International Journal of Psychophysiology 97 (2015) 99–107

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Looking for a precursor of spontaneous Sleep Slow Oscillations in human sleep: The role of the sigma activity

Danilo Menicucci [a,1], Andrea Piarulli [b,1], Paolo Allegrini [c], Remo Bedini [c,d], Massimo Bergamasco [b], Marco Laurino [c], Laura Sebastiani [a], Angelo Gemignani [c,d,e,*]

[a] Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, via Savi 10, 56126, Pisa, Italy
[b] Perceptual Robotics Laboratory, Scuola Superiore Sant'Anna, Pisa, via Alamanni 13b, 56010, Pisa, Italy
[c] EXTREME Centre, Institute of Life Sciences, Scuola Superiore Sant'Anna, Piazza Martiri della Libertà 33, 56127, Pisa, Italy
[d] Institute of Clinical Physiology, National Research Council (CNR), via Moruzzi 1, 56124, Pisa, Italy
[e] Department of Surgical, Medical, Molecular and Critical Area Pathology, University of Pisa, via Savi 10, 56126, Pisa, Italy

ARTICLE INFO

Article history:
Received 27 January 2015
Received in revised form 12 May 2015
Accepted 13 May 2015
Available online 21 May 2015

Keywords:
Bistability
NREM sleep
Sleep slow oscillation
Spindle
Sigma band

ABSTRACT

Sleep Slow Oscillations (SSOs), paradigmatic EEG markers of cortical bistability (alternation between cellular downstates and upstates), and sleep spindles, paradigmatic EEG markers of thalamic rhythm, are two hallmarks of sleeping brain. Selective thalamic lesions are reportedly associated to reductions of spindle activity and its spectrum ~14 Hz (sigma), and to alterations of SSO features. This apparent, parallel behavior suggests that thalamo-cortical entrainment favors cortical bistability. Here we investigate temporally-causal associations between thalamic sigma activity and shape, topology, and dynamics of SSOs. We recorded sleep EEG and studied whether spatio-temporal variability of SSO amplitude, negative slope (synchronization in downstate falling) and detection rate are driven by cortical-sigma-activity expression (12–18 Hz), in 3 consecutive 1 s-EEG-epochs preceding each SSO event (Baselines). We analyzed: (i) spatial variability, comparing maps of baseline sigma power and of SSO features, averaged over the first sleep cycle; (ii) event-by-event shape variability, computing for each electrode correlations between baseline sigma power and amplitude/slope of related SSOs; (iii) event-by-event spreading variability, comparing baseline sigma power in electrodes showing an SSO event with the homologous ones, spared by the event. The scalp distribution of baseline sigma power mirrored those of SSO amplitude and slope; event-by-event variability in baseline sigma power was associated with that in SSO amplitude in fronto-central areas; within each SSO event, electrodes involved in cortical bistability presented higher baseline sigma activity than those free of SSO. In conclusion, spatio-temporal variability of thalamocortical entrainment, measured by background sigma activity, is a reliable estimate of the cortical proneness to bistability.

1. Introduction

Electrophysiological studies in animal models have revealed that during Slow Wave Sleep cortical neurons exhibit slow membrane-potential dynamical oscillations. This neuronal behavior is characterized by the coordinated switching of the membrane potential between a state of hyperpolarization (down state) and a state of firing activity with a rate similar to that of wakefulness (up state) (Steriade et al., 1993a; Vyazovskiy et al., 2009). This behavior, called neural bistability, typically lasts slightly more than 1 s and, when it involves a large amount of neurons in a coordinate way, represents the fundamental network phenomenon underlying different slow EEG patterns of Slow Wave Sleep, such as the K-complexes and the Sleep Slow Oscillations (SSO) (Amzica and Steriade, 1998; Massimini et al., 2004; Menicucci et al., 2009). These waves consist of an early positive deflection followed by a sharp negative peak (related to the cellular down state) and by a shallow positive half wave (related to the cellular up state) (Massimini et al., 2004; Menicucci et al., 2013; Laurino et al., 2014). The early positive deflection, spectrally characterized by the concurrent presence of high frequency activities, acts as a wake-like excitation, whose hypothesized role is that of triggering the down state on large scale (Menicucci et al., 2013; Laurino et al., 2014).

