EFFECTS OF SOMATOSENSORY ALPHA NEUROFEEDBACK TRAINING ON STIMULATION-INDUCED TACTILE LEARNING

by

Marion Brickwedde

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I certify herewith that the dissertation included here was completed and written independently by me and without outside assistance. References to the work and theories of others have been cited and acknowledged completely and correctly. The “Guidelines for Good Scientific Practice” according to § 9, Sec. 3 of the PhD regulations of the International Graduate School of Neuroscience were adhered to. This work has never been submitted in this, or a similar form, at this or any other domestic or foreign institution of higher learning as a dissertation.

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PhD Commission

Chair: Prof. Dr. Stefan Herlitze

1st Internal Examiner: PD Dr. Hubert Dinse

2nd Internal Examiner: PD Dr. Dirk Jancke

External Examiner: Prof. Dr. Guilherme Wood

Non-Specialist: PD Dr. Thorsten Müller

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II. List of Abbreviations

2PD – two-point discrimination task

ADHD – attention deficit hyperactivity disorder

AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

BDNF – neurotrophic factor gene

CaMKII – Ca2+/CaM-dependent protein kinase II

BCI – brain computer interface

BOLD - blood-oxygen-level dependent

EEG – electroencephalography

ERD – event-related desynchronization

ERS – event-related dynchronization

eRSS – electrical repetitive sensory stimulation

fMRI - functional magnetic resonance imaging

GABA - gamma-amino butyric acid

GOT – grating orientation task

ICC – Intraclass correlation

ITPC – inter-trial phase coherence

LTP - long-term potentiation

LTD - long-term depression

NF – neurofeedback

NF-PR – neurofeedback-paradoxical responder

NMDA - N-methyl-D-aspartate

PPS - paired-pulse suppression

PTSD – post-traumatic stress disorder

pRSS – pneumatic repetitive sensory stimulation

RSS – repetitive sensory stimulation

SI – primary somatosensory cortex

SD – standard deviation

SEM – standard error of the mean

SMR – the sensorimotor rhythm

SEP – sensory evoked potential

SSEP – steady-state evoked potential

TMS – transcranial magnetic stimulation

III. Abstract

Oscillations in the alpha frequency range (8 – 12 Hz) are believed to shape the functional architecture of the brain by exerting inhibitory control over neuronal information processing (Klimesch et al., 1999; Klimesch et al., 2007; Jensen and Mazaheri, 2010). This is accomplished by attenuating the processing of irrelevant information, thereby increasing the efficiency of high priority tasks (Jensen et al., 2014; Bonnefond and Jensen, 2015; Gips et al., 2016). Accordingly, alpha oscillations have been linked to perceptual as well as cognitive performance (Ai and Ro, 2014; Linkenkaer-Hansen et al., 2004; Baumgarten et al., 2016; Vernon et al., 2009). Special training protocols have been developed, enabling participants to learn how to volitionally regulate alpha oscillations (Kamiya, 1971; Sterman, 1981). Such neurofeedback trainings have been implemented with great success to enhance cognitive and perceptual performance along with personal well-being (Hanslmayr et al., 2005; Zoefel et al., 2011; Nan et al., 2013; Gruzelier et al., 2014; Okazaki et al., 2015; Hsueh et al., 2016).

So far, it remains elusive whether learning processes would similarly benefit from increased oscillatory alpha activity and whether neurofeedback training could be applied to control learning efficiency. To attend to this matter, a short-term neurofeedback protocol was implemented to up- and down-regulate somatosensory alpha oscillations. Immediately afterwards, a passive, training-free perceptual learning paradigm was applied, by means of repetitive sensory stimulation (Ragert et al., 2008). This particular type of stimulation has been shown to induce reliable tactile acuity increases to the fingertip, accompanied by reorganizational changes in the somatosensory cortex (Pleger et al., 2001; Dinse et al., 2003b; Pleger et al., 2003; Höffken et al., 2007; Heba et al., 2017; Schmidt-Wilcke et al., 2018). The extent of stimulation-induced reorganization occurring has been shown to reflect the extent of tactile acuity improvement on a behavioral level. After only 20 min of stimulation, sufficient perceptual learning is induced, to be measurable on behavioral level (Ragert et al., 2008).

In the present study, it was demonstrated in two separate experiments that short-term neurofeedback training can be successfully applied to up- and down-regulate somatosensory alpha power. This in turn controls subsequent stimulation-induced perceptual learning. In particular, participants who increased somatosensory alpha power via neurofeedback training displayed increased perceptual learning efficiency compared with control participants. By contrast, neurofeedback-induced down-regulation of somatosensory alpha oscillations disrupted the learning process. The relationship between somatosensory alpha oscillations and

perceptual learning efficiency was especially pronounced in neurofeedback groups, explaining up to 59% of the perceptual learning outcome and markedly reducing interindividual learning variance.

Furthermore, analysis of cortical processing mechanisms during repetitive sensory stimulation revealed distinct patterns for neurofeedback groups. Heightened alpha power levels were maintained throughout the whole duration of stimulation. Additionally, participants who increased somatosensory alpha power showed sustained activation in the stimulated frequency (20 Hz) in between stimulation trains. Participants who decreased somatosensory alpha power revealed increased lower beta (14 – 19 Hz) activation after completion of neurofeedback training. The interaction of both neural processes was directly connected to the extent of alpha power changes during neurofeedback training and the extent of stimulation-induced perceptual learning. Accordingly, both factors represent possible mediators for the effect of alpha oscillations on perceptual learning efficiency.

Alpha neurofeedback training is a promising procedure with high potential for the application in clinical, rehabilitational and pedagogical environments, as well as in daily life.

1 – Introduction

1.1 – Neural Plasticity and Learning

Our potential to adapt and to learn enables human life as we know it. It is the basis of any development and while a coherent perception of ourselves over time is a crucial part of human identity, we never stop developing and are actually constantly changing (James, 1892; Chandler et al., 2003; Becker et al., 2017). Even as adults, our nervous system is continuously forming and dissolving connections between cells, cell assemblies and networks (Fuchs and Flügge, 2014). This unique quality of our brain, it's capability for neural plasticity, enables our survival by facilitating rapid adaptions to our environment.

However, our capability for neural plasticity varies over time. The substantial plasticity unfolding in critical phases of the developing brain (ontogenetic plasticity), is unequaled in any other phase of life (Hubel and Wiesel, 1970; Berardi et al., 2000). This large-scale structural plasticity permits growth and maturation through forming of new synaptic connections (Stiles and Jernigan, 2010). Although structural plasticity to some extent also occurs in the adult brain, post-ontogenetic plasticity is largely functional, induced by training and learning (Berry and Nedivi, 2016). But even within this scope, the adaptations occurring in the brain as a consequence of learning processes, vary intra- and inter-individually. As maximal learning efficiency is desirable in most cases, it appears unfavorable that plasticity processes are limited in the adult brain. The drawback of heightened plasticity, on the other hand, is reduced stability, which risks affecting the reliability of information storage and processing, a problem known as the plasticity-stability dilemma (Abraham and Robins, 2005). Nevertheless, some circumstances demand maximal efficiency in learning and plasticity. For example, the reorganization occurring shortly after a traumatic injury like a stroke, determines the course and extent of recovery (Bernhardt et al., 2017). It is critical lesions that particularly drive compensatory structural plasticity even in the adult brain. In fact, research on grown animals undergoing deafferentation or limb amputation first revealed strong reorganization of cortical representational maps post-ontogenetically (Kalaska and Pomeranz, 1979; Kelahan et al., 1981; Kaas et al., 1983). As a consequence, the predominant opinion at that time, that plasticity only occurred during development, was revised. A few years later, the first evidence emerged for use-dependent plasticity in the adult brain. After a tactile frequency-discrimination training,

adult monkeys showed increased cortical hand representations in the somatosensory cortex (Recanzone et al., 1992).

Beyond vital compensatory plasticity, it is likewise desirable to maximize use-dependent plasticity as required in daily life situations, e.g. important exams or memorization of critical information, like a return route. To understand how to maximize the capability for plasticity and therefore for learning, it is vital to understand its physical foundation.

1.2 – Cellular Components of Learning and Plasticity

Plasticity appears in many forms and certainly not all of them are understood well today. However, when considering learning, long-term potentiation (LTP) and long-term depression (LTD) seem to be key mechanisms. One of the most prominent research fields in neuroscience today began 1966 in Oslo, as a small side project of the PhD student Terje Lømo. He stimulated cells in the perforant path of the hippocampal dentate area in anesthetized rabbits with high frequency tetanic bursts and observed a persistent increase in efficiency of synaptic transmission, the first evidence of LTP (see Fig 1; Bliss and Lømo, 1973; Lømo, 2018).

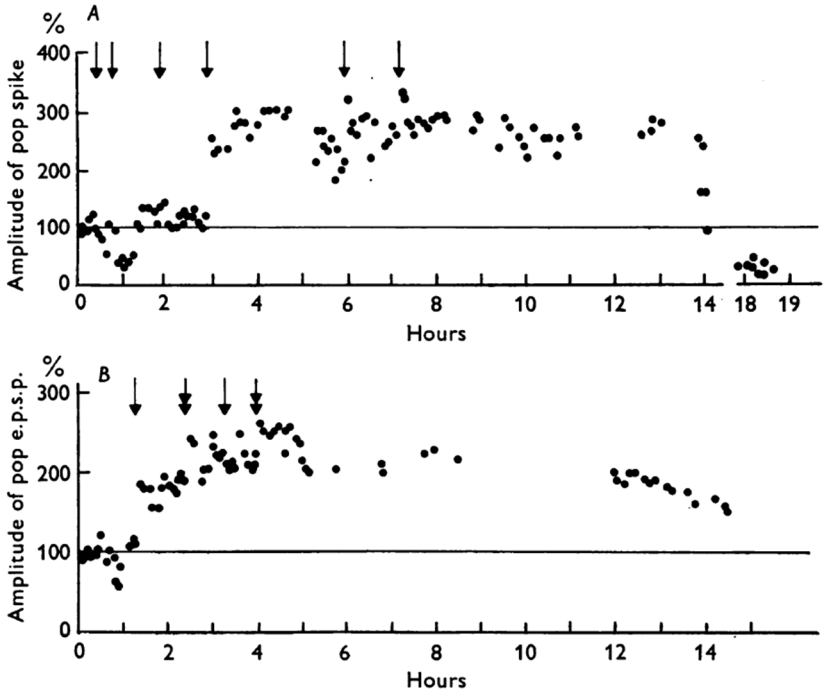

Figure 1 | **Long-term potentiation**. The first published evidence of long-term potentiation A, arrows indicate 15 Hz electrical stimulation trains for 15 sec. b, arrows indicate 15 Hz electrical stimulation trains for 15 sec (single headed arrow) as well as 100 Hz electrical stimulation trains for 3 sec (double headed arrow; modified from Bliss and Lømo, 1973).

It is known today, that LTP cannot only be induced in the perforant path, but also in a wide range of different neurons in various brain areas, possibly also, as Malenka and Bear state, at every excitatory synapse in the mammalian brain (Malenka and Bear, 2004). There is not just one way to elicit LTP, however, the focus in this thesis lies on the extensively studied NMDA (N-methyl-D-aspartate)-receptor dependent LTP, as it is relevant for the experiments conducted in this project.

LTP requires repeated stimulation of one or several synapses. This precondition is manifested in the NMDA-receptor, which has to be activated for LTP to occur, but is blocked by a magnesium protein during resting potentials. To remove this protein, two conditions have to be met. First, the postsynaptic cell has to be depolarized, which can only be achieved by well-timed and repeated stimulation of the presynapse. Second, glutamate has to be released presynaptically, which then binds to the NMDA-receptor postsynaptically. If both conditions are fulfilled, the magnesium block is lifted, and there is a calcium influx into the cell. This in turn activates CaMKII (Ca2+/CaM-dependent protein kinase II), which initiates the LTP cascade. One important structural change induced by this cascade, is an increase in the number of AMPA (α- amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) -receptors in the postsynaptic plasma membrane. The accumulation of AMPA-receptors lowers the threshold of depolarization, which facilitates LTP. This chain of events strongly enhances synaptic transmission efficiency (Lüscher and Malenka, 2012; Nicoll, 2017; Lømo, 2018; Baltaci et al., 2019). As coupled pre- and the postsynaptic activation is necessary to activate the NMDA-receptor, it is frequently referred to as a coincidence-detector (Lüscher and Malenka, 2012; Lømo, 2018; Baltaci et al., 2019) and has therefore been established as cellular model for associative learning. However, there are factors that can interfere with LTP-induction even if all conditions are met. It has been shown for example, that stress can elicit a negative effect on LTP, disrupting its induction (Maggio and Segal, 2010; Fa et al., 2014). Of course, there is also an opposing mechanism, LTD, that dampens the efficiency of synapse transmission. Unlike LTP, it is induced by low frequency stimulation (Malenka and Bear, 2004; Lüscher and Malenka, 2012).

1.3 – From cellular processes to behaviour

Knowledge concerning the molecular bases for plasticity and learning is difficult to translate into daily life situations, where learning largely depends on repetition. Are processes like practicing to play the piano connected to LTP or LTD processes in our brain? Practice leads to

use-dependent plasticity, which is reflected in superior abilities of experts like musicians or blind braille readers (Pascual-Leone et al., 1993; Elbert et al., 1995). These superior abilities are apparent in increased brain representations in task-relevant brain areas of these individuals, for example increased finger representations in the somatosensory cortex of blind braille readers. The opposite effect is also true, as a decline in use of the lower arm and hand due to cast fixation after a broken bone, leads to a decline in the representation of that limb in the primary somatosensory cortex (SI), as well as decreased tactile acuity on the fingers of this arm (Lissek et al., 2009). Whether the underlying processes of such representation changes are LTP- and LTD-dependent is still elusive. Cell cultures and animal models do not always yield results that are consistent with and transferable to humans (Seok et al., 2013). Furthermore, learning tasks in animal models are prone to be very specific and hard to compare with complex learning situations, which humans are confronted with in daily life. Nonetheless, some evidence is suggestive for the interpretation of LTP and LTD in human learning processes. For example, blocking of NMDA-receptors disrupts learning processes, while leaving information processing intact – an effect that has been shown in rats as well as humans (Morris et al., 1986; Dinse et al., 2003b; Cooke and Bear, 2010). Additionally, the effect of in vivo high frequency stimulation on LTP in rats is enhanced and prolonged if performed during learning tasks, indicating a state of preparedness for the acquisition of new information (Davis et al., 2004; Kemp and Manahan-Vaughan, 2004). In human learning tasks, it has been shown that new information cannot be acquired well immediately after a previous learning task has been performed – an effect that mirrors LTP induction, which is occluded for a certain period of time after previous induction of LTP (Rioult-Pedotti et al., 1998; Cantarero et al., 2013). Nonetheless, it is difficult to connect cellular stimulation mechanisms to everyday learning.

1.4 – Perceptual Learning

While we do not usually consider our senses when we think of learning, our sensory capabilities are not simply defined by physical constraints. Sensory abilities improve with use, for example in the process of learning to play a musical instrument. One compelling example was conducted by Deveau and colleagues (2014), who could show that training the visual performance of baseball players improved their success in the next season.

Perceptual learning is an example of use-dependent plasticity in the adult brain, leading to long-lasting adaptations most likely in early stages of sensory processing (Goldstone, 1998). It directly affects conscious perception as processing of categories, dimensions and features of

the environment can be altered with training (Goldstone, 1998; Gold and Watanabe, 2010). For example, trained clinicians are able to quickly identify tumorous tissue in x-ray images, whereas the untrained person cannot detect any abnormality (Sasaki et al., 2010; Shibata et al., 2014). Furthermore, the aforementioned musicians and blind braille readers are remarkable examples of perceptual learning leading to permanent structural changes (Elbert et al., 1995; Seitz and Dinse, 2007; Pascual-Leone et al., 1993) Similarly, structural changes have been shown in the hippocampal area of taxi drivers (Maguire et al., 2000) and participants who learned to juggle, displayed alterations in grey-matter volume related to visual motion perception (Draganski et al., 2004). Perceptual learning is distinguishable from other forms of learning by several core features. Particularly, no feedback, reward, attention or cognition are necessary for perceptual learning to occur and learning in most cases is very specific to the trained content (Goldstone, 1998; Watanabe et al., 2001; Fahle and Poggio, 2002; Seitz and Dinse, 2007). It appears puzzling that learning can occur even in the absence of conscious perception. However, it is conceivable that changes in afferent input patterns stimulate cortical areas processing sensory information. If this stimulation then exceeds a certain threshold, plasticity processes are likely facilitated (Fahle and Poggio, 2002; Seitz and Dinse, 2007; Dinse and Tegenthoff, 2015). Based on this theory, it should be possible to induce perceptual learning by mere stimulation of sensory modalities. These considerations led to an approach that eloquently bridges the gap between cell culture or animal model studies and human training studies: repetitive sensory stimulation

1.5 – Repetitive Sensory Stimulation

Repetitive sensory stimulation (RSS) combines the idea that changes in sensory input patterns initiate perceptual learning processes, with the concept of LTP and LTD eliciting plasticity processes in the brain. It does so by administering high-frequency (LTP-like) or low-frequency (LTD-like) stimulation to the sensory periphery (see Fig. 2). Merely applying such a high-frequency stimulation protocol to the finger, reliably increases tactile acuity unaffected by confounding factors like attention or motivation (Godde et al., 2000; Dinse et al., 2005; Ragert et al., 2008). This procedure functions passively, as no training is necessary to induce plasticity changes. Furthermore, following RSS, major reorganization can be observed, correlating with the induced tactile acuity changes (Dinse et al., 2003b; Pleger et al., 2003). These effects only take 20 min of RSS to become reliably measurable (Ragert et al., 2008). Without further training or stimulation, tactile acuity thresholds return to baseline again after 24 hours. Accordingly,

this particular approach provides a very strong and efficient tool to study plasticity and learning processes in the brain.

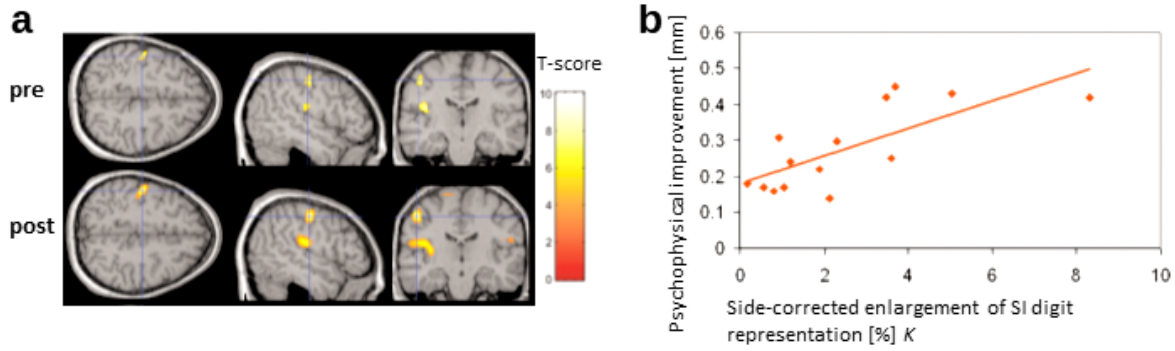

Figure 2 | **Repetitive sensory stimulation**. a, BOLD signals before and after repetitive sensory stimulation in the contralateral SI in the postcentral gyrus and in the contralateral SII in the parietal operculum. b, the observed changes correlated with stimulation-induced tactile acuity changes. (modified from Pleger et al., 2003).

To what extent LTP truly is the underlying process of RSS-induced plasticity changes taking place in somatosensory cortex, remains to be proven. However, on top of theoretical considerations, there is also insinuating evidence for this interpretation. Just like LTP on a cellular level, RSS leads to major reorganization of the somatosensory cortex, such as increased BOLD (blood oxygenation level dependent) signals (Pleger et al., 2003), changes in grey matter volume (Schmidt-Wilcke et al., 2018), cortical excitability (Höffken et al., 2007), expansion of cortical representational areas (Pleger et al., 2001), and enhanced functional connectivity between the somatosensory and motor cortex (Freyer et al., 2012; Heba et al., 2017). These reorganizational changes correlate with improvement of tactile acuity at the stimulated skin site. It is also known, that LTP processes are NMDA-receptor dependent and so is RSS-induced perceptual learning. Dinse and colleagues were able to show, that administration of drugs in the form of an NMDA-antagonist prior to RSS nullified learning and reorganization effects, while an agonist enhanced them (Dinse et al., 2003b). Interestingly, single site stimulation, did not lead to tactile acuity improvements, indicating the necessity of coactivation of multiple cells for reorganization to occur (Pleger et al., 2003). It is conceivable that the coincidence detector, the NMDA-receptor, could be responsible for this limitation. Additionally, RSS-induced perceptual learning has been shown to be disrupted by stress, much like cellular LTP effects (Dinse et al., 2017). However, so far it could not be shown that RSS leads to continuous activation in the somatosensory cortex, a prerequisite for LTP to occur (Nicoll, 2017).

Independent of the underlying mechanism, it is peculiar that, just like in other forms of learning, substantial variance in inter- and intra-individual perceptual learning can be observed (Godde et al., 2000; Pleger et al., 2001; Dinse et al., 2003b; Pleger et al., 2003; Dinse et al., 2005; Schlieper and Dinse, 2012; Freyer et al., 2013; Heba et al., 2016; Dinse et al., 2017; Muret and Dinse, 2018). This is surprising, as all participants receive identical input for exactly the same amount of time. If this kind of learning process is simply a stimulus-response process, no variation between individuals should be apparent. Therefore, empirical evidence points to the existence of additional factors modulating learning efficiency, even in such a standardized and basic induction of learning as it occurs during RSS.

1.6 – Factors determining Learning Success

Exploring beneficial and disruptive influences on learning has inspired a wide range of research and while it was not possible to identify *the* major variable determining learning success, many different factors have so far been identified.

1.6.1 – Research on conditions of learning

When trying to explain differences in learning success, an obvious starting point is to look at physical differences in each individual. Not surprisingly, genetic predisposition does play a major role for our capability to learn. As such, the polymorphism val66met in the neurotrophic factor gene (BDNF) decreases training-dependent plasticity changes compared the polymorphism variant val66val, which leads to common plasticity changes (Kleim et al., 2006). Interestingly, these findings have also been connected to a reduced susceptibility for LTP-like effects in met allele carriers (Cheeran et al., 2008). Grey matter volume constitutes another physical factor influencing learning success (Conde et al., 2012).

There is general agreement that attention positively influences learning success (Le Pelley et al., 2016). This effect can be further enhanced by motivational factors and rewards (Jovanovic and Matejevic, 2014), even to a point where attention is uncontrollably directed towards cues predicting high value stimuli (Le Pelley et al., 2016).

Alongside the strong effect of mental states on learning success, some lifestyle decisions also appear to be influential. Particularly, diet, physical activity, and sleep elicit strong impacts on our learning success. While high-fat, refined sugar and high salt diets seem to be detrimental to

plasticity and learning (Molteni et al., 2002; Cordner and Tamashiro, 2015; Ge et al., 2017), reduced calorie intake, intermittent fasting, or omega-3 fatty acids and polyphenol intake show beneficial effects on plasticity processes (Murphy et al., 2014). The universally positive effects of physical activity on plasticity and learning have been shown repeatedly (Hötting and Röder, 2013; Cassilhas et al., 2016; Cooper et al., 2018). Sleeping behaviour affects plastic processes on several levels. Enough sleep is a prerequisite for high learning success (Kreutzmann et al., 2015; Areal et al., 2017) and sleep is necessary to consolidate what we learn (Timofeev and Chauvette, 2017). Additionally, the time of day, depending on our natural sleep cycle, also affects how well we are able to learn (Facer-Childs et al., 2018). It is further conceivable, that one can 'learn to learn' by developing beneficial dispositions through regular engaging in diverse and demanding tasks, such as action video games (Bavelier et al., 2012). Lastly, contextual factors can also prove detrimental or beneficial to learning success. Among them, reinforcement (Dayan and Niv, 2008; Wehe et al., 2015) and stress (Schwabe et al., 2012) can both boost and dampen learning and plasticity, respectively.

1.6.2 – Research on Stimulation-induced Perceptual Learning

However, most of the above-mentioned factors cannot easily be targeted, or they only have comparably small influences on actual learning outcomes. Additionally, learning studies usually involve complex cognitive processes and apart from sleep consolidation, it is difficult to conclude at what stage of the process the intervention was beneficial or disruptive. Studies applying RSS however, can precisely target the process of perceptual learning, as cognitive processes like memorizing or recalling are not involved and confounding factors such as motivation or attention do not interfere with the learning process (Godde et al., 2000; Dinse et al., 2005). Accordingly, a multitude of factors have been researched regarding their effects on stimulation-induced perceptual learning.

Just as stress has been shown to impair LTP processes (Maggio and Segal, 2010; Fa et al., 2014) and elicit negative effects on behavioral learning processes (Schwabe et al., 2012), it likewise disrupts stimulation-induced perceptual learning (Dinse et al., 2017).

Concerning tactile acuity, there also seems to be a 'learning to learn' effect, as piano players who already show superior tactile acuity compared to non-musicians, display increased benefits from repetitive sensory stimulation compared to non-musicians (Ragert et al., 2004).

In recent years, another line of perceptual learning predictors emerged, involving brain states connected to inhibition and excitation – states that also constitute key roles in cellular LTP (Bliss and Collingridge, 1993; Lüscher and Malenka, 2012; Nicoll, 2017).

One of these predictors is GABA (γ-aminobutyric acid) concentration. Administering the GABA-agonist lorazepam completely blocks the effects of repetitive sensory stimulation (Dinse et al., 2003a). However, in another study without drug administration, baseline levels prior to the application of repetitive sensory stimulation were able to explain 57% of the interindividual learning variance (Heba et al., 2016). In particular, high baseline GABA-concentration in sensorimotor areas led to high stimulation-induced tactile acuity gains (see Fig. 3a).

A similar pattern can be observed for another physiological marker associated with inhibition: alpha oscillations. Electroencephalography (EEG) was recorded for 15 min while participants watched an animal documentary. Immediately afterwards, repetitive sensory stimulation was applied. The oscillatory power in the alpha frequency range averaged over the 15 min recording explained up to 36% of the interindividual stimulation-induced learning variance (Freyer et al., 2013). Again, the relationship was positive, where stronger oscillatory power resulted in an elevated learning outcome (see Fig. 3b).

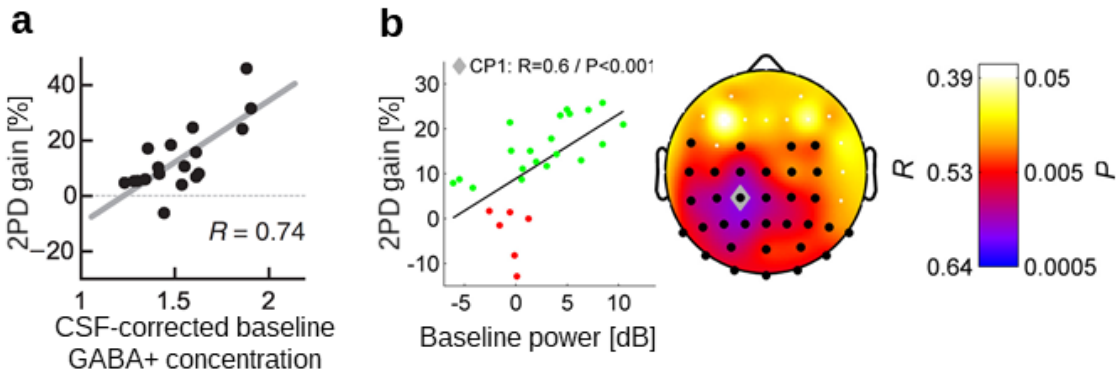

Figure 3 | **Predictors of stimulation-induced perceptual learning**. a, baseline sensorimotor GABA levels correlate with stimulation-induced tactile acuity gains (modified from Heba et al., 2016). b, baseline alpha power levels over the somatosensory cortex correlate with stimulation-induced tactile acuity gains (modified from Freyer et al., 2013); successful learners are illustrated in green, other participants in red.

The right balance of inhibition and excitation does not only seem to be crucial in preparation for learning processes, but also during the process. Changes in cortical excitability measured by paired-pulse suppression, also correlate with stimulation-induced tactile acuity increases (Höffken et al., 2007). In this paradigm, a sensory evoked potential (SEP) is measured as a

cortical response to the stimulation of the median nerve on the lower arm. If a second electrical pulse follows the first one in short succession, a decline in the evoked reaction can be observed when compared to the first SEP. The extent of this decline serves as a marker for cortical excitability, where low excitability indicates strong cortical suppression, which is observable in a strong decline of the second pulse. High excitability on the other hand, is indicated by minor suppression of the second potential. Measured before and after repetitive sensory stimulation, it was revealed that increases in cortical excitability correlate with higher stimulation-induced tactile acuity gains (Höffken et al., 2007).

The high amount of interindividual learning variance that GABA, alpha oscillations and cortical excitability each explain individually, strongly suggests that they are interconnected. This notion is also supported by the fact, that all of them are associated with inhibition and or excitation of brain regions. While GABA concentration and cortical excitability are difficult to target at will, alpha oscillations are affected by top-down processing and can therefore be actively modulated. This circumstance is a great opportunity, as it provides a possibility to study the optimal brain-state for efficient learning. Furthermore, the relationship between brain-state defining factors like GABA, cortical excitability, and alpha oscillations can be explored, as well as the effect that changes in alpha oscillations might elicit on learning and plasticity processes.

1.7 – Alpha Oscillations

Inspired by the works of Caton, Beck, Cybulski and others, who implemented Galvanometers to measure electrical currents on the cortical surface of several animal species, Hans Berger searched for a non-invasive way to repeat these experiments in humans. Almost 100 years ago, his milestone research resulted in the development of the electroencephalogram (EEG). Extensive study on, among others, himself and his son, lead to the discovery and precise description of the alpha rhythm (see Fig. 4), although some of the previously described currents, by measure of the galvanometer, had most probably picked up the same phenomenon (Berger, 1929).

The alpha rhythm is the most prominent oscillatory rhythm measurable with EEG and is strongest over occipital areas. Alpha activity oscillates in a frequency between 8 and 12 Hz. Berger discovered, that opening the eyes or engaging in arithmetic tasks, led to a suppression of the alpha rhythm, a circumstance which was later called the alpha-block or berger-block. As a consequence, the alpha rhythm was interpreted to reflect an ‘idle’ state of the brain (Adrian and Matthews, 1934).

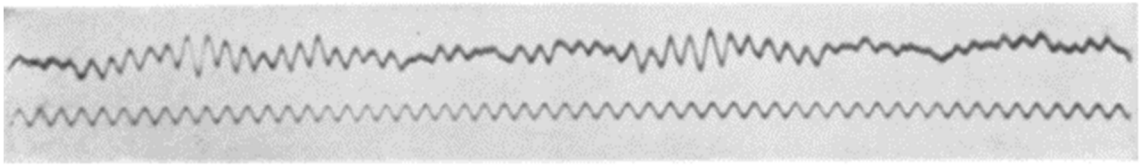

Figure 4| **First measured alpha traces with an electroencephalogram (EEG)**. An EEG recording performed on Klaus Berger (the son of Hans Berger). The upper trace shows the recorded signal, the bottom trace reflects time in tenths of seconds (Berger, 1929).

This interpretation remained prevalent for decades until in the 1990s, it was finally challenged. For instance, it was found that demanding working memory tasks caused strong alpha synchronization in task-irrelevant regions (Klimesch et al., 1999) and it was therefore concluded that alpha oscillation do not reflect an idle state of the brain, but an active inhibition process (Klimesch et al., 2007). Based on these findings, a thorough framework of the mechanism and functionality underlying alpha oscillations was developed. Accordingly, alpha oscillations emit pulses of inhibition at the oscillatory peaks, permitting information processing only during troughs of the oscillatory cycle. The magnitude of the oscillatory peaks defines the time-window available for information processing. Higher alpha power reflects increased synchronous neuronal activity in the alpha rhythm, leading to wider peaks and shorter troughs, which in turn greatly limits processing capabilities. It is further assumed, that information processing is arranged sequentially, in order of priority, so that the most relevant information is processed first and less relevant information is inhibited. This way, a network architecture is achieved, which prevents information overload and gates as well as allocates neural resources according to priority (Jensen and Mazaheri, 2010; Jensen et al., 2014).

Evidence for this theory has accumulated through empirical data and computational models. Information processing is believed to be reflected in high-frequency gamma-band (> 30 Hz) activity (Kaiser and Lutzenberger, 2005; Crone et al., 2006; Jensen et al., 2007). Indeed, it has been shown that gamma-band activity is rhythmically inhibited in line with the alpha cycle (Haegens et al., 2011b; Bonnefond and Jensen, 2015). Furthermore, cortical excitability proved to be higher during troughs than during peaks of the alpha cycle (Haegens et al., 2011b; Zrenner et al., 2018). Incorporating this framework into a computational model allowed for successful prediction of neural firing patterns, in line with experimental data (Gips et al., 2016). The inhibiting effect of alpha oscillations is likely caused by GABAergic interneurons (Haegens et al., 2015; Gips et al., 2016), again suggesting a connection between GABA concentration, alpha oscillations, and cortical excitability.

The gating of neural resources, accomplished by alpha oscillations, could be conceived to manifest in task performance, where optimal allocation should result in increased performance.

This relationship has been suggested in a multitude of studies, for various cognitive as well as perceptual tasks. Particularly, alpha synchronization in task-irrelevant cortical areas during demanding tasks, has positive effects on task performance (Thut et al., 2006; Klimesch et al., 1999; Händel et al., 2011; Haegens et al., 2011a). Furthermore, the amount of alpha synchronization in a critical time window before task onset, correlates with performance on a trial by trial basis (Linkenkaer-Hansen et al., 2004; van Dijk et al., 2008; Ai and Ro, 2014; Baumgarten et al., 2016).

The importance of alpha oscillations for information processing is evident. However, so far, the connection between alpha oscillations and learning processes has been widely neglected. Only a few studies have explored this relationship (Freyer et al., 2013; Bays et al., 2015), with inconsistent results. The fact that alpha oscillations can be targeted with brain-computer interfaces, introduces promising possibilities for in depth research on relationships and effects of alpha power on information processing as well as learning and plasticity processes.

