Eötvös Loránd University, Budapest

Biology Doctorate School, Head: Anna Erdei, DSc

Ethology Doctorate Program, Head: Ádám Miklósi, DSc

The dog as a model-animal in comparative sleep spindle research

Booklet of Thesis

Ivaylo Borislavov Iotchev

Supervisor: Enikő Kubinyi, PhD

Eötvös Loránd University, Department of Ethology

1117 Budapest, Pázmány Péter sétány 1/c

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INTRODUCTION

The canine EEG literature is currently dominated by a focus on sleep macro-structure and epilepsy (Pákozdy et al. 2012; Kis et al. 2017a; Bunford et al. 2018). These constitute holistic brain-state changes, however, that cannot always be traced back to a specific source (Blumenfeld and Taylor 2003). Sleep spindles, due to well-studied underlying mechanisms (Steriade and Llinás 1988), might be a helpful target in increasing the informative value of canine EEG.

Sleep spindles are brief, 1-6 seconds long (Dutertre 1977) bursts in the sigma (9-16 Hz) frequency range (Bódizs et al. 2009), generated during non-REM sleep by the reticular thalamic nucleus (RTN) (Steriade and Llinás 1988). They can be subdivided into a slow (≤ 13 Hz, predominantly found over anteriorly placed channels) and fast (≥ 13 Hz, predominant over central and posterior channels) subtype.

Sleep spindles were found to reflect a variety of capacities and brain states. Mechanistic (Rosanova and Ulrich 2005) and correlational (Gais et al. 2002; Mölle et al. 2009) evidence from humans and rats, support their involvement in memory consolidation. Spindle density (occurrence per minute) increases in response to novel information and these increases predict better recall (Gais et al. 2002). Other changes in spindle attributes were also found to reflect important changes in the brain. Spindle amplitude and occurrence are lower in the elderly (Landolt and Borbély 2001; Crowley et al. 2002; Martin et al. 2012; Gorgoni et al.

2016), while frequency increases (Crowley et al. 2002). Sleep spindles are also reduced in various psychiatric conditions (De Dea et al. 2018; Merikanto et al. 2019). Early development is in turn characterized by increases in fast spindles (Hahn et al. 2018). Finally, sleep spindles are also subject to sexual dimorphism and in particular fast spindle occurrence and frequency are shaped by the menstrual cycle, peaking at the high progesteron luteal phase (Baker et al. 2007; Bódizs 2017).

So far our knowledge of canine sleep spindles has been mostly annecdotal. The few studies mentioning spindles in the dog, refrain from quantifying the events or their relationship with other variables (Petersen et al. 1964; Pákozdy et al. 2012; Kis et al. 2014). Because sleep spindles are not universal in the animal kingdom (Rattenborg et al. 2011; Shein-Idelson et al. 2016) their existence in the dog remains to be demonstrated with more certainty.

Thesis I.: Canine sleep spindles oscillate in the sigma frequency-range and predict recall performance

The sigma (9-16 Hz) frequency range characterizing human sleep spindles (Bódizs et al. 2009) is not assumed to be universal across mammalian species (Steriade and Llinás 1988; Kryger et al. 2011) and contradicting accounts about the frequency of canine spindles are derived from visual inspection (Pákozdy et al. 2012; Kis et al. 2014). One aim was therefore to narrow down the characteristic frequency of canine spindles. Another important goal was to investigate if in dogs exposure

to novel information is associated with an increase in spindles and if spindle occurrence can predict their recall performance. Hypotheses on the possible frequency range of canine spindles were determined a priori, based on the literature, and we employed search criteria validated in humans (Nonclercq et al. 2013).

A data-set previously used to study EEG correlates of learning in the dog (Kis et al. 2017b) was analyzed. Dogs were required to learn new words for familiar commands. Testing performance on the novel words constituted a learning condition, while performance with the old commands was used as a control. A positive, linear association was discovered between detections/minute (density) in the 9-16 Hz range and post-sleep improvement on the novel task, as well as a higher density on the learning condition, compared to the control condition. Female dogs, moreover, displayed both a higher density and novel task improvement. When looking at fast ($\geq$ 13 Hz) and slow ($\leq$ 13 Hz) spindles separately, effects associated with learning were specific to the slow subtype, but sex differences remained significant for each.

Thesis II.: Age and sex differences in the expression of sleep spindles are similar between humans and dogs

Recordings obtained prior experimental manipulation (N = 155 dogs) were analyzed for interindividual differences in spindle features based on sex, reproductive status and age.

Similar to humans the amplitudes of frontally detected slow spindles were lower (Landolt and Borbély 2001; Martin et al. 2012). A decline in centrally detected spindling events (density) resembled a pattern of fast spindle decline associated with pathological aging in humans (Gorgoni et al. 2016), but was specific to slow spindles in the dog. Another age-related change similar to humans was an increase in spindle frequency (Crowley et al. 2002), in dogs expressed for central, fast spindles across all animals and central slow spindles in males. Different from humans, however, older dogs displayed a higher occurrence of frontal, fast spindles.

An interaction between sex and reproductive status concerning associations with fast spindle density and frequency (highest values for intact females) suggest that canine fast spindles might be under similar hormonal modulation as in humans (Baker et al. 2007). Topographic differences resembled those of humans as well (Gibbs and Gibbs 1961), characterized by more fast spindles over central, compared to frontal recording channels.

GENERAL CONCLUSION

The results satisfy criteria of face validity and the broad definition of predictive validity (van der Staay et al. 2009). Arguments for construct validity indirectly emerged from effects of neutering suggesting a similar modulation of fast spindle density and frequency by sexual hormones as in humans and therefore in turn similar generating mechanisms. We

therefore conclude that the dog is a promising model animal for studying sleep spindles. Similarities between human and dog sleep spindles also support the external validity of our instrument for detecting spindles. The reliability of the detection algorithm is supported by replicated results: higher fast spindle denstiy in female dogs and a higher density of frontally detected spindles in old dogs.

PUBLICATIONS

Publications related to the thesis

Iotchev, I. B., Kis, A., Bódizs, R., Van Luijtelaar, G., & Kubinyi, E. (2017). EEG transients in the sigma range during non-REM sleep predict learning in dogs. *Scientific reports*, *7*(1), 12936.

Iotchev, I. B., Kis, A., Turcsán, B., de Lara, D. R. T. F., Reicher, V., & Kubinyi, E. (2019). Age-related differences and sexual dimorphism in canine sleep spindles. *Scientific reports*, *9*(1), 10092.

Other publications

Iotchev, I. B., & van Schie, H. T. (2017). When a model becomes the real thing: A neuro-cognitive account of 'demonic' possession. *Medical hypotheses*, *106*, 35.

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