OPTIMISING PERCEPTUO-MOTOR PERFORMANCE AND LEARNING WITH EEG NEUROFEEDBACK

A Dissertation Presented for the
Philosophy Doctor Degree
in Psychology

Goldsmiths
University of London
United Kingdom

Tomas Ros, MSc

2010

Declaration

I declare that the work presented in this thesis is my own, and that no portion of this work has been submitted in support of an application for another degree of this or any other university, or institute of learning.

Abstract

The neurobiological functions of an organism serve to assist its adaptation to behaviourally challenging environments, which commonly involves the learning and refinement of perceptuo-motor skills. The intensity and time scale at which this occurs is critical towards survival. Previous work has observed that the neurochemical and neuroelectric (EEG) operation of specific functional systems is upregulated during so-called 'activated' states of behaviour. Thus it has recently been shown that artificial (i.e. exogenous) stimulation of such systems via pharmacological or electrical means can successfully modulate as well as enhance learning and associated behavioural performance. We hypothesized that neurofeedback, which is implemented through non-invasive volitional control of electrocortical rhythms (EEG), offers an alternate and natural (i.e. endogenous) way to modulate and thereby stimulate analogous systems.

Study 1 shows that neurofeedback is a viable and beneficial method for improving the acquisition and performance of perceptuo-motor skills in trainee microsurgeons, when compared to a wait-list control group. With the aid of transcranial magnetic stimulation (TMS), Study 2 demonstrates for the first time that 30 minutes of a single neurofeedback session directly leads to a robust and correlated change in corticomotor plasticity which is usually associated with learning or observed after exogenous stimulation. Lastly, Study 3 investigates the short-term modulation of one session of 'excitatory' neurofeedback on the subsequent performance of a serial reaction-time task (SRTT), an experimental paradigm widely used as a model for procedural perceptuo-motor learning.

In conclusion, this thesis contributes original evidence of *direct* as well as *long-term* functional enhancements following EEG neurofeedback, and supports its use as a safe, non-invasive and natural method for improving human perceptuo-motor performance and learning.

to my Mother: this is the flower of all your hard Work

to my Wife: thank you for believing in me Most

to John & Lesley: without you this bird could never Fly

Acknowledgements

This dissertation is the visible culmination of an incalculable number of individual efforts and exchanges that occurred over many years. Although I am able to acknowledge only a few, an even greater part remains unspoken. As the saying goes, "What is essential is invisible to the eye".

I would firstly like to thank the two people without whom this doctoral work would surely not have taken place. In 2006, while my hopes for a future in neuroscience were beginning to fade, Prof. John Gruzelier accepted me into his research group with open arms and blind faith. With astonishing optimism, he entrusted me with running a pioneering study with NHS surgeons based at the Western Eye Hospital. He has been my supervisor and mentor ever since. Around the same time, I was fortunate to meet Dr. Lesley Parkinson, a clinical psychologist practicing in London. In a gesture that can only be described as incredibly magnanimous, Lesley offered to sponsor my PhD studies on neurofeedback at Goldsmiths. Suffice to say that scientific interest and research funding for the field of neurofeedback was, and still is, very scarce to say the least. The present work is therefore a testament to the extraordinary dedication both of them have shown towards me, and this small yet avant-garde field. It is my conviction that since neurofeedback has survived such a deep hibernation, it will experience a still greater awakening!

I would also like to extend my deepest thanks to Prof. John Rothwell, Dr. Diane Ruge, and Moniek Munneke from the Sobell Department of the Institute of Neurology, London. Our joint collaboration during the second study led to some remarkable findings which would never have been possible without their expertise, open-mindedness, and generous offer to make use of the magnetic nerve stimulators. I will fondly remember my time at Queen Square.

I should like to mention Alex Howard, who initially lent me his NeXus-10 neurofeedback unit for a week in order to get my opinion on the interface. It has been more than 2 years now and I am still 'testing' it. Thank you Alex, its impressive recording quality has yielded invaluable results!

Of course, I am equally indebted to all those who have donated their own neural substrates for experimentation: without you dear participants, there would simply be no 'data'. Your brains did all the hard work!