1.8 – Brain Computer Interfaces

The term brain computer interface (BCI) comprises all methods that open up information exchange between the central nervous system and an external device. The idea of using EEG to read out or alter neuronal activity is almost as old as EEG itself (See Fig. 5)

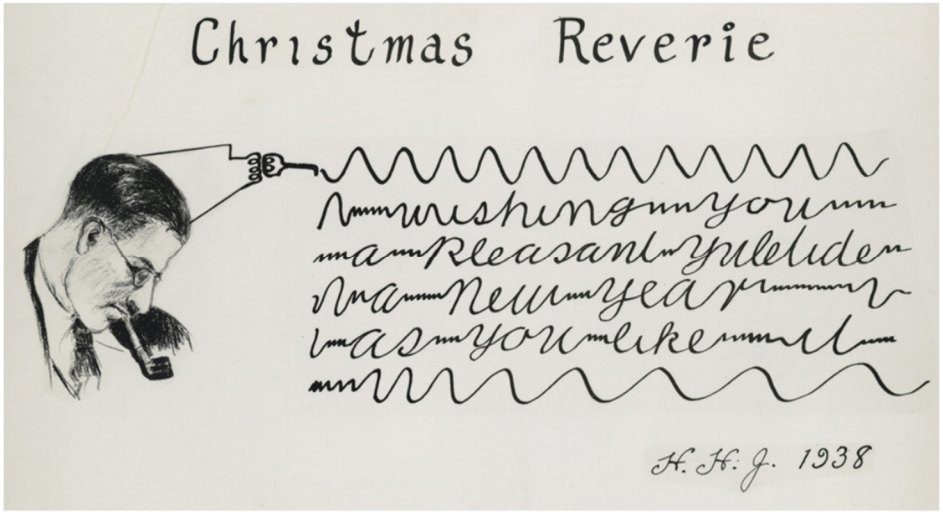

Figure 5 | **Holiday card sent from Herbert Jasper to Hans Berger in 1938.** This is one of the oldest illustrations depicting a concept of a brain computer interface to read out thoughts (modified from Vos and Debener, 2014).

Various forms of BCI exist, most prominent among them are systems reading out brain signals to extract functionality. For example, computers can be trained to recognize certain brain signals, that are then transferred into adaptive functions such as moving a robot arm to the left (Velliste et al., 2008; Klaes et al., 2014). The goal of such BCI systems is to enable patients, who are partially or completely paralyzed, to interact and communicate with the outside world. Another line of BCI aims at the reverse process, using machines to alter neuronal activity. In most cases, sensory input (for example pictures eliciting different neuronal reactions) is presented to the participant, who controls his neural reactions by looking at the stimuli (Williams et al., 2006; Chen et al., 2017; Han et al., 2018). A special form of BCI is called neurofeedback, where participants are trained to actively alter certain neuronal activities, without external induction of brain responses.

1.9 – Neurofeedback Training

Bergers alpha block inspired a line of research that involved classical conditioning to inhibit the observed alpha desynchronization. On this basis, the idea was born that alpha power itself could be conditioned. Joe Kamiya was the first person to teach participants to control their occipital alpha rhythm (Nowlis and Kamiya, 1970; Kamiya, 1971; Ancoli and Kamiya, 1978). He synchronized the appearance of occipital alpha oscillations in the EEG with a tone. By alternating between simply passive sequences, where participants observed the on-set and off-set of the tone, and trial sequences, where participant actively tried to reproduce or suppress the tone, participants could successfully facilitate occipital alpha oscillations. Usually, 15 minutes were sufficient for the participants to achieve first accomplishments.

Roughly at the same time, following the observation that cats show very distinct EEG-patterns during food conditioning experiments, Barry Sterman and colleagues likewise had the idea, to reinforce the EEG-pattern itself with food rewards. Consequentially, Sterman's cats were the first to successfully perform neurofeedback (NF) training on the sensorimotor (SMR)-rhythm (Wyrwicka and Sterman, 1968; Roth et al., 1967). This particular rhythm occurs in the frequency range between 12 and 15 Hz and is connected to suppression of motor tasks. Most interestingly, cats trained to produce SMR-rhythm developed a resistance against drug-induced seizures. Sterman quickly extended his research to humans and attained great achievements in the field of epilepsy treatment, as participants were able to learn how to successfully suppress seizures, a method still applied today (Sterman, 1981; Egner and Sterman, 2006).

The possibilities NF training was offering, quickly led to widespread application of various neurofeedback protocols, for medical treatment of many mental health conditions and diseases. Today, NF training of slow cortical potentials, alpha rhythm, beta rhythm (13 – 30 Hz), theta rhythm (4 – 8 Hz), and even ratios of these are commonly applied. However, thorough methodological studies are rare, as most research focuses on clinical administration, often with poor experimental designs (for example a lack of or a badly chosen control group) and unstandardized training protocols. While a growing body of research advocates the positive effects of NF training in mental diseases like attention deficit hyperactivity-disorder (ADHD; Gevensleben et al., 2009; van Doren et al., 2018), some also find no superior effect to sham neurofeedback or behavioural therapy sessions (Schönenberg et al., 2017). This has led to a collaborative outreach for standardized, controlled and transparent methods applied to neurofeedback research. Interventions like NF training can elicit various effects not explicitly related to the training, e.g. possible placebo effects and side-effects of the training as well as the received attention (Ros et al., 2019). It can be concluded that while promising, NF training research requires well-planned experimental designs, in clinical environments as well as with healthy individuals, to establish functioning and standardized protocols.

1.10 – Alpha Neurofeedback Training

Since the early beginnings of NF training, alpha oscillations have received special attention. Thanks to their connection to task performance, it was the obvious next step to test, whether task performance could be improved by alpha NF training. Results were promising, as participants showed elevated performances in various tasks.

For instance, alpha NF training was implemented to increase memory performance (Wei et al., 2017), working memory (Hsueh et al., 2016), cognitive performance in mental rotation tasks (Hanslmayr et al., 2005; Zoefel et al., 2011), motor performance in stroke patients (Mottaz et al., 2015), and creativity in performing arts (Gruzelier, 2014).

Considering the universally positive effects of alpha NF training, it is not surprising, that it was similarly implemented in clinical environments. Especially in ADHD treatment, alpha NF training seems promising (Vernon et al., 2009; Escolano et al., 2014a). However, successful implementations (with varying protocols involving the alpha band) were also reported in alcohol-related depression (Saxby and Peniston, 1995), post-traumatic stress-disorder (Peniston and Kulkosky, 1991), and treatment for drug abuse (Scott et al., 2005). Nonetheless, more reliable research is necessary and study results require replication.

Resulting from many years of accumulated research on NF training, some methodological insights have been gained. Particularly, some participants learn to alter alpha oscillations more easily than others (Hanslmayr et al., 2005; Vernon et al., 2009). As a possible explanation, spontaneous alpha levels before NF training have been identified as a predictor for alpha neurofeedback success (Wan et al., 2014). However, assessment of uncorrected baseline levels is difficult as differences in skin conduction, bone density, dipole arrangement, and electrode placement strongly decrease signal to noise levels in EEG recordings.

Concerning the duration of alpha power training, sessions should ideally last around 20 to 30 minutes. Another important parameter is the targeted training frequency. Most effective results seem to arise from training on the individual alpha peak frequency, as opposed to training a broad frequency range from 8 to 12 Hz (Vernon et al., 2009). However, the majority studies focus on occipital alpha oscillations, as they are the most prominent and therefore easiest to apply. Participants commonly perform NF training over several weeks before task performance changes are assessed. However, for practical reasons it would be preferable to apply short-term neurofeedback protocols in healthy individuals, to test immediate effects of NF training on cortical processing. Moreover, alpha NF training has not yet been applied in combination with learning or plasticity processes.

1.11 – Aims of this dissertation

High interindividual learning variability can be observed in different learning paradigms, while their root remains elusive. Experimental data suggests, that the balance between cortical excitation and inhibition seems to play an important role in explaining this variance, a factor likewise important for cellular LTP- and LTD processes, which are believed to be the neural substrate of learning. Alpha oscillations are known to gate inhibition and excitation and can be targeted with NF training. The aim of this project was therefore to implement a short-term neurofeedback protocol to up- and down- regulate alpha oscillations. Accordingly, by combining this protocol with a perceptual learning paradigm, it was attempted to decrease perceptual learning variance and to control the perceptual learning outcome. Furthermore, the role of enhanced or decreased alpha power for perceptual learning and plasticity on a behavioural as well as neuronal basis will be analysed. This way, critical insight can be gained on optimal neuronal states to initiate perceptual learning and plasticity processes and on how NF training alters information processing in the brain. Accordingly, five main research questions are examined in this thesis:

(1) Can short-term neurofeedback training be applied to successfully up- and down-regulate somatosensory alpha power?

(2) Can short-term neurofeedback training be applied to control the efficiency of subsequent perceptual learning and to reduce perceptual learning variance?

(3) Are there any additional oscillatory predictors for the perceptual learning outcome?

(4) Is there a relationship between oscillatory alpha power and cortical excitability as assessed with the paired-pulse paradigm?

(5) What causes the effect of neurofeedback training on perceptual learning, can any relevant responses during repetitive sensory stimulation be identified?

In order to answer these questions, a series of five experiments was conducted. First, short-term neurofeedback training was implemented and combined with repetitive sensory stimulation. Baseline tactile acuity thresholds were compared with post-stimulation thresholds as a marker of perceptual learning. It was expected that training-induced increases in somatosensory alpha

power will lead to a heightened perceptual learning outcome. As tactile acuity was not measured in between NF training and repetitive sensory stimulation, it is conceivable that NF training influences tactile information processing as opposed to perceptual learning. To rule out this possible confound, a second neurofeedback experiment was conducted without repetitive sensory stimulation, monitoring tactile acuity thresholds before and after NF training. Additionally, on a separate day, before and after NF training, cortical excitability was measured with paired-pulse suppression. As alpha power is assumed to be connected to inhibition, it is assumed that increases in alpha power will lead to stronger paired-pulse suppression.

Given that electrical repetitive sensory stimulation, which was applied in the first experiment, creates artefacts in EEG-signals, an air-puff driven pneumatic stimulation protocol was implemented. With this approach, the first experiment was repeated in three steps to replicate the data and to enable EEG recording during repetitive sensory stimulation. Additionally, further exploratory analysis of neurofeedback-induced alterations in cortical processing during stimulation-induced perceptual learning was applied.

2 – Materials and Methods

In the following, five experiments with the goal of analysing the effects of somatosensory alpha neurofeedback (NF) training on tactile perceptual learning processes are described (For an overview see 6.2 – Appendix Figure 44).

2.1 – Combination of alpha neurofeedback training with electrical repetitive sensory stimulation

In the first experiment, neurofeedback training was analysed regarding its efficacy in up- and down-regulating somatosensory alpha power. Furthermore, the effect of neurofeedback-induced somatosensory alpha power changes on perceptual learning efficiency was studied.

2.1.1 – Participants

Altogether, 76 healthy, right-handed volunteers participated in this experiment (mean age: 24.4 ± 3.1 SD; 36 women). Their handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971; mean laterality quotient: 81.8 ± 19.8 SD). No participant took regular medication (excluding contraceptives). Participants were randomly assigned to three groups, two experimental groups with NF training and one control group. After completion of the experiment, they received monetary compensation. The study protocol was approved by the Ethics Committee of the Ruhr-University Bochum and in accordance with the Declaration of Helsinki. All participants provided written informed consent.

By consequence of insufficient data quality, eight participants were excluded from further analysis. Specifically, participants who fell asleep or closed their eyes for more than two seconds during EEG recordings were removed from further analysis (n = 2). Additionally, participants unable to perform the tactile acuity task, due to poor sensitivity of their fingers (n = 2), and participants showing strong occipital alpha activity with eyes open, thereby concealing somatosensory alpha peaks measured at CP1 (according to international 10-20 system; n = 2), were also excluded. One participant fell ill during the experiment and one participant utilized excessive eye-blinking as a strategy during NF training. Both participants were removed from data analysis. Accordingly, final group sizes consisted of n = 17 in the

group training to increase alpha power (alpha up), n = 15 in the group training to decrease alpha power (alpha down), n = 20 in the control group, and NF-paradoxical-responders (NF-PR) with n = 16 (9 from the alpha up group and 7 from the alpha down group). NF-paradoxical-responders were defined as participants from the alpha up who on average decreased alpha power and participants from the alpha down group, who on average increased alpha power and were therefore handled as a separate group.

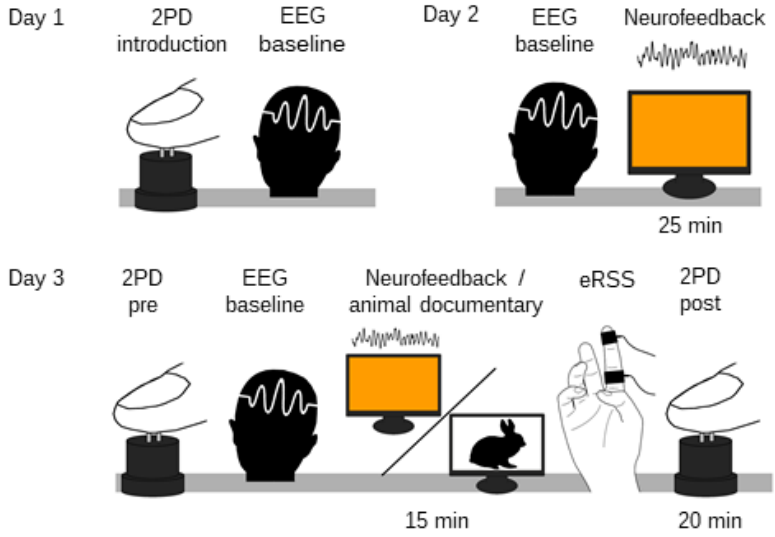

Figure 6 | **Experiment 1 – schedule**. The experiment took place on three subsequent days. The first day included an introductory tactile acuity measure (2PD) as well as a first EEG baseline recording. The second day consisted of another EEG baseline recording and NF training. The last day started with a tactile acuity pre measure, followed by interventions in form of NF training, watching of an animal documentary and electrical repetitive sensory stimulation (eRSS). At the end, one last tactile acuity post measure was performed.

2.1.2 – Experimental Schedule

The experiment spanned over three consecutive days. On the first day, all participants performed a practice tactile acuity measure and for both neurofeedback (NF) groups a baseline EEG recording was applied. The second day started with an EEG baseline recording followed by the respective NF training. Participants from the control group did not attend this day. The final day started with two baseline measures of tactile acuity and one baseline recording of EEG. Subsequently, both NF-groups performed their respective NF training, while the control group watched a muted animal documentary. Immediately afterwards, while continuing to or

starting to watch the documentary, electrical repetitive sensory stimulation (eRSS) was applied to all participants. The experiment concluded with a last tactile acuity measure, to compare the effects of repetitive sensory stimulation on touch sensitivity between groups (see Fig. 6).

2.1.3 – Tactile Acuity

Tactile acuity of the right index fingertip was assessed using a modified version of the two-point discrimination task (2PD), a two-alternative forced-choice task using the method of constant stimuli (Ragert et al., 2008; Muret and Dinse, 2018, 2018). The fingertip was placed on a custom-made device with an armrest, consisting of a rotatable disc with quickly interchangeable test stimuli. All stimuli were locked into position before contacting the fingertip, ensuring standardized assessment (see Fig. 7). The disc contained 8 stimuli, one with a single tip and seven with two tips separated by varying distances (0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5 mm). Each stimulus was presented 8 times in a pseudorandomized order resulting in a total of 64 trials. Immediately after application of the stimulus, participants reported whether they perceived one or two stimuli. Opposed to the classical task, where two tips are tested against one, participants had to differentiate between the perception of two clearly separated tips and the perception of two tips still feeling as one when the distance of two stimuli was too small to be perceived individually. As a marker of tactile acuity, thresholds were defined as the minimal distance where at least 50% of the stimuli were correctly perceived as two. Tactile acuity thresholds were estimated by plotting participants' responses against needle distances and fitting them to a psychometric curve using binary logistic regression. The 50% criterion applied in this experiment is equivalent to the 75% criterion used in the well-known visual GOT (grating orientation task; Johnson and Phillips, 1981), where the 50% criterion equals the chance level. The average of both baseline measures on day three served as the 2PD-baseline used for further analyses (test-re-test reliability was high; $ICC_{(3,2)} = .881$)

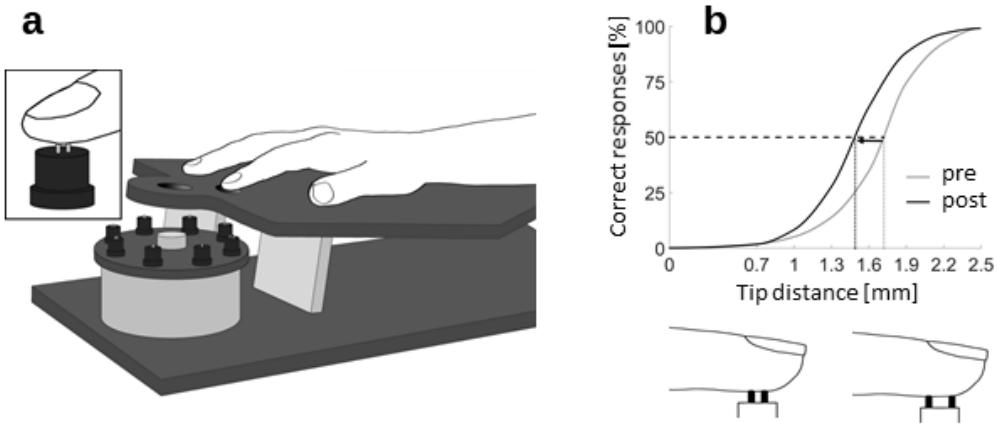

Figure 7 | **Tactile acuity measure**. Stimuli consisting of two metal tips with varying distances between each other, are repeatably presented to the fingertip in a standardized procedure (a). Participants answer, whether they can clearly feel two individual tips, or whether the two tips are so close, they feel as one. Regressing their answers to the actual tip distance will result in a psychometric curve (b). A shift of this curve to the left indicates improved tactile acuity, as the distances between two tips, that is necessary to perceive each of them individually, grew smaller.

2.1.4 – Electrical Repetitive Sensory Stimulation

Electrical repetitive sensory stimulation (eRSS) was applied to the right-hand index finger for the duration of 20 min. The electrical stimulation was delivered with an ELPHA II 3000 (Danmeter A/S) stimulation device, via adhesive surface electrodes fixed to the first and third finger-segment (cathode proximal). The protocol consisted of high-frequency (20 Hz) stimulation train (200 µs pulse duration) for the duration of 1.5 sec additional to 0.3 sec and 0.2 sec of a ramp and fall time respectively, followed by 5 sec inter-train intervals. This protocol has been successfully applied in multitudes of studies had has been proven to reliably induce perceptual learning processes (Ragert et al., 2008; Freyer et al., 2013; Heba et al., 2017; Dinse et al., 2017; Heba et al., 2016; Muret and Dinse, 2018; Schmidt-Wilcke et al., 2018)The stimulation intensity varied between individuals, as it was adjusted to the highest threshold value that the participant could easily tolerate for an extended period (range 3-5 mA).

2.1.5. – EEG and Neurofeedback Training

Both EEG recordings and NF training were performed with a 13-channel DC-EEG amplifier by NeuroConn (Thera Prax® Mobile) and sampled at 512 Hz. During recordings, participants sat in a comfortable chair inside of a Faraday cage. At the electrode sites, the scalp of all participants was prepared with alcohol and SkinPure gel. Afterwards, the Ag/AgCl electrodes were placed with Elefix conduction gel and arranged according to the international 10-20 system (F3, F4, CP1, CP2, PO3, PO4, ground: forehead, reference: linked mastoids). Four additional electrodes were placed around the eyes to record ocular activity.
Before every EEG recording, baseline measures were performed. They alternated between two eyes-open and two eyes-closed condition each lasting 1 min with a random starting condition. Both eyes-open recordings were combined to constitute a stable baseline measure, while the eyes-closed conditions were used to identify occipital alpha peaks in order to differentiate them from somatosensory alpha peaks.

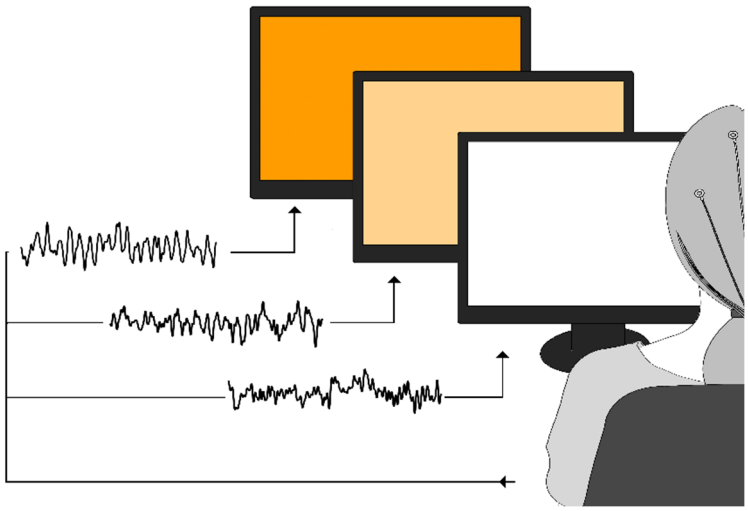

Figure 8 | **Illustration of example neurofeedback training**. Visualization of a participant from the alpha up group performing NF training. The amount of alpha oscillations measured at CP1 determines the color of the screen. At baseline alpha levels, the screen is white. With increasing alpha levels, the screens colour changes to orange. The same is true for participants in the alpha down group, however, their screen turns orange when their alpha oscillations decrease.

The oscillatory frequency targeted by NF training was adjusted to each participant's individual alpha peak, which was identified in the first EEG baseline recording. The provided feedback was extracted from the signal of the CP1 electrode, which is located above the left somatosensory cortex. Real-time processing of the signal was conducted using fast Fourier

transformation on sliding 1 sec Hann windows with an update rate of 100 ms. The amount of alpha power change from baseline was visualized with different color saturations from white to orange. Specifically, the screen was white at baseline power levels and reached a deep orange at 10 mV change of alpha power. This could either be an increase or a decrease of alpha power, depending on the respective condition (see Fig. 8). While the alpha up group trained to increase alpha power, the alpha down group trained to decrease alpha power. Both groups where blind regarding their condition and were simply instructed to increase the color saturation of the screen only using their mind.

On the first NF training day, participants trained over three blocks, while on the testing day, they trained over two blocks. Each block consisted of a 15 sec baseline measurement while fixating a cross in the centre of the screen followed by six training phases. The training phases each consisted of a 1-min training and a 15-s break.

2.1.6 – Data Processing and Analysis

The EEG signal was filtered between 1 and 40 Hz with a linear finite impulse response (FIR) filter and subsequently separated into 2 sec epochs. Ocular artefacts were removed using least mean squares regression (Gómez-Herrero et al., 2006). The corrected signal was manually inspected for remaining artefacts using the EEGLAB toolbox (Delorme and Makeig, 2004). Less than 5 % of the signal was removed, indicating good data quality. Afterwards, power spectra were computed using Morlet wavelet convolution (1-25 Hz; 15-25 dynamic cycles) and then averaged over epochs. Formula (1) was implemented to correct the data for baseline power. *Activity* marks the EEG data of interest and *baseline* the baseline applied for normalization.

$$10 * \log_{10}\left(\frac{activity}{baseline}\right) \quad (1)$$

The peak of the power spectrum between 8 to 12 Hz was manually identified and served as indicator for peak alpha power.

Changes of alpha power and tactile acuity changes were tested on a group level with mixed factorial *ANOVAs* and Bonferroni post hoc tests. A group analysis of perceptual learning success was performed with a one-way *ANOVA* and Fisher's LSD post hoc test. Normal distribution for both types of *ANOVAs* was confirmed for all entered variables with the

Kolmogorov-Smirnov test. Furthermore, power distributions of different frequency bands and electrode positions and their relation to perceptual learning were inspected with regression analyses. Outliers were excluded, if they diverged more than two standard deviations from the mean of the population (outliers – alpha: 0; theta: 2; lower beta: 2; upper beta: 0; low gamma: 0; CP2: 1; PO3: 1; F3: 1). Local maximum values were taken as power markers for the following frequency bands: theta: 4-7 Hz, lower beta: 13-20 Hz, upper beta: 21-30 Hz, and lower gamma: 31-40 Hz. Scalp distributions were interpolated using MATLABs griddata function. Regression analyses (adjusted R^2 are reported) and *ANOVAs* were performed in IBM® SPSS® V25; all other analyses were performed in MathWorks® MATLAB R2015a. Unless states otherwise, all data are presented as *mean* ± *SEM* (standard error of mean).

2.2 – Alpha neurofeedback training and follow-up EEG recordings

The aim of the second experiment was to test the stability of neurofeedback induced alpha power changes and whether these changes affect tactile acuity even in the absence of repetitive sensory stimulation. This way, the possibility of alpha NF training affecting processing of afferent sensory inputs during tactile acuity measures, rather than affecting perceptual learning processes, can be out ruled. Additionally, the relationship between neurofeedback- induced alpha oscillations and cortical excitability was explored.

2.2.1 – Participants

In the second experiment, 38 healthy, right-handed volunteers participated (mean age 25.7 ± 3.2 SD; 24 women). Their handedness was confirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). No participant took regular medication (excluding contraceptives). Participants were randomly assigned to two NF training groups. In one group participants trained to increase their alpha power (alpha up) and in the second group, participants trained to decrease their alpha power (alpha down). After completion of the experiment, they received monetary compensation. The study protocol was approved by the Ethics Committee of the Ruhr-University Bochum and in accordance with the Declaration of Helsinki. All participants provided written informed consent.

As a consequence of insufficient data quality, several participants had to be removed from further analysis. For 6 participants, no tactile acuity data could be collected because of poor sensitivity at the fingertips. A total of 9 participants had to be excluded from cortical excitability analyses, as no N20 and P25 components could be identified during PPS measurement. Another 5 participants had to be removed from EEG analyses, as signal to noise ratios were deficient and the data could not be used for further processing. Final group sizes consisted of n = 6 in the alpha up group, n = 6 in the alpha down group and and NF-paradoxical-responders (NF-PR) with n = 19 (9 from the alpha up group and 10 from the alpha down group). NF-paradoxical-responders were defined as participants from the alpha up who on average decreased alpha power and participants from the alpha down group, who on average increased alpha power and were therefore handled as a separate group.

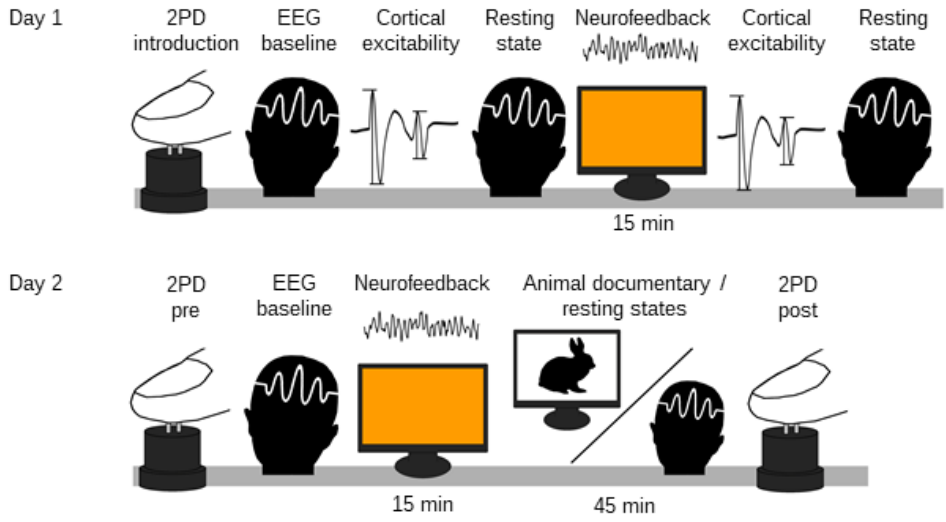

Figure 9 | **Experiment 2 – schedule**. The experiment took place on two consecutive days. The first day started with an introduction measure of tactile acuity (2PD) followed by multiple EEG recordings, paired-pulse suppression measures (cortical excitability) and NF training. The second day started again with tactile acuity measures, followed by an EEG baseline recording, NF training and afterwards 50 minutes of alternation between animal documentary and spontaneous EEG recordings. At the end, one last post measure of tactile acuity was conducted.

2.2.2 – Experimental Schedule

The experiment took place on two consecutive days. On the first day, all participants performed a practice tactile acuity measure. The measure was equivalent to the procedure introduced in the previous experiment (for a detailed description, see 2.1.3– Tactile Acuity). Then, a baseline EEG recording was conducted. Immediately afterwards, cortical excitability was measured

through paired-pulse median nerve stimulation, followed by a two-minute EEG recording of spontaneous activity. During the following 15 minutes, all participants engaged in their respective NF training. Subsequently, a second cortical excitability measure was performed, and the day was concluded by one last EEG recording of spontaneous activity. The second day was almost identical to the last day of experiment 1, except for the missing application of eRSS. It started with two baseline measures of tactile acuity and one baseline recording of EEG. Subsequently, participants performed their respective NF training and afterwards watched an animal documentation for 50 minutes. Every 3 minutes, the documentation was paused for a two-minute EEG recording of spontaneous activity, resulting in 10 EEG measures. The experiment was concluded with one last tactile acuity assessment (see Fig. 9).

2.2.3 – EEG Recording and Neurofeedback Training

EEG recordings and NF training were almost identical to the procedures applied in experiment 1 (see 2.1.5 – EEG Recording and NF training). However, some variations have been introduced, with the goal to simplify NF training. On the first day of training, NF training was only performed for 2 blocks (compared to 3 blocks in the previous experiment). Furthermore, instead of adjusting the NF training to the individual alpha peak frequency, a general frequency range between 8 – 12 Hz has been applied for all participants.

2.2.4 – Cortical Excitability

Median nerve stimulation induces sensory evoked potentials (SEPs) at the somatosensory cortex. If a second stimulus is applied in short succession, the cortical response will be reduced (paired-pulse suppression). This suppression of the second pulse is a marker for cortical excitability, where strong suppression is equivalent to low excitability (Höffken et al., 2007; Stude et al., 2016). Stimulation and recordings were conducted with the NeuroPack S1 MEB-9400 system by Nihon Kohden and filtered between 0.1 and 1000 Hz. After cleaning the skin with alcohol and SkinPure gel, Ag/AgCl electrodes were placed at CP1 and Cz with Elefix conduction gel (according to the international 10-20 system, impedances were kept below 5 kΩ). The Cz electrode served as reference and an additional velcro electrode was wrapped

around the upper left arm and served as ground. A block electrode was used as stimulator and placed at the inner side of the right-hand wrist. The strength of stimulation was individually adjusted so that the thenar muscles were slightly twitching (between 2.6 and 6.8 mA). First 200 single-pulse SEPs were recorded, delivered at the frequency of 1 Hz with 0.2 ms pulse duration. Afterwards, paired-pulses were delivered in the same frequency with an interstimulus interval of 30 ms.

2.2.5 – Data Processing and Analysis

The first two measures of tactile acuity of the right index finger were averaged and used as baseline measure. However, signal to noise ratio for tactile acuity measures in this experiment was poor (test-re-test reliability was only moderate; $ICC_{(3,2)} = .603$), a limitation that has to be taken into account. Data processing of EEG baseline and spontaneous EEG recordings as well as neurofeedback recordings were processed and analysed the same way as in experiment 1 (see 2.1.6 – Data Processing and Analysis). Less than 5 % of the signal was removed, indicating good data quality. Additionally, EEG recordings performed during the cortical excitability measure were averaged over all trials and N20 as well as P25 components were identified. As a marker for paired-pulse suppression (PPS), the following formula (3) was applied:

$$\frac{\Delta N20P25_2}{\Delta N20P25_1} \tag{3}$$

As such, the difference between the second pulse response components N20 and P25 was divided by the difference between the first pulse response components N20 and P25. Small ratios reflect strong suppression, while a ratio of 1 would reflect a complete lack of suppression (Höffken et al., 2007; Stude et al., 2016).

Because of small and strongly diverging group sizes, no inferential statistics were applied on group level. To test possible perceptual learning effects in the absence of eRSS on all participants, repeated measures *ANOVA*s were conducted. Additionally, to explore the relationship between alpha oscillations and cortical excitability, regression analyses (adjusted R^2 are reported) were conducted. Both types of analyses were performed in IBM® SPSS® V25. All entered variables followed a normal distribution as confirmed with the Kolmogorov-Smirnov test and unless states otherwise, data are reported as *mean* ± *SEM*.

2.3 – Pneumatic repetitive sensory stimulation to induce perceptual learning

In the following experiment, a pneumatic stimulation protocol was piloted to ensure the induction of tactile perceptual learning, a prerequisite for all further experiments.

2.3.1 – Participants

In this pilot experiment, 14 healthy, right-handed volunteers participated (8 women, mean age 24.2 ± 3.0). Handedness of participants was confirmed using the Edinburgh Handedness Inventory (Oldfield, 1971; mean laterality quotient 81.2 ± 15.7). No participant took regular medication (excluding contraceptives and in two cases thyroid hormones). At the end of the experiment, all participants received monetary compensation. The study protocol was approved by the Ethics Committee of the Ruhr-University Bochum and in accordance with the Declaration of Helsinki, all participants provided written informed consent. Four participants were removed from further analysis, by consequence of insufficient sensitivity at their right-hand fingertips to perform the tactile acuity measure.

2.3.2 – Experimental Schedule

The experiment started with a practice measure of tactile acuity (2PD). The procedure was equivalent to the one applied in experiment 1 (see 2.1.3 – Tactile Acuity). After the introduction, participants performed a baseline measure of tactile acuity on the right index finger (pre1-right). Then, another two baseline measures were assessed: one on the right (pre2-right) and on the left index finger (pre1-left), in randomized order. During the next 30 minutes, participants watched an animal documentary while pneumatic repetitive sensory stimulation (pRSS) was applied. Finally, a post measure of tactile acuity was assessed on the index finger of each hand, in randomized order (post-right and post-left; see Fig. 10).

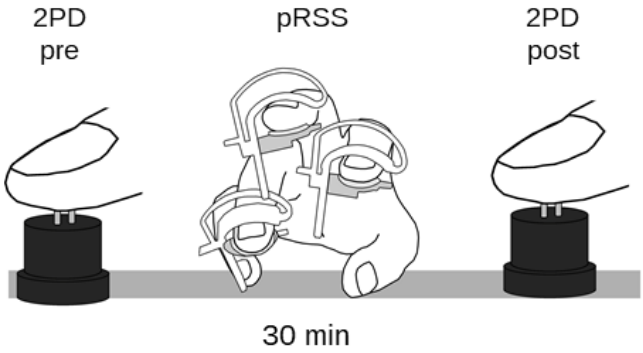

Figure 10 | **Experiment 3 – schedule**. The experiment consisted of one session, where the effect of pneumatic repetitive sensory stimulation (pRSS) on tactile acuity (2PD) was assessed on the index fingers of both hands (stimulated and unstimulated).

