

FAST TRACK PAPERS

Sleep architecture in agenesis of the corpus callosum: laboratory assessment of four cases

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SUMMARY Whether the corpus callosum is essential for normal human sleep cannot be decided from current knowledge. We thus studied sleep architecture in four subjects with agenesis of the corpus callosum (ACC) and four control subjects matched for age, gender, and hand preference. All-night EEG, EOG, and EMG activity were monitored in the laboratory for one adaptation night and one data acquisition night. Standard sleep variables were calculated for the second night.

Agenesis subjects were found to have a greater percentage of stage 3 + 4 sleep and a lower percentage of stage 2 sleep than control subjects. Agensis subjects also tended to have more REM sleep periods and a shorter REM cycle length than controls.

The pattern of results is similar to that produced by partial callosotomy. It is also relevant to two hypotheses about the function of the corpus callosum in sleep. First, the corpus callosum may facilitate synchronization of activity between homologous regions in the two hemispheres but interfere with synchronization of neuronal populations within each hemisphere. Its absence may thus explain both an augmentation of slow-wave activity (and thus more slow-wave sleep) and a decrease in interhemispheric EEG coherence. Secondly, the corpus callosum may play a role in the regulation of the ultradian rhythm which underlies timing and duration of REM sleep.

KEYWORDS agenesis of the corpus callosum, cortical synchronization, REM sleep, slow-wave sleep, ultradian rhythms

INTRODUCTION

Experimental study of agenesis of the corpus callosum (ACC) in human subjects has shed considerable light on the functional and developmental status of the corpus callosum (e.g. Jeeves 1986; Lassonde *et al.* 1988; Lassonde *et al.* 1991). However, little is yet known about how sleep is affected by chronic absence of the corpus callosum or about the functions of the corpus callosum in normal human sleep.

An early study with cats (Berlucchi 1965) revealed that callosal activity is typically reduced during sleep, especially

during desynchronized or REM sleep. The exception to this reduction is the occurrence of periodic phasic bursts of activity concomitant with stage 2 spindles and REM sleep eye movements. However, the results of this study of sleep in cats are not necessary compatible with those of human sleep. Human studies typically suggest that callosal activity—as measured by the interhemispheric EEG coherence function—is greater during all stages of sleep than during wakefulness (e.g. Dumermuth *et al.* 1981, 1983; Banquet, 1983; Nielsen *et al.* 1990).

Specific effects of an absence of the corpus callosum on the architecture of human sleep are also not well known. One group has reported disturbed sleep in two megalencephalic subjects with ACC; both showed restricted percentage of REM sleep, and one a virtual absence of

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stages 3 and 4 sleep (Lynn *et al.* 1980). By comparison, a study of sleep in one partial callosotomy subject in our laboratory (Côte 1986; Montplaisir *et al.* 1990) found that posterior section of the corpus callosum led to a decrease in stage 2 sleep time, an increase in stage 3 + 4 sleep time, and no change in REM sleep.

To summarize, the question of whether and how the corpus callosum may be implicated in normal sleep cannot be decided definitely on the basis of current knowledge. We therefore undertook to further explore the role of the corpus callosum in human sleep by assessing the sleep profiles of four subjects with ACC and four subjects matched for age, gender and hand preference.

SUBJECTS

Two male and two female subjects with ACC (age range: 17–29, $M = 23.0$ years) and four age- and gender-matched controls (age range: 18–32, $M = 24.5$ years) were studied. Three of the acallosal subjects (MG, LG, and SG) are siblings in a French-Canadian family of four children. Additional information concerning the psychiatric, neuropsychological, and cognitive status of these subjects has been described extensively elsewhere (Sauerwein *et al.* 1981; Sauerwein *et al.* 1983; Lassonde *et al.* 1988; Lassonde *et al.* 1991). Diagnoses of ACC in all cases were confirmed using computerized axial tomography (CAT) scan and/or nuclear magnetic resonance imaging (MRI).

Case 1. MG, a 19-year-old left-handed male, is the youngest of the family. He scored a full-scale IQ of 77 (Verbal: 71, Performance: 87) on a French version of the WAIS-R. At age 4 he was seen in neurology because of chronic enuresis and other motor and language difficulties. He attended special classes for children with learning disabilities and is presently unemployed.

Case 2. LG, a 27-year-old right-handed female, is the second child of the family. She has a full-scale IQ of 78 (Verbal: 81, Performance: 81) on the Ottawa-Wechsler scale. She had a premature birth, and at age 6 exhibited a temporary mutism and ataxia which prompted neurological examination. She is married, has a child and is gainfully employed.