Last but never least, I would like to express my gratitude to all colleagues, friends and family who have given me the intellectual and emotional support other PhD students would envy. Thank you for your enduring patience with regard to my ramblings on the brain, and many other philosophies. Tony Steffert, Joe Leach, Max Chen, Trevor Thompson, Helen Brinson, Deborah Bowden, Julia Ovenden, and Alan Parkinson, it has been a memorable three years...I wish you all the best and count on seeing you in London or on conferences around-the-globe. To my dear sister Hana, thank you for the greatest service a researcher could wish for: unbridled access to the world's most and least known journals, I have enjoyed gazing from the mountaintop. To my caring mother, for all your investment in my life-long education, the pancakes, and 400^{+} references. And finally, to Iva, my loving wife, for moving continents so that we may be close together —no matter the weather!

*

The quality of mercy is not strain'd,
It droppeth as the gentle rain from heaven
Upon the place beneath. It is twice blest:
It blesseth him that gives and him that takes.

"Plasticity [...] means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once."

William James
The Principles of Psychology (1890)

I. BACKGROUND

The strict definition of being *plastic* refers to the ability to undergo a change in shape. The thesis of the present work rests upon the principle that the brain (and the nervous system as a whole) has a natural and extraordinary capacity to change and regulate *itself*. In other words, it is the one organ that has evolved to be plastic par excellence. That is after all the characteristic of its basic constituents, the neurons. It is this inherent flexibility of the central nervous system (CNS) that gives the more complex organisms an advantage in the most important of sectors: adaptation. To learn is ultimately, to adapt. An organism is capable of both short-term and long-term change through learning, and therein is its dilemma. To refer to James's citation above, it must be "weak enough to yield to an influence, but strong enough not to yield all at once". This chapter will serve to introduce the behavioural and neurophysiological processes which have been widely linked to the concept of 'neuromodulation', which is proposed here as the ability to *appropriately adjust the nervous system towards optimal function within a given environmental context.* The aim is to provide a framework of converging evidence which logically supports the use of a variety of modern neuromodulation techniques – culminating in neurofeedback - towards promoting or "optimizing" the neurocognitive mechanisms responsible for the acquisition and performance of perceptuo-motor skills.

'Activated' states of performance and learning

In an ingenious experiment, Bergan et al. (Bergan et al. 2005) observed that owls who were made to hunt (a pursuit involving motivation and arousal) whilst wearing displacing prisms exhibited more rapid adaptation compared to those who wore prisms for an equal amount of time but were fed dead prey. This sends a clear message that learning during different behavioural states leads to different outcomes. It is also evident that our own bodies respect a diurnal cycle, with greater activity during the day followed by rest during the night time. In a marvel of adaptation, our organism has set-aside a time for action and a time for rest. If we were to look even closer, the same could

be said of the smaller cycles that have evolved within the larger ones, such as the multiple stages of sleep, or hormonal variations during the daytime. Especially during the latter, managing the organism's needs and metabolic expenses is a balancing act (Shin et al. 2009). In the diurnal animal at least, the daytime holds greater responsibilities towards its survival, and it is common knowledge that at least one such regulatory mechanism operates through the so-called autonomic nervous system, consisting of mutually antagonistic effects between the sympathetic ('fight-or-flight') and parasympathetic ('rest-and-digest') modes of neuro-endocrine function (Teff 2008). During wakeful rest or digestion for example, more insulin is secreted to augment the efficacy of glucose absorption (Frohman 1983). On the other hand, during the fight-or-flight response, adrenalin is released to increase glucose production (Frohman 1983). Hence, akin to a wise accountant, the body is continuously adapting to its environment by balancing its imports and exports. Since, it is the direct experience of every organism that natural resources are limited, and the preservation of such an economical modus operandi has enabled its survival over other competition.

A logical question that follows is: what processes actually characterise the neurobiological states which appear to be beneficial for learning and/or performance in general? Historically speaking, they have often been referred to as increased states of 'arousal' (Neiss 1988; Paisley & Summerlee 1984). In the operational sense one may regard such states as 'activated', in light of evidence that they require a concerted upregulation of central nervous system (CNS) and metabolic activity (Ursin H. 2004), which are summarised in the forthcoming sections. As will be related, it is the prominent *intersection* of several behavioural and neurophysiological processes that allows a more integrated picture to be assembled of this phenomenon.

