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# Brain fragility among middle-aged and elderly patients from the anaesthesia induction EEG

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1 Cognitive decline (CD) is a common condition amongst elderly, affecting memory, language or thinking. Patients experiencing  
2 CD have a higher incidence rate of post-operative neurocognitive disorders<sup>1</sup>. Moreover, for a fraction of these patients,  
3 occurrence of intra-operative burst-suppressions will result in post-operative delirium<sup>1</sup>. It is therefore important to know early  
4 on patients' cognitive status for adapting anaesthesia and post-operative care. CD is routinely assessed through neurocognitive  
5 evaluation with first onsets occurring around 50 years old, and affecting about 40% of patients<sup>1</sup>. However, with one third of  
6 people over 50 years old programmed for a surgery, a systematic evaluation beforehand is difficult if not impossible in clinical  
7 practice.

8 We propose to take advantage of general anaesthesia (GA) to address this issue; a controlled procedure where the cerebral  
9 activity can be monitored with a frontal ElectroEncephaloGram (EEG). Specifically, propofol-induced GA exhibits a characteristic  
10 EEG signature composed of simultaneous frontal slow (<1 Hz) and  $\alpha$  (8-14Hz) waves with several studies outlining the  
11 association between  $\alpha$  waves and CD or burst-suppressions<sup>2-4</sup>. However, both CD and alpha-wave changes are age-dependent<sup>5</sup>.  
12 In this letter, we proceed with a prospective study, for patient age above 50yo. and for whom the propofol target brain  
13 concentration was systematically set to 5 $\mu$ g/ml during the GA induction.

14 We focus on predicting CD, characterized using the Montreal Cognitive Assessment method (MoCA), performed one day before  
15 GA. From anaesthesia's induction period, we analyse  $\alpha$ -band power ( $\alpha$ Pow) and  $\alpha$  waves transient amplitude decrease: TAD  
16 (Fig 1A-C), the low amplitude components of intra-operative alpha-oscillations that have been shown to predict burst-  
17 suppression onsets<sup>6</sup>. Given the non-stationarity of the EEG signal during the induction period, we tested a dynamic biomarker  
18 (TAD) and compared it to ( $\alpha$ Pow), a standard parameter of EEG spectral analysis.

19 We included 38 patients (69 $\pm$ 10.6yr., 34.2% female), twenty-five underwent an orthopaedic surgery and 13 a neuroradiology  
20 intervention. Patients were divided into two groups: CD (n=18(47%), MoCA < 25 points) and NoCD (n=20(53%), MoCA  $\geq$ 25  
21 points). The total dose of propofol administered during induction and the age were not significantly different between the two  
22 groups (see Table 1).

