Schizophrenia Research 155 (2014) 31–38

Contents lists available at ScienceDirect

Schizophrenia Research

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

A microstructural study of sleep instability in drug-naive patients with schizophrenia and healthy controls: Sleep spindles, rapid eye movements, and muscle atonia

Fabian Guénolé [a,1], Élyse Chevrier [a], Emmanuel Stip [c,d], Roger Godbout [a,b,c,d,*]

[a] Sleep laboratory & clinic, Hôpital Rivière-des-Prairies, Montréal, Québec, Canada
[b] Centre de recherche, Hôpital Rivière-des-Prairies, Montréal, Québec, Canada
[c] Research Center, Institut universitaire en santé mentale de Montréal, Montréal, Québec, Canada
[d] Department of Psychiatry, Faculty of Medicine, Université de Montréal, Montréal, Québec, Canada

ARTICLE INFO

Article history:
Received 9 September 2013
Received in revised form 11 March 2014
Accepted 13 March 2014
Available online 13 April 2014

Keywords:
EEG
EMG
EOG
Schizophrenia
Sleep
REM sleep behavior disorder

ABSTRACT

This study aimed at characterizing the functional stability of sleep in schizophrenia by quantifying dissociated stages of sleep (DSS), and to explore their correlation with psychopathology. The sleep of 10 first-break, drug-naive young adults with schizophrenia and 10 controls was recorded. Four basic DSS patterns were scored: 1) the transitional EEG-mixed intermediate stage (EMIS); 2) Rapid-eye-movement (REM) sleep without rapid eye movement (RSWR); 3) REM sleep without atonia (RSWA); and 4) non-REM sleep with rapid eye movements. An intermediate sleep (IS) score was calculated by summing EMIS and RSWR scores, and the durations of intra-REM sleep periods IS (IRSPIS) and IS scored "at the expense" of REM sleep (ISERS) were determined. Patients were administered the Brief Psychiatric Rating Scale (BPRS) at the time of recording. Proportions of each DSS variables over total sleep time and proportions of IRSPIS and ISERS over REM sleep duration were compared between patients and controls. Correlation coefficients between DSS variables and BPRS total scores were calculated. The proportion of total DSS did not differ between patients and controls. Among DSS subtypes, RSWA was significantly increased in patients while other comparisons showed no significant differences. Significant positive correlations were found between BPRS scores and proportions of DSS, IS, RSWR, IRSPIS and ISERS over total sleep and REM sleep durations. These results demonstrate the functional instability of REM sleep in first-break, drug naive young adults with schizophrenia and unveil a pattern reminiscent of REM sleep behavior disorder. The significant correlation suggests that schizophrenia and REM sleep share common neuronal control mechanisms.

1. Introduction

The manifestation of sleep relies on a dynamic interaction between distributed neural networks (Brown et al., 2012). Such networks include those responsible for the circadian alternation of wake and sleep (Fuller et al., 2006; Brown et al., 2012), those responsible for the cyclic alternation between non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Fuller et al., 2006; Saper et al., 2010), and finally those responsible for the organization of NREM sleep and REM sleep themselves (Brown et al., 2012).

NREM sleep normally appears with sleep onset and is divided into four successive stages, corresponding to a progressive slowing and synchronization of the electroencephalogram (EEG) (Rechtschaffen and Kales, 1968). Stage 2 sleep predominates among the NREM stages, and is characterized by two phasic EEG events considered to reflect the activity of sleep protective mechanisms (Bastien et al., 2009; Forget et al., 2011): sleep spindles (bursts of 0.5–5.0 s waveforms) and K-complexes (0.5–1.5 s high-voltage triphasic waves). The generation of sleep spindles involves a sequence of inhibitory GABAergic and excitatory glutamatergic influences onto the thalamocortical loop (Brown et al., 2012); K-complexes are thought to be generated exclusively at the cortical level, with a combination of hyperpolarizing and depolarizing current flows (Cash et al., 2009).

