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Placebo hampers ability to self-regulate brain activity: A double-blind sham-controlled neurofeedback study

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ABSTRACT

It is still poorly understood how unspecific effects peripheral to the supposed action mechanism of neurofeedback (NF) influence the ability to self-regulate one's own brain signals. Recently, skeptical researchers have even attributed the lion's part of therapeutic outcomes of NF to placebo and other psychosocial factors. Here, we investigated whether and by which mechanisms unspecific factors influence neural self-regulation during NF. To manipulate the impact of unspecific influences on NF performance, we used a sham transcranial direct current stimulation (tDCS) as active placebo intervention suggesting positive effects on NF performance. Our results show that the expectation of receiving brain stimulation, which should boost neural self-regulation, interferes with the ability to self-regulate the sensorimotor rhythm in the EEG. Hence, these results provide evidence that placebo reduces NF performance, and thereby challenge current theories on unspecific effects related to NF.

In Neurofeedback (NF) applications, brain signals are recorded, processed in real-time and fed back to the user with the aim of improving motor functions, cognitive performance, emotional regulation or behavior (Gruzelier, 2014a; Kropotov, 2009; Wolpaw et al., 2002). Most research in this field focused on specific effects of engineering factors on the ability to modulate one's own brain activity during NF training and its outcome (Gruzelier, 2014b; Kober et al., 2016, 2018; Lotte et al., 2007; Neuper and Pfurtscheller, 2010). Beyond engineering, new studies suggest that unspecific influences peripheral to the supposed action mechanism of NF may account for a substantial part or in some cases even for the entirety of NF effects (Blankertz et al., 2010; Halder et al., 2013; Hammer et al., 2012; Kleih et al., 2010a; Kober et al., 2013; Kübler et al., 2004; Neuper and Pfurtscheller, 2010; Nijboer et al., 2008; Witte et al., 2013). For instance, there is evidence that motivation or subjective control beliefs affect the ability to self-regulate one's own brain activity (Kleih et al., 2010a; Witte et al., 2013).

Understanding specific and unspecific effects is crucial for the practical application of NF. Recently, it has been controversially discussed whether NF itself is a kind of placebo or not (Fovet et al., 2017; Schabus et al., 2017; Thibault et al., 2017; Witte et al., 2018). On the one hand, a large number of studies has reported clinical benefits and validation of cognitive and/or affective gains in healthy participants after NF training (Gruzelier, 2014a; Kober et al., 2015b, 2015c; Kropotov, 2009). On the other hand, NF has been put on a level with “neuroenchantment” (Thibault et al., 2017). Thibault et al. (2017) even describe NF as a “superplacebo”, defined as a treatment that is actually a placebo although neither the experimenter/practitioner nor the NF user is aware of the absence of its effectiveness. Placebo effects of NF may be therapeutically more valuable than the specific effects of neural self-regulation themselves (Thibault et al., 2017). If NF exerts its effects via unspecific placebo effects, why spending a large amount of money to use expensive EEG equipment for NF training rather than buying a cheap hair-dryer that looks like cutting-edge technological equipment suggesting the NF users that this hair-dryer will lead to specific improvements (Ali et al., 2014)?

Placebo interventions indeed affect hemodynamic and electrical brain activity as well as connectivity (Beauregard, 2007; Meyer et al., 2015; Schienle et al., 2014a, 2014b; Volkow et al., 2006; Wager et al., 2011; Wager, 2005). Prior fMRI studies reported on increased

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connectivity between frontal and more posterior sites after different placebo interventions (Schienle et al., 2014a, 2017; Wager et al., 2011). Moreover, Meyer et al. (2015) found a placebo intervention to increase connectivity between frontal and more posterior brain areas recorded with EEG (Meyer et al., 2015). In contrast, up-regulation of the EEG sensorimotor rhythm (SMR, 12–15 Hz) by means of NF training reduces the connectivity between central and more posterior brain areas (Kober et al., 2015c; Pfurtscheller, 1992; Sterman, 2000b, 1996). Therefore, placebo effects and SMR up-regulation seem to modulate brain connectivity patterns in opposite directions and the existence of interactions between both effects is unclear.

These contradictory findings call for a more precise investigation of the effects of placebo (Raz and Michels, 2007) on NF results to determine the extent to which training outcomes are due to neural self-regulation or some unspecific aspect of NF training. Accordingly, in a first step one has to determine whether placebo treatments interfere with the ability to self-regulate brain signals. In the present study, we used a sham transcranial direct current stimulation (tDCS) as placebo intervention, which was applied directly before one session of NF training, to manipulate expectations of participants concerning their ability to self-regulate their own brain signals during NF (Wager, 2005). Hence, we investigated the effects of a placebo intervention on the ability to control one's own brain activity.