2.3.3 – Pneumatic Repetitive Sensory Stimulation

Pneumatic repetitive sensory stimulation (pRSS) was applied to the index-, middle- and ring-fingers of the right hand for 30 minutes using an airflow-driven membrane (Festo®; see Fig. 11). The stimulation of multiple fingers was implemented to increase the efficacy of the stimulation to drive cortical responses. The stimulation protocol was equivalent to the one previously used for eRSS and consisted of a 20 Hz stimulus train for 2 sec, with a 5 sec inter-train interval (single air-puff duration: 20ms). The stimulation sequence was generated with a Master 8 (A.M.P.I), which forwarded TTL pulses to the EEG-trigger module (NeuroConn) as well as to the pneumatic interface (Wienbruch et al., 2006). The TTL pulses were used to control magnetic solenoid valves (operating pressure: 5 bar; Festo®). The valves were placed in an adjacent room to reduce operating noise. The airflow was transmitted to the participant using plastic standard tubes (Festo®), which inflated the circular membrane attached to the skin (~0.8 cm^2; 4D Neuroimaging Inc.). The latency between the Master 8 trigger output and the air-puff arriving at the membrane was 33 ms. This latency was subtracted in the presented data, ensuring that the latency of 0 in all illustrations reflects the arrival of the stimulus on the skin. For a detailed description see Wienbruch et al. (2006).

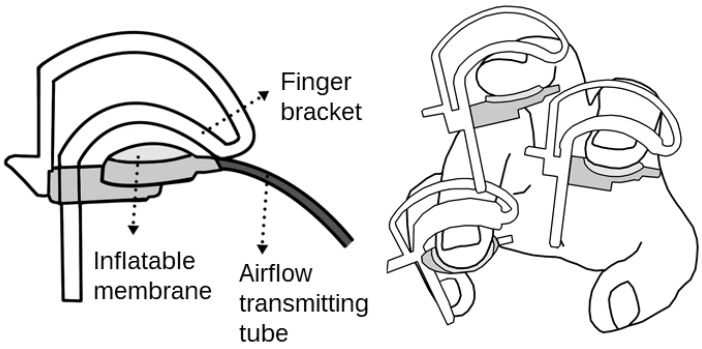

Figure 11 | **Pneumatic repetitive sensory stimulation**. Inflatable membranes were attached to the right index- middle- and ring-finger with adjustable brackets. Magnetic solenoid valves in the adjacent room, controlled airflow through a transmitting tube which lead to in- or deflation of the membrane. This way, precisely timed stimuli could be transmitted to the fingers.

2.3.4 – Data Processing and Analysis

The first two measures of tactile acuity of the right index finger were averaged and used as baseline measure (test-re-test reliability was high; $ICC_{(3,2)} = .966$). In order to test the effect of pRSS on tactile acuity for each hand (stimulated and unstimulated), paired T-Tests were applied in IBM® SPSS® V25. All entered variables followed a normal distribution and mean values are reported in *mean* ± *SEM*.

2.4 – EEG recording of pneumatic repetitive sensory stimulation

The following experiment explored cortical responses to pneumatic repetitive sensory stimulation.

2.4.1 – Participants

In this experiment, 15 healthy, right-handed volunteers (9 women, mean age 23,3 ± 2.9) participated. Handedness of participants was confirmed using the Edinburg Handedness Inventory (Oldfield, 1971; mean laterality quotient: 94.3 ± 9.0). No participant took regular medication. At the end of the experiment, all participants received monetary compensation. The study protocol was approved by the Ethics Committee of the Ruhr-University Bochum and in

accordance with the Declaration of Helsinki, all participants provided written informed consent. One participant was removed from data analysis as a consequence of poor EEG data quality

2.4.2 – Experimental Schedule

The experiment started with a 4-minute EEG baseline recording (2 x 1 min eyes open and 30 sec eyes closed), which was used as a reference for later EEG recordings. Afterwards, pneumatic repetitive sensory stimulation (pRSS) was applied for 40 min, during which participants watched an animal documentary. The duration of stimulation was increased compared to the previous experiment, to study possible changes over time of the cortical response pattern to the stimulation. Otherwise, the procedure was exactly the same as reported in the previous experiment (see 2.3.3 – Pneumatic Repetitive Sensory Stimulation). During the whole time, scalp EEG was continuously recorded (see Fig. 12).

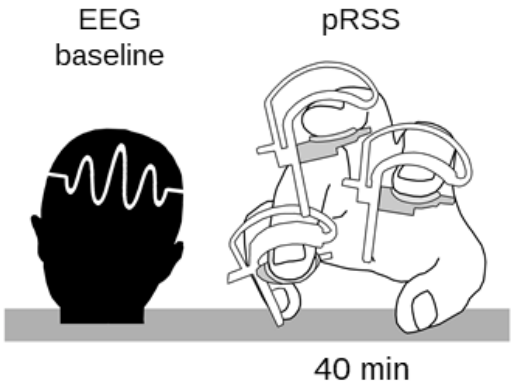

Figure 12 | **Experiment 4 – schedule**. First, a baseline EEG recording was conducted and then pneumatic repetitive sensory stimulation (pRSS) was applied for 40 min. During this time, participants watched an animal documentary. Additionally, scalp EEG was recorded for the whole duration of pRSS.

2.4.3 – EEG Recording

Like in experiment 1, EEG recordings were performed using a 13-channel DC-EEG amplifier by NeuroConn (Thera Prax® Mobile). Participants sat in a comfortable chair inside of a Faraday cage. Before electrode placement, the skin was cleaned with alcohol and prepared with SkinPure preparation gel. The Ag/AgCl electrodes were placed with Elefix conduction gel and

arranged according to the international 10-20 system (F3, F4, CP1, CP2, PO3, PO4; ground: forehead; reference: linked mastoids). Additionally, four ocular electrodes were applied. The sampling rate of the signal was 512 Hz. Baseline measures alternated between two eyes-open (each lasting 1 min) and eyes-closed conditions (each lasting 30 s). Both eyes-open conditions were combined to serve as the baseline measure all further EEG data was normalized to.

2.4.4 – Data Processing and Analysis

Ocular artefacts were removed from the EEG signals using least mean squares regression (Gómez-Herrero et al., 2006). The corrected signal was then manually inspected for remaining artefacts using the EEGLAB toolbox (Delorme and Makeig, 2004). In total, 12.7% of the EEG signal was removed, indicating good data quality considering the length of trials (7 s) and the continuous recording. The EEG signal of the somatosensory electrode (CP1) was high pass filtered above 1 Hz and a notch filtered around 47 and 53 Hz with a linear finite impulse response (FIR) filter and segmented into 7 sec epochs. Sensory evoked potentials (presented in µV) were generated by computing the grand average of EEG signal epochs over all trials and subsequently all participants.

To illustrate the characteristics of SEPs induced by single pneumatic stimuli, single air-puffs to four participants with a 1 Hz intertrial interval were applied. Figure 13 depicts an example of a SEP following a single air-puff stimulation, otherwise recorded and processed identically to the 20 Hz train air-puff stimulation described above.

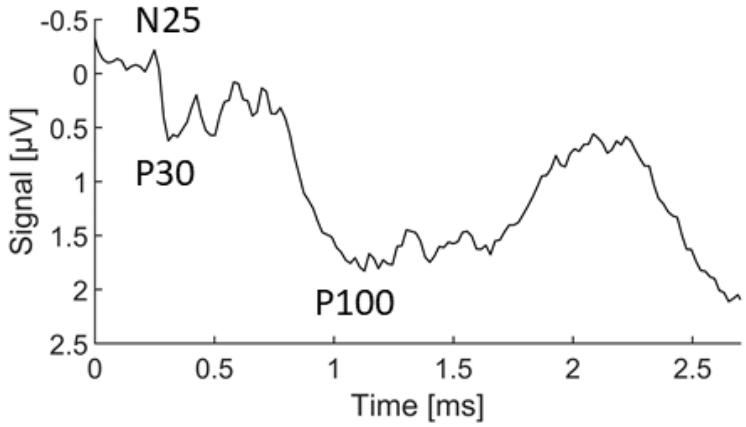

Figure 13 | Illustration of an airpuff-induced somatosensory evoked potential. Average of 200 trials pneumatic stimulation averaged over representative participants (repetition rate 1 Hz).

Time-frequency analyses were performed using Morlet wavelet convolution (3-60 Hz; 8-15 dynamic cycles). Baseline correction was applied with formula (1; see 2.1.1.6 – Data Processing and Analysis), where the EEG-baseline measure was applied as baseline and EEG-measure of interest is referred to as activity.

Stimulus evoked power- and phase-changes from baseline were analyzed using non-parametrical permutation testing (Maris and Oostenveld, 2007) in MATLAB R2015a. The time-frequency decomposed signal was tested against a null-hypothesis distribution, which consisted of the average of 1000 permutations, shuffled in the temporal domain. More specifically, in each iteration, the time series data was shifted around a random offset. Significance was tested by applying a T-test to each data point and corrected for multiple comparisons using a cluster-based procedure. In this approach, the 1% largest clusters, referring to adjacent data points reaching significance, were identified for each iteration. Only clusters the size or larger than 1% of the largest of these clusters, were considered significant. To analyse possible signal processing dynamics over 40 minutes of stimulation, the first and last ten minutes of stimulation were compared. To this end, a similar procedure was used with shuffled conditions (first and last ten-minute recordings) instead of the shuffled temporal domain in each iteration. Furthermore, condition differences were tested with Welch's Test appropriate for within subject designs. The same multiple comparison correction was applied.

2.5 – Combination of alpha neurofeedback training and pneumatic repetitive sensory stimulation

In the last experiment, the effects of somatosensory alpha NF training on subsequent cortical processing of pneumatic repetitive sensory stimulation and perceptual learning were analysed.

2.5.1 – Participants

A total of 41 healthy, right-handed volunteers (21 women, mean age 24,4 ± 3.0) participated in this experiment. Handedness of participants was confirmed using the Edinburg Handedness Inventory (Oldfield, 1971; mean laterality quotient: 76.8 ± 19.0). No participant took regular medication. The study protocol was approved by the Ethics Committee of the Ruhr-University Bochum and in accordance with the Declaration of Helsinki, all participants provided written

informed consent. All participants were randomly assigned to one of two groups performing NF training to either increase (alpha up) or decrease (alpha down) their somatosensory alpha power. By consequence of violations of inclusion criteria or insufficient data quality, 6 participants were excluded from further analysis. One participant aborted the experiment early, as she felt uncomfortable sitting for 20 minutes and one participant fell asleep during repetitive sensory stimulation. Both were removed from further analysis. Two participants were removed as they were unable to perform the tactile acuity measure due to insufficient sensitivity at their fingertips. One participant showed strong occipital alpha activity with eyes open, thereby concealing somatosensory alpha peaks measured at CP1 (according to international 10-20 system). One last participant was excluded, as he had already taken part in one of our studies and was therefore omitted from participation. Final group sizes consisted of n = 13 in the alpha up group, n = 11 in the alpha down group, and n = 12 NF-paradoxical-responders (NF-PR; 5 from the alpha up group and 7 from the alpha down group). NF-paradoxical-responders were defined as participants from the alpha up who on average decreased alpha power and participants from the alpha down group, who on average increased alpha power and were therefore handled as a separate group.

2.5.2 – Experimental Schedule

The first day of the experiment started with a practice tactile acuity measure (2PD). The procedure was the same as described previously (see 2.3.3 – Tactile Acuity). Afterwards, all participants took part in a 4-min EEG baseline recording before they performed their respective NF training for 25 minutes. The second day of the experiment began with a tactile acuity baseline assessment at the right index finger. Subsequently, another two baseline measure of tactile acuity were assessed, one on the right and one on the left index finger in randomized order. Following this, an EEG baseline recording took place before participants performed their respective NF training for 25 minutes. Immediately afterwards, pneumatic repetitive sensory stimulation (pRSS) was applied to the right index finger for 30 minutes, while scalp EEG was recorded, and participants watched an animal documentary. The procedure of pRSS was identical to the one applied in previous experiments (see 2.2.1.3. Pneumatic Repetitive Sensory Stimulation). Lastly, another two tactile acuity assessments were performed, one on the right and one on the left index finger in randomized order (see Fig. 14).

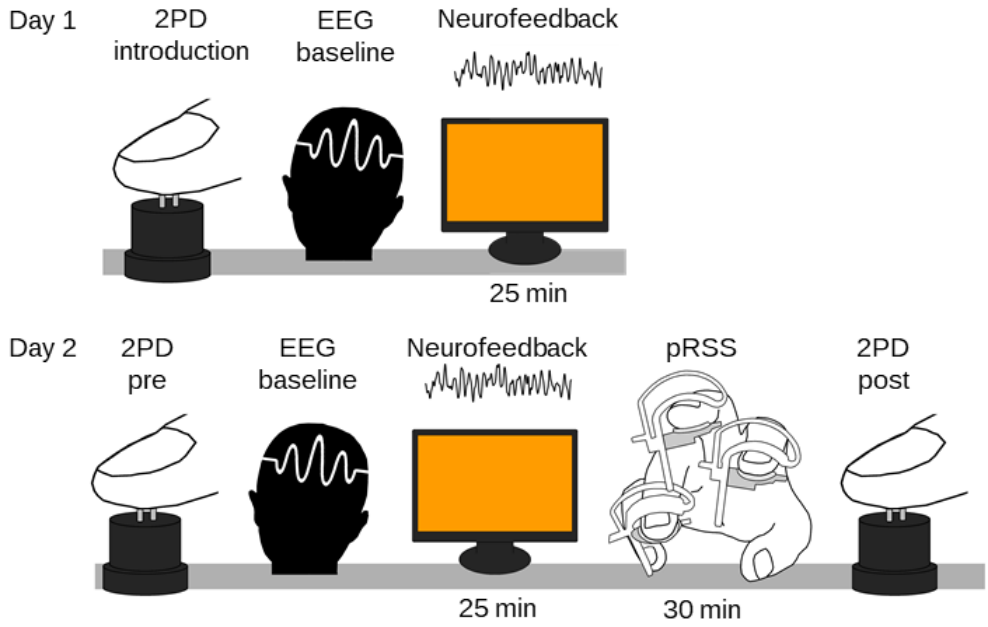

Figure 14 | **Experiment 5 – schedule**. The experiment took place on two consecutive days. The first day introduced the procedure of measuring tactile acuity (2PD), followed by an EEG baseline recording and NF training. The second day started with baseline tactile acuity measure on the index fingers of both hands, followed by an EEG baseline recording, NF training, pneumatic repetitive sensory stimulation (pRSS) and was concluded with one last measure of tactile acuity on each index finger.

2.5.3 – EEG Recording and Neurofeedback Training

EEG recordings and NF training were identical to the procedures applied in experiment 1 (see 2.1.5 – EEG Recording and NF training). However, on the second day of training, NF training was performed for 3 blocks (compared to 2 blocks in the experiment 1).

2.5.4 – Data Processing and Analysis

The first two measures of tactile acuity of the right index finger were averaged and used as baseline measure (test-re-test reliability was high; $ICC_{(3,2)} = .837$). Data processing of EEG baseline and spontaneous EEG recordings as well as neurofeedback recordings were processed and analysed the same way as in experiment 1 (see 2.1.6 – Data Processing and Analysis). Less than 10 % of the signal was removed, indicating good data quality. Time frequency analyses were performed the same way as in experiment 2.4 (see 2.4.4 – Data Processing and Analysis).

Additionally, group-level analysis was performed to identify differences in oscillatory responses to pRSS. Therefore, two different intervals of interest were created and averaged over the temporal domain (0.5 – 2 sec to account for processing during stimulation trains and 4 – 6 sec to account for oscillatory processes between stimulation trains). *T*-tests for each data point were performed between all pairs of groups. To correct for multiple comparisons, a cluster-based procedure was applied. To this aim, group-level the same *T*-tests were applied 1000 times while permutating the group membership of participants. This way, the two groups that were tested against each other were artificially created anew in each iteration by assigning participants to them randomly independent of their experimental condition. For each iteration, the 1% largest clusters, that is adjacent data points reaching significance, were identified. In the final *T*-test between the two experimental conditions, only clusters the size or larger than 1% of the largest clusters found in the random group membership permutations, were considered significant.

To compare tactile acuity and perceptual learning between groups and to explore the relationship between alpha power changes and perceptual learning and oscillatory processes, a mixed factorial and one-way *ANOVA*s as well as regression analyses (adjusted R^2 are reported) were performed in IBM® SPSS® V25. All entered variables followed normal distributions as confirmed by the Kolmogorov-Smirnov test and unless stated otherwise, all data are presented as *mean* ± *SEM*.

3 – Results

3.1 – Efficacy of short-term neurofeedback training

To ensure that neurofeedback training was successfully implemented and accordingly, that somatosensory alpha oscillations were modulated, mixed factorial *ANOVA*s were applied. The data was collected in three separate experiments.

3.1.1 – First neurofeedback study

Grand average spectral power changes between first EEG baseline recordings on day 1 and the last minutes of NF training on day 2 show significant group differences (see Fig. 15c-e; two-way mixed *ANOVA*; main effect time: $F_{(1,45)} = 8.73$; $p < .01$; interaction: $F_{(1,45)} = 8.73$; $p < .01$; for post hoc analysis, see 6.1 – Appendix Table 1). Participants from the alpha up group were able to markedly increase somatosensory alpha power levels, while the alpha down group slightly decreased their alpha power, though not significantly. No changes were apparent for NF-paradoxical-responders. Baseline levels did not differ significantly between groups.

Analysis of the alpha power development during NF training was performed on the average alpha power relative to baseline for each block of training (see Fig. 15a-b). Significant differences over time and between conditions were revealed for the first day (two-way mixed *ANOVA*; main effect condition: $F_{(2,45)} = 6.49$; $p < .01$; main effect NF-block: $F_{(2,90)} = 11.24$; $p < .001$; interaction: $F_{(4,90)} = 3.40$; $p < .05$; for post hoc analysis, see Appendix 6.1 – Table 2). Throughout all three blocks of NF training, the alpha up group showed steady increases in alpha power. In contrast, the alpha down group stayed below baseline levels for the whole duration of the training. NF-paradoxical-responders slightly increased their alpha power levels over time. On the second day of NF training, significant differences became apparent between groups with slight increases in alpha power levels for both NF groups, while the control group and NF-paradoxical-responders remained slightly above baseline levels (two-way mixed *ANOVA*; main effect NF-block: $F_{(1,64)} = 4.26$; $p = .043$; main effect condition: $F_{(3,64)} = 6.79$;$p < .001$; for post hoc analysis, see 6.1 – Appendix Table 3).

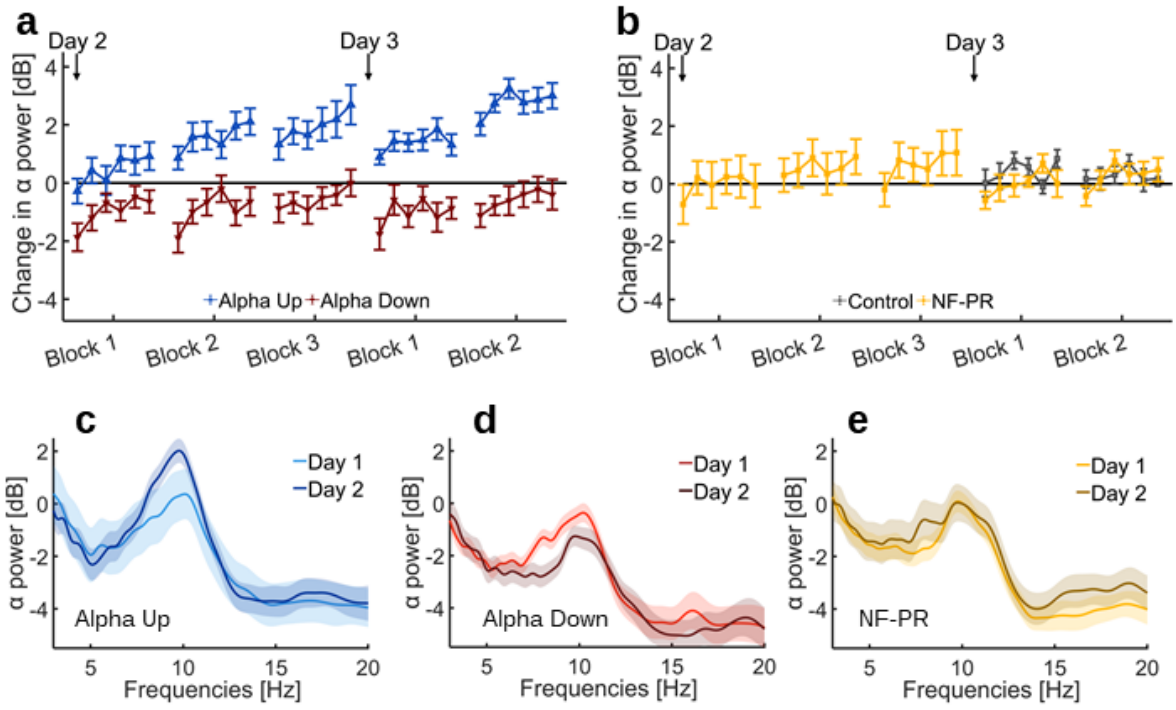

Figure 15 | **Efficacy of neurofeedback training (experiment 1)**. Temporal development over both days of NF training are illustrated for both NF groups (a) and NF-paradoxical-responders as well as the control group (b). All data are presented relative to the baseline of the respective day. Each time point represents 1 min of NF training. c-e, Comparisons between the first baseline recording on day 1 and the last minute of NF training across groups. All data are presented as *mean ± SEM (Brickwedde et al., 2019)*.

While a group of non-responders were unable to alter somatosensory alpha power levels in the targeted direction, two thirds of the participants were able to perform the task as intended. For these participants, the NF training induced remarkable group differences in somatosensory alpha oscillations and can therefore be considered successful.

3.1.2 – Second neurofeedback study

To test the isolated effect of NF training on tactile acuity, the second experiment aimed at replicating the results of experiment 1, without applying subsequent repetitive sensory stimulation. However, on the first day of NF training only 2 blocks of training were applied, opposed to 3 blocks in the previous experiment. While the data show a similar pattern to the results observed in experiment 1 on a group level (see Fig. 16 a-e), the majority of all participants responded to NF training paradoxically. As a consequence, the alpha up and alpha

down groups were too small for reliable inferential analysis (alpha up: n = 6; alpha down: n = 6; NF-PR: n = 16). Therefore, no group-level inferential statistics were performed on the data.

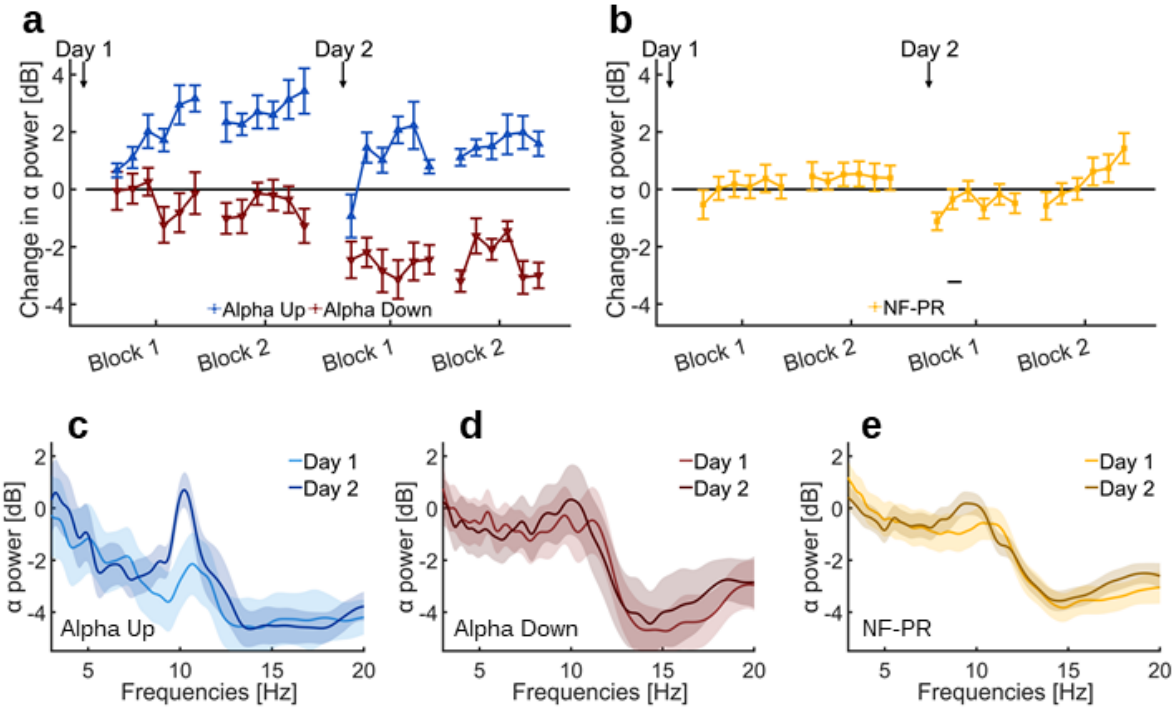

Figure 16 | **Efficacy of neurofeedback training (experiment 2)**. Temporal development over both days of NF training are illustrated for both NF groups (a) as well as NF-paradoxical-responders (b). All data are presented relative to the baseline of the respective day. Each time point represents 1 min of NF training. c-e, Comparisons between the first baseline recording on day 1 and the last minute of NF training across groups. All data are presented as *mean* ± *SEM*.

The alterations applied to the NF training in this experiment were unsuccessful. Nevertheless, numerically the data shows the same pattern as could be observed in neurofeedback study 1.

3.1.3 – third neurofeedback study

In this experiment, the same neurofeedback procedure as in experiment 1 was applied, with an additional block of NF training on the last (second) day. Grand average spectral power changes between first baseline measurements on day 1 and the last minutes of NF training on day 2 revealed a significant interaction (two-way mixed *ANOVA*; interaction: $F_{(2,32)} = 4.26$; $p = .023$; see Fig. 17c-e; for post hoc analysis, see Appendix 6.1 – Table 7). Similar to the observations of experiment 1, participants from the alpha up group were able to markedly increase somatosensory alpha power levels (however, after correcting for multiple comparisons, this

effect no longer reached significance), while the alpha down group slightly decreased their alpha power, though not significantly. No changes were apparent for NF-paradoxical-responders. Baseline levels did not differ significantly between groups.

Analysis of the alpha power development during NF training was performed on the average alpha power relative to baseline for each block of training (see Fig. 17a-b). Significant differences over time and between conditions were revealed for the first day (two-way mixed *ANOVA*; main effect condition: $F_{(2,32)} = 4.04$; $p = .027$; main effect NF-block: $F_{(2,64)} = 16.46$; $p < .001$; for post hoc analysis, see Appendix 6.1 – Table 8). Throughout all three blocks of NF training, the alpha up group showed steady increases in alpha power. In contrast, the alpha down group stayed below baseline levels for the first two blocks and in the last block, alpha levels receded back to baseline. NF-paradoxical-responders slightly increased their alpha power levels over time. After correction for multiple comparisons, group differences for day 1 no longer reached significance.

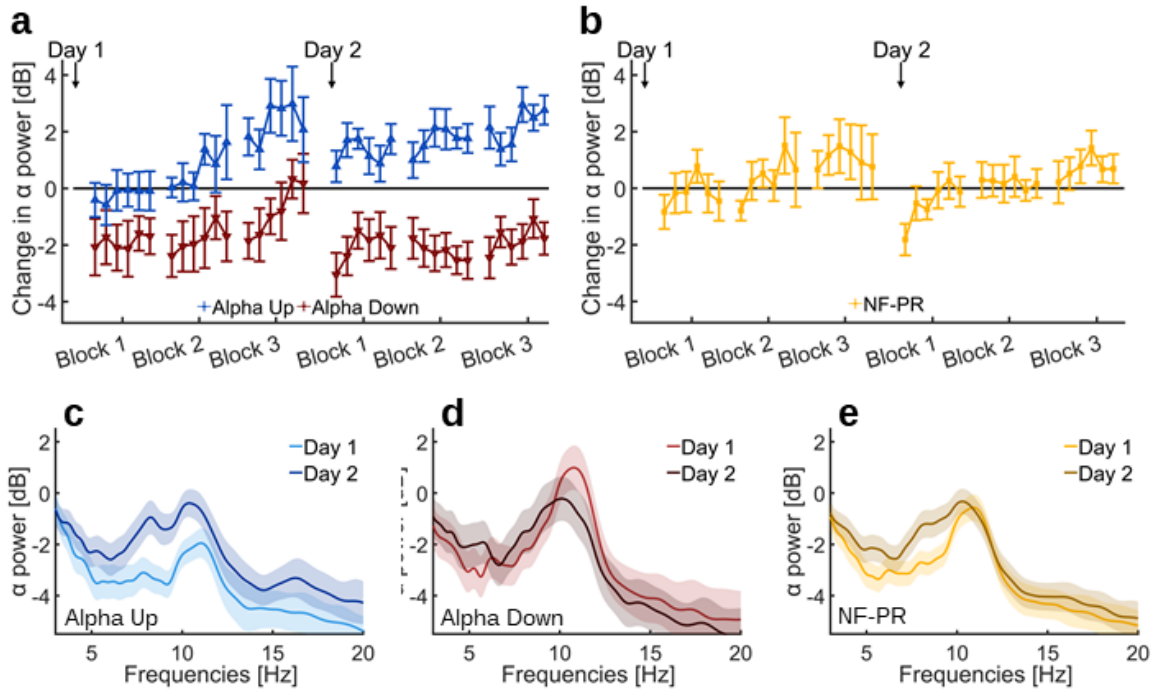

Figure 17 | **Efficacy of neurofeedback training (experiment 5)**. Temporal development over both days of NF training are illustrated for both NF groups (a) as well as NF-paradoxical-responders (b). All data is presented relative to the baseline of the respective days. Each time point represents 1 min of NF training. c-e, Comparisons between the first baseline recording on day 1 and the last minute of NF training across groups. All data are presented as *mean* ± *SEM*.

On the second day of NF training, significant differences became apparent between groups and over time with slight increases in alpha power levels for all groups, while the alpha down group

remained clearly below baseline, contrasting the alpha up group, already starting above baseline levels. NF-paradoxical-responders started below baseline levels, but alleviated alpha levels to slightly above their baseline from the second block onwards (two-way mixed *ANOVA*; main effect NF-block: $F_{(2,64)} = 5.75$; $p = .005$; main effect condition: $F_{(2,32)} = 22.15$; $p < .001$; for post hoc analysis, see Appendix 6.1 – Table 9). Differences between NF groups were significant in all blocks. In the first block, NF-paradoxical-responders differed significantly from the alpha up group. In the last block, instead they differed significantly from the alpha down group.

NF training in this experiment provided similar results to experiment 1 with two thirds of the participants successfully modulating their somatosensory alpha oscillations and one third of the participants responding paradoxically.

The results show that short-term neurofeedback can successfully be applied to up- and – down regulate somatosensory alpha oscillations. A training of only 2 blocks (12 min in total) seemed too short to elicit alpha power changes. In experiment 1, differences between groups were already significant on the first day of training. However, applying the same neurofeedback protocol, the effect of NF training in the third neurofeedback study only became significant on the second day of training. Further experiments are necessary to gain deeper knowledge about the optimal amount and duration of training.

3.2 – Effects of neurofeedback training on perceptual learning

After showing that somatosensory alpha power levels were successfully altered, the effect of neurofeedback training on subsequent perceptual learning processes was analysed. The data for these analyses were collected in three separate experiments.

3.2.1 – Electrical repetitive sensory stimulation

On average, repetitive sensory stimulation induced tactile acuity improvements, however, not equally for all groups (see Fig. 18a-d; two-way mixed *ANOVA*; main effect pre-post: $F_{(1,64)} = 40.13$; $p < .001$; interaction: $F_{(3,64)} = 13.66$; $p < .001$). Post hoc tests (see Appendix 6.1 – Table 4) revealed that participants of the alpha up group showed the strongest tactile acuity changes, whereas the discrimination performance of participants from the alpha down group remained unchanged. Participants from the control group displayed an intermediate

improvement commonly observed for this kind of repetitive sensory stimulation protocol (Ragert et al., 2008; Schlieper and Dinse, 2012; Freyer et al., 2013; Heba et al., 2016; Dinse et al., 2017; Muret and Dinse, 2018; Schmidt-Wilcke et al., 2018), while NF-paradoxical-responders slightly, yet non-significantly improved. Fig. 18e displays the extent of perceptual changes compared between groups. Differences between participants from the control group and NF-paradoxical-responders were minor; however, both NF groups differed significantly from them and between each other (one-way *ANOVA*; $F_{(3,64)} = 12.44$; $p < .001$; for post hoc analysis, see Appendix 6.1 – Table 5).