Case 3. SG, a 29-year-old right-handed woman, is the second of four children and the sister of MG and LG described above. Her history was unremarkable apart from a slow acquisition of walking. She has a global IQ of 84 (Verbal: 88, Performance: 82) on the revised WAIS, has finished high school and works part-time in a home for the elderly.

Case 4. SB, a 17-year-old right-handed male, was adopted at 6 months. His development was slow and he started absence seizures accompanied by manual and buccal automatisms at

age 6. He is dyslexic and his seizures are presently well-controlled with Carbamazepine. He scored 68 on the global IQ of the WISC-R (Verbal: 58, Performance: 81).

Control Subjects. Control subjects were persons known to members of the research team and were recruited informally to match the age, gender, and hand preference of the agensis group. None reported a history of neurological, psychiatric, or sleep problems.

METHODS

Each subject spent two consecutive nights in the sleep laboratory where all-night polysomnograms were recorded according to the 10–20 EEG montage (Jasper 1958) and the standard, EEG, EOG, and EMG montage for sleep staging (Rechtschaffen *et al.* 1968). Subjects were awakened from the last REM period of both nights to report dream mentation; the results of these analyses are not reported here. The first night of sleep was for adaptation to the laboratory and was not considered further. Records for the second night were visually scored and coded by an experienced technician and the following standard sleep parameters calculated: total sleep time (TST); number of awakenings, sleep efficiency, REM sleep efficiency, number of REM sleep periods, sleep latency, latency to stages 1, 2, 3, 4 and REM sleep, time and percent (of TST) of awake and stages 1, 2, 3 + 4, and REM sleep, and length of the REM cycle. Mean scores were calculated for each subject and statistical estimates of group differences were calculated with *t*-tests.

RESULTS

Two major differences between the sleep profiles of the acallosal and control subjects were found (Table 1). First, several variables indicated differences in the occurrence of slow wave sleep. Acallosal subjects spent more minutes in stages 3 + 4 sleep ($M = 122.3$) than controls ($M = 84.9$; $t_{(6)} = 2.61$, $P = 0.04$); this difference also approached significance when expressed as a percentage of TST ($M = 25.6$ vs $M = 16.6$; $t_{(6)} = 2.14$, $P = 0.08$). A similar effect was observed for each subject when individually compared with his/her matched control. A complementary difference was observed for stage 2 time ($t_{(6)} = -2.36$, $P = 0.06$) and percent ($t_{(6)} = -4.38$, $P = 0.005$). Again, the effect was observed for each subject when individually compared with his/her control.

Second, two variables suggested an alteration of the ultradian biorhythm in ACC. There was a tendency for acallosal subjects to have more REM sleep periods ($M = 5.8$) than controls ($M = 4.5$; $t_{(6)} = 2.24$, $P = 0.07$), a trend that was not diminished by controlling for TST ($t_{(6)} = 2.14$, $P = 0.08$). There was also a tendency for the mean duration of the REM sleep cycle to be shorter for acallosal subjects ($M = 84.0$) than for controls ($M = 100.2$; $t_{(6)} = -2.12$, $P = 0.08$).

Table 1 Comparisons of the sleep architecture of subjects with agenesis of the corpus callosum and controls.

Sleep variable	Agenesis			Control			p
	Mean	±	s.d.	Mean	±	s.d.	
Total time in bed	498.5	±	57.2	460.6	±	39.1	—
Total Sleep Time (TST)	506.5	±	52.9	469.8	±	59.6	—
# awakenings	23.8	±	16.1	14.3	±	9.3	—
Sleep efficiency ¹	92.4	±	3.7	96.8	±	4.1	—
Sleep latency	10.1	±	9.8	15.9	±	16.1	—
Stage 1 latency	6.8	±	6.1	14.3	±	14.3	—
Stage 2 latency	17.8	±	9.7	18.2	±	18.3	—
Stage 3 latency	24.7	±	13.5	26.8	±	19.3	—
Stage 4 latency	30.6	±	14.3	51.6	±	52.8	—
REM sleep latency	77.5	±	13.9	88.1	±	26.2	—
Total time awake	40.7	±	21.2	16.4	±	22.3	—
% time awake	7.6	±	3.7	3.2	±	4.1	—
Total time Stage 1	50.4	±	24.5	33.8	±	12.6	—
% time Stage 1	10.2	±	4.5	7.3	±	2.6	—
Total time Stage 2	218.7	±	27.7	252.7	±	8.1	0.056
% time Stage 2	45.3	±	2.8	55.6	±	3.7	0.005
Total time Stage 3 + 4	122.3	±	24.3	84.9	±	15.1	0.040
% time Stage 3 + 4	25.6	±	6.0	18.6	±	2.7	0.076
Total time REM sleep	90.8	±	6.7	86.3	±	26.0	—
% time REM sleep	19.0	±	2.6	18.7	±	4.1	—
REM sleep efficiency ²	83.2	±	3.8	79.0	±	10.9	—
# REM sleep periods	5.8	±	1.0	4.5	±	0.6	0.067
REM cycle duration	83.6	±	5.3	100.1	±	4.5	0.080