Attention and Vigilance

The positive effect of increased vigilance on performance is due in part to the activation of cerebral mechanisms that act to facilitate input detection and processing of relevant information, which are otherwise referred to as "attention". This process has been described as 'sensory gain control' (or amplification) (Hillyard et al. 1998). Attention has been reported to enhance receptive field properties of sensory neurons in cortical plus subcortical areas (Corbetta & Shulman 2002; Wager et al. 2004), or to inhibit activity in regions which process irrelevant or competing inputs (Shulman et al. 1997; Smith

et al. 2000). For example, functional MRI (fMRI) studies report increased metabolic activity of cortical areas involved in the detection of attended target stimuli (Serences et al. 2005), while reduction of activity in regions representing unattended stimulus features has been also observed (O'Connor et al. 2002). Conversely, distracters that capture attention produce increases in visual cortex representing their location (Kastner et al. 1999). In light of such evidence of resource allocation, another leading concept in theories of attention in the last decade has been the notion of capacity limitation, which may be understood as an upper limit on the amount of processing resources that are available for perception and action (Broadbent 1965; Wickens & Kessel 1980). According to this model, allocating more resources to a certain task will improve its performance, but there will be a trade-off with resources that are available for performance of other concurrent tasks. Hence the principal role of attention would be to allocate neuronal resources appropriately in order for high-priority tasks to receive a greater share than low-priority tasks (Peterson et al. 1999). Wachtel (Wachtel 1968) was one of the first to observe that anxiety provoked by threat of electric shock over which subjects had no control lead to reduced performance and responsiveness to peripheral stimuli, when compared to an unthreatened control group. A third group, who was also threatened with shock but told that it could be avoided with good performance on both central and peripheral tasks, responded as rapidly to the peripheral stimuli as did the control group. Attentive mechanisms therefore seem to reduce distraction and improve performance only when deployed in a task-relevant manner. To cite Wachtel: "When an individual is additionally anxious, attention is diverted inward to perception of his anxiety and therefore less attention is available for external stimuli".

On the other hand, what is known about the relationship between attention and its impact on sensorimotor *learning*? Firstly, collective evidence of performance decrements directly implicates attention in learning during multi-tasking experiments (Nissen 1987). Moreover, the first stages of motor learning are attentionally demanding, when movements are not very skilled and highly-feedback dependent (Atkeson 1989). Upregulation of prefrontal areas is frequently seen during the early phases of explicit motor learning, which is in accordance with the observed involvement of the prefrontal cortex in action selection and attentional processes (Deiber et al. 1997; Jueptner & Weiller 1998). Motor skills then develop from initial explicit control to more automatic or 'implicit' control when mastered (Halsband & Freund 1993). Still, the role of attention in generating motor memories remains controversial principally

because it is difficult to separate the effects of attention from changes in kinematics of motor performance. Nevertheless, in an elegant study Stefan et al. (Stefan et al. 2004) attempted to disentangle attention from performance effects by varying attention while associative plasticity was induced in human primary motor cortex by external stimulation, passively and in the absence of any voluntary movement. Associative stimulation failed to induce plasticity while the person's attention was directed to their left hand, away from the right hand whose cortical representation was being stimulated. Induction of plasticity was greatest when the person viewed their right hand, and this effect diminished at lower attention levels (e.g. when the person was asked to only feel their hand). Likewise, plasticity was blocked when the person's attention was deployed to a competing cognitive task. Interestingly, these findings offer a tempting explanation for the clinical observation that motor recovery is more impaired in stroke patients with unilateral spatial neglect (Denes et al. 1982). It is plausible that the failure to deploy attention to the side of the motor disability may compromise the brain's capacity to create effective and long-term memory traces of newly acquired motor skills.

Skin Conductance

In the past, electrodermal activity had been the most frequently used biological marker of arousal in psychophysiological research (Christie 1973). The skin conductance response (SCR) can indicate the state of arousal expressed by the activity of sympathetic cholinergic neurons at the level of eccrine dermal sweat glands (Freedman et al. 1994). This method has also been traditionally used in lie-detector tests to probe for autonomic shifts in arousal (Gamer et al. 2008). New studies using functional imaging techniques demonstrate descending cortical (ventromedial prefrontal) and sub-cortical (amygdala) co-activation associated with sympathetic arousal (Critchley 2002; Critchley et al. 2002). Orbitofrontal, cingulate, and insular cortices have also been implicated in autonomic control from electrostimulation and lesion studies (Cechetto & Saper 1990). These particular regions have also been linked to emotional and motivational behaviours (Dolan 2007). Such findings indicate the close association of central and peripheral measures of arousal, and emphasize that activated states impact the body as a whole, and not only the brain.