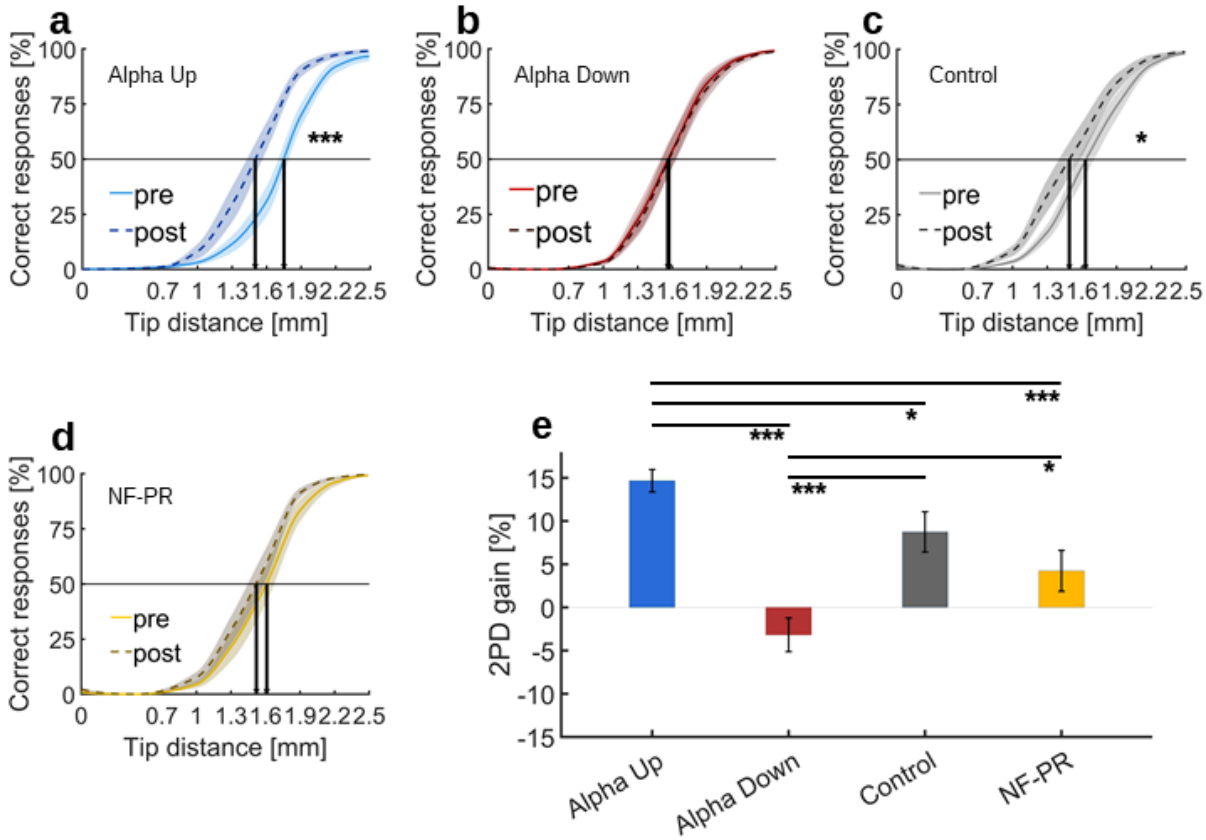

Figure 18 | **Effect of neurofeedback training on perceptual learning (experiment 1)**. a-d, psychometric curves before and after eRSS for all conditions. A shift of the curve to the left indicates improved tactile acuity (a marker for perceptual learning). Data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$; two-way mixed *ANOVA*; e, tactile acuity improvements compared between groups. Data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$; one-way *ANOVA (Brickwedde et al., 2019)*;

The data clearly shows that the neurofeedback intervention elicited a strong effect on subsequent stimulation-induced perceptual learning, increasing learning success in the alpha up group and disrupting learning processes in the alpha down group.

3.2.2 – Effects of alpha neurofeedback training on tactile acuity without induction of perceptual learning

To rule out that the observed learning processes were not simply an effect of improved sensory processing of afferent inputs during tactile acuity measures, NF training was applied without repetitive sensory stimulation. While no group-level statistic was performed on tactile acuity changes due to the unsuccessful implementation of NF training, tactile acuity did not increase overall (repeated measures *ANOVA;* $F_{(1,29)} = .93$; $p = .931$) Independent of alpha power levels, no relevant tactile acuity changes were observable in the alpha up group and in NF-paradoxical responders, while the alpha down group showing slight declines (see Fig. 19).

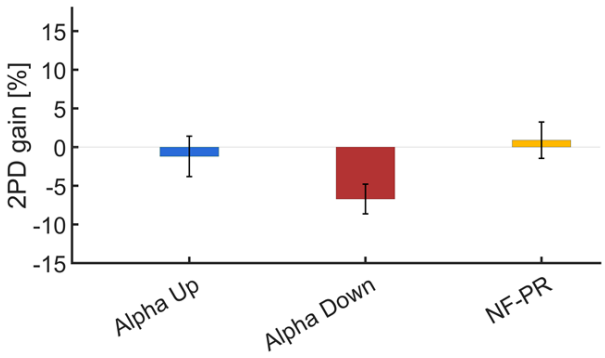

Figure 19 | **Perceptual learning compared between groups**. As a consequence of small and strongly diverging group sizes, no statistical analysis was applied on group level. Data are presented as mean ± SEM.

It is apparent that in the absence of repetitive sensory stimulation, no perceptual learning occurred, independent of alpha power levels prior to tactile acuity measurements.

3.2.3 – Pneumatic repetitive sensory stimulation

Similar to the observations from experiment 1, repetitive sensory stimulation induced tactile acuity improvements on the right index finger (stimulated with pRSS), again, not equally for all groups (see Fig. 20a-c; two-way mixed *ANOVA*; main effect pre-post: $F_{(1,32)} = 4.41$; $p = .045$; interaction: $F_{(2,32)} = 17.89$; $p < .001$). Post hoc tests (see Appendix 6.1 – Table 10) revealed that participants of the alpha up group showed the strongest tactile acuity changes,

whereas the discrimination performance of participants from the alpha down group decreased. NF-paradoxical-responders slightly, yet non-significantly improved.

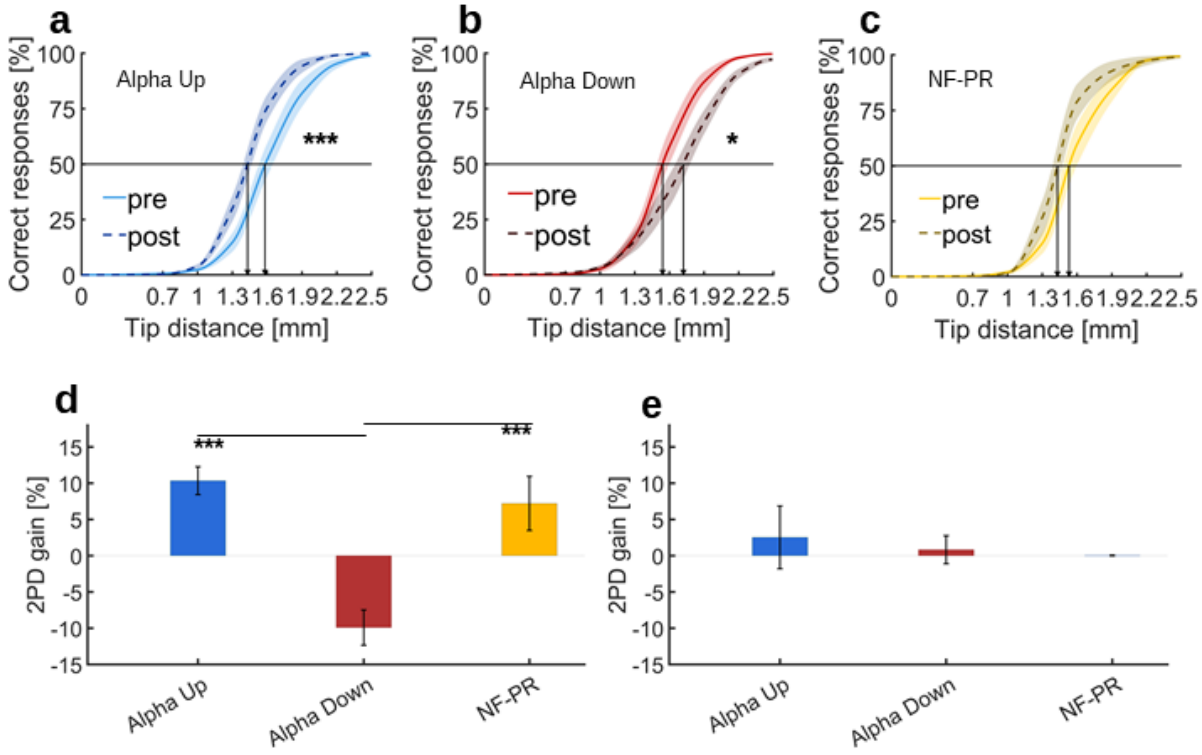

Figure 20 | **Effect of neurofeedback training on perceptual learning (experiment 5)**. a-c, psychometric curves before and after pRSS for all conditions. A shift of the curve to the left indicates improved tactile acuity (a marker for perceptual learning). Data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$; two-way mixed *ANOVA*; d, tactile acuity improvements compared between groups for the right (stimulated) hand. Data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$; one-way mixed *ANOVA*; e, tactile acuity improvements compared between groups for the left (unstimulated) hand. Data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$; one-way mixed *ANOVA*;

Figure 20d displays the extent of perceptual changes compared between groups. Differences between participants from the alpha up group and NF-paradoxical-responders did not reach significance. However, the alpha down group differed significantly from both other groups (one-way *ANOVA*; $F_{(2,32)} = 18.66$; $p < .001$; for post hoc analysis, see Appendix 6.1 – Table 11). Analysis of the left index finger (see Fig. 20e; unstimulated hand) did not reveal any changes in tactile acuity (repeated measures *ANOVA*; $F_{(1,34)} = 2.41$; $p = .130$). or any differences between groups (one-way *ANOVA*; $F_{(2,32)} = .10$; $p = .902$).

The results of experiment 1 could be replicated. Additionally, data of the unstimulated hand presents a strong case for the effect of NF training on perceptual learning, as opposed to processing of afferent inputs during tactile acuity measures.

The first and the third neurofeedback study show strong effects of NF training on tactile acuity changes. NF-paradoxical-responders neither showed alpha power changes, nor stimulation-induced tactile acuity changes. Additionally, the second neurofeedback experiment was performed without RSS, which left tactile acuity thresholds at baseline levels. In the third neurofeedback study, no tactile acuity changes were observable for the unstimulated hand. Both results indicate, that NF training elicits effects on stimulation-induced perceptual learning processes, rather than information processing during tactile acuity measures.

3.2.4 – Relationship between alpha oscillations and perceptual learning efficiency

To gain deeper insight into the relation of alpha power and perceptual learning, regression analyses between neurofeedback-induced changes in alpha oscillations and changes of discrimination thresholds were conducted. The data was collected from three separate experiments.

3.2.4.1 – Electrical repetitive sensory stimulation

As initially hypothesized, learning variability as indicated by standard deviations was strongly reduced within conditions (Fig. 21a-c). Particularly the alpha up group was very homogenous (alpha up: ± 5.4; alpha down: ± 7.5). In contrast, standard deviations were higher for the control group (± 10.4), NF-paradoxical-responders (± 9.5), and all participants combined (± 10.5). When comparing both NF groups, striking clusters become apparent (Fig 21a). These results emphasize the remarkable effect of alpha power, explaining up to 59% of the interindividual perceptual learning variability ($p < .001$; $R^2 = .59$). Participants from the control group showed a similar relationship, although less pronounced (Fig 21b; $p < .05$; $R^2 = .18$). By contrast, NF-paradoxical responders barely showed any perceptual learning, independent of their alpha power levels (Fig 21c; $p = .343$; $R^2 = -.002$).

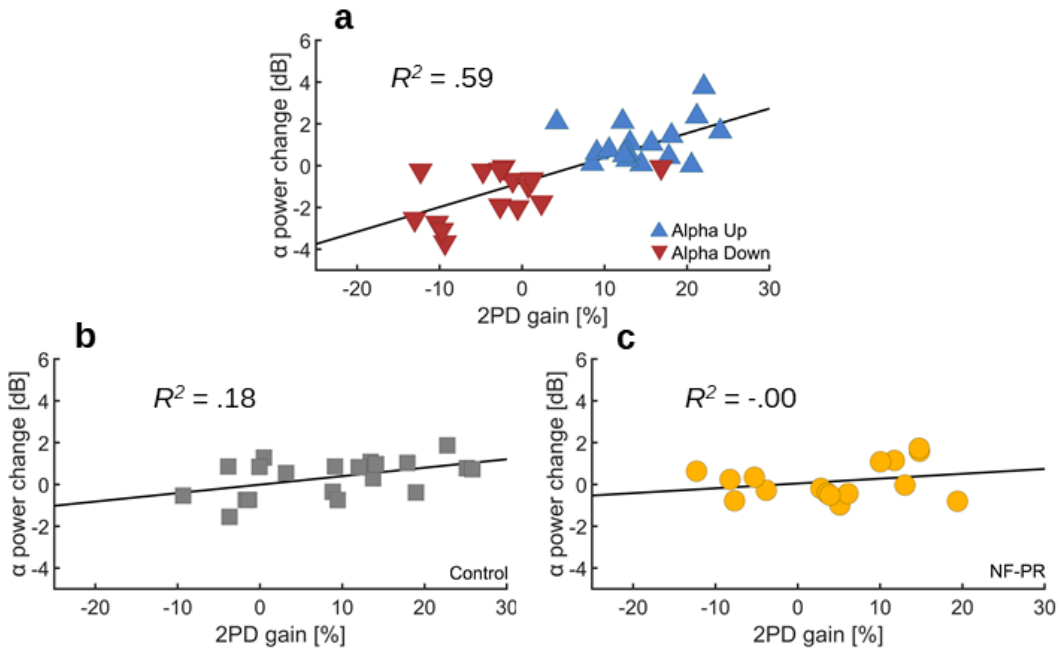

Figure 21 | **Relationship between somatosensory alpha oscillations and perceptual learning (experiment 1)**. a-c, regression analysis between alpha power change during NF training relative to the EEG baseline recording of day 2 and perceptual learning (2PD gain) for all conditions (Brickwedde et al., 2019). Adjusted R^2 are reported.

These analyses show that there is a strong connection between alpha oscillations and perceptual learning, which is especially pronounced for NF groups. NF-paradoxical-responders fail to show this relationship.

3.2.4.2 – Effects of alpha neurofeedback training on tactile acuity without induction of perceptual learning

In the absence of repetitive sensory stimulation, considerably fewer participants displayed relevant tactile acuity changes. For the NF groups, no relationship between alpha power and tactile acuity changes could be found (see Fig. 22a; p =.277; R^2 = .039). Similarly, NF-paradoxical-responders showed no relationship between alpha power and tactile acuity changes (see Fig. 22b; p =.267; R^2 = .022).

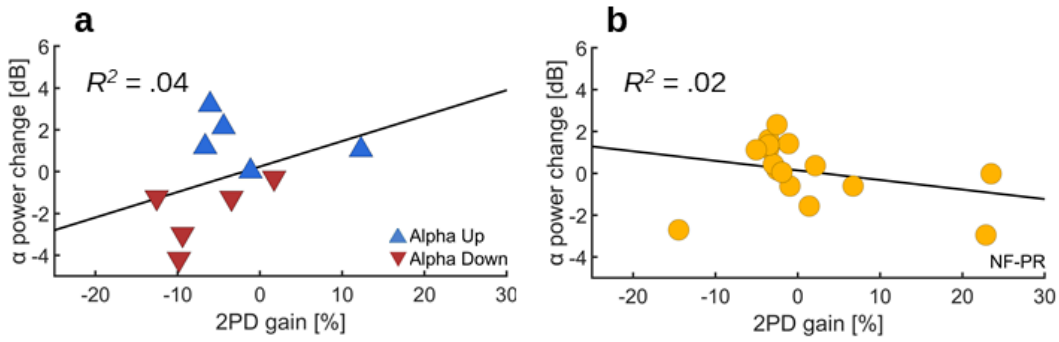

Figure 22 | **Relationship between somatosensory alpha oscillations and tactile acuity changes (experiment 2)**. a-b, regression analysis between alpha power change during NF training relative to the EEG baseline recording of day 2 and perceptual learning (2PD gain) for all conditions. Adjusted R^2 are reported.

The data of this experiment revealed that alpha power levels did not elicit a relevant effect on tactile acuity changes.

3.2.4.3 – Pneumatic repetitive sensory stimulation

Paralleling the results of experiment 1, learning variability as indicated by standard deviations was strongly reduced within NF groups (Fig. 23a; alpha up: ± 6.7; alpha down: ± 8.1). In contrast, standard deviations were higher for NF-paradoxical-responders (Fig. 23b; ± 11.2), and all participants combined (± 12.5). When comparing both NF groups, the same striking clusters as in experiment 1 become evident (Fig 23a). Intriguingly, the same effect was found for NF-groups, explaining up to 59% of the interindividual perceptual learning variability (p < .001; R^2 = .59). Again, NF-paradoxical responders showed the same trend for increased perceptual learning after alpha power increases. However, this effect failed to reach significance (Fig 23b; p =.104; R^2 = .185).

The same analyses were performed for the relationship between tactile acuity changes on the left index finger (unstimulated hand) and alpha power changes over the right somatosensory cortex (see Fig. 23c-d). While no clear trend of improvement or decline in tactile acuity was apparent, interindividual variance was strong, particularly in the alpha up group (alpha up: ± 14.4; alpha down: ± 6.4; NF-PR: ± 9.8; all participants: ± 10.7). No relationship between pre-RSS somatosensory alpha power levels over the right hemisphere and tactile acuity changes on the left index finger could be found for any group (NF-groups: p < .745; R^2 =-.04; NF-PR: p < .697; R^2 =-.09).

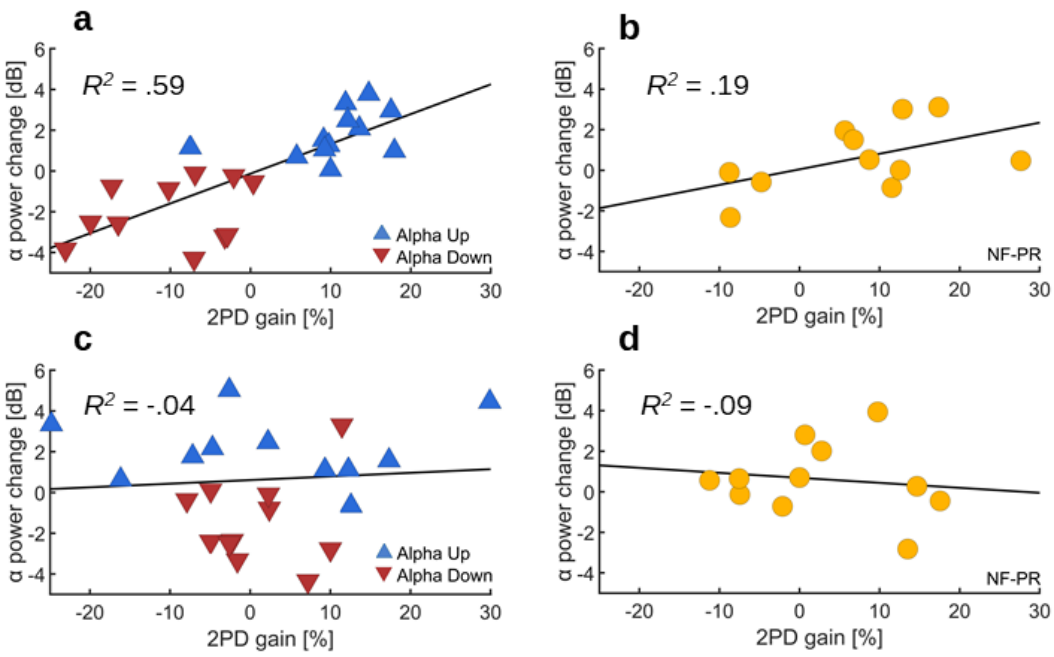

Figure 23 | **Relationship between somatosensory alpha oscillations and perceptual learning (experiment 5)**. a-b, regression analysis between alpha power change over the left somatosensory cortex during NF training relative to the EEG baseline recording of day 2 and perceptual learning (2PD gain) measured on the right index finger (stimulated hand) for all conditions. c-d, regression analysis between alpha power change over the right somatosensory cortex during NF training relative to the EEG baseline recording of day 2 and perceptual learning (2PD gain) measured on the left index finger (unstimulated hand) for all conditions. Adjusted R^2 are reported.

This experiment could replicate the results of experiment 1, reconfirming the lack of a relationship between alpha power and perceptual learning for NF-paradoxical-responders. Furthermore, the lack of a connection between tactile acuity changes on the left (unstimulated) index finger and right somatosensory alpha oscillations, presents further evidence for the effect of NF training on perceptual learning rather than on tactile processing during tactile acuity measurements.

Neurofeedback study 1 revealed a strong relationship between neurofeedback-induced alpha oscillations and stimulation-induced perceptual learning. The results could be replicated in neurofeedback study 3. Both experiments also illustrated, that NF-paradoxical-responders did not show this relationship. Neurofeedback study 2 explored the relationship between alpha oscillations and tactile acuity without induction of perceptual learning. No connection could be found. This result is further verified by neurofeedback study 3, where no relationship between alpha oscillations measured above the right somatosensory cortex and tactile acuity changes on the left (unstimulated) hand could be observed.

3.3 – Additional oscillatory predictors for perceptual learning

3.3.1 – Relationship between perceptual learning and additional oscillatory frequency bands

It is possible, that alpha oscillations are not the only frequency band showing strong relationships to perceptual learning. Therefore, the relationship between additional oscillatory frequency bands and perceptual learning, was analysed.

Regression analyses of the effects of different oscillations prior to repetitive sensory stimulation on perceptual learning yielded no substantial results. No relevant learning variance (< 10%) could be explained by theta (p = .909; R^2 =-.015), lower (p = .028; R^2 = .059) and upper beta (p = .012; R^2 = .078) as well as lower gamma (p =.030; R^2 = .055) oscillations (Fig. 24a-e).

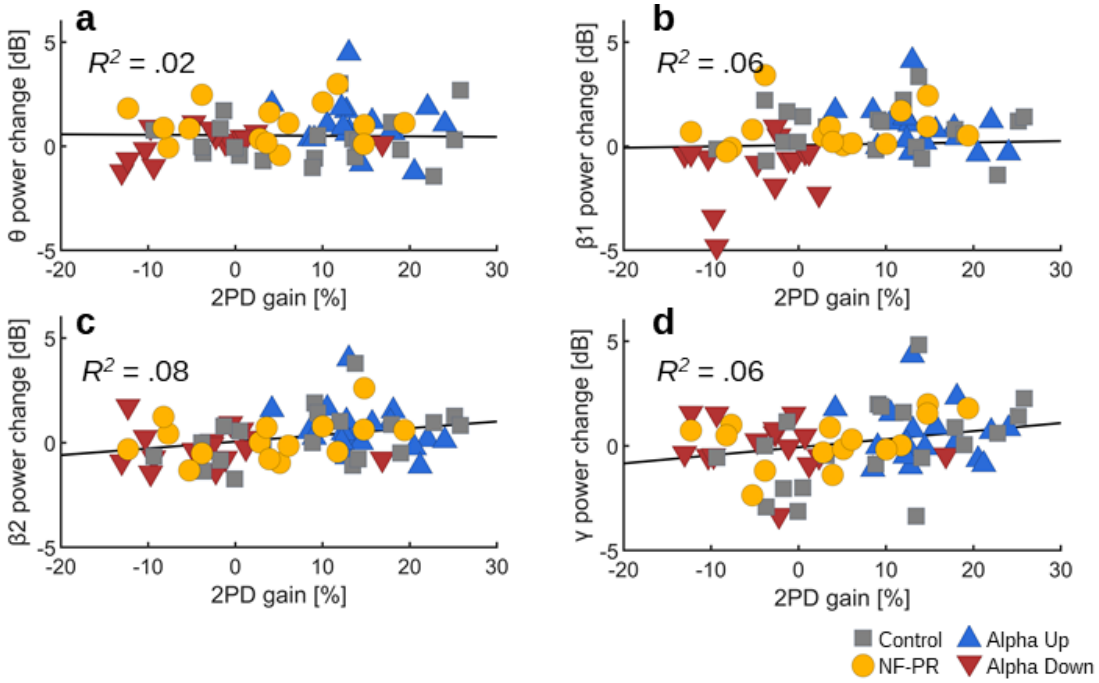

Figure 24 | **Relationship between somatosensory oscillations and perceptual learning**. a-d, regression analysis between perceptual learning (2PD gain) and oscillatory changes during NF training relative to the EEG baseline recording of that day in the theta (a, 4 – 8 Hz), lower beta (b, 13 – 20 Hz), upper beta (c, 21 – 30 Hz) and low gamma (d, 30 – 40 Hz); (Brickwedde et al., 2019). Adjusted R^2 are reported.

These analyses indicate that alpha oscillations are the relevant oscillations determining perceptual learning success prior to repetitive sensory stimulation.

3.3.2 – Relationship between perceptual learning and alpha power measured over additional cortical areas

To analyse, whether alpha oscillations in other cortical areas further contribute to - or have an even stronger impact on perceptual learning success than left somatosensory alpha power, signals recorded at additional electrode sites were analysed.

Left somatosensory alpha oscillations had the strongest connection to perceptual learning (59% of explained variance; Fig. 21a). This connection was still prevalent, but substantially reduced over the right hemisphere (Fig. 25a; $p < .01$; $R^2 = .116$) as well as over the left frontal areas (Fig. 25b; $p < .001$; $R^2 = .171$). Over left occipital areas, no relationship between alpha power and perceptual learning could be observed (Fig. 25c; $p = .440$; $R^2 = -.006$).

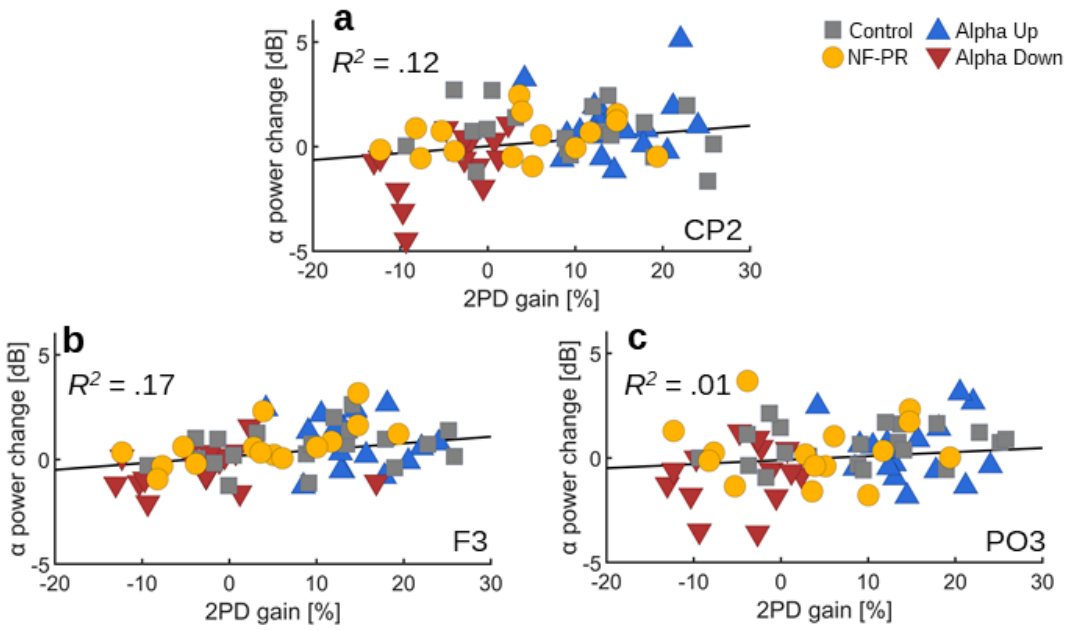

Figure 25 | **Relationship between alpha oscillations recorded over different cortical areas and perceptual learning**. a-c, regression analysis between perceptual learning (2PD gain) and oscillatory changes during NF training relative to the EEG baseline recording of the same day recorded at CP2 (a, right somatosensory cortex), F3 (b, left frontal area) and PO3 (c, left occipital cortex); (Brickwedde et al., 2019). Adjusted R^2 are reported.

It can be concluded that the effect of alpha oscillations on perceptual learning was strongest measured over the somatosensory cortex. No substantial additional oscillatory predictors for perceptual learning were identified.

3.4 – Relationship between alpha oscillations and cortical excitability

Much like alpha oscillations, baseline cortical excitability, has been connected to perceptual learning success. Furthermore, both alpha oscillations and cortical excitability are considered to reflect manifestations of inhibition and excitation. Therefore, the relationship between paired-pulse suppression – a marker of cortical excitability – and alpha oscillations, before and after NF training, was analysed.

Recordings of spontaneous activity before and after paired-pulse suppression (PPS) surprisingly revealed a strong effect of the paired-pulse measurement on alpha oscillations (see Fig. 26; repeated measures *ANOVA;* $F_{(3,84)} = 3.62$; $p = .016$) Particularly, alpha oscillations were considerably increased after PPS. This effect was found before, however not after NF training (for post hoc analysis, see Appendix 6.1 – Table 12) – an observation possibly based on altered alpha power levels at the time of the second paired-pulsed measurement. Descriptively however, a shift of alpha power levels can be observed converging to the initial alpha power levels seen after the first PPS measurement.

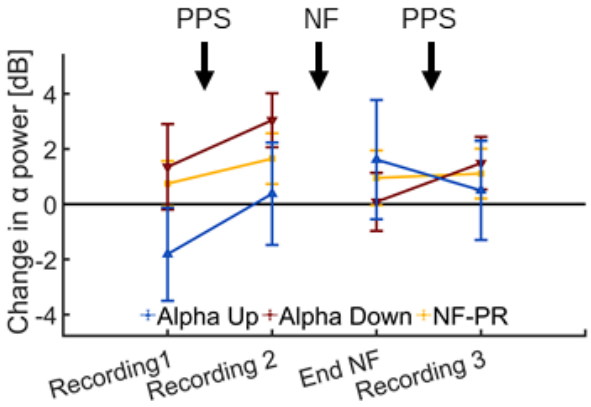

Figure 26 | **Effect of paired-pulse suppression recordings on alpha oscillations**. As group sizes were small and strongly diverging, no group level statistics were performed. Compared are four time points over all participants. First, an EEG recording of spontaneous activity was performed followed by paired-pulse suppression (PSS) and immediately after PPS, another EEG recording was performed. Then, alpha levels during the last minute of NF training are depicted and another EEG recording of spontaneous activity after the second time PPS was measured. Data are presented as *mean* ± *SEM*.

To gain deeper insight into the relationship between cortical excitability and alpha oscillations, regression analyses were conducted for different time points. Uncorrected baseline alpha oscillations show no connection to baseline PPS (see Fig. 27a; $p = .537$; $R^2 = .136$). Although numerically, there was an impression of a stronger baseline PPS paralleling an increase in subsequent alpha power levels, it did not reach significance (see Fig. 27b; $p = .121$; $R^2 = .068$).

Following NF training, no relationship between alpha power changes from baseline and PPS could be found both before and after PPS measurement (before: see Fig. 27c; $p = .276$; $R^2 = .012$; after: see Fig. 27f; $p = .298$; $R^2 = .006$).

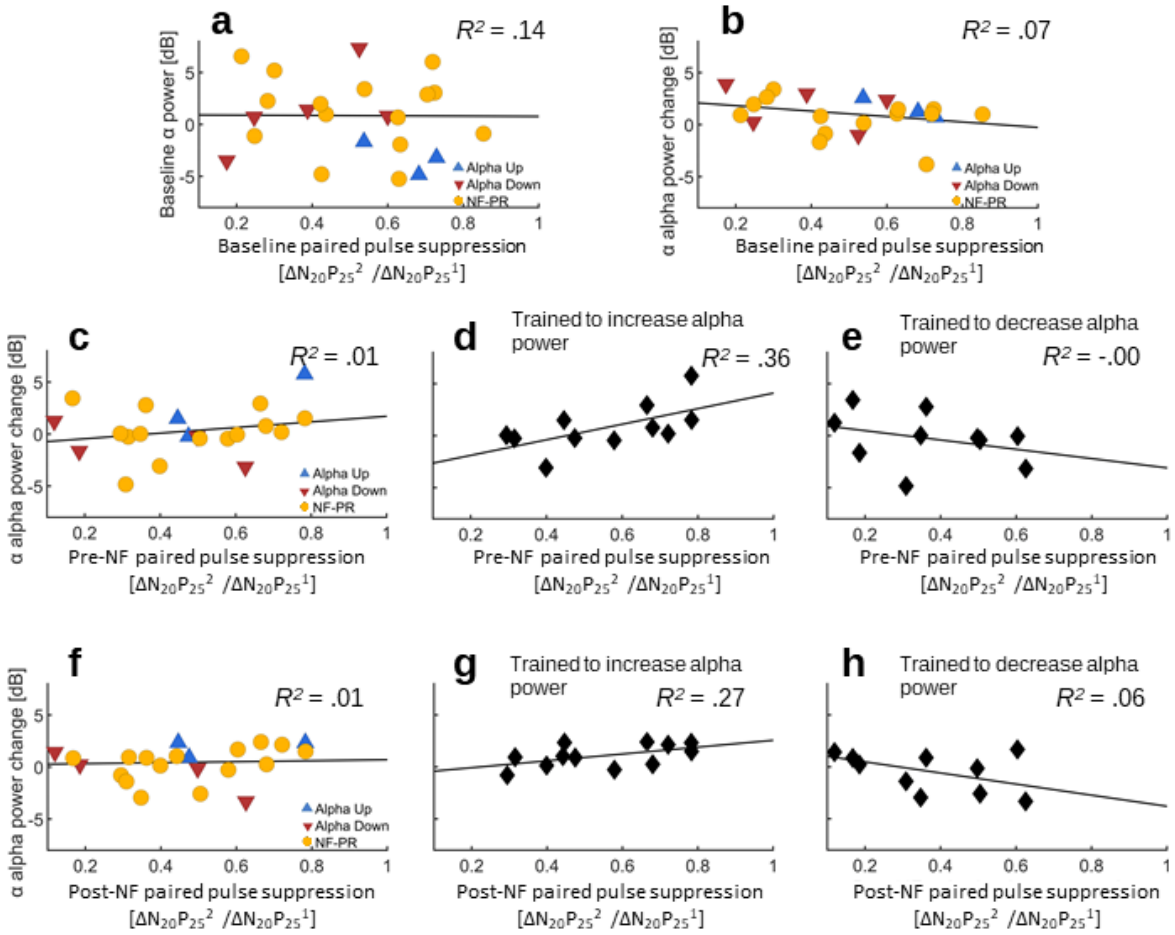

Figure 27 | **Relationship between cortical excitability and alpha oscillations**. a, regression analysis of paired pulse suppression (PPS, a marker for cortical excitability) on baseline alpha oscillations. b, regression analysis of spontaneous alpha oscillation after the first PPS measurement on PPS. c-e, regression analysis of PPS on alpha oscillations during the last minute of neurofeedback for all participants (c), participants who trained to increase alpha power (d) and participants who trained to decrease alpha power (e). f-h, regression analysis of spontaneous alpha oscillations after the PPS measurement on PPS for all participants (f), participants who trained to increase alpha power (g) and participants who trained to decrease alpha power (h). Adjusted R^2 are reported.

Even though NF training was not successful in this experiment, it might still elicit effects. Intriguingly, participants who trained to increase alpha power, independently of their success, showed diverging relationships between alpha power and cortical excitability compared to participants training to decrease alpha power. For those participants, who trained to increase alpha power, a stronger increase in alpha power was accompanied by higher cortical excitability before (see Fig. 27d; $p = .022$; $R^2 = .364$) and again, yet only marginally significant, after (see

Fig. 27g; $p = .069$; $R^2 = .269$) the second PPS measure. No such relationship could be observed for participants, who trained to decrease alpha power (before: (see Fig. 27e; $p = .350$; $R^2 = -.002$; after: see Fig. 27h; $p = .242$; $R^2 = .062$).

No relationship between cortical excitability and alpha oscillations was found. However, participant numbers were unsatisfactory and further experiments are needed to validate the results. Furthermore, it became apparent that PPS measures increase oscillatory alpha power.