¹ Sleep efficiency = (TST/Total time in bed) × 100

² REM sleep efficiency = (Total time REM sleep/TST) × 100

DISCUSSION

There is only a meagre literature on sleep and ACC with which to compare the present results. Two relevant studies both concern subjects who differ in age and clinical history from those participating in the present study, i.e. infant subjects in one study (Kuks *et al.* 1987) and two megalencephalic subjects in the other (Lynn *et al.* 1980). The 35-year old patient in the latter study showed an abnormal absence of stage 3 + 4 sleep (1%); however, his 11-year old son showed a stage 3 and 4 percentage (23%) comparable to the present acallosal group mean of 25.6%.

On the other hand, the present results may be usefully compared to those of a prior study of a patient who underwent posterior partial callosotomy (Côté 1986; Montplaisir *et al.* 1990). Such comparisons reveal that the sleep of acallosal subjects resembles that of the callosotomized patient in two ways. First, callosotomy led to a 19.7% increase in stage 3 + 4 sleep time (from 5.6% to 25.3%) and a corresponding 19.0% decrease in stage 2 sleep time (from 68.0% to 49.0%). The pre-/post-surgery changes are in the same direction as the differences found in the present study. Secondly, the percentages of stages 2 and 3 + 4 post-surgery sleep in the callosotomy patient closely resemble values observed in the acallosal subjects in the present study. Thus, the sleep of both acallosal and partial callosotomy subjects seems to be similarly affected by absence of the corpus callosum, specifically, both are characterized by more stage 3 + 4 and less stage 2 sleep.

The present results thus implicate the corpus callosum in

at least two functions relevant to the regulation of sleep. One is the synchronization of slow waves and may be explained as follows: individual cortical regions receive an initial synchronizing influence from thalamo-cortical projections, particularly from fibres in non-specific intralaminar thalamic nuclei (e.g. Macchi 1990). Intracortical mechanisms further enhance synchronization within limited cortical regions. Contralateral callosal fibres exert a desynchronizing effect on these cortical regions, thereby reducing slow-wave activity and consequently stages 3 and 4 sleep. Nevertheless, the callosal fibres also enhance synchrony between homologous interhemispheric regions. In cases of callosotomy or ACC, local cortical regions will be released from the desynchronizing influence of the callosal fibres, but will no longer be well-synchronized with regions in the opposite hemisphere. The lack of interhemispheric synchrony will appear as lower interhemispheric EEG coherence (Montplaisir *et al.* 1990; Nielsen *et al.*, in press).

A second possible function of the corpus callosum suggested by the present results is that the corpus callosum may play a role in the timing of ultradian biorhythms. Absence of the corpus callosum may disrupt the periodicity of sleep-related processes associated with ultradian pacemakers, producing a rhythm with a higher than normal frequency. The present finding that acallosal subjects tend to have more REM sleep periods and a REM cycle shorter than the normal 90–100-minute ultradian cycle (Kleitman 1963) are consistent with this possibility. Further support for this possibility comes from a previous pilot study (Nielsen *et*

al. 1989) of the Basic Rest-Activity Cycle (BRAC) of 2 of the present acallosal subjects: one subject showed a BRAC periodicity shorter than that of the control subject.

In sum, the present results implicate the corpus callosum in two basic features of sleep architecture: the generation of slow-wave sleep and the timing of ultradian rhythms. However, the results should be interpreted with caution. The small sample size combined with the large number of variables compared severely limits the extent to which the results may be generalized. Furthermore, it should be reemphasized that 3 of the 4 acallosal subjects in this study were genetically related; their results may thus be affected by common inherited factors which influence the proportion of stages 2, 3, and 4 sleep (Lonkowski *et al.* 1989). Notwithstanding these caveats, however, acallosal subjects who also do not suffer from neurological impairments or serious mental deficiencies have a limited availability for this type of research; the present results thus bolster the view that further studies of this rare disorder may provide insights into functioning of the corpus callosum during sleep.

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