Furthermore, by simply utilising SCR, it has recently been shown that activation can be usefully dissociated from overall arousal per se, if the former is considered as the *relative* change between the resting baseline and the on-

task situation, while the latter is simply the *overall* electrodermal state on-task. It has then been observed that overall arousal levels do not affect behavioural measures in a rifle shooting task (Vaez et al. 2008). In contrast, changes in *activation* were successful predictors of performance. Hence, the degree of activation from baseline appears more influential in modulating performance than either high or low initial arousal levels with no major shifts on task. As will be related below, SCR measures have also been found to be correlated to cerebral neuroelectric (EEG) activities.

The Electroencephalogram (EEG)

Cortical electrical oscillations (also known as brainwaves), are recorded by the electroencephalogram (EEG), and reflect rhythmic fluctuations in the excitability of underlying neural populations (Neuper et al. 2006; Niedermayer & Lopes Da Silva 1999; Rossini et al. 1991). Brainwave synchronisation covaries reliably with both gross and subtle changes in brain state and function (during sleep (Steriade & Timofeev 2003), pathophysiology (Uhlhaas & Singer 2006) or following pharmacological treatment (Gross et al. 2004), having been shown to be sensitive to behavioural modifications of various anatomical (e.g. sleep spindle (Sterman et al. 1970)) and neurochemical (e.g. noradrenergic (Rougeul-Buser & Buser 1997)) systems. Cortical oscillations have moreover been linked to many cognitive and behavioural processes, including learning (Axmacher et al. 2006), decision-making (Cohen et al. 2009), and motor processing (Zhang et al. 2008). Crucially, both long-term *tonic* (hours-days) and short-term *phasic* (milliseconds-seconds) oscillatory dynamics are modulated in the brain during different states of CNS arousal or vigilance. In fact, the first neurophysiological approaches to brain activation had their origin in the EEG. In 1934, a few years after the initial discovery of the EEG by Hans Berger, the British magazine *Spectator* reported on a remarkable public demonstration (Walter, 1934, p. 479):

"Adrian and Matthews recently gave an elegant demonstration of these cortical potentials. [. . .] When the subject's eyes were open the line was irregular, but when his eyes were shut it showed a regular series of large waves occurring at about ten a second. [. . .] Then came the surprise. When the subject shut his eyes and was given a simple problem in mental arithmetic, as long as he was working it out the waves were absent and the line was irregular, as when his eyes were open. When he had solved the problem, the waves reappeared. [. . .] So, with this technique, thought would seem to be a negative sort of thing:

a breaking of the synchronized activity of enormous numbers of cells into an individualized working."

Particular patterns of brain waves were quickly observed to differentiate levels of psychological arousal in the progression from deep sleep to wake, to high alertness (Jasper & Droogleever-Fortuyn 1948). As can be seen in Fig 1.1 below, low-frequency delta waves mostly dominate deeper sleep states, while during lighter or more activated (REM) sleep the frequencies are more accelerated, but slower than in waking states. In relaxed wakefulness there is an emergence of the alpha (8-12 Hz) rhythm that gives rise to faster beta (approx. 18-30 Hz) and gamma (>30 Hz) frequencies upon activation of cognitive or attentional resources (Steriade et al. 1993). In parallel to the acceleration of frequencies seen during heightened states of arousal, there is also a robust reduction in the overall synchronisation of the brainwaves to a more irregular 'desynchronized' tracing of reduced amplitude (as reported by Grey Walter above).