To test unspecific effects on the NF performance, half of our participants received a sham tDCS as placebo intervention before NF training. The other half received no intervention before NF. Participants are generally not able to distinguish between active and sham tDCS (Palm et al., 2013). A cover story suggested positive effects of tDCS on the capacity to control one's own brain activation during the subsequent NF training. Most placebo studies that report on significant placebo effects use pills (Price et al., 2008; Shapiro and Shapiro, 1997). The type of placebo intervention influences the strength of placebo effects. For instance, colored pills work better than white ones, the larger the pill the stronger the effects, expensive pills work better than cheap ones, and two pills are better than one (Raz and Harris, 2016; Thibault et al., 2017). Even the clothes of the experimenter turned out to influence placebo effects (Schienle et al., 2014a, 2014b). Generally, there is evidence that placebo effects induced by medical devices (such as a needle or technical equipment) are as strong or even superior to orally administered placebo pills. Hence, sham tDCS was an optimal placebo intervention for the purpose of our study (Turi et al., 2017). Using sham tDCS, we could manipulate unspecific influences on NF performance, and this manipulation was active, controllable, and comparable across participants receiving sham tDCS.

Concerning the effects of a placebo intervention on the ability to up-regulate SMR during NF, three different outcomes are likely. First, placebo may hamper the ability to up-regulate SMR given the opposing effects on brain connectivity (placebo should increase connectivity (Meyer et al., 2015) while SMR up-regulation should reduce brain connectivity (Kober et al., 2015c; Reichert et al., 2016; Sterman, 2000b, 1996). Second, if the brain networks involved are independent from each other, no negative effects of a placebo intervention on the ability to up-regulate SMR are expected. Third, if the involved brain networks do not interfere with each other, even positive effects of placebo on the NF performance due to motivation, expectation, or suggestion are likely (Thibault et al., 2017). For instance, there is evidence that participants' motivation is associated positively with the ability to modulate one's own brain activity (Kleih et al., 2010b). A placebo intervention may thus influence motivation and expectancies of participants in a way boosting NF learning (Colagiuri et al., 2011).

Besides our main research question addressing placebo effects on NF performance, we investigated whether placebo effects differ depending on the NF training protocol used (see Fig. 1, study design). Therefore, we used two different NF training protocols: Half of all participants should enhance (SMR up-regulation NF) and the other half should reduce (SMR down-regulation NF) the sensorimotor rhythm (SMR, 12–15 Hz) over central brain areas (Cz) recorded with EEG. Investigating SMR up- and down-regulation groups can help to answer the question whether possible placebo effects are independent of the used NF protocol or protocol specific. Additionally, half of all groups received real NF, while the others did not get real feedback about their own brain activity during NF training. Instead, they saw a video of another participant's EEG recording, which is called sham NF (Kober et al., 2015c). The sham groups should not be able to modulate SMR activity voluntarily during NF training (Kober et al., 2015c).

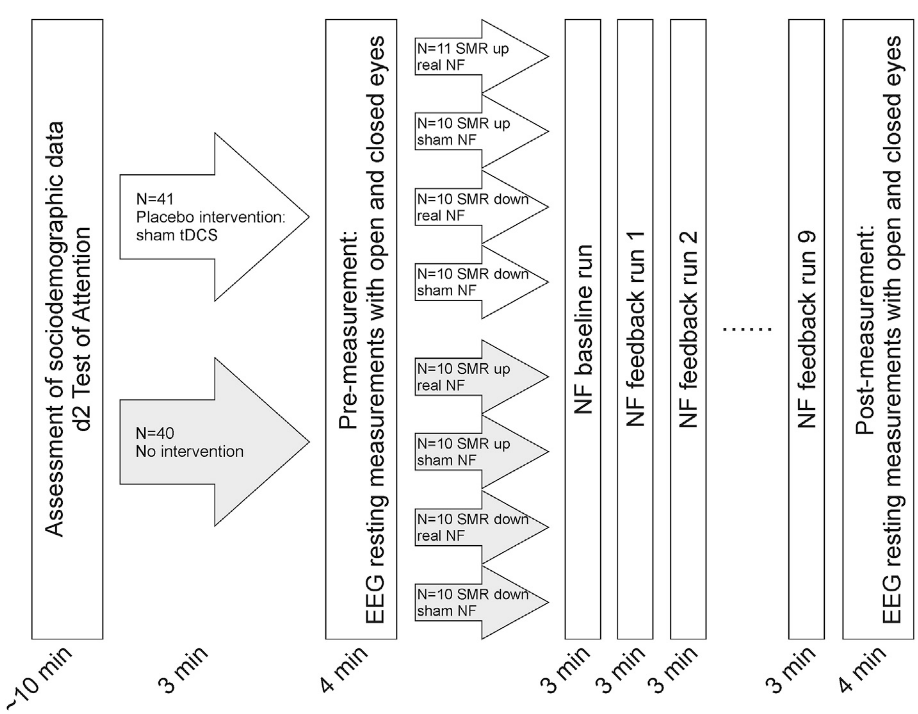

Fig. 1. Procedure and study design. After filing out questionnaires assessing sociodemographic and personal data and the d2 Test of Attention, participants were split up in placebo groups receiving sham tDCS and groups that received no placebo intervention. Then all groups performed resting EEG measurements. The placebo and no placebo groups were split up again in groups receiving either real or sham NF and groups that trained to increase or decrease SMR during NF training. In sum, eight different groups were tested. The NF training consisted of a 3-min baseline run and nine 3-min feedback runs. After the NF training, the EEG resting measurements were performed again.