The concept that an early excitation favors the transition into the down state has been corroborated both theoretically and experimentally. In general, a perturbation acting on a system with two metastable states can force the transition to the lowest-energy one and this holds true also for the sleeping neurons (Wilson et al., 2006; Frohlich et al., 2006). At a computational level, depolarization-activated K^+ channels have been used to model bistability in the thalamo-cortical system:

Abbreviations: SSO, Sleep Slow Oscillation; NREM sleep, Non-Rapid-Eyes-Movement sleep; FRD, False Discovery Ratio; d.f., degrees of freedom.

* Corresponding author at: Department of Surgery, Medical, Molecular and Critical Area Pathology, University of Pisa, via Paradisa 2, 56124, Pisa, Italy. Tel.: +39 050 315 2686; fax: +39 050 580018.
E-mail address: gemignan@dfb.unipi.it (A. Gemignani).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ijpsycho.2015.05.006
0167-8760/

simulations showed that the amount of depolarization influences the intensity of the K^+ current that induces the down state (Hill and Tononi, 2005). This mechanism has then been experimentally validated in ferret slices (Sanchez-Vives et al., 2010) and indirectly observed in humans. Specifically, Laurino et al. (2014), in a multisensory evoked K-complex experiment, showed that the higher the amplitude of the evoked wake-like excitation (P200), the higher the probability of effectively evoking the down state (N550). In principle, cortical proneness to bistability must depend on (i) the number of activity-dependent K^+ channels and (ii) their opening synchronization (Compte et al., 2003; Vyazovskiy et al., 2009; Sanchez-Vives et al., 2010). At the EEG level, both for SSO and K-complex, these two information are respectively estimated by means of the amplitude of the negative peak and by the "slope 1", i.e. the velocity of reaching the negative peak (Riedner et al., 2007; Laurino et al., 2014). Fig. 1 provides an illustration of the two features for a typical isolated SSO.

Once the aforementioned measures are adopted, it follows that the cortical proneness to bistability in humans displays a spatial variability across cortical areas with an antero-posterior gradient (Massimini et al., 2004; Menicucci et al., 2009). This kind of variability, stemming from averages over a sleep cycle, does not take into account time-varying properties. In general, however, a temporal variability of the proneness may take place, due, in turn, to variability in neural activity. Indeed, each SSO traveling event has its own topology and amplitude (Massimini et al., 2004; Riedner et al., 2007; Menicucci et al., 2009).

These two sources of variability, spatial and temporal, may be respectively associated to differences in anatomical structures, possibly explaining the antero-posterior gradient, and in functional modulations of GABAergic and glutamatergic neurons in the cortex (Steriade, 2000; Shu et al., 2003; Sanchez-Vives et al., 2010; Piantoni et al., 2013a).

Cortical proneness to bistability is influenced by subcortical structures, among which thalamus, up to now, seems to play a crucial role. The recent review of Crunelli and Hughes (2010) describes the emergence of the SSO as the product of the interaction between three cardinal oscillators: the cortical synaptically-based oscillator and two thalamic oscillators, the thalamocortical cells and the reticular thalamic neurons. On this basis,

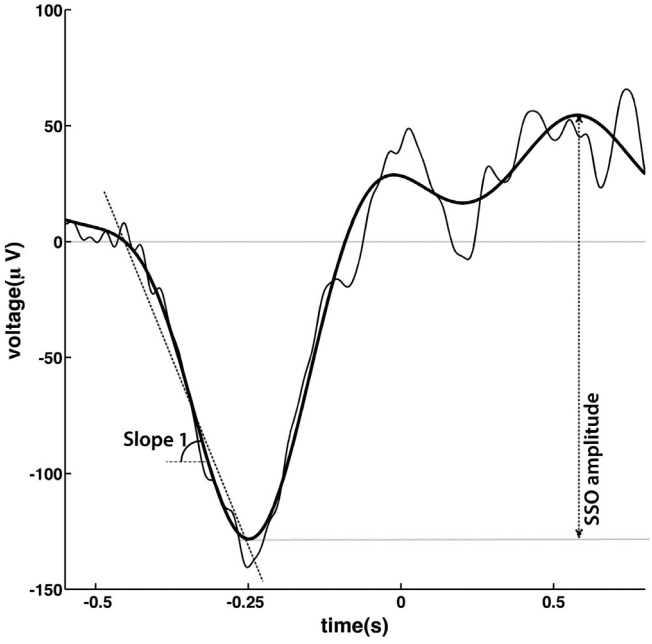

Fig. 1. Graphical definition of the SSO morphological features. The two superimposed lines represent the raw EEG trace of a SSO wave (thin line) and the corresponding delta-band filtered trace (thick line). Each detected wave is characterized by means of the SSO amplitude and the absolute value of the slope between the first zero crossing and the negative peak (slope 1) measured on the filtered signal according to the specifications in the Materials and methods section.

