Drowsiness during resting-state fMRI: a major confounder for intrinsic connectivity analysis

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Introduction

- As practiced in human functional MRI, the resting paradigm induces drowsiness despite the noise generated by the scanner[1]. Falling asleep causes respiratory disturbances, such as a decrease in chemoreceptor sensitivity or delay in the feedback loop, leading to instability in the respiratory control system. Periodic breathing, characterized by short hyper and hypoventilation alternations, can occur even under normal physiological conditions in adults[2]. Beyond the loss of vigilance, drowsiness is likely to induce changes in the brain's physiological signal that may impact the resting state intrinsic connectivity.

This work aims to identify cerebral biomarkers of drowsiness and evaluate techniques for correcting functional connectivity differences between subjects fully awake and those falling asleep.

Methods

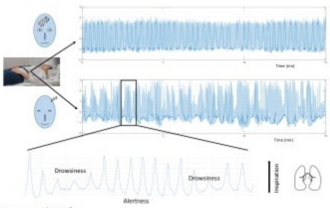
Resting state imaging

- 1870 healthy individuals of the MRI-Share database with eyes closed [3];
- T1-weighted and fMRI (15mn, Tr=850ms, multiband 6, 2.5^3 mm^3 voxel size);
- Recording of 2 physiological parameters: blood volume changes in the microvascular bed of finger tissue (photoplethysmography[4]) and respiration rate (using a thoracis belt).

Vigilance assessment

- We extracted 164 out of 1870 participants whose breathing patterns (Fig.1) show either a continuous pattern of alertness (N=97) or an alternate pattern of drowsiness and alertness (N=66). The top trace of Fig 1. shows breathing cycles of regular frequency and amplitude that are typically observed in awake subject. The bottom trace shows a "periodic breathing" pattern characterized by a regular waxing and waning of breathing amplitude ranging from 25 to 100 s. This pattern is observed, in healthy subjects, at high altitudes or during exercise. It can also be observed in some subjects while falling asleep.

Fig. 1 : Breathing patterns of awake (top) or drowsy (bottom) subject.



Resting state processing

- State-of-the-art standards rs-fMRI data preprocessing[4];
- Quality control markers (Inverse temporal signal to noise ratio: ItSNR and Framewise displacement: FD[5]).

Correction of the effect of the drowsiness

- No correction (NoC);
- Physiological response function (PRF[6]) including RETROICOR[7] ;
- Global normalization (GN) using regression by the whole grey matter BOLD time course.

Biomarkers

- Two BOLD signal markers corresponding to the Regional Homogeneity (ReHo[8]) and amplitude of low-frequency fluctuation (ALFF[9]) were estimated on both cortical cerebral tissue and subcortical nuclei (defined individually using Freesurfer[10]).
- Inter-regional intrinsic connectivity (CoAi) was computed using the AICHA[11] atlas (384 regions) and AvCoAi with the average of 73k CoAis.

Vigilance cross correction analysis

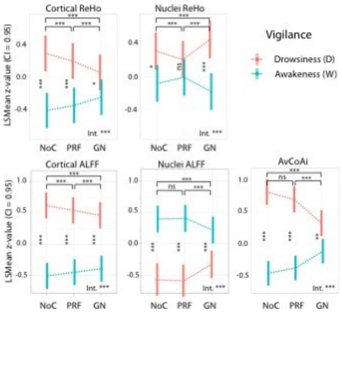
- For the three biomarkers (ReHO, ALFF, and AvCoAi), the significance of the interaction between the correction technique (NoC, PRF and GN) and vigilance (drowsiness, awakeness) was assessed through ANOVA components based on a mixed-effect linear regression model with the random effects fitted at the participant level. All analyses were adjusted for age, sex, and brain volume.
- The vigilance effect was independently computed on CoAis for each of the three correction techniques. Significant differences were reported at a p-value threshold of 0.05 Bonferroni corrected. The results were also synthetized for each AICHA region (# of significant effects including a region).

