On assessing neurofeedback effects: should double-blind replace neurophysiological mechanisms?

Thomas Fovet, Jean-Arthur Micoulaud-Franchi, François-Benoît Vialatte, Fabien Lotte, Christophe Daudet, Jean-Marie Batail, Jeremie Mattout, Guilherme Wood, Renaud Jardri, Stefanie Enriquez-Geppert, et al.

On assessing neurofeedback effects:
should double-blind replace neurophysiological mechanisms?

Thomas FOVET[1*], Jean-Arthur MICOULAUD-FRANCHI[2], François-Benoît VIALATTE[3,4], Fabien LOTTE[5], Christophe DAUDET[6], Jean-Marie BATAIL[7], Jérémie MATTOUT[8], Guilherme WOOD[9], Renaud JARDRI[1], Stefanie ENRIQUEZ-GEPPERT[10], Tomas ROS[11]

1 - Univ. Lille, CNRS UMR 9193, Laboratoire de Sciences Cognitives et Sciences Affectives (SCALab-PsyCHIC), F-59000 Lille, France & CHU Lille, Pôle de Psychiatrie, Unité CURE, F-59000 Lille, France
2 - Services d'explorations fonctionnelles du système nerveux, Clinique du sommeil, CHU de Bordeaux, Place Amélie Raba-Leon, 33076 Bordeaux, France & USR CNRS 3413 SANPSY, CHU Pellegrin, Université de Bordeaux, France.
3 - CNRS UMR 8249, Brain Plasticity Unit, Brain-Computer Interface team, 10 rue Vauquelin, 75231 Paris Cedex 05, France.
4 - ESPCI Paris, PSL Research University, 10 rue Vauquelin, 75231 Paris Cedex 05, France.
5 - Inria Bordeaux Sud-Ouest / LaBRI / Univ. Bordeaux / CNRS / IPB – 200 avenue de la vieille tour, 33405, Talence Cedex, France
6 - Université de Bordeaux, 33000 Bordeaux, France.
7 - Academic Psychiatry Department, Centre Hospitalier Guillaume Régnier, Rennes, France ; Inserm, Visages U746, IRISA, Campus de Beaulieu, F-35042 Rennes, France ; "Behavior and Basal Ganglia" research unit (EA 4712), University of Rennes 1, Rennes, France
8 - Brain Dynamics and Cognition Team, Lyon Neuroscience Research Center, INSERM U1028-CNRS UMR5292-University Lyon 1, Lyon F-69000, France
9 - Department of Psychology, Karl-Franzens-University Graz Graz, Austria ;BioTechMed Graz, Austria.
10 - Department of Clinical and Developmental Neuropsychology, University of Groningen, Groningen, the Netherlands
11 - Laboratory Behavioral Neurology and Imaging of Cognition, Department of Neuroscience, University Medical Center and Campus Biotech, Geneva, Switzerland.

* Corresponding author
Dr. Thomas FOVET
Unité hospitalière spécialement aménagée, Chemin du Bois de l'Hôpital, 59113 SECLIN, FRANCE.
E-mail adress: thomas.fovet@chru-lille.fr

***Running title*: On assessing neurofeedback effects**

ABBREVIATIONS

NFB: neurofeedback

SMR: sensorimotor rhythm

Madam, Sir,

We read with great interest the recent article of Schabus et al. entitled "Better than sham? A double-blind placebo-controlled neurofeedback study in primary insomnia" published in *Brain* (Schabus *et al.*, 2017) and its commentary "Neurofeedback or neuroplacebo?" (Thibault *et al.*, 2017). In recent years, EEG-neurofeedback (NFB) has benefited from a revival of interest, although its clinical efficacy remains a controversial and delicate issue (Micoulaud-Franchi and Fovet, 2016; Thibault and Raz, 2016; Sitaram *et al.*, 2017). In the context of a general reproducibility crisis in science (Baker, 2016), we can only be delighted that negative results are being recognised in leading neurology journals such as *Brain*. The findings of Schabus et al. are of great scientific interest, contributing to a stimulating debate in the domain of EEG-NFB. However, we believe that caution is needed before generalizing these results to SMR frequency training as well as the entire field. This is because irrespective of whether results from a single study are positive or negative, "one swallow does not a summer make". Moreover, despite the study's double-blind design, inconsistencies exist between earlier and current results published by the same research group.