REM sleep cyclically follows NREM sleep, and displays three main conjugate electrophysiological features (Rechtschaffen and Kales, 1968): 1) a desynchronized, mixed-fast EEG activity; 2) rapid eye movements; and 3) muscle atonia. REM sleep desynchronized EEG originates from phasic electrical potentials in the pons, which trigger bursts in cholinergic neurons projecting to thalamocortical networks and basal forebrain (Brown et al., 2012). This activity begins a few dozens of seconds before the onset of REM sleep, i.e., the so-called transitional period, and continues during REM sleep per se (Datta, 1997). Rapid

* Corresponding author at: Sleep Laboratory and Clinic, Hôpital Rivière-des-Prairies, 7070 boul. Perras, Montréal, Québec H1E 1A4, Canada. Tel.: +1 514 323 7260x2657; fax: +1 514 328 3504.
E-mail address: roger.godbout@umontreal.ca (R. Godbout).
[1] Present address: Service de psychiatrie de l'enfant et de l'adolescent, Centre Hospitalier Universitaire de Caen, avenue Clemenceau, 14033 Caen cedex 9 France.

http://dx.doi.org/10.1016/j.schres.2014.03.013
0920-9964/

eye movements occur simultaneously with pontine ascending bursts (Escudero and Marquez-Ruiz, 2008), and are due to action potentials in neurons of the abducens motor nucleus, resulting from inputs in adjacent paramedian reticular formation (Brown et al., 2012). REM sleep muscle atonia is induced by glutamatergic neurons in the laterodorsal tegmental nucleus, via their descending projections to the pre-motor GABA/glycinergic neurons of the ventral gigantocellular reticular nucleus (Luppi et al., 2011). REM sleep generating neurons are located in the dorsolateral pons, with ascending glutamatergic neurons in the laterodorsal tegmental nucleus being responsible for the onset of the REM state (Clément et al., 2011), and positive feedback between cholinergic and glutamatergic reticular neurons stabilizing it (Brown et al., 2012).

The dynamic interaction of sleep-regulating neural networks can be unstable in some physiological or pathological circumstances. To begin, intermediate sleep (IS) is the polysomnographic pattern of the transitional period between NREM sleep and REM sleep, during which EEG shows desynchronized, low voltage and mixed-frequency activity, similar to that found in REM sleep, together with bursts of spindles and/or K-complexes otherwise typical of NREM stage 2 sleep (Ey et al., 1975; Gottesmann, 1996; Salzarulo et al., 1997). IS represents 1 to 10% of sleep in healthy human adults (Goldsteinas et al., 1966; Lairy, 1967; Halasz et al., 1985), and has been conceptualized as sate entailing concomitant manifestation of NREM–REM brainstem and forebrain neural mechanisms (Gottesmann, 1996). More recently, the concept of IS was expanded to include all electrophysiological sleep patterns exhibiting simultaneous occurrence or rapid oscillation of any sleep stages components, coined under the term “dissociated stages of sleep” (DSS) (de Barros-Ferreira and Lairy, 1976; Smith and Cohen, 1988; Mahowald and Schenck, 1992; Salzarulo et al., 1997; Mahowald et al., 2011). DSS reflect various levels of instability within sleep's regulating networks, and can be considered as a marker of dysfunctional binding between brain oscillatory systems (Mahowald et al., 2011). Together with IS, DSS include: 1) REM sleep without rapid eye movement (RSWR), a pattern which is functionally linked to IS (Ey et al., 1975; Gottesmann, 1996); 2) REM sleep without atonia (RSWA), which is found mainly in association with neurodegenerative diseases (Gagnon et al., 2006), and which pathophysiology involves abnormal functioning in several areas of the dorsolateral pons (Luppi et al., 2011); and 3) NREM sleep with rapid eye movement (NRSWR), which is seen in patients under antidepressant medication (Passouant, 1974; Schenck et al., 1992; Armitage et al., 1995).