3.5 – Neurofeedback-induced alterations in cortical activity and their effect on perceptual learning

3.5.1 – Stability of neurofeedback-induced alpha power changes

To acquire deeper knowledge on the mechanism behind the effect of alpha oscillations on learning processes, it is critical to know, how stable the induced changes in alpha oscillations are and if they persevere during learning processes.

3.5.1.1 – Alpha neurofeedback training and 50 min follow-up

After the conclusion of NF training, recordings of spontaneous EEG were performed every 5 min for 50 min (2 min duration). Although NF training was not successful, there were still strong variations in alpha power changes from baseline, with participants strongly increasing and participants strongly decreasing alpha power (see Fig. 28).

A repeated measure *ANOVA* for all participants and a reliability analysis to assess the stability of alpha power levels were performed (repeated measures *ANOVA;* $F_{(9,261)} = 2.03$; $p = .071$; Greenhouse-Geisser correction for sphericity: .664). The analysis reveals a marginally significant effect for changes over time. Post hoc tests revealed, (see Appendix 6.1 – Table 13), that after the initial EEG recording, a slight increase in alpha power was observable across all participants. However, performing the same analysis only including the 9 following EEG recordings, presents a stronger case for stability of alpha oscillations (repeated measures *ANOVA;* $F_{(8,216)} = 1.07$; $p = .380$; Greenhouse-Geisser correction for sphericity: .703). Furthermore, test-re-test reliability over all 10 EEG recordings was very high ($ICC_{(3,10)} = .966$).

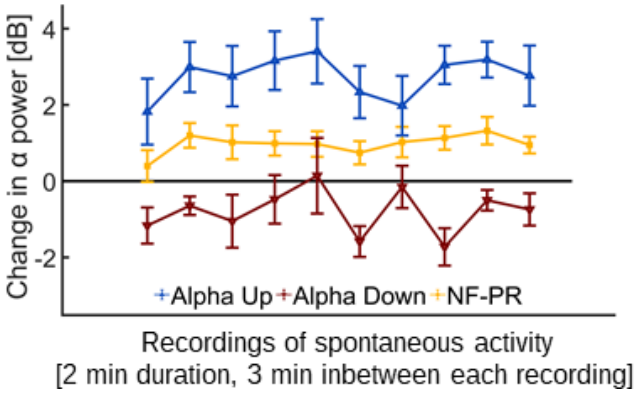

Figure 28 | **Stability of alpha oscillations subsequent to neurofeedback training**. Because of small and strongly diverging group sizes, no group level statistics were administered. Illustrated are alpha power levels of participants from the alpha up group, participants from the alpha down group and participants who responded paradoxically to NF training during 50 minutes of alternating between watching an animal documentary and performing EEG recordings. Data are presented as *mean* ± *SEM*.

Alpha oscillations remained stable over a period of 50 min without signs of decline.

3.5.1.2 – Alpha power during pneumatic repetitive sensory stimulation

In addition to analysing the stability of somatosensory alpha power without deliberate tactile input, it is of great interest to see what actually happens to alpha oscillations during stimulation-induced perceptual learning. It is known that sensory stimuli lead to alpha desynchronization (Pfurtscheller et al., 1996; Freyer et al., 2013). Therefore, alpha power levels over the course of 30 min of stimulation in-between stimulation trains, averaged over 10 min intervals, were analysed. There was no sign of a decline in alpha power back to baseline levels across all participants but also within groups. However, group differences were significant. (see Fig. 29; two-way mixed *ANOVA*; main effect condition: $F_{(2,31)} = 4.10$; $p = .026$; main effect time: $F_{(2,62)} = .66$; $p = .522$; interaction: $F_{(4,62)} = 1.23$; $p = .31$; for post hoc analysis, see Appendix 6.1 –Table 14). Test-re-rest reliability was again, very high ($ICC_{(3,3)} = .954$).

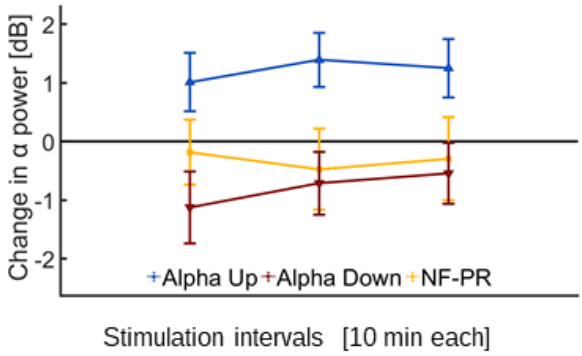

Figure 29 | **Stability of alpha oscillations during pneumatic repetitive sensory stimulation**. Between stimulation trains at an interval of 4 – 6 sec, alpha oscillations are illustrated for the first, the second and the third ten minutes of stimulation for all three groups. Data are presented as *mean* ± *SEM*.

Surprisingly, alpha oscillations remained stable over 30 min of pRSS and group differences persevered without any sign of a decline in alpha power levels back to baseline.

3.5.2 – Efficacy of pneumatic repetitive sensory stimulation

Effects of NF training have so far been largely analysed on a bases of behavioural outcomes (e.g. improved cognitive performance). There is sparse data on the effects of NF training on stimulus processing. As eRSS elicits strong artefacts in the EEG data, pneumatic repetitive stimulation (pRSS), was implemented. Therefore, as a first step, the efficacy of pRSS to induce tactile learning was analysed.

Both baseline measures of tactile acuity on the right index finger were stable (pre1: 1.70 mm; pre2: 1.69mm). After pRSS, 2PD-thresholds were significantly reduced (post: 1.55mm; $T_{(9)} = 3.18$; $p = .011$; $d_z = 1.01$), indicating improved tactile acuity (see Fig. 30). In contrast, no changes were observed on the left, at the unstimulated index finger (pre: 1.74 mm; post: 1.71 mm; $T_{(9)} = .80$; $p = .447$).

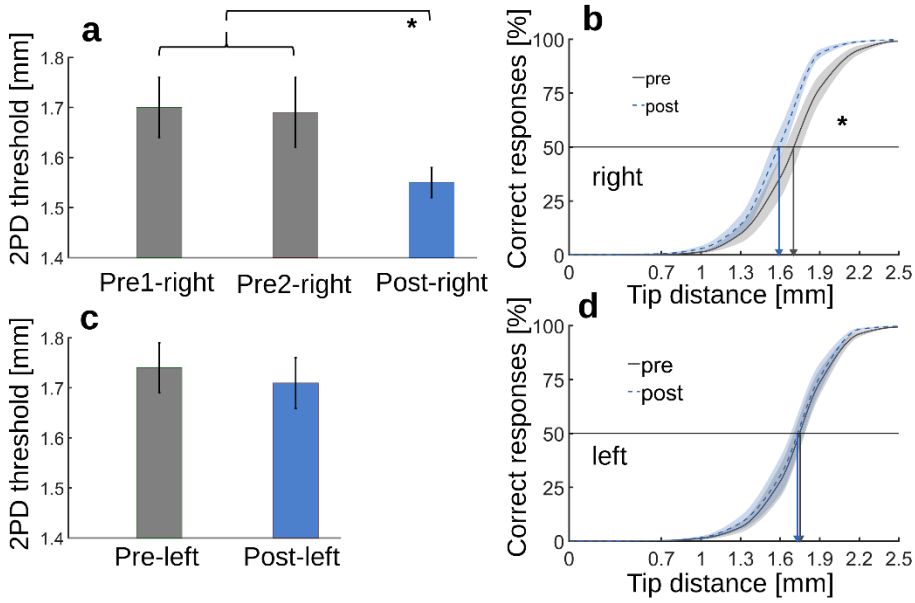

Figure 30 | **Efficacy of pneumatic repetitive sensory stimulation**. a, tactile acuity thresholds at baseline (Pre1-right and Pre2-right) and after pRSS (Post-right) on the right (stimulated) hand index finger. b, psychometric curves of tactile acuity measured before and after pRSS on the right (stimulated) hand index finger. c, tactile acuity thresholds at baseline (Pre-left) and after pRSS (Post-left) on the left (unstimulated) hand index finger. d, psychometric curves of tactile acuity measured before and after pRSS on the left (unstimulated) hand index finger. All data are presented as *mean* ± *SEM*. * $p < .05$; *** $p < .001$;

It can be concluded, that pneumatic repetitive sensory stimulation inducing tactile perceptual learning.

3.5.3 – Cortical processing during pneumatic repetitive sensory stimulation

Based on the results of the previous experiment, EEG during 40 min of pRSS was recorded, to analyse common oscillatory brain responses during stimulation-induced perceptual learning as well as their development over time.

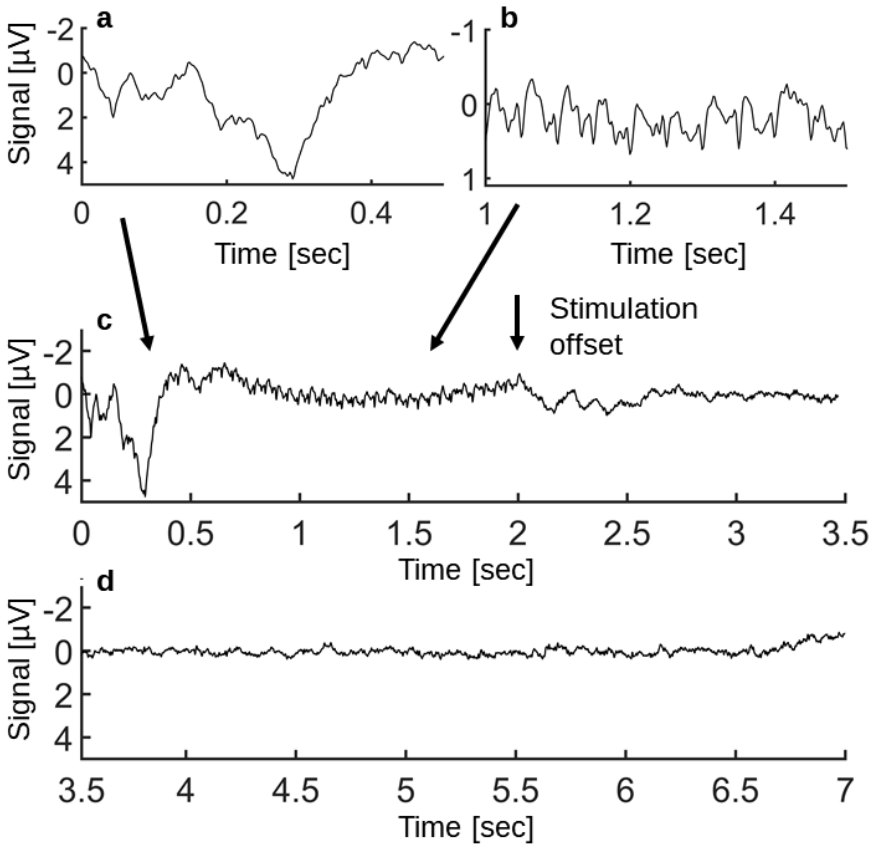

Figure 31 | **Event-related potentials during pneumatic repetitive sensory stimulation.** a, illustration of the first 0.5 sec of pRSS reveal several SEP components. b, illustration of the SEP of the seady-state response induced by pRSS. c, illustration of the SEP during the first half of the stimulation interval, where stimulation trains take place from 0 to 2 sec. d, illustration of the SEP during the second half of the stimulation interval, where no stimuli are presented onto the skin.

Sensory-evoked potential (SEP) analysis of the 7 sec stimulation intervals averaged over all participants revealed several clearly discernible components (see Fig 31a,c). Among them, P50 (43 ms; 2.0 µV), N70 (66 ms; 0 µV), P100 (84-109 ms; 1.2 µV), N150 (148 ms; -0.5 µV), P200(193 ms; 2.6 µV) and P 300 (293 ms; 4.8 µV) are observable.

During the 20 Hz stimulation train interval, between about 0.5 - 2 sec, components converge into a steady-state response which accurately follows the stimulation (see Fig. 31b-c). Two different 20 Hz components are visible, the first one with an amplitude of roughly -0.7 µV, followed by a smaller component with an amplitude of roughly -0.3 µV. During the inter-train interval between 2 - 7 sec, no clear potentials are detectible (see Fig. 31d).

Time frequency analysis of the EEG signal recorded during the 20 Hz intermittent stimulation revealed several significant clusters of stimulus evoked power changes, in line with the components seen in the SEP-analysis (see Fig. 32a-b).

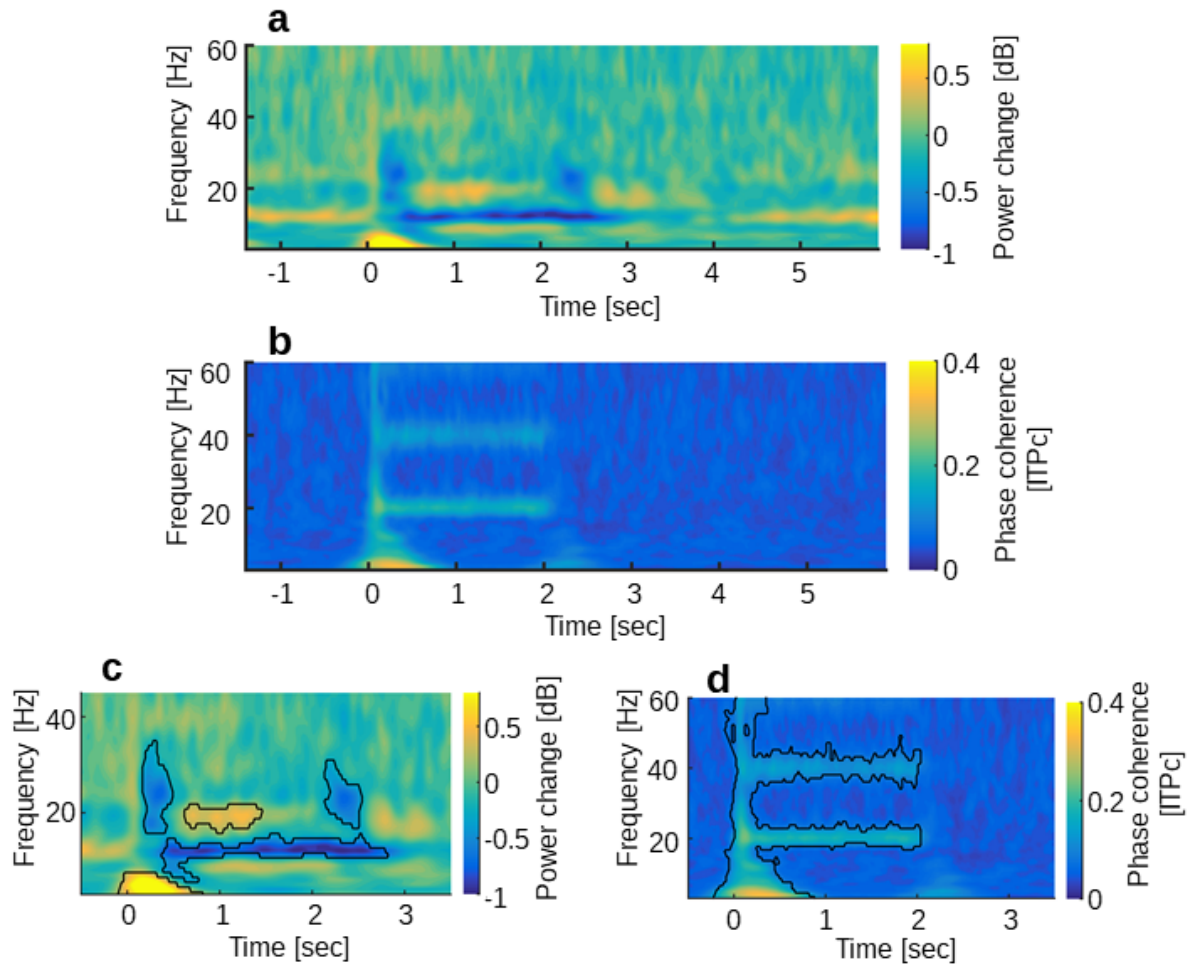

Figure 32 | **Time-frequency analysis of recordings performed during pneumatic repetitive sensory stimulation** a, illustration of stimulation induced and evoked power changes during 40 min of pRSS for the whole stimulation cycle of 7 sec. The stimulation train occurs between 0 and 2 sec. b, illustration of stimulation evoked inter trial phase coherence (ITPC) during 40 min of pRSS for the whole stimulation cycle of 7 sec. The stimulation train occurs between 0 and 2 sec. c, significant clusters ($p < .01$; corrected for multiple comparisons with $p < .01$) obtained from the time-frequency analysis shown in (a) for the time epoch -0.5 to 3.5 sec. d, significant clusters ($p < .01$; corrected for multiple comparisons with $p < .01$) obtained from the inter-trial phase coherence analysis shown in (b) for the time epoch -0.5 to 3.5 sec.

A strong event-related synchronisation immediately following stimulation onset between 0 and 600 ms is apparent in the lower frequency range of the delta and theta band (3 – 8 Hz) with a maximum of 1.26 dB power change from baseline. Furthermore, between 600 to 1400 ms after stimulus onset, an event-related synchronization is visible in the 18-21 Hz range of the beta band (with a maximum of 0.54 dB power change from baseline). Shortly after both stimulus on- (+150 ms) and offset (+500 ms), a notable event-related desynchronization (-0.73 dB maximum change from baseline) between 16 and 35 Hz occurred in the beta and low gamma band. Additionally, with a latency of 350 ms from stimulus onset, an event-related desynchronization (-1.02 dB maximum change from baseline) in the upper alpha and beta band

(10 to 15 Hz) develops, which is maintained until shortly after the conclusion of the stimulation train (2800 ms compared to end of stimulation train: 2000 ms). While not significant, increased power in the 20 Hz band can be observed even between stimulation trains. As they this effect is neither visible in the SEP analysis, nor in the phase analysis, it could be assumed that this activation varies strongly between participants and reflects induced, rather than evoked oscillatory responses.

A grand average inter-trial phase coherence (ITPC) analysis revealed a large synchronous activation right after stimulus onset, which comprises all measured frequencies from 3 to 60 Hz. For the 3 Hz band, this synchronization lasts up to 850ms, but for higher oscillatory frequencies lasts up only for 200 ms (see Fig 32c-d). Importantly, a significant phase synchronicity in the 20 Hz (max phase synchronicity is 0.25 ITPC) as well as the 40 Hz (max phase synchronicity is 0.17 ITPC) band is visible for 15 to 2050 ms, reflecting the entire duration of the 20 Hz stimulation train.

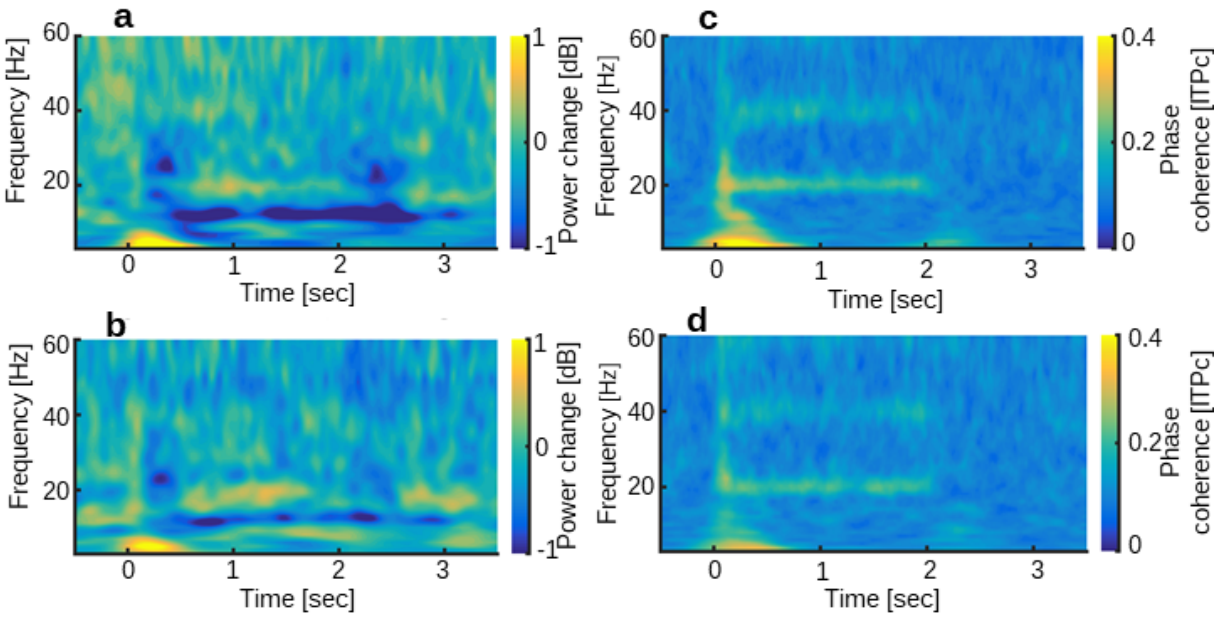

Figure 33 | **Comparison of the first and last ten minutes of pneumatic repetitive sensory stimulation.** a, Time-frequency analysis of the first ten min of stimulation analysed between -0.5 and 3 sec. b, time-frequency analysis of the last ten min of stimulation analysed between -0.5 and 3 sec. Permutation test yielded no significant results compared to a. b, Inter trial phase coherence (TIPC) analysis of the first ten min of stimulation analysed between -0.5 and 3 sec. b, ITPC analysis of the last ten min of stimulation analysed between -0.5 and 3 sec. Permutation test yielded no significant results compared to c.

It is conceivable that cortical responses to the 20 Hz stimulation would wane over time as habituation slowly takes effect. Therefore, the first and the last ten minutes of the 40 min stimulation period were compared.

Both power and phase coherence analysis showed no sign of habituation (see Fig. 33), as no significant clusters differentiated between both time points. Descriptively it seems as if stimulus on- and off-set responses have declined slightly, along with the alpha desynchronization, whereas the 20 Hz activation during and in between stimulus trains slightly increased.

Pneumatic repetitive sensory stimulation evokes sensory potentials as well as a steady state response over the somatosensory cortex. Particularly, next to event-related potentials, a suppression of alpha power and a synchronization of 20 Hz activity can be observed during stimulation trains. These cortical responses remain stable over the course of 40 min of stimulation.

3.5.4 – Effects of neurofeedback training on cortical processing during pneumatic repetitive sensory stimulation

To assess the effect of NF training on cortical responses during repetitive sensory stimulation, EEG recordings during pRSS immediately after NF training were performed.

When analysing changes in oscillatory responses, the point of reference as baseline should always be considered. As this analysis is of exploratory nature, three different baseline references were of interest, as all of them reflect different processes and should be looked at independently.

In the first analysis, the first baseline measure on the last day prior to any interventions was chosen. It reflects the overall change in oscillatory activity relative to baseline levels, timelocked to the 7 sec stimulation interval. For each condition, a time frequency decomposition was performed (see Fig. 34). Based on this, two intervals of interest (during stimulation trains: 0.5 – 2 sec and in between stimulation trains: 4 - 6 sec) where averaged in the temporal domain. Afterwards, between condition permutation tests were administered for all condition-combinations. It is immediately noticeable, that alpha power levels are markedly increased in the alpha up group compared to the other two conditions. During the stimulus-train interval, a distinction can be seen between lower (8-10 Hz) and upper alpha (10-13 Hz), as stimulus-evoked desynchronization occurred mostly in the upper alpha band. In this interval, group differences in the alpha band did not reach significance. When regarding 20 Hz oscillatory activity however, the alpha down group showed significantly less activation than

NF-paradoxical-responders and the alpha up group. These differences did not survive multiple comparison correction. The second interval of interest, between stimulation trains, exposed stronger group differences. Especially the alpha up and alpha down group strongly diverge in the alpha band (9-13 Hz) as well as 20 Hz (20-24 Hz) oscillatory activity. In both cases, the alpha up group shows markedly stronger synchronization. NF-paradoxical-responders showed both differences to the alpha up and the alpha down group in these frequency bands, which did not withstand multiple comparison correction, however.

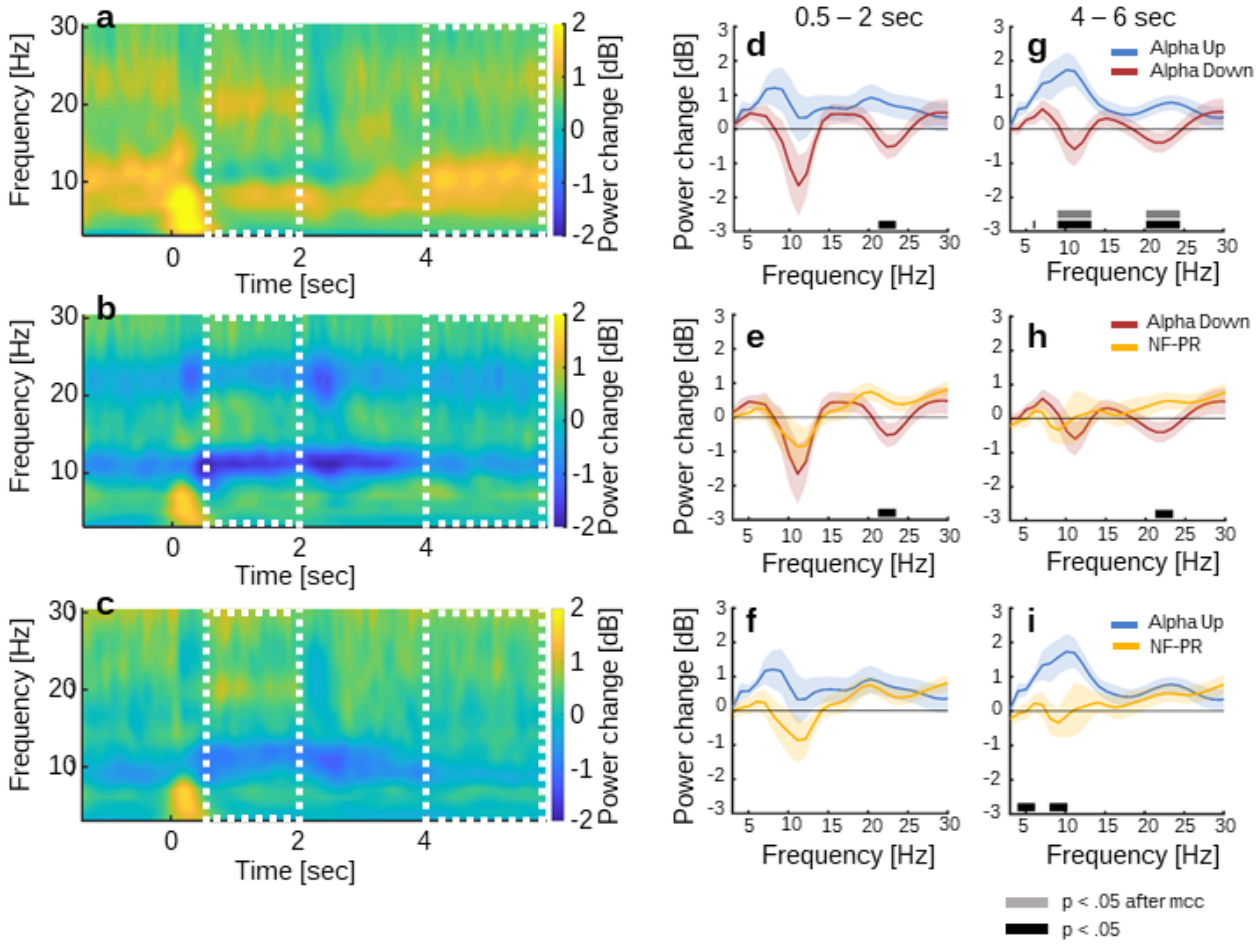

Figure 34 | **Time-frequency analysis of pneumatic repetitive sensory stimulation compared between groups relative to baseline.** a-c, Time-frequency analysis of 30 min of stimulation analysed for the whole stimulation cycle of 7 sec relative to the baseline recording of this day for the alpha up (a), the alpha down (b) groups and for NF-paradoxical-responders (c) respectively. d-f, group comparisons of the average power spectra between 0.5 and 2 sec for both NF groups (d), for the alpha down group and NF-paradoxical-responders (e), and for the alpha up group and NF-paradoxical-responders (f). g-i, group comparisons of the average power spectra between 4 and 6 sec for both NF groups (g), for the alpha down group and NF-paradoxical-responders (h), and for the alpha up group and NF-paradoxical-responders (i). significant clusters are marked by a black block ($p < .01$). If clusters are still significant after multiple comparison correction ($p < .01$) they are additionally marked by a grey block. Power spectra are presented as *mean* ± *SEM*.

The second baseline reference of interest is the last minute of NF training. When comparing stimulation-induced cortical processes with this time period, adaptation processes to the stimulation compared with the state right before the onset of stimulation can be observed. While alpha up and NF-PR groups show mostly the same pattern, the alpha down group shows a glaring deviation from that pattern in the beta band (14 -19 Hz), producing a strong synchronization throughout the whole 7 sec interval (Fig. 35). Interestingly, in this band, no differences could be seen between groups when using the first baseline as a reference.

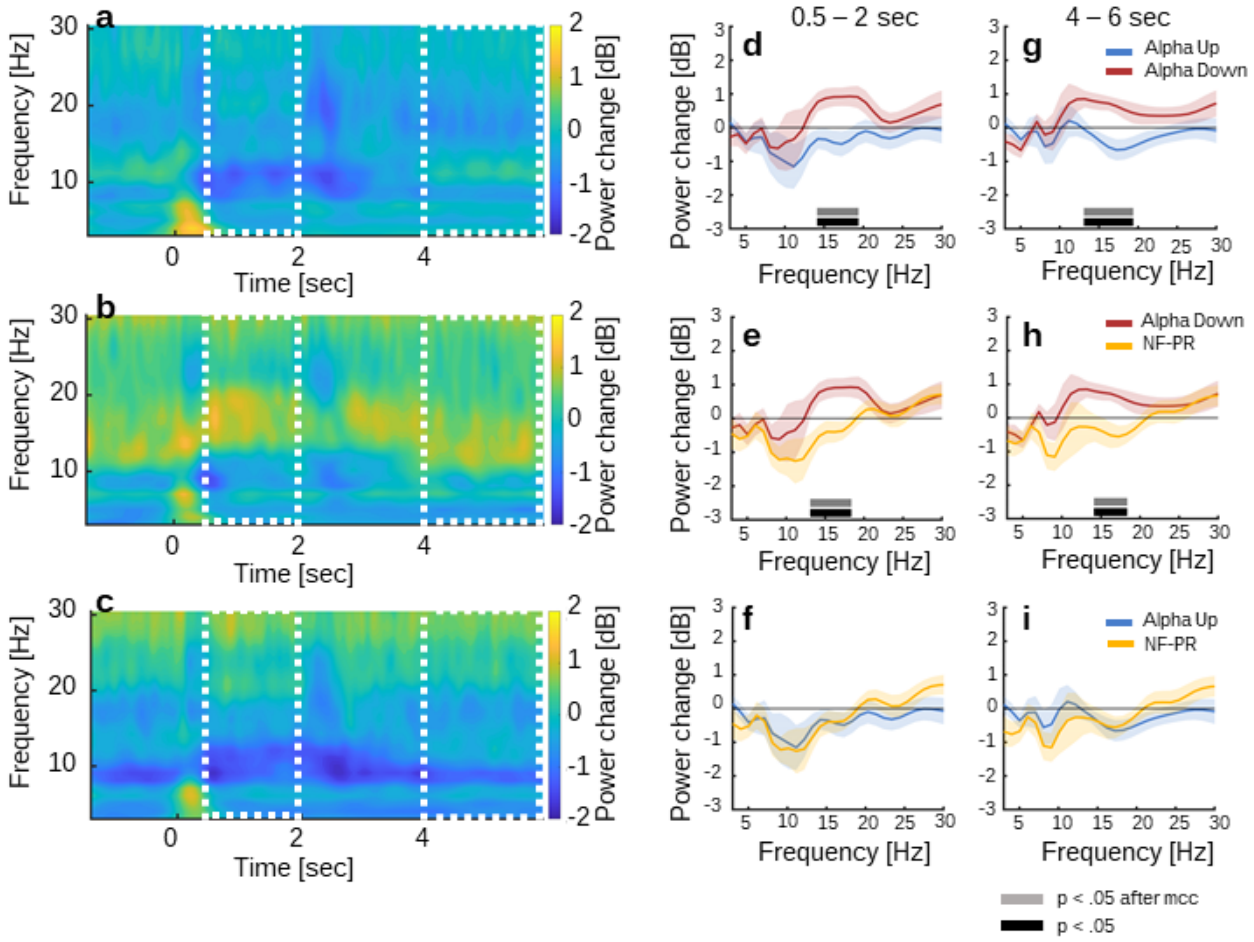

Figure 35 | **Time-frequency analysis of pneumatic repetitive sensory stimulation compared between groups relative to neurofeedback.** a-c, Time-frequency analysis of 30 min of stimulation analysed for the whole stimulation cycle of 7 sec relative to the end of NF training for the alpha up (a), the alpha down (b) groups and for NF-paradoxical-responders (c) respectively. d-f, group comparisons of the average power spectra between 0.5 and 2 sec for both NF groups (d), for the alpha down group and NF-paradoxical-responders (e), and for the alpha up group and NF-paradoxical-responders (f). g-i, group comparisons of the average power spectra between 4 and 6 sec for both NF groups (g), for the alpha down group and NF-paradoxical-responders (h), and for the alpha up group and NF-paradoxical-responders (i). significant clusters are marked by a black block ($p < .01$). If clusters are still significant after multiple comparison correction ($p < .01$) they are additionally marked by a grey block. Power spectra are presented as *mean* ± *SEM*.

The final reference of interest is a baseline period taken from the actual time of stimulation in-between stimulation-trains shortly before stimulation onset (-0.7 - -0.4 sec). This period was then averaged over all trials. As a consequence, stimulation-evoked reactions are based on pure cortical responses without considering previous oscillatory architecture.

