Sleep and Wakefulness Affect GABA Levels in the Dorsolateral Prefrontal Cortex

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Introduction

Brain γ-aminobutyric acid (GABA) levels have been measured by MEGA-PRESS [1], with reliable coefficients of variation throughout the day [2]. While this and other brain ^{1}H MRS sequences have been used to study GABA in chronic sleep disorders [3-5], it has not been previously reported whether the act of sleeping itself may affect GABA measurements. Given that the sleep-wake state is generally not controlled for in human studies, we asked whether GABA signals from the left dorsolateral prefrontal cortex (DLPFC) differed during sleep and wakefulness.

Methods

Participants. The local Institutional Review Board approved this study. A total of 5 subjects were recruited. All subjects were healthy and on no medications. Scans occurred around the same time at night (9 P.M.). All participants were experienced scan subjects, instructed to fall asleep for the first (baseline sleeping) portion of the scan, and confirmed to have fallen asleep after the initial, baseline MEGA-PRESS scan. After being awakened, a series of repeated MEGA-PRESS acquisitions were taken during a working memory task to ensure ongoing wakefulness.

Working memory task. To maintain a controlled state of wakefulness during the awake acquisitions, subjects (eyes closed) were presented with an aural Sternberg working memory task, using non-repeating, pseudo-randomly generated strings of 5 or 7 letters and a one-letter probe. Subjects were asked to move the right foot if they thought the probe letter was present in the string; they were instructed to move the left foot if not.

MRS data acquisition. Data were acquired on a Siemens Tim Verio 3T magnet (Erlangen, Germany) running Syngo VB17A, using a 32-channel head coil and a vendor-supplied MEGA-PRESS sequence (TE 71 ms, TR 1800 ms, edit pulse frequency 1.90 ppm, edit pulse bandwidth 43 Hz, 160 averages). After each MEGA-PRESS acquisition, a water-unsuppressed PRESS spectrum was acquired (TE 70 ms, TR 1800 ms, 16 averages). A 4 x 2.5 x 3 cm voxel was placed over the left DLPFC [6]. The duration of each scan pair was 10 min, 19 s. Subjects underwent one or two baseline scans while asleep. In 4 subjects, three MEGA-PRESS scans were repeated while awake. One subject underwent one baseline scan while asleep and 5 repeated scans while awake.

MRS analysis. Spectra were analyzed using LCModel 6.3-1B (Oakville, Ontario) using the provided basis set for MEGA-PRESS, which includes resonances for GABA, glutamate, glutamine, and N-acetylaspartate (NAA). For quality control, a signal-to-residual threshold of ≥20 was used, which except for some of the lower GABA values, yielded Cramér-Rao lower bounds of <20%.

Results

Out of 5 recruited subjects, the data from 4 subjects met quality-control criterion (16 out of 25 scans). Compared to the baseline sleeping state, GABA signals detected by MEGA-PRESS appeared to decline after awakening, and continued to decline during a controlled state of wakefulness (Fig. 1*A*). In contrast, concentration estimates for glutamate and glutamine (Glx; Fig. 1*B*) and NAA (Fig. 1*C*) remained comparatively stable throughout both conditions.

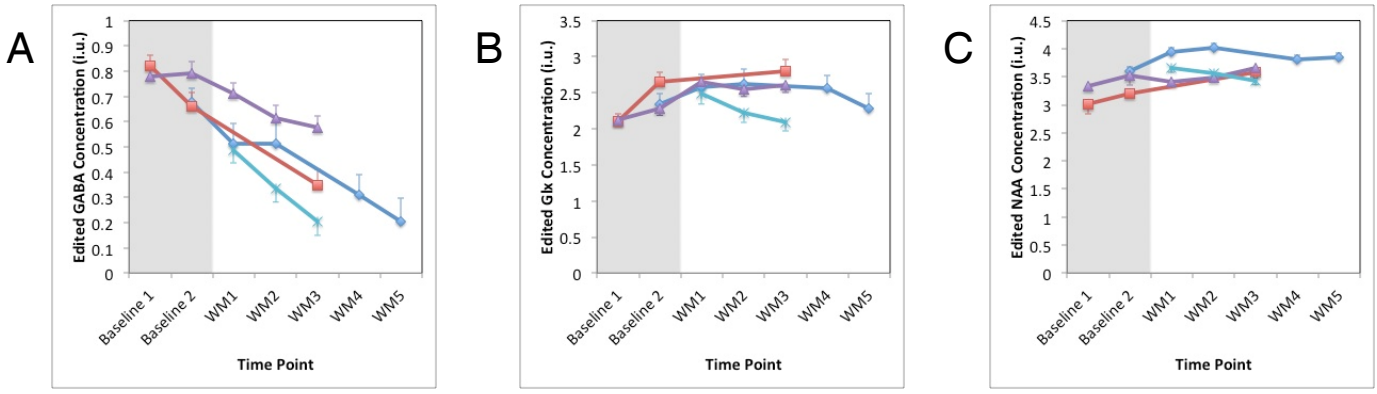

Figure 1. Detected levels of (*A*) GABA, (*B*) Glx, and (*C*) NAA in the left DLPFC during sleep (gray background) and wakefulness (white background). Error bars denote Cramér-Rao lower bounds. *WM*, working memory.

Discussion

Sleep is a distinct physiological phenomenon that depends, in part, on GABA signaling [7]. By controlling for sleep at baseline, this study permits a delineated comparison between sleep and wakefulness. Our observations suggest that increased GABA concentrations may either mediate or result from sleep—and that this increase in GABA can be detected non-invasively. The subsequent decline in GABA levels with continued, controlled wakefulness is also in line with prior work employing a visual Sternberg working memory task [8].

One weakness of this study is its small sample size. Another potential concern would be motion artifact during the awake scans. However, the stability of detected Glx and NAA levels argues against this possibility.

Conclusion

Overall, MEGA-PRESS detection of GABA is sensitive to whether subjects are asleep during scanning. We would recommend controlling for this effect to maximize measurement precision and the power to detect true pathologic changes, especially in studies with inexperienced scan subjects.

References

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