Sleep in schizophrenia displays dysfunctional binding between brain oscillatory systems (Rockstroh et al., 2007; Vukadinovic, 2011) in association with severe psychopathology, including atypical polysomnographic patterns (Poulin et al., 2003; Chouinard et al., 2004; Benson, 2008) and a high occurrence of IS (Koresko et al., 1963; Lairy et al., 1965, 1968a, 1968b; Lairy, 1967; Salzarulo et al., 1968; Ey et al., 1975; Julien et al., 1980). A recently increasing number of publications also documented disconnections between EEG network components (Roschke et al., 1995; Tekell et al., 2005; Poulin et al., 2008; Ferrarelli et al., 2010), thus opening a window onto neural dynamics by investigating sleep microstructure in schizophrenia. The present paper reports such a microstructural analysis of sleep organization in schizophrenia, aiming at characterizing the frontiers between NREM and REM sleep and their functional stability. We quantified DSS in drug-naive patients with first-episode schizophrenia, in comparison to healthy controls. We hypothesized that DSS scores would: 1) be significantly increased in patients; and 2) correlate with psychopathology.

2. Material and methods

2.1. Participants

Fourteen patients diagnosed with a schizophreniform disorder according to DSM-IV-R criteria (American Psychiatric Association, 2000) gave their informed consent to sleep for two consecutive nights in our sleep laboratory during their first week of hospitalization. None of them had a history of antipsychotic medication and patients using drugs of abuse were excluded. All patients were unmedicated inpatients, controlled for drug-intake. Two patients could not complete a full night of recording and returned to the emergency ward, and four patients could complete only the first night of sleep recording. All patients were experiencing their first acute schizophrenic episode at the time of sleep recording. The Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was administered at the time of sleep recording.

Six months after the first clinical evaluation, the diagnosis of schizophrenia was confirmed by a trained psychiatrist using DSM-IV-R in all but one of the 12 patients who completed at least one night of sleep recording. The data from one of the 11 remaining patients were removed because of his advanced age (64 years old). Thus, the clinical group comprised 5 women and 5 men with a mean age of 24.9 ± 11.1 years (Table 1); this is a subset of the clinical group in a previous publication of ours on sleep patterns in drug-naive, first-episode schizophrenia (Poulin et al., 2003).

The control group included 10 healthy volunteers, 4 women and 6 men, with a mean age of 23 ± 8 years (range 18–42). Exclusion criteria were a personal or first degree relative with a psychiatric or neurological disorder, a complaint of sleep disorder and use of CNS-active drugs.

Control subjects were asked to keep a regular sleep–wake schedule for the 2 weeks preceding the recordings. On the days before recordings, all participants were asked not to nap and not to have caffeine after noon. Bedtime was set at the participant preferred time.

The protocol was approved by the Ethics Committee of the Fernand-Seguin Research Center, Louis-H. Lafontaine Hospital site, in accordance with the Declaration of Helsinki.

2.2. Polysomnographic recordings and scoring

Polysomnographic recordings were performed in individual bedrooms using a Grass Neurodata Model 12 Acquisition System assisted by Eclipse 3.0® software (Stellate Systems, Montreal, Canada). Ten EEG electrodes (Fp1, Fp2, F7, F8, C3, C4, T3, T4, O1 and O2) were applied to the scalp using the 10–20 system (Jasper, 1958). Two electrooculogram (EOG) electrodes were applied, one 1 cm below the left outer cantus and one 1 cm above the right outer cantus. Three surface electromyogram (EMG) electrodes were applied over chin muscles: one midline 1 cm above the inferior edge of the mandible, one 2 cm below the inferior edge of the mandible and 2 cm to the right of the midline and 2 cm below the inferior edge of the mandible and 2 cm to the left of the midline. EEG and EOG electrodes were referenced to linked earlobes (A1 + A2); each reference had a serial 10 KΩ resistor for impedance equilibrium purposes (Pivik et al., 1993). EMG recording was in bipolar mode. Filter settings and amplification factors were as follows: EOG: 1/2 amplitude high pass = 0.1 Hz, 1/2 amplitude low pass = 100 Hz, amplification × 1000 = 20; EMG: 1/2 amplitude high pass = 10 Hz, 1/2 amplitude low pass = 100 Hz,

Table 1
Age, sex, and total BPRS score for each patient.

	Age	Sex	BPRS score
1	23	F	44
2	37	F	–
3	23	M	44
4	18	F	56
5	20	F	42
6	19	M	50
7	54	M	43
8	21	F	53
9	22	M	51
10	24	M	47