It may at first appear surprising that Schabus et al. were not able to replicate some key neurophysiological relationships that have consistently emerged in their previous work. In 2008, with a sample of 27 healthy subjects, the same team demonstrated that 10 NFB sessions of sensorimotor rhythm (SMR, 12-15 Hz) up-regulation was successful in: (1) conditioning an increase in relative SMR amplitude; (2) eliciting positive changes in sleep parameters (sleep spindle number and sleep onset latency); (3) eliciting changes in declarative memory performance (enhancement in retrieval score computed at immediate cued report) (Hoedlmoser *et al.*, 2008). In the same vein, in 2014, Schabus et al. reported in 24 patients with insomnia disorder (4) a positive correlation between SMR-NFB training enhancement, overnight memory consolidation and sleep spindle changes; (5) a significant effect of SMR-NFB on objective sleep quality (a decrease in the number of awakenings, a trend towards decreased sleep onset latency and an increase in slow wave sleep) (Schabus *et al.*, 2014).

Paradoxically, in their double-blind study involving 16 patients with insomnia disorder and 9 patients with misperception insomnia, they did not reproduce a significant effect of SMR-NFB on objective measures of sleep quality neither in the active nor in the placebo group (Schabus *et al.*, 2017). However, in a well-controlled double-blind study unrelated to insomnia, Kober et al. replicated finding (1) and extended (3) from immediate recall to 24-hours delayed response (Kober *et al.*, 2015a). Therefore, the use of double-blind control alone cannot explain all the null-results of Schabus et al. (2017). Definite conclusions can only be drawn on the basis of more solid data.

In particular, we think any discussion of NFB is incomplete without considering its basis from the point of view of *neurophysiological mechanisms*. Indeed, the previously established correlations between post-NFB sleep spindle generation and within-session NFB control highlight key neurophysiological mechanisms that are difficult to be reduced to simple placebo processes and/or a single-blind design (Hoedlmoser *et al.*, 2008; Schabus *et al.*, 2014). From a historical perspective, seminal experiments by Sterman and colleagues (Sterman *et al.*, 1970) were the first to show that waking SMR activity may be operantly-conditioned to be more strongly expressed during subsequent sleep. Since long-term effects manifest in the same direction dictated by the training, a candidate mechanism may be Hebbian plasticity (see (Ros *et al.* 2014) for a review). In fact, a host of other NFB studies indicate a similar Hebbian relationship between within-session and post-session EEG changes (*e.g.* Cho *et al.*, 2008; Zoefel *et al.*, 2011; Engelbregt *et al.*, 2016). Importantly, online control of spectral power is necessary but insufficient as a demonstration of brain plasticity induction (*i.e.* a lasting change outside of the training session). Hence, a crucial question of mechanistic importance is why there was no association between the NFB training in the current study with any change in offline spindle activity and offline SMR activity; as observed twice in the team's previous work (Hoedlmoser *et al.*, 2008; Schabus *et al.*, 2014)?

In that respect, we noticed a potentially important methodological change between their 2008, 2014 and 2017 studies. Each time the authors used a different rule for setting and adapting the reward threshold. They decreased the threshold based on no particular rule in 2008, following "< 5 success in a 3 min block" in 2014, and "< 13 success in a 5 min block" in 2017. We wonder why such changes have been made, since the last two rules are not proportionally related, while in contrast the proportionality between the rules governing the threshold increase were preserved. Since this modification effectively makes the NFB task less challenging, it may have led to a decrease in the SMR activity during the 3-second baseline periods preceding each trial and used as references for each trial when compared with the spontaneous *resting-state* SMR activity of each subject prior to NFB. Hence, given that *Figure 2* only displays percent evoked power *from* this respective 3-second baseline, it is hard to verify whether absolute SMR power during NFB actually exceeded the values of the resting-state activity recorded before the start of NFB training. From a mechanistic standpoint, altering EEG activity significantly from its spontaneous value may be a critical determinant of plasticity induction (Ros *et al.*, 2014). We therefore invite Schabus et al. to clarify this issue by submitting supplementary data providing absolute SMR changes during NFB relative to the initial 2-minute resting-state, unreferenced to the (potentially variable) 3-second baseline(s) before each trial. Interestingly, while changes from baseline roughly score between 115% and 125%, in 2014, in the current study they lie only between 14% and 23%. Such differences may arise by simply using different learning indices, and/or the influence of the experimenter's knowledge/un-blindness; however, they might also reflect differences in NFB learning and ultimately contribute to a reduced impact on brain plasticity.

Finally, and regardless of whether brain plasticity was actually induced by Schabus et al.'s (2017) paradigm, logical reasoning should have restricted Thibault et al. to a simpler claim: that this specific NFB training, for this specific application, was not better than placebo. Instead, they appear to overgeneralize the null findings in the treatment of insomnia to the greater field of EEG-NFB. Such a position appears to us to be more ideological than scientific and contradicts the overall spirit necessary for advancing medical research. By jumping to conclusions, Thibault et al. forget that caution needs to be applied to both positive and negative findings. NFB should be considered as a unique tool for targeting specific neural activities rather than as a panacea for all brain disorders. Successful deployment of NFB critically depends on our knowledge of the brain's inner-workings, which still remains incomplete. Hence, to properly exploit this approach, there is an urgent need for more research in order to both optimize NFB learning (*e.g.* number of trials in a NFB block, threshold rules, number of training sessions) (Micoulaud-Franchi *et al.*, 2016; Enriquez-Geppert *et al.*, 2017) and to select the most appropriate training protocol for each disorder (Kober *et al.*, 2015b).