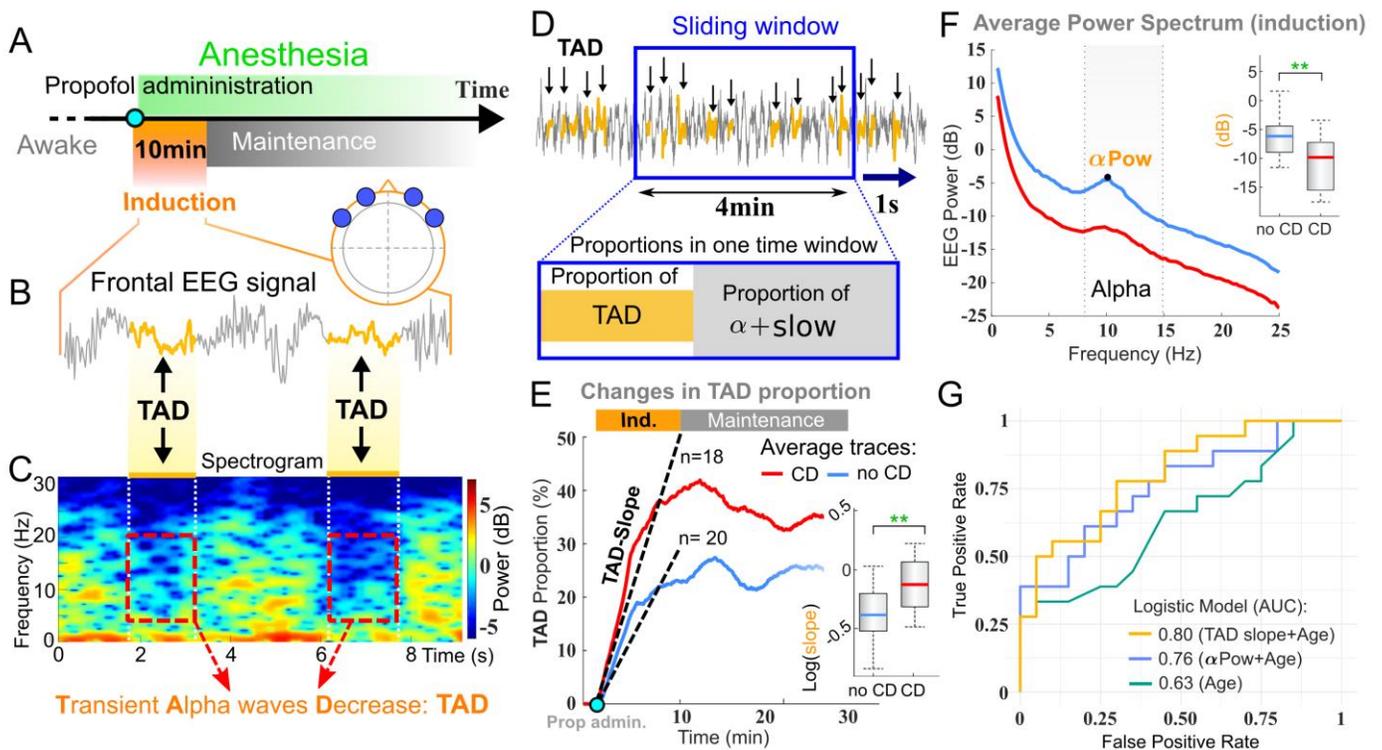
23 Every second, we estimated the fraction of the EEG signal represented by TADs over the last 4 minutes (Fig 1D) and used the  
24 slope of this time series as a variable (TAD-slope, Fig. 1E, dashed-black). We found that: 1.  $\alpha$ Pow and TAD-slope measured during  
25 the first 10 minutes of induction were significantly different between CD and NoCD groups ( $p=0.007$  and  $p=0.004$  respectively,  
26 Fig. 1E,F); 2. A larger TAD-slope was associated with CD (or was a biomarker of CD), independently of age (Adjusted OR =  
27  $4.01[1.44, 11.20]$ ,  $p=0.008$ , AUC = 0.80, logistic model); And 3. A weaker  $\alpha$  Pow was significantly linked with CD  
28 (Adjusted/Corrected OR =  $0.33[0.14, 0.78]$ ,  $p = 0.011$ , AUC = 0.76, Fig. G).

29 In summary, a rapid TAD increase as well as  $\alpha$ Pow decrease measured during the first 10 minutes of a Propofol-induced GA  
30 were associated to lower preoperative MOCA scores. These results confirm previous findings from Giattino, Koch, and recently  
31 Shao and their colleagues, retrospectively linking intra-operative  $\alpha$ -band measured during the maintenance period to pre-  
32 existing cognitive impairments<sup>2-4</sup>. We also confirm that this effect persists independently of patients' age and the dose of  
33 propofol administered during anaesthesia induction. In addition, we show that the EEG brain response to GA, captured during  
34 induction, could be a proxy for CD.

35 Although our study focused on the relationships between alpha-band (maximal alpha power) variables and CD, a larger EEG  
36 database might improve CD detection using multivariate analysis of EEG variables and comorbidities. Furthermore, the  
37 systematic initial  $5\mu g/ml$  target concentration used here would not suit very fragile patients (despite infusion models adapting  
38 for age, sex, height and weight). Thus, further studies should explore the present findings for various propofol TCI.

