550 P900	3	KC amplitude increased from B to 1 month; no change 1-2 months.

Legend: ^a Number of females reported at baseline available only. Abbreviations: Heart Rate Variability (HRV), heart rate (HR), total power (TP; an index of total HR variability), high frequency power (HF_a; an index of cardiac vagal modulation), HF proportion of total power (HF_{prop}; an index of sympathovagal balance) and HF peak frequency (HF_{pf}; an index of respiration rate).

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