the detection on the cortex of SSO and its coalescing rhythms can only occur when the cortical and thalamic oscillators are entrained (Crunelli et al., 2015).

The contribution of the *thalamo-cortical entrainment* on the generation and synchronization of the cortical SSO has been highlighted or inferred by many studies in vitro (Rigas and Castro-Alamancos, 2007; Hirata and Castro-Alamancos, 2010; Wester and Contreras, 2013) and in vivo (Contreras et al., 1996a; Steriade, 2006; Gemignani et al., 2012; David et al., 2013; Menicucci et al., 2013; Piantoni et al., 2013b; Laurino et al., 2014).

As a recent confirmation of this viewpoint, a paradigmatic sign of thalamo-cortical activity, the sigma rhythm ~14 Hz (Contreras et al., 1996b, 1997; De Gennaro and Ferrara, 2003), was shown to characterize the spectrum of the positive deflection preceding spontaneous down states (Menicucci et al., 2013). More recently, Laurino et al. (2014), stimulating sensory cortices via afferent core thalamic projections, have confirmed the triggering of bistability (Laurino et al., 2014) only if the priming excitatory wave, along its travel towards integrative areas, undergoes a waxing mechanism, possibly thalamically driven. In addition, pathological models of thalamic degeneration and stroke highlight the fundamental role of the thalamo-cortical interaction for the SSO expression (Santamaria et al., 2000; Montagna et al., 2002; Gemignani et al., 2012).

The sigma rhythm observed at the cortical level corresponds to an intra-thalamic resonant activity in which thalamocortical cells are synchronized with the intrinsic oscillatory pattern of reticular thalamic neurons (Fuentealba and Steriade, 2005; Timofeev and Chauvette, 2011). This intra-thalamic activity becomes detectable on the EEG when the excitatory thalamocortical cells fire on their cortical targets (Fuentealba and Steriade, 2005; Timofeev and Chauvette, 2011). The cortex, however, does not play the role of a passive signal receiver but contributes to the within-thalamus synchronization via corticothalamic firing, which excites both reticular thalamic neurons and thalamocortical cells (Contreras et al., 1997; Timofeev and Chauvette, 2011; Bonjean et al., 2011). This cortico-thalamo-cortical entrainment has been reported to explain the occurrence of sigma-rhythm spindles upon the depolarizing phase of the SSO after the down state (Timofeev and Chauvette, 2011).

Notice that the described circuits have been recently proved to only sustain the so-called fast sigma activity (Doran, 2003). Indeed, a lower limit at ~12 Hz for the sigma activity related to *thalamo-cortical entrainment* has been better defined by recent studies on the differential properties of slow (centered around 10 Hz) and fast (centered around 14 Hz) sleep spindles. Indeed, the thalamo-cortical network seems involved only in the generation of fast spindles as they are selectively reduced after blocking low-threshold Ca^{2+}-dependent spike bursts in the reticular thalamic nucleus (Ayoub et al., 2013; Timofeev and Chauvette, 2013).

The aim of the present work is to describe whether the time-dependent proneness to bistability is marked by the presence of sigma rhythm, in other words, whether a pre-existing *thalamo-cortical entrainment* leads to an increase in the expression of SSOs in human EEG.

In order to provide evidence of this link we have studied temporally isolated SSOs and measured the sigma activity seconds before these SSOs (we call this temporal window "baseline").

In the following we report results showing baseline sigma activity as a reliable estimator of cortical proneness to bistability, able to predict SSO structure, mapping and dynamics.

2. Materials and methods

2.1. Subjects and sleep recordings

Ten non-sleep-deprived male volunteers (age 18–30, right-handed according to the Edinburgh Handedness Inventory, EHI) participated in the study. Inclusion criteria were: not taking any medication for at