Results

Uncorrected data

- Vigilance did not induce differences for F.D. (movement) but drowsiness significantly increased itSNR ($p<0.0001$).
- AvCoAi, cortical ReHo and ALFF were significantly higher in drowsy participants than awake ones (Fig 2.).
- Nuclei ALFF was significantly higher in awake participants than in drowsy ones, while the reverse was observed for ReHo (Fig 2.).

Fig. 2 : Vigilance x Correction techniques interaction (Int.) p-bonferroni: ***<0.001, **<0.01, *<0.05



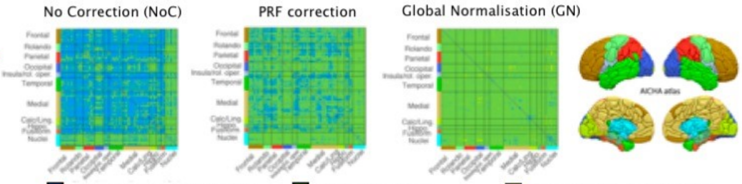
Correction effects

- **PRF** significantly lowered vigilance-induced differences of ReHo and cortical ALFF but not Nuclei ALFF nor AvCoAi (Fig 2.).
- **GN** significantly lowered vigilance-induced differences of AvCoAi, Cortical ReHo and ALFF, Nuclei ALFF, but it increases the Nuclei ReHo (Fig 2.).

Vigilance effect on intrinsic connectivity

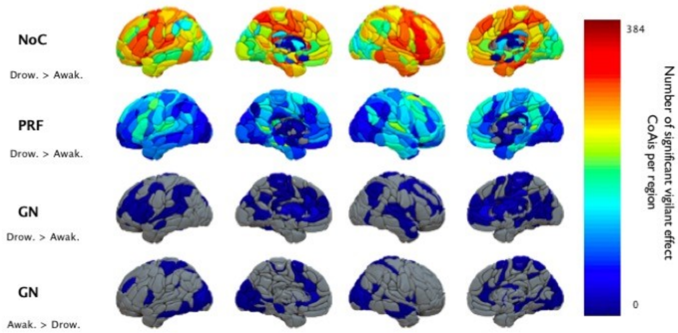
- Regarding CoAis, 59.7% were significantly higher in the drowsiness than awakeness state with NoC (Fig. 3); PRF lowered this number to 22.9%, but only GN corrected almost all differences (1.9%). The CoAis that survived the correction involved at least 30% of nuclei, including the Putamen and Amygdala.

Fig. 3 : Significant vigilance effect on the inter-regional intrinsic connectivity (CoAis) for the 3 types of corrections



- Fig. 4 illustrates the variability of the vigilance effect at the regional level. Without correction, the effect is present in all the cortical regions, being higher in the frontal regions and lower in the occipital lobes. PRF-based correction lowered the vigilance effect in all the cortical regions and the GN-based correction even more. It is only with this latter correction that some CoAis (0.7%) were found higher in awake than drowsy subject, both in regions belonging to visual (in the occipital lobes) and salient networks (both dorsal and ventral[12]).

Fig. 4 : Vigilance effect on the inter-regional intrinsic connectivity synthetized per regions.



Discussion

- Vigilance is a major confounder of intrinsic connectivity.
- In the drowsiness state like in sleep[1], regional and inter-regional correlations were strongly increased, such as the amplitude of the BOLD oscillations and regional homogeneity.
- Regions get a different susceptibility to drowsiness. It is crucial to understand whether it could be attributed to physiological "noise" or neural processes (see poster Kuldavletova ??).
- While state of the art physiological-based correction[6,7], the difference between the two states decreases but is still significant in all the cortical regions.
- Global regression-based correction is the most effective correction method
- After the global normalization, only a few regions show an effect than can be attributed either to the neural impact of the drowsiness or to an imperfect correction.
- The correction highlight some regions in which connectivity is higher in awake than drowsy subjects, notably areas belonging to the salience (dorsal and ventral) networks[12].

Conclusion

- **Global correction is strongly recommended when the vigilance state cannot be established and entered as a confounding factor in the analysis.**
- **Regional differences were uncovered or emphasized by the processing, pointing out a careful interpretation when those regions are involved in a study.**

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