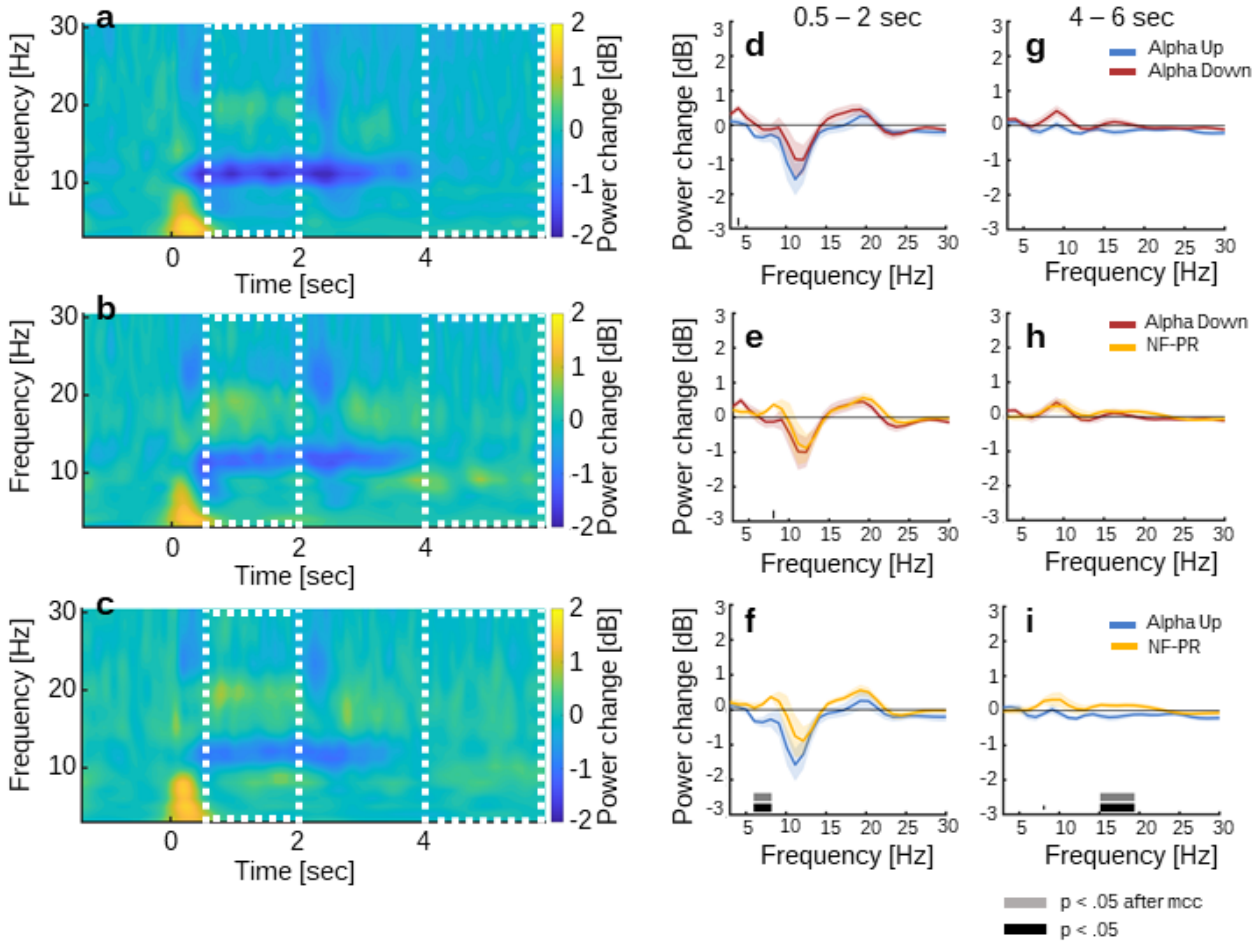

Figure 36 | **Time-frequency analysis of pneumatic repetitive sensory stimulation compared between groups relative to stimulation baseline.** a-c, Time-frequency analysis of 30 min of stimulation analysed for the whole stimulation cycle of 7 sec relative to -0.7 – -0.4 sec of the stimulation period for the alpha up (a), the alpha down (b) groups and for NF-paradoxical-responders (c) respectively. d-f, group comparisons of the average power spectra between 0.5 and 2 sec for both NF groups (d), for the alpha down group and NF-paradoxical-responders (e), and for the alpha up group and NF-paradoxical responders (f). g-i, group comparisons of the average power spectra between 4 and 6 sec for both NF groups (g), for the alpha down group and NF-paradoxical-responders (h), and for the alpha up group and NF-paradoxical responders (i). significant clusters are marked by a black block ($p < .01$). If clusters are still significant after multiple comparison correction ($p < .01$) they are additionally marked by a grey block. Power spectra are presented as *mean* ± *SEM*.

While only descriptively, it seems as if the alpha up group shows the strongest desynchronization in the alpha band during stimulation trains (see Fig. 36). NF-paradoxical-responder show a slightly stronger synchronization in the theta to lower alpha band (6 – 8 Hz)

compared to the alpha up group. As would be expected, not much difference can be seen between 4 - 6 sec and -0.7 - 0.4 sec. The only apparent change is a disparity between a slight decrease in beta power (15 – 19 Hz) in the alpha up group compared to a slight increase in beta power in NF-paradoxical-responder.

Taken together, it is apparent that somatosensory alpha NF training evoked group differences in subsequent processing of pRSS. Especially the neurofeedback-induced group differences in alpha power levels between NF groups remained stable during inter-train intervals. Additionally, both groups also differed in their 20 Hz oscillatory activity during inter-train intervals, as the alpha up group showed a synchronization, whereas the alpha down group suppressed 20 Hz activity relative to baseline. Looking at the difference in oscillatory activity between the end of NF training and pRSS, the alpha down group showed increased oscillatory activity in the beta band (14 – 19 Hz), significantly diverging from both the alpha up group and NF-paradoxical-responders during as well as in between stimulation trains. Lastly, no strong group differences were found in the oscillatory response to pRSS. The only apparent differences were in the theta (6 – 8 Hz) band during stimulation trains and in the beta (16 – 19 Hz) band in between stimulation trains. In both cases, NF-paradoxical responders showed increased activity, while the alpha down group suppressed activity slightly.

3.5.5 – Behavioural relevance of neurofeedback-induced alterations in cortical processing of pneumatic sensory stimulation

The exploratory analysis of processing during pRSS compared between NF groups uncovered several interesting oscillatory differences. It is therefore of great interest to analyse, whether these differences can be traced back to pre-stimulation alpha power levels and whether they are behaviourally relevant for perceptual learning. Therefore, the relevant clusters in the temporal and frequency domain were averaged and regression analyses with tactile acuity gains and alpha power were performed.

Oscillatory synchronization compared to the first baseline in the 20 Hz band (20 – 24 Hz) was connected to alpha power (see Fig. 37b; $p = .005$; $R^2 = .194$) as well as tactile learning (see Fig. 37a; $p = .031$; $R^2 = .108$). More precisely, Stronger synchronization was paralleled by both higher alpha power and higher tactile learning.

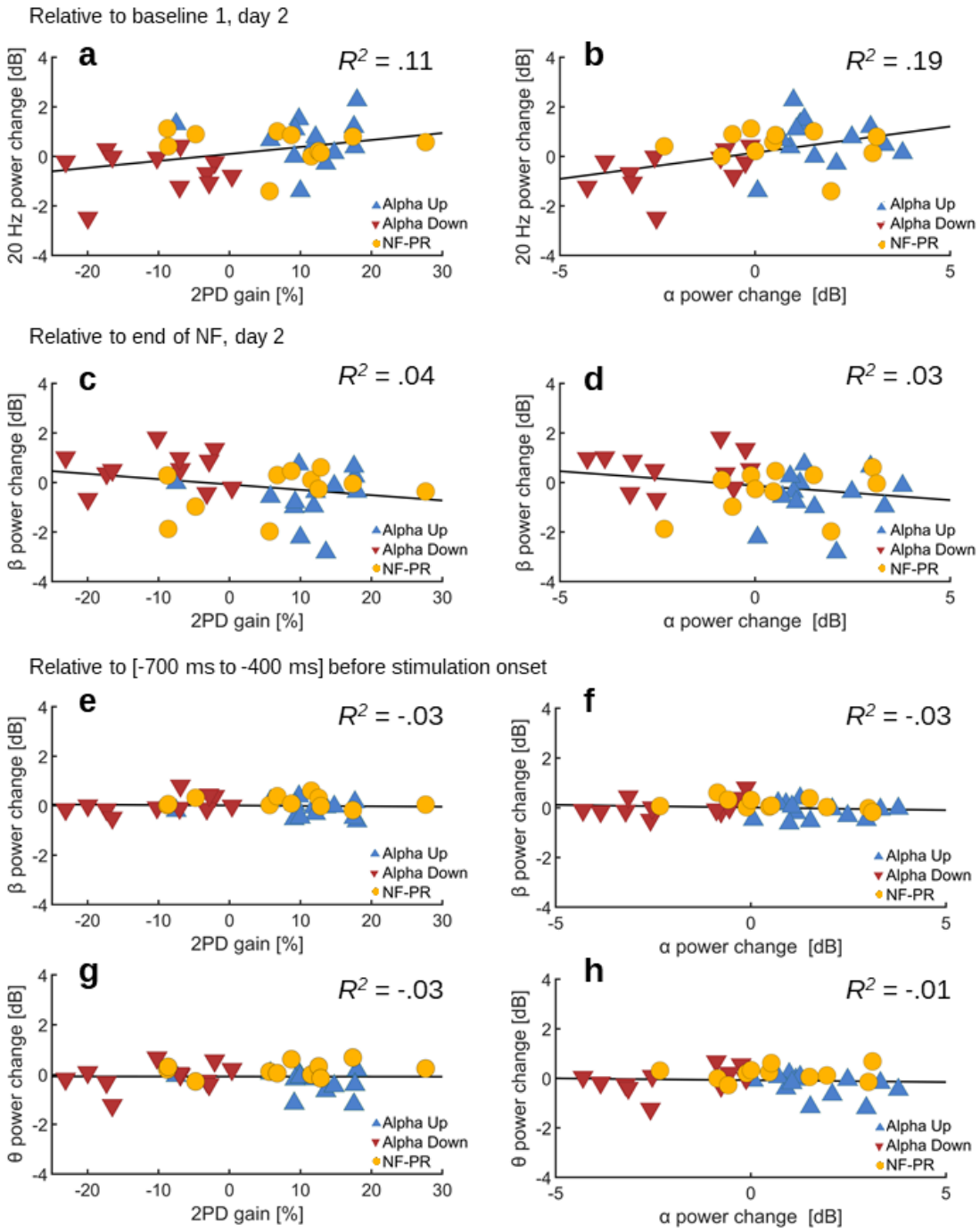

Figure 37 | **Relationship between alpha oscillations, perceptual learning and oscillatory responses during pneumatic repetitive sensory stimulation.** a-b, regression analyses of the relationship between perceptual learning (2PD gain, a) as well as alpha power change during NF training (b) and 20 Hz synchronization during 4 – 6 sec of the stimulation interval relative to the EEG baseline recording. c-d, regression analyses of the relationship between perceptual learning (2PD gain, c) as well as alpha power change during NF training (d) and beta (14 – 19 Hz) power changes after NF training during 4 – 6 sec of the stimulation interval. e-f, regression analyses of the relationship between perceptual learning (2PD gain, e) as well as alpha power change during NF training (f) and beta (13 – 19 Hz) power responses during 4 – 6 sec of the stimulation interval. g-h, regression analyses of the relationship between perceptual learning (2PD gain, g) as well as alpha power change during NF training (h) and theta (6 – 8 Hz) power responses during 0.5 – 2 sec of the stimulation interval. Adjusted R^2 are reported.

Furthermore, enhanced beta power (14 – 19 Hz) after NF training was numerically accompanied with reduced alpha power and reduced tactile learning. This effect was not significant (alpha power: see Fig. 37d; $p = .158$; $R^2 = .031$; tactile learning: see Fig. 37c; $p = .123$; $R^2 = .042$). Cortical reactions in the theta (6 – 8 Hz; alpha power: see Fig. 37f; $p = .700$; $R^2 = -.026$; tactile learning: see Fig. 37e; $p = .980$; $R^2 = -.030$) as well as the beta (15 – 19 Hz; alpha power: see Fig. 37h; $p = .425$; $R^2 = -.010$; tactile learning: see Fig. 37g; $p = .722$; $R^2 = -.026$) band showed no connection to alpha power and tactile learning whatsoever.

It seems irritating, that none of the differences between NF groups can account for relevant variations in the learning outcome between participants. However, it is likely, that changes in oscillations initiate complex oscillatory interactions and that a model of isolated oscillatory activity is too simple to represent real responses. Therefore, the two factors showing connections or indications for connections to alpha oscillations and tactile learning were tested with a multiple regression analysis approach. The interactive effect of 20 Hz oscillatory activity relative to the first baseline (20 Hz) and beta power changes after NF training (beta) was able to explain 20% of the tactile learning outcome (see Fig. 38a; $p = .011$; $R^2 = .198$; $\beta_{(20Hz)} = 5.52$; $\beta_{(beta)} = -4.18$) and showed an even stronger connection to alpha power changes during NF training (see Fig. 38b; $p = .002$; $R^2 = .284$; $\beta_{(20Hz)} = 1.16$; $\beta_{(beta)} = -.70$). Beta weights showed the same pattern in both cases, with 20 Hz oscillations revealing a positive and beta oscillations revealing a negative relationship with both tactile learning and alpha power. On a group level, NF-paradoxical-responder seem to follow a different pattern than the alpha up and alpha down groups. Therefore, the same analyses were performed again, while separating NF-paradoxical-responder from both NF groups. This led to a strong increase of the effect, now explaining up to 41% of the perceptual learning variance (see Fig. 38c; $p = .002$; $R^2 = .410$; $\beta_{(20Hz)} = 6.38$; $\beta_{(beta)} = 5.94$). The relationship to alpha power change during NF training was also enhanced after the removal of NF-paradoxical-responders (see Fig. 38d; $p < .001$; $R^2 = .513$ $\beta_{(20Hz)} = 1.40$; $\beta_{(beta)} = -.99$). Performing these analyses with NF-paradoxical-responders showed that the regression weights contrasted the ones in the alpha up and down group strongly and the analyses did not reach significance (tactile learning: see Fig. 38e; $p = .263$; $R^2 = .104$ $\beta_{(20Hz)} = -7.51$; $\beta_{(beta)} = 7.68$; alpha power: see Fig. 38f; $p = .203$; $R^2 = .161$ $\beta_{(20Hz)} = 1.24$; $\beta_{(beta)} = 1.22$).

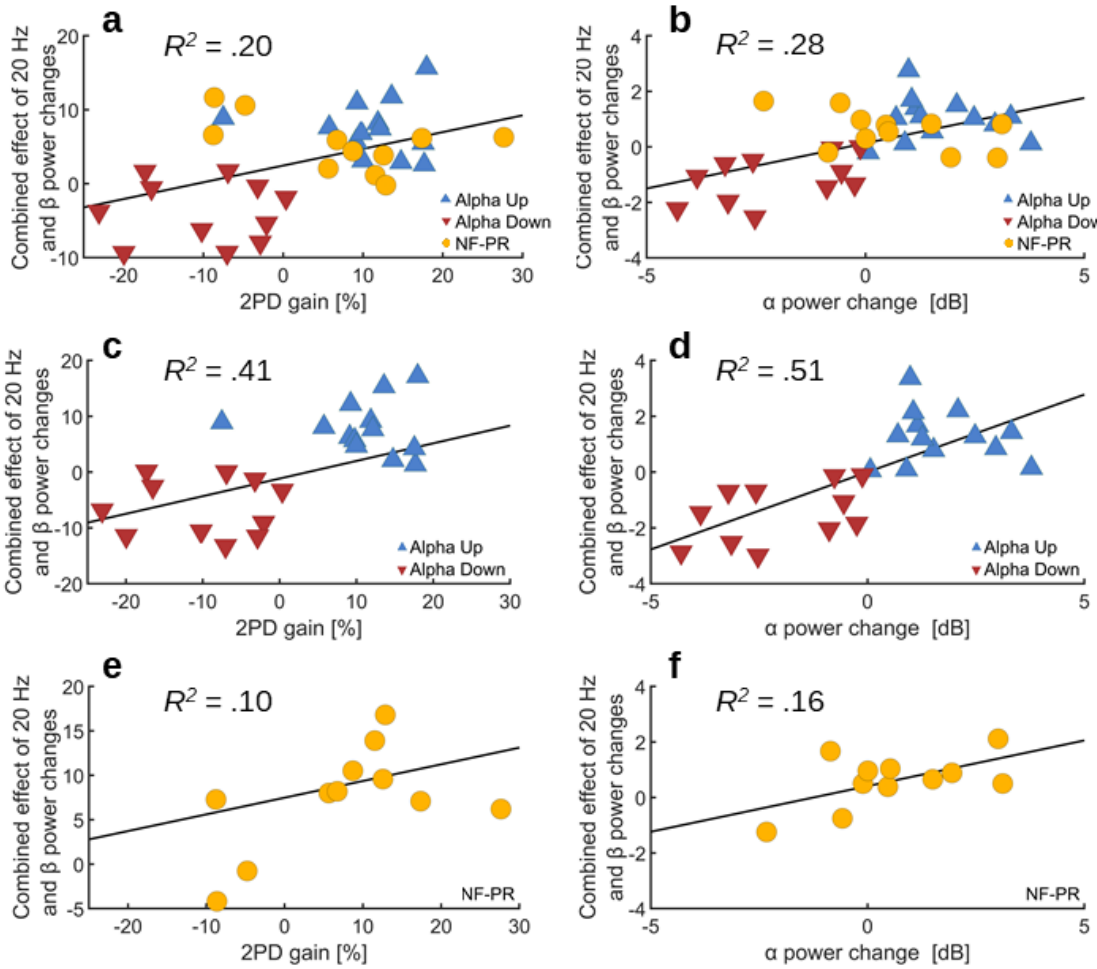

Figure 38 | **Multiple regression model of 20 Hz synchronisation and beta activity on the dependent variables of alpha oscillations and perceptual learning.** For all illustrations, the following formula was applied: a+ β1*20 Hz + β2*beta. a-b, multiple regression analysis with the dependent variable of perceptual learning (a) as well as alpha power (b) and two predictors (20 Hz and beta) for all participants. c-d, multiple regression analysis with the dependent variable of perceptual learning (c) as well as alpha power (d) and two predictors (20 Hz and beta) for NF-groups. e-f, multiple regression analysis with the dependent variable of perceptual learning (e) as well as alpha power (f) and two predictors (20 Hz and beta) for NF-paradoxical-responders. Adjusted R^2 are reported.

It seems that 20 Hz oscillations as well as beta oscillations play a role for perceptual learning and could prove to be possible candidates mediating the effects of NF training on perceptual learning. Specifically, stimulation induced 20 Hz synchronization relative to baseline at the beginning of the experiment, recorded between stimulation trains seems to elicit a positive effect on perceptual learning. Beta synchronization relative to the last minute of NF training right before pRSS seems to dampen the perceptual learning success. Further studies are needed to validate these findings.

4 – Discussion

4.1 – Summary

Whereas several predictors for learning performance are known today, a considerable amount of inter- and intra-individual learning variance is still unresolved (among others, see Dinse et al., 2003b; Pleger et al., 2003; Ragert et al., 2008; Schlieper and Dinse, 2012; Muret and Dinse, 2018). Recent findings identified several markers of neuronal inhibition and excitation as relevant predictors for the efficiency of learning and plasticity processes (Höffken et al., 2007; Freyer et al., 2013; Heba et al., 2016). Cortical alpha oscillations are known to gate information processing through inhibition (Klimesch et al., 1999; Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011b; Jensen et al., 2014; Bonnefond and Jensen, 2015). It is therefore conceivable, that alpha oscillations, just like other markers of inhibition, are likewise relevant for perceptual learning and plasticity processes. First evidence has been presented by Freyer and colleagues (2013), who could demonstrate that somatosensory alpha oscillations during 15 min of watching an animal documentary prior to tactile perceptual learning, were predictive of the perceptual learning outcome. A growing body of research suggests, that alpha oscillations can be voluntarily altered with neurofeedback (NF) training (Kamiya, 1971; Hanslmayr et al., 2005; Vernon et al., 2009; Hsueh et al., 2016). The aim of this thesis was therefore, to implement short-term NF training in order to bidirectionally modify somatosensory alpha oscillations. Afterwards, perceptual learning was induced to analyze whether NF training could control subsequent learning efficiency and inter-individual learning variance. To this end, repetitive sensory stimulation was applied (RSS) – a training-free perceptual learning paradigm, which has been shown to reliably induce tactile learning in form of tactile acuity changes (Ragert et al., 2008). These changes were in line with reorganization occurring in the somatosensory cortex (Pleger et al., 2001; Dinse et al., 2003a; Pleger et al., 2003). Moreover, EEG recordings during pRSS were performed to gain insight into the effect of NF training on cortical processing during stimulation-induced perceptual learning. Finally, possible additional factors predicting perceptual learning as well as their relationships to somatosensory alpha oscillations were explored.

In two experiments, NF training was successfully applied to up- and down-regulate somatosensory alpha power (neurofeedback study 1 and 3). At the end of the training, the alpha power levels of both neurofeedback (NF) groups differed significantly, with both groups

showing changes in alpha power levels in the targeted direction. Furthermore, they also significantly differed from alpha power levels of a control group performing no NF training. In an additional neurofeedback study (neurofeedback study 2), participants were unable to modulate somatosensory alpha power in the desired direction, which could be the consequence of a shortened training phase.

In neurofeedback studies 1 and 3, alpha power levels at the end of NF training could predict perceptual learning success, as induced by repetitive sensory stimulation. Again, the extent of learning differences between all three groups was significant. Participants, who increased their alpha levels by training showed the highest learning performance, significantly higher than controls who just watched an animal documentation instead of NF training. In contrast, the learning process for participants, who successfully trained to decrease their alpha power levels, was disrupted. Furthermore, for both NF groups, learning variance was strongly reduced compared to controls, NF-paradoxical-responders or all participants.

In an attempt to identify further neural predictors of perceptual learning, EEG-recordings from additional electrode sites as well as additional frequency bands were analyzed. No relevant relationship between perceptual learning and the theta (4 – 8 Hz), lower beta (13 – 20 Hz), upper beta (20 – 30 Hz and low gamma (30 – 40 Hz) could be found. Small correlations between alpha power measured over left frontal areas (F3) and right somatosensory cortex (CP2) could be observed. However, they were strongly reduced compared to the relationship between alpha power over the left somatosensory cortex and perceptual learning and it is likely that their origin is in part caused by volume conduction. No relationship between left occipital alpha power PO3) and perceptual learning could be found. Accordingly, out of all tested predictors, left somatosensory alpha power seems to be the critical factor determining perceptual learning success.

As alpha oscillations have been connected to inhibitory processes and other factors related to inhibition and excitation likewise were able to predict perceptual learning, the relationship between cortical excitability and alpha oscillations was analyzed. To this end, the paired-pulse suppression (PPS) paradigm was implemented to assess cortical excitability. EEG recordings were performed before and after PPS. Afterwards, NF training was implemented to up- or down- regulate somatosensory alpha power. Finally, PPS was measured again, followed by one last EEG recording. No relationship between cortical excitability and PPS could be found. Surprisingly, it was shown that the PPS measure itself led to an increase in oscillatory alpha power.

To gain deeper knowledge on the effect of NF training on information processing, EEG was recorded during pneumatic repetitive sensory stimulation. In a first step, the stability of neurofeedback induced alpha power changes was studied. Surprisingly, neither regular follow-up recordings up to 50 min after NF training nor a recording during 30 min of repetitive sensory stimulation provided evidence for declines in alpha power levels. This shows that NF training elicits resilient and stable changes for at least 50 min.

As a next step, EEG-recordings during pneumatic repetitive sensory stimulation were analyzed. During stimulation trains, event-related desynchronization (ERD) in the upper alpha band as well as phase-locked 20 Hz activation could be observed. Evoked potentials were observable at the on- and off-set of the stimulation train. Though not significantly, time-frequency analysis also revealed time-locked (but not phase-locked) activity in the 20 Hz and slightly above the 20 Hz frequency range in between stimulation trains.

In a final study, NF training was applied again to monitor neurofeedback-induced changes in cortical processing of pRSS. NF training elicited strong effects on neuronal activity during repetitive sensory stimulation. Differences in the alpha band were most striking and remained stable over the whole period of stimulation. Furthermore, participants who trained to increase alpha power also showed significantly higher time-locked activity in the 20 Hz frequency range in between stimulation trains. Participants in the alpha down group markedly increased their lower beta activation (14 – 19 Hz) immediately after NF training. In multiple regression analysis, both factors showed strong connections to left somatosensory alpha power and the perceptual learning outcome, indicating their possible mediating role for the effect of alpha power on perceptual learning.

It can be concluded that alpha NF training can be applied to up- and down-regulate somatosensory alpha oscillations, which in turn gates the efficiency of subsequent stimulation-induced perceptual learning. The elicited changes are stable and directly influence neural processing of the perceptual learning process. Two possible mediators for this effect are induced 20 Hz activation in between stimulation trains and increased lower beta activity after NF training.

4.2 – Detailed discussion

In the following, results for each of the five main research questions will be explained and discussed in comparison to current research in the field.

4.2.1 – Efficacy of short-term neurofeedback training

4.2.1.1 – The optimal neurofeedback protocol

Ever since the method of alpha NF training has been developed in the 1960s (Kamiya, 1971), its application in research as well as clinical and rehabilitational settings has strongly increased. However, most studies incorporated NF training in multiple session spread over several days. The most common protocol constitutes 10 sessions of NF training, each lasting between 20 and 30 min (e.g. Dempster and Vernon, 2009; Choi et al., 2011; Gruzelier et al., 2014; Guez et al., 2015; Rogel et al., 2015; Shtark et al., 2018; Lavy et al., 2019). Very few studies reported the application of single-session NF trainings, some of them did not observe influence on behavioural outcomes (Kluetsch et al., 2014; Escolano et al., 2014b; Davelaar et al., 2018). In the present study, a two-day approach was chosen to keep NF training short, but at the same time elicit stronger effects than single-session trainings. Another reason to include a second day of training, was the well-known amplifying effect of sleep consolidation on learning tasks (Timofeev and Chauvette, 2017). The 25-min duration of the first training session was well in line with other studies, while on the second day, 15 min were chosen to avoid possible performance decreases in NF training caused by exhaustion at the end of the training. This approach elicited significant group differences between participants who successfully trained to increase and to decrease somatosensory alpha power. Both NF groups also differed significantly from controls. The same results could be replicated in neurofeedback study 3, applying the same protocol except for an increased training phase on the second day (25 min instead of 15 min). The observed temporal dynamic was the same in both studies. The alpha up group showed steady increases in alpha power and started with elevated alpha levels in the first NF session on the second day. While the alpha down group initially showed strongly decreased alpha power, their alpha power levels slowly returned to baseline levels in the course of NF training, yet remaining below baseline levels most of the time. Steady increases in alpha power

levels over sessions have been commonly reported (e.g. Zoefel et al., 2011; see Fig. 39) until after about ten sessions, where alpha power levels seem to reach a plateau (Dekker et al., 2014).

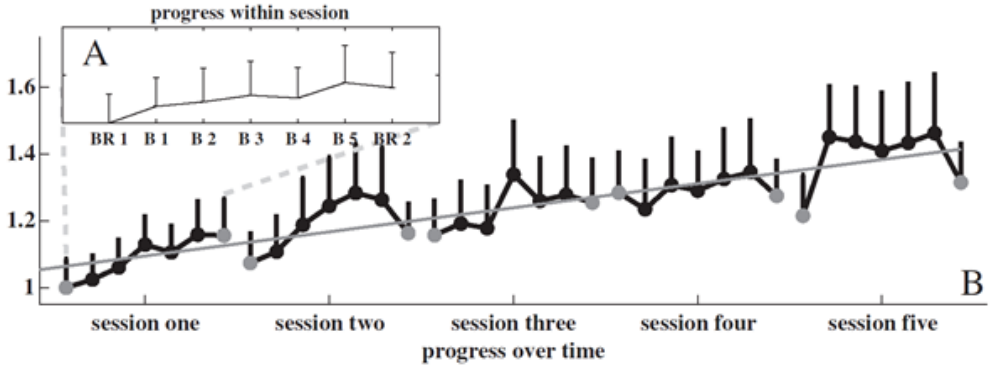

Figure 39 | **Time course of parieto-occipital alpha neurofeedback training over multiple sessions.** A steady increase can be observed over session. Grey dots represent resting states (BR) and black dots represent training blocks of 5-min duration (Modified from Zoefel et al., 2011).

Empirical data on the down-regulation of alpha power is sparse. However, in two studies a slow but steady decrease in alpha power is reported (Wan et al., 2016; Nan et al., 2018). In both studies participants trained to down-regulate their oscillatory alpha power for 3-min training phases totalling into 15 min of training. The same training was repeated on a second day. It is possible that shorter overall training time facilitates the ease to decreasing alpha power. In the present study, participants from the alpha down group reported their training to be particularly exhausting, which could lead to increased difficulties in keeping alpha levels low for longer durations. Furthermore, it is conceivable that 3-min training phases as opposed to 1-min phases in the present study, led to better performances, due to prolonged periods of feedback.

Another possibility is that in this project, bottom effects were reached while down-regulating somatosensory alpha power, rendering further decreases impossible. Potential support for this argument lies in the fact that in both reported experiments (Wan et al., 2016; Nan et al., 2018), occipital alpha power was down-regulated, contrasting the somatosensory alpha power targeted in the present study. Occipital alpha oscillations are the most pronounced cortical rhythm, which might result in higher margins for power variations.

NF training performed in neurofeedback study 2 did not lead to reliable modifications of somatosensory alpha power in the desired directions. The protocol applied was distinguishable from the other two, in that only 15 min of training were performed on the first and the second day respectively. While 15 min seemed to be enough to down-regulate alpha power in some cases (Wan et al., 2016; Nan et al., 2018), there were also reports of unsuccessful NF training with sessions of less than 20 min duration, even if multiple sessions were applied over several

days (Cho et al., 2008). However, in this case parietal alpha oscillations were trained with closed eyes while auditory feedback was provided. The differences in modalities, localization and protocols between alpha neurofeedback studies make comparisons increasingly difficult. The development of optimal protocols for different circumstances warrants further research. Nonetheless, the protocol applied in the present study elicited stable and significant group differences on both days of training.

4.2.1.2 – NF-paradoxical-responders

Despite the fact that most participants successfully altered somatosensory alpha power, some participants, the NF-paradoxical-responders, were not able to alter their oscillatory power in the targeted direction. In both neurofeedback study 1 and 3, this concerned 33% of the participants, well in line with the amount of non-responders commonly reported, which vary between 20 and 50% (Kober et al., 2015; Nan et al., 2018). It is currently unknown what distinguishes responders from paradoxical responders. Nevertheless, there are several possible explanations. As such, resting state central alpha power during eyes-open as well as eyes-closed conditions has been identified as relevant predictor for NF training performance (Wan et al., 2014). It has further been shown that the mental strategy applied during frontal alpha NF training differs between learners and non-learners (see Fig. 40).

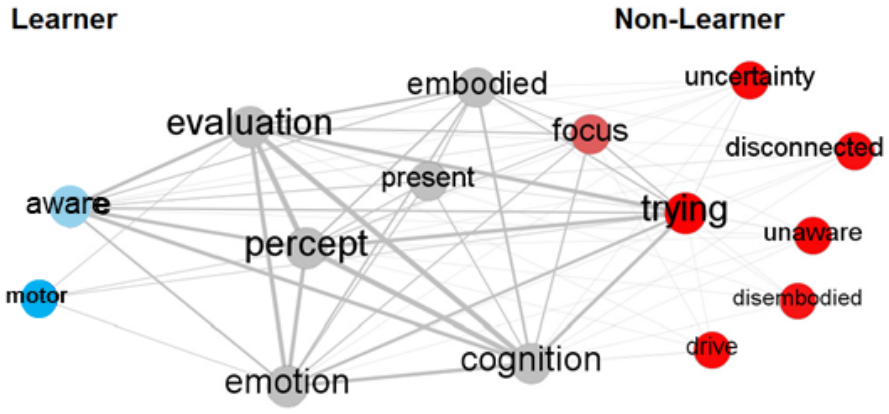

Figure 40 | **Strategies applied for neurofeedback training in learners and non-learners.** The size of a node represents the frequency of reports about this strategy and the width of connections represents the frequency in which two strategies were reported in combination. Red dots represent strategies that were reported more often by non-learners and blue dots represent strategies that were reported more often by learners (Modified from Davelaar et al., 2018).

The authors categorized successful strategies into more intuitive approaches, where participants described “being aware”. Non-learners on the other hand, described mental effort

and purposeful attentional focus (Davelaar et al., 2018). As NF training was kept deliberately short (5 min of training) to enforce sufficient numbers of non-learners (n = 12), there were only very few learners (n = 4). It can therefore be argued, that successful learners might just have coincidentally increased alpha power. Furthermore, the study only covers training to increase alpha power. As such, it is possible that some strategies concern NF training in general, while others are specific to up-regulation of alpha power. Nevertheless, these results are interesting and warrant further research. Some of the non-learners in this study described feeling "uncertainty" and being "disconnected". This fits well to another possible predictor of learning success: experienced stress levels in participants. The evidence on detrimental effects of stress on learning is unequivocal. It has been shown for word learning tasks (Schwabe and Wolf, 2010; Schwabe et al., 2012), associative learning (Ehlers and Todd, 2017) as well as passive stimulation-induced perceptual learning in humans (Dinse et al., 2017). Interestingly, it has also been shown to impair LTP-induction on a cellular level (Maggio and Segal, 2010; Fa et al., 2014). Given the importance of LTP processes for learning and plasticity, it is conceivable that stress has negative effects on NF training, regardless of protocol and direction of training. It has to be taken into account, that most neurofeedback studies are performed with either clinical subpopulations or students. Both of these groups are known to suffer heightened stress levels (Combs et al., 2015; Concerto et al., 2017; Amaral et al., 2018). In part, this might explain high numbers of non-responders. Given that stress can be easily induced (Allen et al., 2017), this relationship could be tested in future studies.

It can be concluded, that short-term NF training was successfully applied to up- and down-regulate somatosensory alpha power. A clear distinction between groups was observed at the end of NF training, permitting tests on subsequent interventions. A two-day training seems to be preferable to training performed on just one day. Varying protocols, localizations and modalities of NF trainings across the literature make comparisons difficult and thorough methodological research on the effectiveness of different protocols is necessary. Furthermore, deeper understanding of the reasons behind paradoxical responses to NF training are of crucial importance.

4.2.2 – Effects of neurofeedback training on perceptual learning

4.2.2.1 – Effect of alpha neurofeedback training on perceptual learning

In the following, the effects of somatosensory alpha NF training on behavioural correlates of perceptual learning and plasticity will be outlined. To test these effects, repetitive sensory stimulation was applied immediately after the completion of NF training. Changes in tactile acuity thresholds were used as markers for perceptual learning and plasticity. In previous studies, they have been shown to reliably correlate with reorganizational changes occurring in the somatosensory cortex induced by repetitive sensory stimulation (Pleger et al., 2001; Dinse et al., 2003a; Pleger et al., 2003). Therefore, baseline tactile acuity measures preceding NF training were compared with post-intervention tactile acuity measures after repetitive sensory stimulation. Four different groups were compared: participants successfully up-regulating alpha power (alpha up), participants successfully down-regulating alpha power (alpha down), paradoxical-responder to NF training (NF-paradoxical-responder) and controls watching an animal documentary without performing NF training.