In conclusion, the negative findings published by Schabus et al. excitingly generate more questions than answers for the field. Moreover, the last fifty years since NFB's discovery cannot be considered a homogenous record, given several decades of relative dormancy in terms of research output, before a resurgence in the early 2000s. Hence, these results call for more research rather than less, including a deeper exploration of the neural mechanisms and methodological nuances emerging from this embryonic field - preferably before premature launches of double-blind clinical studies. It is more conceivable that the story of NFB is a simple reflection of the general scientific process, which, through its twists and turns, remains in the safer judgement of posterity.

DECLARATION OF INTERESTS

FBV received funding from the company *Urgotech* (France) to investigate neurofeedback, however this sponsor had no involvement in the preparation of this letter.

TF, JAMF, FL, CD, JMB, JM, GW, RJ, SEG and TR declare no conflict of interest.

REFERENCES

Baker M. Reproducibility: Seek out stronger science. Nature 2016; 537: 703–704.

Cho MK, Jang HS, Jeong S-H, Jang I-S, Choi B-J, Lee M-GT. Alpha neurofeedback improves the maintaining ability of alpha activity. Neuroreport 2008; 19: 315–317.

Engelbregt HJ, Keeser D, van Eijk L, Suiker EM, Eichhorn D, Karch S, et al. Short and long-term effects of sham-controlled prefrontal EEG-neurofeedback training in healthy subjects. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 2016; 127: 1931–1937.

Enriquez-Geppert S, Huster RJ, Herrmann CS. EEG-Neurofeedback as a Tool to Modulate Cognition and Behavior: A Review Tutorial. Front. Hum. Neurosci. 2017; 11.

Hoedlmoser K, Pecherstorfer T, Gruber G, Anderer P, Doppelmayr M, Klimesch W, et al. Instrumental conditioning of human sensorimotor rhythm (12-15 Hz) and its impact on sleep as well as declarative learning. Sleep 2008; 31: 1401–1408.

Kober SE, Witte M, Stangl M, Väljamäe A, Neuper C, Wood G. Shutting down sensorimotor interference unblocks the networks for stimulus processing: An SMR neurofeedback training study. Clin. Neurophysiol. 2015a; 126: 82–95.

Kober SE, Schweiger D, Witte M, Reichert JL, Grieshofer P, Neuper C, et al. Specific effects of EEG based neurofeedback training on memory functions in post-stroke victims. J. Neuroengineering Rehabil. 2015b; 12: 107.

Micoulaud-Franchi J-A, Fovet T. Neurofeedback: time needed for a promising non-pharmacological therapeutic method. Lancet Psychiatry 2016; 3: e16.

Micoulaud-Franchi J-A, Salvo F, Bioulac S, Fovet T. Neurofeedback in Attention-Deficit/Hyperactivity Disorder: Efficacy. J. Am. Acad. Child Adolesc. Psychiatry 2016; 55: 1091–1092.

Ros T, J Baars B, Lanius RA, Vuilleumier P. Tuning pathological brain oscillations with neurofeedback: a systems neuroscience framework. Front. Hum. Neurosci. 2014; 8: 1008.

Schabus M, Griessenberger H, Gnjezda M-T, Heib DPJ, Wislowska M, Hoedlmoser K. Better than sham? A double-blind placebo-controlled neurofeedback study in primary insomnia. Brain J. Neurol. 2017; 140: 1041–1052.

Schabus M, Heib DPJ, Lechinger J, Griessenberger H, Klimesch W, Pawlizki A, et al. Enhancing sleep quality and memory in insomnia using instrumental sensorimotor rhythm conditioning. Biol. Psychol. 2014; 95: 126–134.

Sitaram R, Ros T, Stoeckel L, Haller S, Scharnowski F, Lewis-Peacock J, et al. Closed-loop brain training: the science of neurofeedback. Nat. Rev. Neurosci. 2017; 18: 86–100.

Sterman MB, Howe RC, Macdonald LR. Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. Science 1970; 167: 1146–1148.

Thibault RT, Lifshitz M, Raz A. Neurofeedback or neuroplacebo? Brain 2017; 140: 862–864.

Thibault RT, Raz A. When can neurofeedback join the clinical armamentarium? Lancet Psychiatry 2016; 3: 497–498.

Zoefel B, Huster RJ, Herrmann CS. Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. NeuroImage 2011; 54: 1427–1431.