39 We previously showed that the TAD-slope measured during induction captured patient propensity to burst-suppression<sup>6</sup>. We  
40 now suggest that it also correlates with patient's cognitive status. TAD measured at the beginning of GA might reflect brain  
41 sensitivity to anaesthetics and probably reveal cognitive impairment, while also screening for patients for whom maintaining an  
42 appropriate depth of anaesthesia will be challenging.

43 The present method is not a substitute for a neurocognitive evaluation, but a possible complementary examination for guiding  
44 the post-operative care, optimizing intra-operative anaesthesia or even referring patients to a neurologist.



**Figure 1: Increase of TAD during the 10 first minutes of GA is linked to pre-operative CD.** **A:** Schematic representation of peri-anaesthesia periods. **B:** Example of EEG signal (grey) with two TADs (yellow). **C:** Spectrogram associated to B revealing two spots with low alpha power. **D:** TAD proportion estimation every second using a sliding window. **E:** Time series of TAD proportion. Averaged traces for patient with (red) and without (blue) CD. TAD-slope are shown as black dashed lines. **F:** Average power spectral density for CD (red) and no CD (blue) patients. **G:** ROC curves and their AUC obtained from adjusted logistic models.

**METHODS:** Study PROBRAIN ID NCT0387637, approved by the Société de réanimation de langue française ethics committee CE SRLF 11-356 05/01/2016 (Chairperson Dr Jean Reignier, 48, avenue Claude Vellefaux, Paris, France). Patients were provided an information letter and verbal consent was obtained before anaesthesia. Patient selection, anaesthetic protocol, EEG collection/analysis, MoCA for CD assessment, and  $\alpha$  Pow detection are described in<sup>7</sup>. The TAD-slope was computed then log-transformed using the alpha-suppression pipeline in<sup>6</sup>. The induction period corresponds to the first ten minutes following alpha waves onset. Sample size (n=32) estimated for  $\alpha=0.05$  and  $\beta=85\%$  (OR=3, P0=0.46, R2=0.05, age adjusted logistic models). Two-tailed Mann-Whitney test used for group comparison. For OR estimation,  $\alpha P \leq -13\text{dB}$  were mapped to  $-13\text{dB}$ . Authors declare no conflict of interest. JC-CT-CP-FV design the study and wrote the manuscript. JC-CT-PP-EG-CP-FV analysed and interpreted the data.

**Table 1:** Main characteristics of patients with and without cognitive decline (CD). ‘BS’ Burst-Suppression; ‘αPow’ frontal alpha rhythm power; ‘TAD’ transient alpha decrease, ‘TCI’ target controlled infusion.

Variables	All (n = 38)	CD (n=18)	No CD (n=20)	p
Age (yr.), Mean±SD	69.3±10.7,	72.2±11.8,	66.7±9.2,	0.058
Gender (female), n (%)	13 (34.2%)	7 (38.9%)	6 (30.0%)	0.495
Education level (≤12yr), n(%)	19 (50%)	11 (61%)	8 (40%)	0.194
Hypertension, n(%)	25 (65.8%)	13 (72.2%)	12 (60%)	0.728
Smoker; Obese; Diabetes (%)	5.3; 21.1; 13.1%	11.1; 22.2; 11.1%	10%; 20%; 15%	-
<b>INDUCTION EEG MARKERS (10 FIRST MINUTES)</b>				
TAD-Slope (percentage per min.)	8.9[5.1, 6.5]	11.47[7.5, 8.2]	5.9[4.1, 4.9]	<u>0.004</u>
αPow (dB), Median[IQR]	-8.3[-11.1, -4.9]	-9.9[-15.3, -7.3]	-6.2[-8.8, -4.5]	<u>0.007</u>
Propofol Dose (mg), Median[IQR]	195[187, 208]	194[177, 201]	201[191, 213]	0.058
Time in BS (s), Median[IQR]	5.3[0, 12.3]	10.6[2.2, 93.3]	1.46[0, 8.4]	<u>0.031</u>

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