After NF training, participants from the alpha up group displayed markedly elevated tactile acuity while NF-paradoxical responder did not. Additionally, in the first neurofeedback study the control group also showed improved tactile acuity. This observation affirms that perceptual learning was successfully induced in the alpha up and control group. In the first study, participants from the alpha down group did not show any tactile acuity changes overall, while in the neurofeedback study 3, their tactile acuity even decreased. It is difficult to say, whether in this case repetitive sensory stimulation elicited negative effects on tactile acuity thresholds, or if the reported exhaustion in the alpha down group affected tactile acuity performance. In a neurofeedback study 2, no repetitive sensory stimulation was applied. Therefore, potential effects of NF training on tactile acuity changes beyond perceptual learning processes could be assessed. Numerically, the alpha down group likewise decreased in tactile acuity performance, while participants from the alpha up group and NF-paradoxical responders remained at baseline performance. As participant numbers were too low in NF groups and the protocol did not successfully induce alpha power changes in a sufficient number of participants, results should be considered with caution. However, the data still suggests that found reductions in tactile acuity thresholds in the alpha down group might be caused by exhaustion rather than reverse effects of repetitive sensory stimulation.

Nevertheless, downregulation of somatosensory alpha power via NF training disrupts stimulation-induced learning. This is evident as the observed tactile acuity changes were comparable across studies (with and without repetitive sensory stimulation) and fingers (stimulated and unstimulated). As down-regulation of alpha power has recently been discovered to decrease signal-to-noise ratio in steady-state-visual-evoked-potential BCIs (Wan et al., 2016) and has also been applied as treatment for post-traumatic-stress disorder (PTSD; Kluetsch et al., 2014), these findings are important. However, the authors of this study suggest that patients suffering from PTSD display abnormally low alpha levels and by further trying to decrease them, a subsequent "rebound" is elicited, inducing increased alpha levels after training. The same effect was not found in healthy controls. Possible negative side effects of down-regulating alpha oscillations should be considered, especially regarding long-term application in clinical populations. It is also not clear, why down-regulating alpha oscillations would be preferable over up-regulating alpha oscillations when the desired outcome is elevated levels of alpha oscillations.

4.2.2.2 – Effect of alpha neurofeedback training on perceptual learning efficiency

To see whether alpha NF training actually increased perceptual learning efficiency, tactile acuity gains were compared between groups. The first neurofeedback study showed that participants from the alpha up group depicted higher perceptual learning than any other group. Controls and NF-paradoxical-responders differed only numerically, with controls showing slightly higher tactile acuity increases. Both groups displayed significant higher perceptual learning than participants from the alpha down group. The third neurofeedback study replicated these results for the three tested groups (alpha up, alpha down and NF-paradoxical responders). However, the difference between the alpha up group and NF-paradoxical responders did not reach significance. There are two possible explanations for this. Firstly, it is possible that pneumatic repetitive sensory stimulation applied in the second neurofeedback study was slightly less efficient compared to its electrical counterpart. Some data supports this theory, as the average tactile acuity increase in the alpha up group was 14.7% in the first study, compared to 10.4% in the second study. Secondly, perceptual learning of NF-non-responders was increased in the second study (7.2%) as opposed to the first study (4.2%). This could in turn be explained by a decreased number of non-learners in the alpha up in the second study (n = 5) as compared to the first study (n = 9), while numbers in the alpha down group were identical in

both studies (n = 7). As a consequence, more participants would paradoxically increase alpha power levels resulting in a slightly higher perceptual learning outcome.

In conclusion, perceptual learning outcomes were markedly increased for the alpha up group and decreased for the alpha down group, with NF-paradoxical-responders and controls showing low to commonly reported (e.g. Ragert et al., 2008; Schlieper and Dinse, 2012; Freyer et al., 2013; Heba et al., 2016; Dinse et al., 2017) learning outcomes.

4.2.2.3 – Relationship between neurofeedback-induced alpha power changes and perceptual learning

A closer look at the relationship between neurofeedback-induced alpha power levels and perceptual learning on individual subject level was gained with regression analyses. In neurofeedback study 1 and 3 respectively, neurofeedback induced alpha power changes could explain up to 59% of the perceptual learning variance for NF groups. Furthermore, intragroup variance was strongly reduced, which speaks for the potential of NF training to control the perceptual learning outcome.

The same connection was also observable for controls, where 18% of the perceptual learning variance could be explained. It can only be speculated why the relationship was stronger for NF groups. Controls displayed almost the same extent variance in tactile acuity performance changes as both NF groups combined. However, the observed variance in alpha power levels was distinctively smaller than in NF groups. It is also possible, that induced alpha power changes beyond natural fluctuations elicit stronger or additional effects on information processing. Given that participants in the control group watched an animal documentary, it cannot be ruled out, that the documentary itself had an effect on subsequent perceptual learning for some participants more than others. For example, one participant reported after the documentary, that she had to look away for a brief period during the movie, as a mouse appeared, which scared her. Such diverse effects on participants cannot be avoided and might explain why Freyer and colleagues (2013) found a stronger relationship between somatosensory alpha power during an animal documentary and subsequent stimulation-induced perceptual learning, explaining 35% of the observed interindividual variance. The nature of the documentary might have been slightly different (e.g. calmer sequences or more pleasant sequences). For example, it could be shown that different meditation methods facilitate distinct effects on alpha oscillations, where some lead to alpha level increases, others to decreases

(Travis, 2001; Cahn et al., 2013; Lee et al., 2018). It makes sense that such alterations depend on the content of meditation (or of a movie) as well as the individual experience of the participant.

In the first neurofeedback study, no relationship between somatosensory alpha oscillations and perceptual learning could be found for NF-paradoxical responders. If stress was a possible reason for their paradoxical response to NF training, as has been previously discussed, then perceptual learning would equally be affected, independent of alpha power levels. While pre-learning oscillatory states possibly constitute different levels of preparedness for upcoming tasks, the actual task processing still needs to be performed accordingly. As such, it has been shown that the right timing of oscillatory alpha fluctuations in hippocampus during execution of a working memory task are decisive for task success (Leszczyński et al., 2015). In the third neurofeedback study however, NF-paradoxical-responders displayed a similar pattern as participants in the control group of the first neurofeedback study, as 19% of their interindividual perceptual learning variance could be explained by alpha oscillations. This puzzling result is difficult to interpret. However, NF-paradoxical-responder might be a heterogenous group and, all of the previously mentioned factors as well as others could be causing the disruption in learning effects, to different extents in different participants. Furthermore, the classification of NF-paradoxical-responders is arbitrarily chosen. In this study, as in many others (e.g. Hanslmayr et al., 2005), they were defined as participants unable to change alpha oscillations in the targeted direction. This on the other hand means that participants, increasing their alpha oscillations by 0.2% are in a different category than participants decreasing their alpha oscillations by 0.2%. When interpreting such results however, it should be considered that the truth is probably a continuum, where participants display different extents of learning success, influenced by several beneficial and detrimental effects and measured with a varying signal-to-noise ratio. Therefore, it is possible, that the distribution factors disrupting NF training success in NF-paradoxical responders, diverged in neurofeedback study 1 and 3.
Nevertheless, the data clearly provides strong evidence for the relationship between alpha oscillations and perceptual learning, especially for NF groups.

Taken together, the strength of the relationship between alpha oscillations and perceptual learning varied and was strongest for NF groups, where 59% of the interindividual learning variance could be explained. NF-paradoxical-responders provide an interesting research field, as factors determining their lack of learning success both in neurofeedback and perceptual learning are still mostly elusive.

4.2.2.4 – Effect of neurofeedback training on tactile processing during tactile acuity measures

One limitation to the reported results so far lies in the fact that the effect of NF training on perceptual learning cannot be distinguished from the effect of NF training on tactile acuity performance during post measurement.

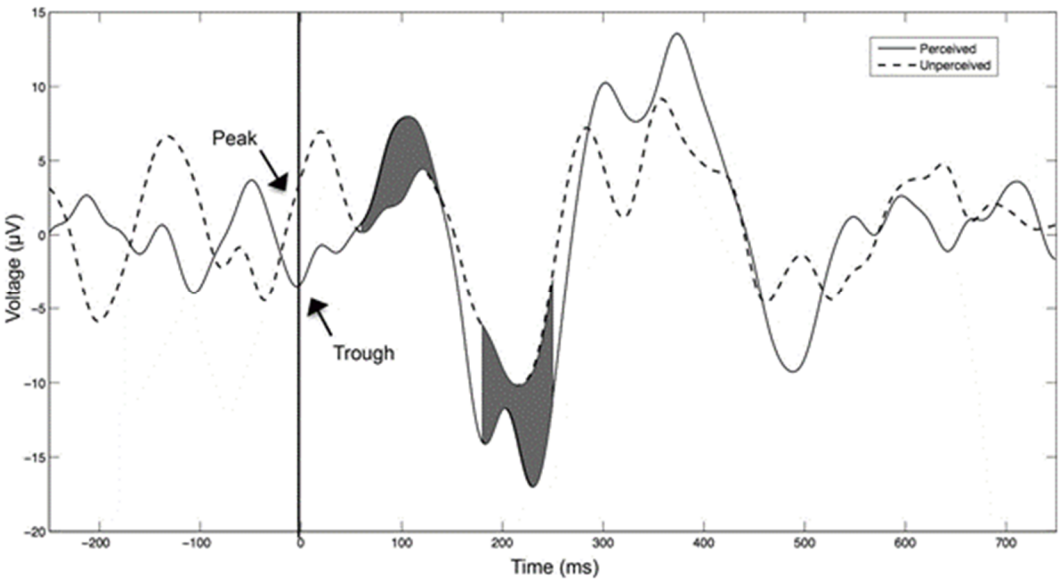

Figure 41 | **Perception of near-threshold stimuli is influenced by oscillatory alpha phase.** Electrical stimuli were administered to the left-hand middle finger. Grand average somatosensory-evoked potentials (SEP) over right primary somatosensory cortex for perceived (solid) and unperceived (dotted) target-present trials, showed the influence of the oscillatory alpha phase on perception. The shaded areas represent significant differences (Modified from Ai and Ro, 2014).

Given that alpha oscillations influence tactile perception performance on a trial by trial level (see Fig. 41; Linkenkaer-Hansen et al., 2004; Ai and Ro, 2014; Baumgarten et al., 2016), it is well possible that pre-stimulation alpha oscillations affect the sensory processing of afferent stimuli during tactile acuity measures after repetitive sensory stimulation. To rule out this possible confound, additional analyses were performed. In the second study of this project, alpha NF training was applied without subsequent application of repetitive sensory stimulation. As previously described, the majority of participants were unable to alter somatosensory alpha power in the targeted direction. However, participants still elicited distinct levels of alpha power, which remained stable up to 50 min after completion of NF training. In a subsequent tactile acuity measure no tactile acuity changes from baseline could be observed for the alpha up group and NF-paradoxical responders. Numerically, there was a slight decrease in tactile acuity for participants from the alpha down group. Moreover, no relationship between alpha power levels during the 50 min period after NF training and tactile acuity changes could be

found. These results strongly suggest, that altered alpha power levels in neurofeedback study 1 and 3 affected perceptual learning processes as opposed to tactile acuity processing.
Furthermore, in the third neurofeedback study, tactile acuity changes at the left (unstimulated) index finger were measured in addition to measures on the right (stimulated) index finger. No overall tactile acuity changes could be observed for the left hand independent of participants conditions. There was also no apparent connection between alpha power measured above the right somatosensory cortex (where left-hand sensory input is processed) and tactile acuity changes at the left-hand index finger.
Taken together, it seems unlikely that observed effects are elicited by altered sensory processing of afferent input during tactile acuity measures. However, replication in additional neurofeedback studies without repetitive sensory stimulation, but also without a break between NF training and tactile acuity measures would provide further evidence.

Taken together, much evidence suggests that alpha NF training gates stimulation-induced perceptual learning efficiency.

4.2.3 – Additional oscillatory predictors for perceptual learning

While alpha oscillations constitute the most prominent oscillatory rhythm measurable on the cortical surface, a multitude of oscillations interact to ensure efficient information processing. It therefore makes sense to consider the predictive effects of additional oscillations in other frequency ranges on perceptual learning. No effect could be found for theta oscillations. However, lower beta (13 – 19 Hz), upper beta (20 – 30 Hz) and low gamma (30 – 40 Hz) displayed small predictive value on perceptual learning, each explaining between 6% and 8% of observed interindividual variance. These effects could well be caused by underlying interactivity with the alpha frequency band, eliciting only small predictive value on their own. Given the fact that gamma oscillations have previously been shown to commonly occur phase-locked to alpha oscillations especially at high alpha power levels (Haegens et al., 2011b; Bonnefond and Jensen, 2015), it a connection between gamma-band power and perpetual learning could have been expected. However, gamma oscillations in this study only reflected the lower end of the gamma frequency range compared to higher frequency oscillations reported in other studies (e.g. 80-120 Hz in Bonnefond and Jensen, 2015).

Furthermore, alpha oscillations measured above left frontal and occipital areas as well as right somatosensory areas were analysed for their effect on perceptual learning. No predictive effect could be found for occipital areas. By contrast, alpha oscillations over frontal and right somatosensory areas could explain 17% and 12% of the stimulation-induced perceptual learning variance, respectively. As left and right somatosensory electrodes were in close proximity to each other, the found effect over the right somatosensory cortex could be partly due to volume conduction. However, alpha power measured over frontal areas showed an even stronger relationship, while locally further apart from the electrode over the somatosensory cortex. It should therefore be at least partly be considered to explain additional perceptual learning variance. Frontal alpha oscillations have previously been linked to enhanced attentional control (Berger and Davelaar, 2018). Even though, it is unlikely that attention alters perceptual learning, as previous experiments have shown that repetitive sensory stimulation can be applied independent of attentional processes (Godde et al., 2000). A more likely explanation is that increased functional connectivity constitutes for this relationship, as previous studies have shown that alpha neurofeedback training enhances network connectivity (Imperatori et al., 2017; Kozlova et al., 2017; Shtark et al., 2018).

Taken together, the results suggest that pre-learning somatosensory alpha oscillations are the critical variable predicting perceptual learning success. However, they reflect a state of preparedness before induction of learning. There is some research on oscillatory processes effecting performance during learning processes. It is conceivable that optimal performance can only be achieved, if both processes are executed at their most efficient level. For example, beta-band synchronization especially during early stages of a learning process has been reported to be beneficial for the learning outcome in rhythm learning and statistical learning (Skrandies and Klein, 2015; Edagawa and Kawasaki, 2017). Furthermore, pre-stimulus alpha power as well as alpha desynchronization during visual stimulus presentation steadily and significantly increased with training in a visual perceptual learning task (Bays et al., 2015). Another study showed that associative learning performance was dependent on early alpha and beta desynchronization during target presentation and frontal theta synchronization during a delay period before a response prompt (Clarke et al., 2018). At this stage, it is difficult to consolidate findings, as different modalities, tasks and analysed time periods impose hurdles to compare oscillatory processes. Especially when active cognitive processing is involved in the learning task, it can be expected that additional complex networks are recruited, when compared to passive sensory induction of learning. However, one important finding is that flexibility in the oscillatory domain is a strong predictor for learning success (Bassett et al., 2011). It makes

sense to assume that optimal preparation in combination with fast neural adaptations to the relevant learning task, will elicit the most effective outcome.

4.2.4 – Relationship between alpha oscillations and cortical excitability

Given the fact that GABA concentration, cortical excitability and alpha oscillations are all connected to perceptual learning (Höffken et al., 2007; Freyer et al., 2013; Heba et al., 2016; Brickwedde et al., 2019) and also describe different states of inhibition and excitability, it makes sense to assume that they are somehow connected. To test this hypothesis for alpha oscillations and cortical excitability, we implemented the paired-pulse suppression (PPS) paradigm.

No relationship could be found for uncorrected baseline alpha oscillations and subsequent PPS. However, uncorrected power values display decreased signal-to-noise ratios, as interindividual differences in volume conduction, electrode placement, cortical structure and bone density all affect power values beyond actual differences in oscillatory power.

However, PPS was similarly unpredictive for subsequent spontaneous alpha oscillations. Surprisingly, the measurement of PPS induced a rapid rise in oscillatory alpha power. During measurement of paired-pulse suppression, electrical impulses are administered to the median nerve, eliciting slight twitches in the thumb. It is conceivable that observed alpha power increases reflect adaptive changes in cortical inhibition as a response to a high priority stimulus. These coincidental findings are important, as they suggest that measures of cortical excitability possibly influence factors directly related to the intrinsic measure. It would be interesting to analyse, whether multiple measurements of paired-pulse suppression in short succession would reflect such changes.

Afterwards, NF training was applied for 15 min. As neurofeedback was very short, only few participants showed learning success, possibly due to natural fluctuations more than NF training. Nevertheless, change in alpha power during neurofeedback was unrelated to PPS before and after NF training. One last measure of spontaneous alpha oscillations succeeding the second PPS measure did not display any relationship either. This time, alpha oscillations did not increase in the wake of PPS. However, a trend of alpha power levels shifting into the direction of alpha power levels after the first PPS measurement was observable. This could

possibly indicate a constant level of oscillatory alpha activity, which is accomplished in response to PPS measures, independent of previous alpha power levels.

Therefore, no relationship between oscillatory alpha power and cortical excitability as measured with PPS could be found. The results are limited by small participant numbers as well as unsuccessful application of NF training, which might still induce unspecific effects influencing further measurements. For example, participants could have experienced frustration, which might affect the flexibility of neuronal adaptation processes.

Recent findings oppose the result of the present study. By administering transcranial magnetic stimulation (TMS) pulses tailored to the individual intrinsic alpha rhythm, cortico-spinal excitability differences could be observed (see Fig. 42). Pulses arriving at the peak of the cycle reflected low excitability, while pulses arriving at the trough of the cycle displayed highly excitability responses (Thut et al., 2017; Zrenner et al., 2018).

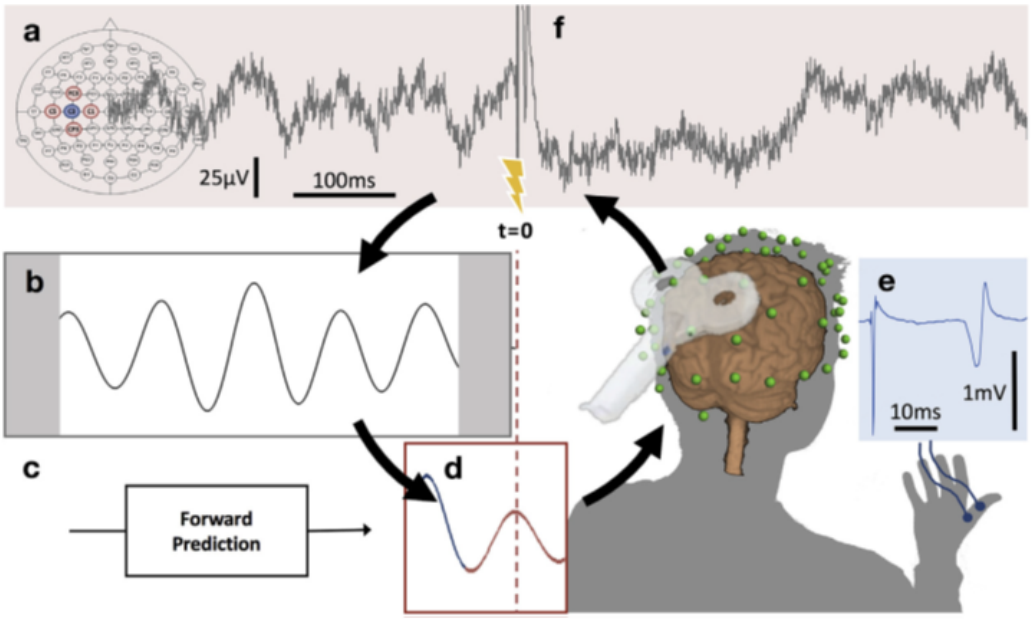

Figure 42 | **Administration of TMS pulses tailored to the intrinsic alpha phase of the participant.** a, recording of real-time EEG; b, the alpha phase is extracted with a bandpass filter and edge artefacts are removed; c, phase predictions are calculated; d, forward prediction of the signal determines the timepoint of the TMS pulse; e, motor evoked potentials can be measures with EMG electrodes at the hand; f, after about 300 ms, the intrinsic alpha rhythm is resumed; (Modified from Zrenner et al., 2018)

In neurofeedback study 1 and 3 respectively, neurofeedback-induced alpha power changes could explain up to 59% of the perceptual learning variance for NF groups. Intriguingly, baseline GABA levels measured right before application of repetitive sensory stimulation similarly explained 57% of the perceptual learning variance (Heba et al., 2016). While the direct

connection between alpha oscillations and GABA concentration has not been studied yet, some suggestive evidence exists. Administration of the drug lorazepam, a GABA-agonist, leads to consistent decreases in posterior alpha power (Schreckenberger et al., 2004; Ahveninen et al., 2007). These counterintuitive results were interpreted as a challenge to the theory of the inhibitory function of alpha oscillations (Lozano-Soldevilla, 2018). However, it has also been found that lorazepam reduces paired-pulse suppression, which is likewise counterintuitive as this suppression is believed to be GABAergic (Stude et al., 2016). An explanation possibly unifying these results, is that lorazepam, as suggested by Stude and colleagues (2016), actually decreases GABAergic inhibition. If this was true, the above-mentioned studies would provide evidence for a close connection between GABA concentration and alpha oscillations. However, it remains difficult to interpret neuronal processes on a cellular level with macro-level measuring methods. EEG can only pick up synchronized alpha oscillations. It is possible that more cells engage in oscillatory alpha activity, which are shifted in phase, thereby cancelling each other out on the scalp surface. Furthermore, it is possible that in the same region, different cell assemblies process different information. With EEG, we can only interpret functions eliciting the strongest synchronized oscillations. It is conceivable for example, that high alpha power measured over a certain cortical area can be traced back to a big cell assembly, while at the same time another cell assembly in the same area emits only very reduced oscillatory activity in the alpha band, thereby allowing increased information processing. If the second cell assembly would be of high importance for the performed task, increased alpha activity would be measured in EEG, while task processing would still be elevated and possibly performed very efficiently, as the first assembly reduces potential interferences though rivalling processes. Such circumstances would lead to inconsistent results.

It can be concluded that the results of the present study do not support recent findings and the theory that alpha oscillations and cortical excitability are connected. However, much still speaks for a connection between alpha oscillations, cortical excitability and GABA concentration, which should be explored in further experiments.

4.2.5 – Neurofeedback-induced alterations in cortical response patterns and their effect on perceptual learning

4.2.5.1 – Stability of neurofeedback-induced alpha power changes

A prerequisite for the facilitation of neurofeedback-induced changes in subsequent cortical processing, is that these changes are sustained after the completion of NF training. In the present study we could show that alpha levels were stable for at least 50 min after completion of the training while watching an animal documentary. Furthermore, alpha power levels assessed in between stimulation trains during 30 min of pRSS likewise remained robust, maintaining significant group differences up to the end of the stimulation (and likely beyond).

Literature regarding these findings are mixed. While some studies report no alterations in baseline alpha power levels (e.g. Berger and Davelaar, 2018), others report steady increases in baseline alpha levels with each session spread over several days or weeks (Escolano et al., 2011; Zoefel et al., 2011; Escolano et al., 2013; López-Larraz et al., 2012; Mennella et al., 2017)

Remarkably, a two year follow up after 20 sessions of alpha/theta NF treatment of children with "academic difficulties", showed differences in cortical processing compared to controls (Becerra et al., 2006). Given the young age of participants, it is conceivable that NF training directly influenced developmental processes. It is unclear whether a two year follow up assessment in adults would similarly show maintained alterations after such a long time period.

Taken together, growing evidence suggests that neurofeedback-induced alpha power changes elicit robust changes in cortical processing. The temporal dynamics of declines back to baseline levels are not yet fully understood and warrant further research.

4.2.5.2 – Sensory processing of repetitive sensory stimulation

Electric repetitive sensory stimulation (eRSS) elicits artefacts in EEG recordings. In order to still measure neural processing during repetitive sensory stimulation, a pneumatic stimulation protocol was implemented, delivering 20 Hz air-puff stimuli onto the fingertip. In a pilot study, it was shown that pneumatic repetitive sensory stimulation (pRSS) increased tactile acuity at the fingertips to an extent commonly reported in studies applying eRSS (Ragert et al., 2008; Schlieper and Dinse, 2012; Freyer et al., 2013; Heba et al., 2016; Schmidt-Wilcke et al., 2018).

No changes in tactile acuity were found for the unstimulated left-hand fingertip. It was therefore concluded that pRSS successfully induces perceptual learning processes.

Processing dynamics of cutaneous stimulation at the fingers has been extensively studied. Mechanoreceptors in the glabrous skin of the fingertip transmit tactile stimuli. Determining the particular receptor transmitting 20 Hz air-puffs is intricate, as multiple receptor types are likely involved. Presumably, FA-1 (fast-adapting type I) Meissner endings, which are sensitive to high-frequency dynamic skin deformation, and FA-II (fast-adapting type II) Pacini endings, which respond to mechanical transient and high-frequency vibrations, are responsible for the transmission of pRSS stimulation (Johansson and Flanagan, 2009). The received information is then forwarded via dorsal columns and the ventroposterior thalamic nuclei to the somatosensory cortex (Pons et al., 1992), resulting in sensory evoked potentials (SEPs) recordable with EEG.

While descriptions on SEPs induced by air-puff stimulation are sparse, a large body of research has accumulated, describing SEPs elicited by electrical stimulation of the median nerve. The first negative N20 component is thought to originate mainly from the granular layer (layer IV) of Brodmann's area 3b, occupying the posterior bank of the Rolandic fissure (Allison et al., 1989; Allison et al., 1991; McLaughlin and Kelly, 1993; Rossini et al., 1997; Balzamo et al., 2004). The second component, the P25, is more difficult to place. It has been suggested to be caused by depolarization of the superficial portion of apical dendrites from cortical layers 2 and 3 (Mitzdorf, 1985; Arezzo and Vaughan, 1980; Allison et al., 1991; McLaughlin and Kelly, 1993; Peterson et al., 1995). However, there was also evidence for an origin in Brodmann's area 1, at the apex of the postcentral gyrus (Arezzo et al., 1979; Allison et al., 1989; McCarthy et al., 1991). There is general agreement though, that on a broader scale, the N20 component reflects thalamocortical input to S1, while the P25 component represents intracortical processing (Wolters et al., 2005). Components of longer latencies like P45, N60 and P/N100 show greater variance between participants and are more susceptible to cognitive modulations such as attention or motivation (Michie et al., 1987; Hämäläinen et al., 1990; Ito et al., 1992; Eimer and Forster, 2003; Montoya and Sitges, 2006; Schubert et al., 2006).

Air-puff stimulation likely causes less synchronized afferent activation compared to electrical stimulation. It can therefore be assumed, that latencies would be delayed. In single air-puff recordings, instead of N20 and P25 components, N25 and P30 components were observable, introducing a 5 ms shift in latencies. In another study, similarly neglectable latency shifts between electrical and air-puff stimulation have been described (Kawohl et al., 2007).

Potentials evoked by the 20 Hz pRSS administered in this study, display increased latencies. The first clearly discernible positive component emerged at 43 ms. At this stage, it is difficult to say, whether this observed P43 reflects a delayed P25 (or P30 for pneumatic stimulation), or whether it reflects an early P50 and N20 as well as P25 components are not visible. Later components are even more difficult to interpret, as they are confounded by the repetitive character of pRSS, where incoming stimuli interact in complex ways with processing of previous ones (Schubert et al., 2006; Wan et al., 2008; Terrasa et al., 2018).

After about 500 ms following stimulation onset, the evoked potentials accumulate into steady-state evoked potentials (SSEP) in a 20 Hz frequency range. Repeated stimulation in certain frequency ranges elicit higher amplitude SSEPs than others, depending on the modality of stimulation. As such, the visual system favours frequencies between 18 and 20 Hz for unpatterned flash stimuli and slightly reduced frequencies for patterned stimuli (Regan, 1982). In the somatosensory system, the highest amplitudes of SSEPs have been registered between 21 and 26 Hz (Snyder, 1992; Tobimatsu et al., 1999; Colon et al., 2012), well in line with the protocol applied in the present study. The generation of steady-state responses is controversial. It is possible, that superstition of independent transient responses causes the observed SSEPs, that neurons simply respond to the stimulated frequency, or both mechanism are present simultaneously (Colon et al., 2012; Lütkenhöner, 2016). However, recent data from the auditory cortex suggests that independent transient responses generate SSEPs (Lütkenhöner, 2016).

In the present study, observed SSEP characteristics are also reflected in phase coherence analysis, where the initial SEP components, as well as the steady-state response at 20 Hz and harmonics at 40 Hz can be observed. Repeated measure comparison of the first and the last 10 minutes of stimulation revealed no sign of decline, suggesting a maintained SSEP response over 40 min of stimulation without habituation processes.

The same processes can also be observed when analysing the time-frequency decomposition of the signal. Additionally, there is a strong event-related desynchronization (ERD) visible during stimulation train in the upper alpha frequency. This process likely reflects sensory encoding, which has been connected to ERD in the upper alpha band (Pfurtscheller and Klimesch, 1991; Freyer et al., 2013). Again, no significant decline in stimulation processing could be observed over 40 min of stimulation.

These findings provide further evidence for the hypothesis, that RSS induced LTP-like processes in the cortex, as robust and maintained activation of the somatosensory cortex is a prerequisite for LTP-like processes to occur (Nicoll, 2017).

4.2.5.3 – Effects of neurofeedback training on sensory processing during repetitive sensory stimulation

Analysis of neurofeedback-induced changes in cortical processing of pRSS were largely exploratory without directed hypothesis. It should therefore be considered a starting point for future research more than definite evidence.

So far, several studies have analysed neurofeedback-induced alterations of neural processing. For example, several sessions of alpha or alpha/theta NF training enhanced connectivity in the default mode network and the salient network (see Fig. 43; Kluetsch et al., 2014; Imperatori et al., 2017; Kozlova et al., 2017; Shtark et al., 2018). Furthermore, in patients with PTSD, alpha NF training shifted complex amygdala connectivity from areas related to negative affect to areas related to emotion regulation (Nicholson et al., 2016). However, they focused mostly on fMRI scans at rest. It is however of great interest, to see differences in actual information processing after neurofeedback-induced changes.

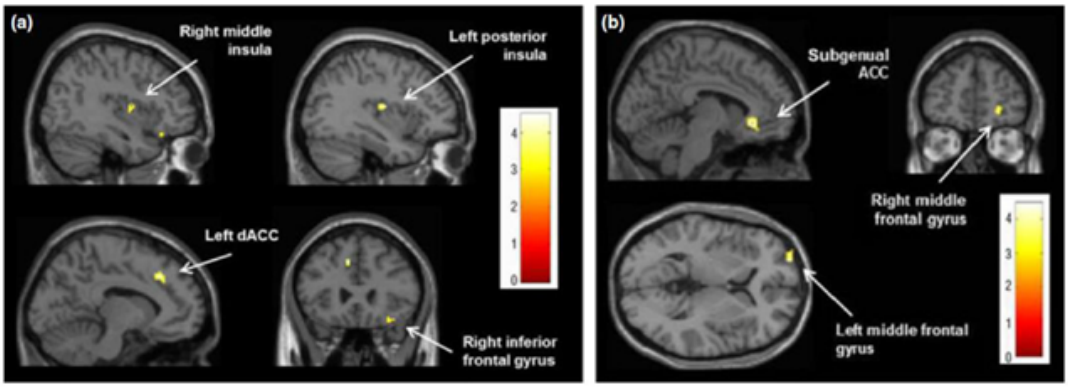

Figure 43 | **Clusters showing increased functional connectivity after neurofeedback in fMRI.** a, salience network; b, default mode network; (Modified from Kluetsch et al., 2014)

During pRSS, significant differences between the alpha up and alpha down group were most prevalent in between stimulation trains, where the alpha up group showed increased upper alpha activity as well as increased 20 Hz activity. As a consequence, it was not the instantaneous reaction to the stimulation train, that was affected, but rather the processing occurring immediately after stimulation trains. Furthermore, sustained 20 Hz activity in between

stimulation trains is highly interesting for two reasons. Firstly, this activity reflects time-locked but not phase-locked activity, which can also be observed in the EEG recordings during pRSS without prior NF training. It can be interpreted as 20 Hz event-related synchronization (ERS), which is not directly induced by the stimulus, but intrinsically maintained after stimulus offset. Secondly, this activity could reflect the induction of LTP-like processes, where maintained activation is required (Nicoll, 2017). Interestingly, levels of this 20 Hz activation are in line with observed perceptual learning outcomes for the respective groups. The alpha up group shows high 20 Hz ERS and high perceptual learning, for NF-paradoxical-responders both factors were numerically reduced. In contrast, participants from the alpha down group, 20 Hz activity was reduced, and no perceptual learning occurred.

Further observation included a strong ERS of beta band activity after the completion of NF training in the alpha down group, which prevailed during and in between stimulation trains. Somatosensory and motor beta activity has been repeatedly linked to movement, passive moment and movement observation (Salmelin and Hari, 1994; Pfurtscheller and Lopes da Silva, 1999; Alegre et al., 2002; Babiloni et al., 2002; Amaral et al., 2018; Espenhahn et al., 2017). Specifically, movement elicits beta desynchronization followed by strong increases in beta power after movement, well above baseline levels. While no specific movement was performed by participants, it is possible that participants from the alpha down group experienced increased difficulties to sit still after NF training and remain still during pRSS, related to the reported exhaustion in their training group. Even if this is largely speculative, it could relate to the sensory gating phenomenon, which describes that movement processes attenuate sensory processing (Song and Francis, 2015; Saradjian, 2015). This in turn could explain impeded perceptual learning outcomes in the alpha down group.

As an immediate reaction to pRSS, NF-paradoxical responders elicited increased theta ERS at the stimulus onset and increased beta ERS in between stimulation trains compared to the alpha down group. However, these effects were small and neither visible when comparing the alpha up with the alpha down group, nor when comparing the alpha up group to NF-paradoxical responders.

No group differences in upper alpha ERD could be found, directly contradicting previously reported results, where upper alpha ERD during stimulation trains predicted large fractions of the perceptual learning outcome (Freyer et al., 2013). Reasons behind this discrepancy are unclear. However, it is conceivable that NF training induces alterations in cortical processing affecting the relevance of different processes for plasticity and learning processes.

It can be concluded that instantaneous responses to pRSS were not different between groups. However, the alpha up group displayed heightened alpha power and 20 Hz ERS in in between stimulation trains, while the alpha down group displayed increased beta ERS after completion of neurofeedback-training. These factors might reflect alterations in underlying plasticity processes crucial for perceptual learning. However, functional connectivity changes after NF training reported across several studies also suggest modifications of complex network interactions by NF training beyond the scope of the present study.

4.2.5.4 – Behavioural relevance of neurofeedback-induced differences in cortical processing

Although it makes sense to assume, that neurofeedback-induced group differences in cortical processing are the cause of differences in perceptual learning efficiency, this is not necessarily the case. It is possible that the underlying factors determining learning success are not visible in somatosensory EEG recordings. Therefore, the identified group differences (lower beta ERS after completion of neurofeedback, theta ERS during stimulation trains and 20 Hz as well as lower beta ERS in between stimulation trains) were analysed concerning their relationship to perceptual learning and alpha oscillations. Theta power and beta power in between stimulation trains were neither connected to alpha oscillations nor to perceptual learning. This is not surprising, as their effect was very small and only observable between participants from the alpha down group and NF-paradoxical responders. Origin and meaning of these group differences for now remain elusive.

On the other hand, lower beta ERS seemed to display an inverse relationship to perceptual learning and alpha oscillations, not reaching significance. Visual inspection of the observed distributions might suggest, that NF-paradoxical responder do not display this relationship, contrasting participants from the alpha up and the alpha down group.

Finally, 20 Hz ERS in between stimulation trains was connected to alpha oscillations and perceptual learning, explaining 19% and 11% of the interindividual learning variance, respectively. Considering that alpha oscillations explained 59% of the subsequent stimulation-induced perceptual learning variance, 11% seems low. However, it is unlikely that there is only one factor modifying sensory processing and perceptual learning. Far more reasonable is a complex interaction of several different factors. Multiple regression analysis of the interactive effect of 20 Hz ERS and lower beta ERS revealed strong connections to both alpha power (R^2 = .513) and perceptual learning (R^2 = .410) for NF groups. Regression weights showed that

20 Hz ERS had a strong positive relationship to both factors, while for lower beta ERS, the relationship was slightly less strong and inversed. Accordingly, it was most beneficial for perceptual learning, if 20 Hz activation was sustained in between stimulation trains and if lower beta oscillations were kept low. No such relationship could be observed in NF-paradoxical responders.

Accordingly, two factors have been identified possibly mediating the effect of alpha NF training on perceptual learning: 20 Hz ERS in between stimulation trains and lower beta ERS after NF training. As this analysis was exploratory, replication of these findings is necessary along with higher subject numbers to allow mediator analysis. Most likely however, there are more factors mediating the effect of alpha NF training on perceptual learning processes and this result should be considered a starting point of a long way to go.

4.3 – Open questions

In the present study, it was demonstrated that somatosensory alpha NF training gates stimulation-induced tactile perceptual learning efficiency. It is conceivable, that this mechanism generalizes to any learning process. So far, no such evidence exists. Positive effects of alpha NF training on memory performance provide first indications for this theory (Nan et al., 2012; Guez et al., 2015; Wei et al., 2017). However, it would be great to monitor oscillatory activity during an active learning task immediately after NF training. This would render results comparable to the data collected in this study. One possible option would be to implement a simple tactile learning task (for example braille reading). It would remain in the same modality, thereby keeping all variables constant apart from active learning as opposed to stimulation-induced learning. From there, other modalities could be integrated and more cognitive tasks like studying vocabularies could be tested.

Alpha NF training has been shown to elicit overwhelmingly positive effects for many different tasks and conditions, which appear to be completely unrelated. For instance, alpha NF training was reported to elicit beneficial effects on ADHD (Vernon et al., 2009; Arns et al., 2012; Escolano et al., 2014a), learning disabilities in children (Becerra et al., 2006), symptom severity, perceived stress, cortisol levels and memory function after traumatic brain injury (Kober et al., 2015; Bennett et al., 2018), attentional control (Berger and Davelaar, 2018), tinnitus (Crocetti et al., 2011), avoidant personality accentuation and depression in and treatment of alcohol and drug abuse (Saxby and Peniston, 1995; Scott et al., 2005; Dalkner et

al., 2017), cognitive enhancements and reduction of negative affect and anxiety in major depression disorder (Choi et al., 2011; Escolano et al., 2013; Escolano et al., 2014b; Ramirez et al., 2015; Mennella et al., 2017), cognitive performance (Hanslmayr et al., 2005; Zoefel et al., 2011; Escolano et al., 2012; Escolano et al., 2014c), working memory performance (Escolano et al., 2011; Xiong et al., 2014; Hsueh et al., 2016), creative performance (Gruzelier et al., 2014), attention (Gruzelier et al., 2014), well-being (Gruzelier et al., 2014; Reddy et al., 2014; Phneah and Nisar, 2017; Wei et al., 2017), memory performance (Nan et al., 2012; Guez et al., 2015; Wei et al., 2017, 2017, 2017) well-being in patients with PTSD (Peniston and Kulkosky, 1991; Kluetsch et al., 2014; Nicholson et al., 2016), memory in patients with mild cognitive impairments (Lavy et al., 2019), visual performance (Nan et al., 2013; Okazaki et al., 2015) and perceptual learning . This non-exhaustive list reveals two main areas of application: emotional wellbeing and increased sensory and cognitive performance, both of which also support many clinical conditions. Interestingly, treatment of tinnitus and reduced symptom severity after traumatic brain injury seem to constitute additional categories of application. However, this effect could possibly be traced back to reduced stress. The present study presents another new field of application: increased perceptual learning efficiency.

The pressing questions are how and why does alpha NF training elicit these universally positive effects? A thorough frameworks exist to answer the question of how cognitive performance improvements can be achieved. There is general agreement that alpha oscillation gate information processing by emitting pulses of inhibition during peaks of the oscillatory cycle (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011b; Jensen et al., 2014; Bonnefond and Jensen, 2015; Gips et al., 2016; van Diepen et al., 2019). This way, the power of alpha oscillations determines how much information can be processes during troughs of the cycle, inhibiting less important information. Accordingly, alpha oscillations shape the neural architecture with a mechanism to allocate neural resources and organize networks to be optimally prepared for upcoming tasks. A positive side effect of increased alpha oscillations can be heightened levels of relaxation. High oscillatory alpha power reflects a state of reduced processing and could probably also be achieved by negative thoughts or emotions, as long as they are immersive. For example, one participant who trained to increase alpha power in the present study, reported to have imagined himself in fearful situations. Furthermore, it has been shown that some forms of meditation are accompanied by increases in alpha oscillations, while others are not (Travis, 2001; Cahn et al., 2013; Lee et al., 2018). Increased relaxation might therefore be a side-effect of instructions, as most neurofeedback-studies report to instruct participants to relax. Consequentially, it should be noted that increased alpha oscillations can

be but do not have to be induced by relaxation. Moreover, there is more to the question of how alpha oscillations elicit those effects, as complex modifications of neuronal processes with potentially long-lasting effects have been discussed. Part of this question can only be answered by conducting longitudinal follow up studies after NF training. This may seem effortful, however, considering the potential of neurofeedback intervention such research is warranted.

The enormous potential of NF training described above leads to the question of why NF training elicits such universally positive effects. It seems irritating, that the human neuronal architecture is not highly efficient for information processing. If higher alpha power had been adaptive throughout evolution, it surely would be higher now. It is possible, that the actual benefit of alpha NF training is not solely the amount of alpha power itself, but the heightened flexibility with which it can be up- and down-regulated according to demand (Bassett et al., 2011). The question remains why we do not incorporate more flexibility then to begin with. It could be argued that as with most factors, the right balance is key. In the busy environments of today's city life, continuous sensory and cognitive stimulation prevails. It is conceivable that in such an environment, the ability to downregulate information processing is impaired. It is therefore possible, that in different environments, for example in a barren and withdrawn monastery, the neural architecture of the brain would be different (Hankey, 2006). Furthermore, it has to be considered that reported short-term effects NF training could have drawbacks in the long run. Similarly to increased plasticity, which seems desirable in all situations at first sight, a drawback could be less reliable storage of former information (Abraham and Robins, 2005). Interferences with the homeostasis of intrinsic, induced and evoked processes our brain preserves, should be closely monitored.

An encouraging example of long-term effects in NF training has been demonstrated in children with learning disabilities, whose neural development was still altered 2 years after neurofeedback intervention (Becerra et al., 2006). However, in this case all children had received personalized NF training, tailored to abnormal oscillatory patterns previously discovered in their scalp EEG. As such, their altered brain pattern was in fact closer to a normal population than to peers with learning disability. Such an approach seems reasonable and has been shown to be effective for ADHD treatment (Arns et al., 2012).

As alpha NF training is a promising candidate for application in pedagogical, clinical and rehabilitational settings, it is vital to assess long-term effects, possible costs, gain deeper understanding of neural modifications and to understand the factors impairing NF training success in NF-paradoxical responders.

4.4 – Conclusions

The present study demonstrated that neurofeedback training can be successfully applied to bidirectionally modulate somatosensory alpha power. This in turn gated stimulation-induced tactile perceptual learning. Accordingly, participants who increased alpha oscillations by neurofeedback training showed increased perceptual learning performance compared to control participants. In contrast, participants who decreased alpha oscillations in the wake of neurofeedback training on average showed no perceptual learning. Interindividual learning variance in NF groups could be substantially reduced.

Induced alpha power changes remained stable over 50 min after neurofeedback training and persisted throughout repetitive sensory stimulation. As a consequence of neurofeedback training, the neural architecture during processing of repetitive sensory stimulation was modified. Participants who increased somatosensory alpha power showed sustained activity in the stimulated frequency range, even in between stimulation trains. This behaviour was contrasted by participants who decreased alpha power and elicited heightened synchronization in the lower beta band after neurofeedback training. In combination, these two factors could be identified to be relevant for perceptual learning, possibly mediating the effect of alpha oscillations on perceptual learning. Future research should focus methodological aspects of neurofeedback training and its short-term as well as long-term effects on neuronal processing.

Neurofeedback training is an exciting and promising candidate for application in rehabilitational, pedagogical and clinical environments or even to improve learning efficiency in everyday life.

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6 – Appendix

6.1 – Post-Hoc Tests

Table 1 | Experiment 1; Two-way mixed *ANOVA* 2 x 3 (time x condition) with raw alpha power comparing baseline day 1 with the last block of NF training;

Alpha power	Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Baseline day 1	Alpha Up	Alpha Down	.28(1.39)	.20(30)	.844	-2.567	3.120
		NF-PR	-.42(1.18)	-.35(31)	.725	-2.827	1.990
	Alpha Down	NF-PR	-.70(1.27)	-.55(29)	.587	-3.234	1.894
Last NF training day 2	Alpha Up	Alpha Down	3.26(1.63)	2.00(30)	.055	1.633	6.597
		NF-PR	.99(1.37)	.72(31)	.476	-1.808	3.788
	Alpha Down	NF-PR	-2.27(1.55)	-1.45(29)	.153	-5.443	.898

Alpha power		Group	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Baseline day 1	Last NF training day2	Alpha Up	-2.55(.65)	-3.94(16)	.001*	-3.930	-1.180
		Alpha Down	.43(.68)	,63(14)	.539	-1.035	1.898
		NF-PR	-1.15(.58)	-1.98(15)	.066	-2.381	.088

*Note. *The level of significance (*p < .05) was obtained after Bonferroni adjustment (.05/9 =.006)*

Table 2 | Experiment 1; Two-way mixed *ANOVA* 3 x 2 (time x condition) with alpha power during NF training on day 2, normalized on baseline day 1;

Group		Alpha power day 2	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	Alpha Down	NF block 1	1.54(.63)	2.46(30)	.020	.260	2.821
	NF-PR		-.65(.65)	-.99(31)	.330	-1.982	.687
Alpha Down	NF-PR		.89(.65)	1.37(29)	.183	.445	2.231
Alpha Up	Alpha Down	NF block 2	2.86(.72)	3.95(30)	.000**	1.378	4.331
	NR-PR		-1.19(.72)	-1.65(31)	.109	-2.652	.280
Alpha Down	NF-PR		1.67(.76)	2.20(29)	.036	.118	3.220
Alpha Up	Alpha Down	NF block 3	3.00(.81)	3.71(30)	.001*	1.347	4.654
	NF-PR		-1.70(.86)	-1.20(31)	.058	-3.454	.063
Alpha Down	NF-PR		1.31(.75)	1.73(29)	.094	-.237	2.848

Group	Alpha power day 2		*Mdiff*(*SEM*)	*t*(*df*)	*P*	95% Confidence interval	
						Lower	Upper
Alpha Up	NF block 1	NF block 3	-1.72(.44)	-3.92(16)	.001*	-2.652	-.791
Alpha Down	NF block 1	NF block 3	-.26(.23)	-1.12(14)	.282	-.763	.240
NF-PR	NF block 1	NF block 3	-.67(.38)	-1.77(15)	.097	-1.485	.137

*Note. *The level of significance (*p < .05; ** p < .01) was obtained after Bonferroni adjustment (.05/12 =.004; .01/9 = .0008)*

Table 3 | Experiment 1; Two-way mixed *ANOVA* 2 x 2 (time x condition) with alpha power during NF training on day 3, normalized on baseline day 1;

Group		Alpha power day 3		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
							Lower	Upper
Alpha Up		NF block 1	NF block 2	-.64(.21)	-3.06(16)	.008	-1.091	-.197
Alpha Down		NF block 1	NF block 2	-.27(.32)	-.84(14)	.415	-.954	.417
NF-PR		NF block 1	NF block 2	-.278(.30)	-.92(15)	.372	-.923	.366
Control		NF block 1	NF block 2	.13(.20)	.644(19)	.528	-.293	.553
Alpha Up	Alpha Down	NF block 1		2.65(.78)	3.39(30)	.002*	1.051	4.238
	NF-PR			-1.04(.82)	-1.26(31)	.216	-2.724	.639
	Control			1.30(.63)	2.05(35)	.048	0.139	2.584
Alpha Down	NF-PR			1.60(.65)	2.45(29)	.021	.265	2.940
	Control			-1.35(.43)	-3.16(33)	.003*	-2.212	-.480
NF-PR	Control			.26(.51)	.50(34)	.620	-.785	1.298
Alpha Up	Alpha Down	NF block 2		3.02(.79)	3.83(30)	.001*	1.411	4.628
	NF-PR			-1.04(.82)	-1.75(31)	.090	-3.049	.233
	Control			2.07(.63)	3.29(35)	.002*	.794	3.352
Alpha Down	NF-PR			1.61(.67)	2.42(29)	.022	.252	2.972
	Control			-.95(.47)	-2.03(33)	.050	-1.895	.001
NF-PR	Control			.67(.51)	1.30(34)	.201	-.465	1.800

*Note. *The level of significance (*p < .05; ** p < .01) was obtained after Bonferroni adjustment (.05/16 =.003).*

Table 4 | Experiment 1; Two-way mixed *ANOVA* 2 x 4 (time x condition) comparing tactile acuity pre and post measures of all groups;

Tactile acuity day 3	Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Pre	Alpha Up	Alpha Down	.13(.08)	1.73(30)	.094	-.023	.285
		Control	.11(.07)	1.47(35)	.152	-.041	.257
		NF-PR	.16(.08)	1.93(31)	.063	-.009	.322
	Alpha Down	Control	-.02(.07)	-.33(33)	.743	-.166	.119
		NF-PR	.03(.08)	.33(29)	.743	-.133	.184
	Control	NF-PR	.05(.08)	.65(34)	.520	-.104	.202
Post	Alpha Up	Alpha Down	-.17(.08)	-2.21(30)	.035	-.331	-.013
		Control	-.01(.08)	-.07(35)	.946	-.174	.163
		NF-PR	-.02(.07)	-.27(31)	.789	-.172	.132
	Alpha Down	Control	.17(.09)	1.93(33)	.061	-.008	.342
		NF-PR	.15(.08)	2.01(29)	.054	-.003	3.07
	Control	NF-PR	-.01(.08)	-.18(34)	.862	-.182	.153
Tactile acuity day 3		Group	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Pre	Post	Alpha Up	.25(.02)	11.07(16)	.000***	.295	.303
		Alpha Down	-.05(.03)	-1,62(14)	.129	-.115	.016
		Control	.14(.04)	3.75(19)	.001*	.062	.219
		NF-PR	.08(.04)	2.10(15)	.053	-.001	.156

*Note. *The level of significance (*p < .05; ** p < .01; *** p < .001) was obtained after Bonferroni adjustment (.05/16 =.003; .01/16 = .0006; .001/9 = .00006)*

Table 5 | Experiment 1; LSD Fisher post hoc test for comparisons of tactile acuity gains between all conditions

Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
					Lower	Upper
Alpha Up	Alpha Down	17.84(3.02)	1.73(30)	.000***	11.80	.285
	Control	5.92(2.82)	1.47(35)	.039*	0.30	.257
	NF-PR	10.42(2.97)	1.93(31)	.001***	4.48	.322
Alpha Down	Control	-11.92(2.92)	-.33(33)	.000***	-17.74	-6.09
	NF-PR	-7.41(3.07)	.33(29)	.019*	-13.54	-1.29
Control	NF-PR	4.50(2.86)	.65(34)	.121	-1.22	10.22

*Note. * p < .05; ** p < .01; *** p < .001;*

Table 6 | Experiment 1; Two-way mixed *ANOVA* 4 x 2 (time x condition) with alpha power during inter-train intervals of repetitive sensory stimulation, normalized on baseline day 1;

Group		Alpha power RSS	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	Alpha Down	0 - 5 min	2.51(.89)	2.82(22)	.010*	.667	4.364
		5 - 10 min	3.31(.93)	3.55(22)	.002**	1.376	5.247
		10 - 15 min	3.10(.88)	3.51(22)	.002**	1.270	4.931
		15 - 20 min	2.15(.84)	2.57(22)	.017	0.415	3.878

*Note. *The level of significance (*p < .05; ** p < .01) was obtained after Bonferroni adjustment (.05/4 =.013; .01/16 = .003)*

Table 7 | Experiment 5; Two-way mixed *ANOVA* 2 x 3 (time x condition) with raw alpha power comparing baseline day 1 with the last block of NF training;

Alpha power	Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Baseline day 1	Alpha Up	Alpha Down	-2.64(1.75)	-1.51(22)	.146	-6.281	.995
		NF-PR	-.14(1.49)	-.09(22)	.928	-3.227	2.954
	Alpha Down	NF-PR	2.51(2.11)	1.19(20)	.249	-1.897	6.911
Last NF training day 2	Alpha Up	Alpha Down	.56(1.88)	.299(22)	.768	-3.336	4.461
		NF-PR	-.29(1.94)	-.151(22)	.881	-4.235	3.659
	Alpha Down	NF-PR	-.85(2.21)	-.29(20)	-704	-5.452	3.751

Alpha power		Group	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Baseline day 1	Last NF training day2	Alpha Up	-1.66(.76)	-2.18(12)	.050	-3.313	-.003
		Alpha Down	1.55(95)	1.63(10)	.134	-.569	3,665
		NF-PR	-1.81(1.02)	-1.77(10)	.107	-4.084	.468

*Note. *The level of significance (*p < .05) was obtained after Bonferroni adjustment (.05/9 =.006)*

Table 8 | Experiment 5; Two-way mixed *ANOVA* 3 x 2 (time x condition) with alpha power during NF training on day 1, normalized on baseline day 1;

Group		Alpha power day 2	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	Alpha Down	NF block 1	1.53(.82)	1.86(22)	.076	-.174	3.236
	NF-PR		-.31(.84)	-.36(22)	.718	-2.038	1.428
Alpha Down	NF-PR		-1.84(1.05)	-1.75(20)	.096	-4.028	.356
Alpha Up	Alpha Down	NF block 2	2.32(.93)	2.48(22)	.021	.383	4.255
	NR-PR		-.087(.81)	-.107(22)	.916	-1.773	1.600
Alpha Down	NF-PR		-2.41(1.08)	-2.23(20)	.037	-4.656	-.154
Alpha Up	Alpha Down	NF block 3	2.68(1.10)	2.44(22)	.023	.404	4.985
	NF-PR		.52(1.91)	.51(22)	.614	-1.578	2.610
Alpha Down	NF-PR		-2.17(.90)	-2.42)20)	.025	-4.031	-.299
Group	Alpha power day 2		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	NF block 1	NF block 2	-2.24(.78)	-2.88(12)	.014	-3.926	-.546
Alpha Down	NF block 1	NF block 2	-1.09(.47)	-2.33(10)	.042	-2.125	-.046
NF-PR	NF block 1	NF block 2	-1,41(.46)	-3.06(10)	.012	-2.445	-.383

*Note. *The level of significance (*p < .05) was obtained after Bonferroni adjustment (.05/12 =.004)*

Table 9 | Experiment 5; Two-way mixed *ANOVA* 3 x 2 (time x condition) with alpha power during NF training on day 2, normalized on baseline day 2;

Group		Alpha power day 2	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	Alpha Down	NF block 1	3.28(.72)	4.55(22)	.000**	1.782	4.771
	NF-PR		1.93(.54)	3.56(22)	.002*	.805	3.048
Alpha Down	NF-PR		-1.35(.77)	-1.76(20)	.094	-2.954	.252
Alpha Up	Alpha Down	NF block 2	3.63(.59)	6.17(22)	.000***	2.40ß	4.851
	NR-PR		1.07(.64)	1.65(22)	.112	-.271	2.400
Alpha Down	NF-PR		-2.57(.75)	-3.41(20)	.003*	-4.137	-.994
Alpha Up	Alpha Down	NF block 3	3.824(.64)	5.997(22)	.000***	2.502	5.147
	NF-PR		1.14(-63)	1.82(22)	.082	-.157	2.44
Alpha Down	NF-PR		-2.68(73)	-3.65(20)	.002*	-4.217	-1.152
Group	Alpha power day 2		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Alpha Up	NF block 1	NF block 3	-.84(.45)	-1.72(12)	.111	-1.900	.224
Alpha Down	NF block 1	NF block 3	-.29(.60)	-.485(10)	.638	-1.625	1.044
NF-PR	NF block 1	NF block 3	-1.62(.44)	-3.66(10)	.004	-2.612	-.636

*Note. *The level of significance (*p < .05; **p < .01; ***p < .001) was obtained after Bonferroni adjustment (.05/12 =.004; .01/12 =.0008; .001/12 =.00008)*

Table 10 | Experiment 5; Two-way mixed *ANOVA* 2 x 3 (time x condition) comparing tactile acuity pre and post measures of all groups;

Tactile acuity day 3	Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
Pre	Alpha Up	Alpha Down	.06(.07)	.81(22)	.427	-.096	.220
		NF-PR	.05(.08)	.62(22)	.541	-.116	.215
	Alpha Down	NF-PR	-.01(.08)	-.144(20)	.887	-.187	.163
Post	Alpha Up	Alpha Down	-.27(.08)	-3.54(22)	.002*	-.429	-.112
		NF-PR	-.01(08)	-.10(22)	.925	-.167	.152
	Alpha Down	NF-PR	.26(.09)	2.90(20)	.009	.074	.453
Tactile acuity day 3		Group	*Mdiff*(*SEM*)	*t*(*df*)	*P*	95% Confidence interval	
						Lower	Upper
Pre	Post	Alpha Up	.18(.03)	6.00(12)	.000***	.115	.246
		Alpha Down	-.15(.04)	-4.12(10)	.002*	-.234	-.070
		NF-PR	.12(.06)	2.16(10)	.056	-.004	.251

*Note. *The level of significance (*p < .05; **p < .01; ***p < .001) was obtained after Bonferroni adjustment (.05/9 =.006; .01/9 =.001; .001/9 =.0001)*

Table 11 | Experiment 5; LSD Fisher post hoc test for comparisons of tactile acuity gains between all conditions

Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
					Lower	Upper
Alpha Up	Alpha Down	20.81(3.58)	6.91(22)	.000***	13.520	28.106
	NF-PR	3.56(3.58)	.96(22)	.327	-3.732	10.854-
Alpha Down	NF-PR	-17.25(3.73)	-4.14(20)	.000***	-24.843	-9.662

*Note. * p < .05; ** p < .01; *** p < .001;*

Table 12 | Experiment 2; Repeated measures *ANOVA* comparing alpha power levels before and after paired-pulse suppression measures

Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
					Lower	Upper
Base1	Post PPS1	-1.29(.39)	-3.34(29)	002**	-2.085	-.500
Post PPS1	End NF	.60(.48)	1.25(28)	.220	-.382	1.589
END NF	Post PPS2	.03(.41)	.08(28)	.932	-.796	.866

*Note. *The level of significance (*p < .05; **p < .01; ***p < .001) was obtained after Bonferroni adjustment (.05/3 =.017; .01/3 =.003; .001/3 =.0003)*

Table 13 | Experiment 2; Repeated measures *ANOVA* comparing alpha power levels 50 min after repetitive sensory stimulation every 5 min

Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
					Lower	Upper
Timep 1	Timep 2	-.82(.26)	-3.07(25)	.005	-1.36895	-.26886
Timep 2	Timep 3	.25(.31)	.76(25)	.455	-.40301	.87350
Timep 3	Timep 4	-.17(.31)	-.56(25)	.583	-.80900	.46510
Timep 4	Timep 5	-.16(.27)	-.58(25)	.566	-.70756	.39608
Timep 5	Timep 6	.68(.38)	1.77(25)	.089	-.11158	1.46945
Timep 6	Timep 7	-.38(.34)	-1.12(25)	.275	-1.07909	.32042
Timep 7	Timep 8	.03(.36)	.09(25)	.933	-.71427	.77587
Timep 8	Timep 9	-.38(.28)	-1.35(25)	.188	-.95520	.19755
Timep 9	Timep 10	.36(.24)	1.52(25)	.142	-.12927	.84787

*Note. *The level of significance (*p < .05; **p < .01; ***p < .001) was obtained after Bonferroni adjustment (.05/3 =.017; .01/3 =.003; .001/3 =.0003)*

Table 14 | Experiment 5; Two-way mixed *ANOVA* 3 x 3 (time x condition) comparing alpha power stability over 30 min of stimulation;

Tactile acuity day 3	Group		*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
0-10 min	Alpha Up	Alpha Down	2.05(.74)	2.76(21)	.012	.507	3.594
		NF-PR	1.25(.76)	1.65(21)	.113	.322	2.822
	Alpha Down	NF-PR	-.80(.79)	-1.01(20)	.324	-2.450	.850
10-20 min	Alpha Up	Alpha Down	2.21(.63)	3.49(21)	.002*	.894	3.531
		NF-PR	2.01(.83)	2.42(21)	.025	.285	3.747
			-.20(87)	-.23(20)	.823	-2.003	1.610
20-30 min			1.74(.68)	2.57(21)	.018	.329	3.150
			1.60(.91)	1.75(21)	.095	-.301	3.497
	Alpha Down	NF-PR	-.14(.88)	-.16(20)	.874	-1.987	1.703
Tactile acuity day 3		Group	*Mdiff*(*SEM*)	*t*(*df*)	*p*	95% Confidence interval	
						Lower	Upper
0-10 min	10-20 min	Alpha Up	.36(.23)	-1.54(11)	.152	-.868	.153
		Alpha Down	-.20(-19)	-1.02(10)	.331	-.621	.231
		NF-PR	.41(.43)	.95(10)	.363	-.547	1.364
	20-30 min	Alpha Up	-.21(.27)	-.75(11)	.470	-.807	.398
		Alpha Down	-.52(-33)	-1.58(10)	.144	-1.241	.210
		NF-PR	.14(.46)	.31(10)	.760	-.872	1.158
10-20 min	20-30 min	Alpha Up	.15(.22)	.69(11)	.506	-.336	.642
		Alpha Down	-.32(.32)	-.99(10)	.345	-1.039	.399
		NF-PR	-.27(.15)	-1.73(10)	.115	-.609	.078

*Note. *The level of significance (*p < .05; **p < .01; ***p < .001) was obtained after Bonferroni adjustment (.05/18 =.003; .01/18 =.0006; .001/18 =.00006)*

6.2 – Additional Material

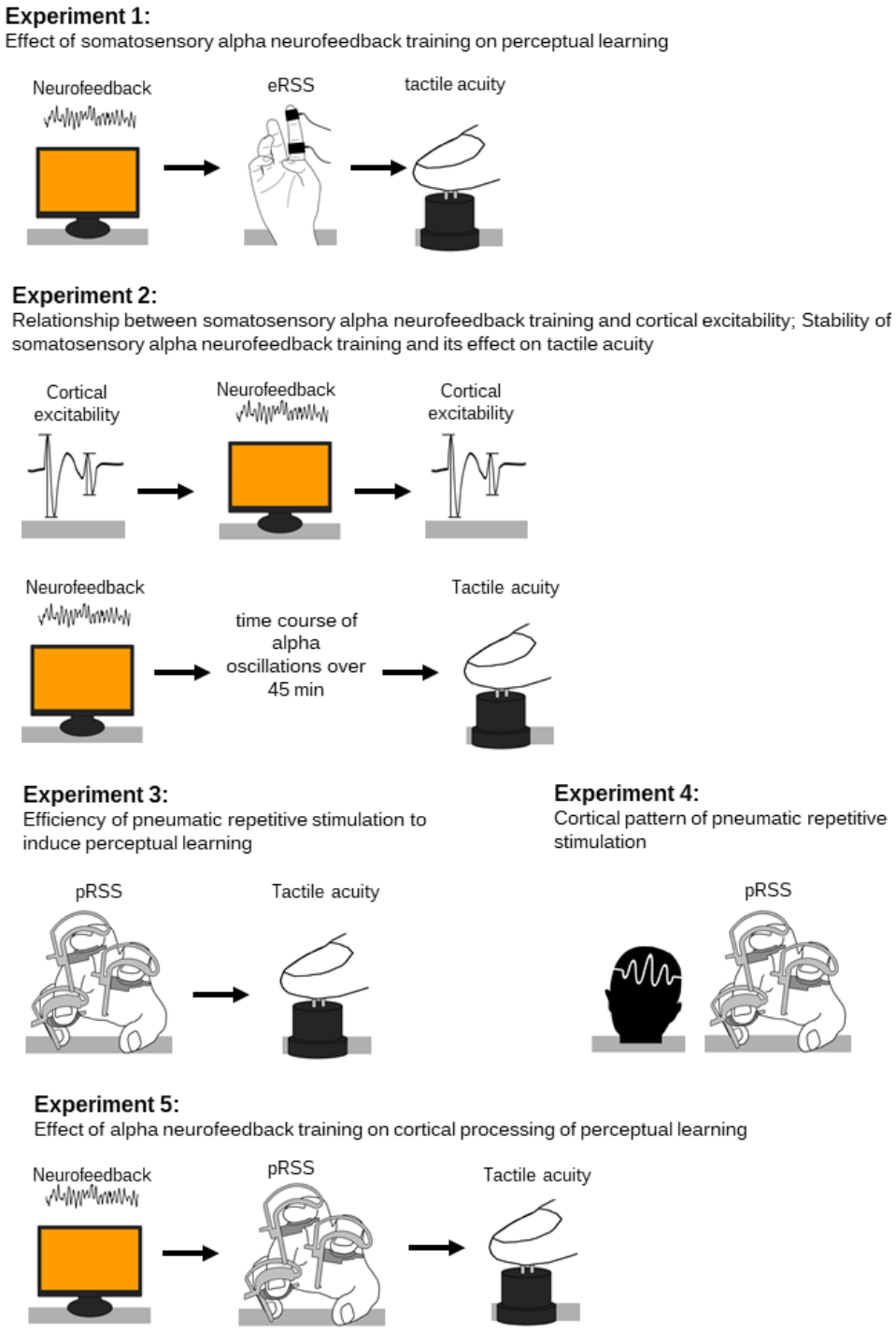

Figure 44 | **Overview of performed experiments.** five experiments were performed in this study. eRSS: electrical repetitive sensory stimulation; pRSS: pneumatic repetitive sensory stimulation;

6.3 - Curriculum Vitae

Graduation

Oct 2010 – Mar 2013: Student of Psychology at the University of Trier – B.S.c

Apr 2013 – Sep 2015: Student of Psychology at the University of Trier – M.S.c

Oct 2015 – Mar 2019: Graduate student at the Ruhr-University Bochum, Neural Plasticity Lab, Institute for Neuroinformatics, vie the International Graduate School of Neuroscience – P.h.D

Academic Career

Aug 2011 – Sep 2011: Internship at the Institute for Psychobiology, University of Trier

Oct 2011 – Jan 2015: Student Assistant and Tutor for test theory at the Department for Giftedness Research and Education, University of Trier

Aug 2014 – Oct 2014: Internship at the Neural Plasticity Lab, Institute for Neuroinformatics, University of Bochum

Jul 2015 – Sep 2015: Student Assistant at the Institute for Neurophysiology, Ruhr-University of Bochum

Oct 2015 – Dec 2018: Research fellow at the Neural Plasticity Lab, Institute for Neuroinformatics, Ruhr-University of Bochum

6.3 – List of Publications

Peer Reviewed Journals

1. Brickwedde M, Krüger MC, Dinse HR (2019) Somatosensory alpha oscillations gate perceptual learning efficiency. Nature communications 10:263.

2. Brickwedde, M., Schmidt, M., D. & Dinse, H. R. (2018). Somatosensory oscillation power and phase responses to peripheral pneumatic finger stimulation (in preparation).

Other

1. "Brickwedde, M., Krüger, M. & Dinse, H. R. (2018). How watching birds fly can train your brain to new feats. IGSN report, 26-29.

2. Niepel, C., Brickwedde, M., & Preckel, F. (2014). Begabtenförderung durch Fähigkeitsgruppierung: Eine wissenschaftliche Begleitung der Sir-Karl-Popper-Klassen am Wiedner-Gymnasium in Wien. ÖzBF news & science, 36/37, 68-74.

Conference Poster Presentations

1. Brickwedde, M. & Dinse, H. R. (2017). Neurofeedback-induced modulation of somatosensory alpha power controls subsequent tactile learning. Annual Meeting of the Society for Neuroscience, Washington, DC, USA.

2. Brickwedde, M., Krüger, M. C. & Dinse, H. R. (2018). Alpha neurofeedback training regulates interindividual variability in tactile learning. International Neuroscience Winter Conference, Sölden, Austria.

3. Brickwedde, M., Krüger, M. C. & Dinse, H. R. (2018). Alpha neurofeedback training modulates perceptual learning by reduction of learning variability. Annual Meeting of the Federation of European Neuroscience Society, Berlin, Germany.

4. Brickwedde, M., Krüger, M. C. & Dinse, H. R. (2018). Somatosensory alpha oscillations gate perceptual learnign efficiency. Hand, Brain and Technology Conference 2018, Ascona, Switzerland.

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