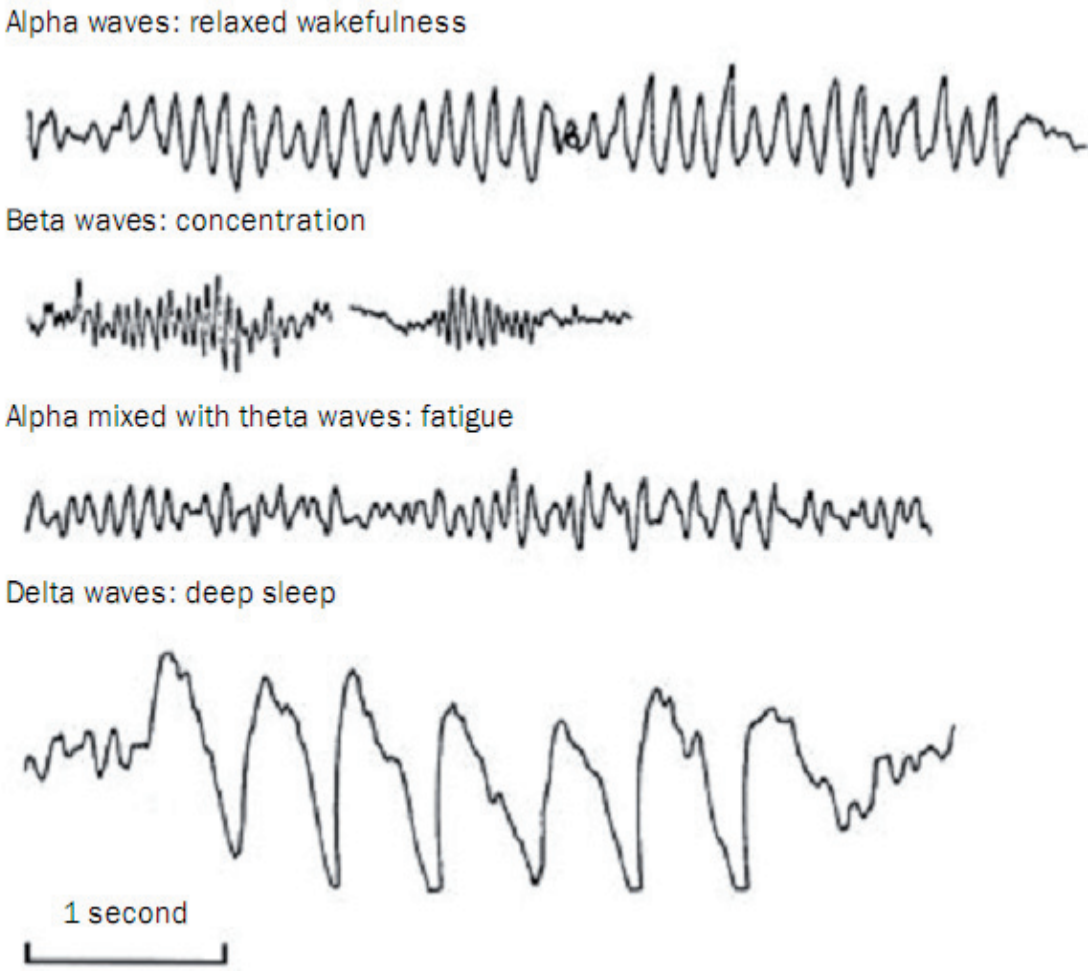

Fig 1.1 Several common brainwave patterns observed in the cortical electroencephalogram

With the discovery that the ascending reticular activating system (ARAS) (Moruzzi & Magoun 1949) was responsible for consciousness and the sleep-wake cycle, some of the most important findings were that lesions in the ARAS abolished the abovementioned "activation" of the EEG whilst increasing episodes of sleep and motor inactivity (Lindsley et al. 1950). Subsequent experiments by Magoun and colleagues (French & Magoun 1952) demonstrated that intact cortical and behavioral activation is retained despite selective lesion of all sensory pathways to the brain, whereas they are not maintained after destruction of the reticular formation in the presence of intact sensory input. The reticular formation is thus regarded to be necessary for the overall wakefulness of the animal and its reactivity to incoming sensory input or motor output. Remarkably, progressively greater degrees of EEG activation pattern could be provoked by simple electrical stimulation of the brainstem (Moruzzi & Magoun 1949). This led to the finding that moderate stimulation of this kind enhanced the precision and speed of visual discrimination in monkeys (Fuster 1958). It was also noted that higher intensities had a counterproductive effect, increasing reaction times and error rates. Recently, the EEG correlates of skin-conductance arousal have also been investigated (Barry et al. 2004), where a high arousal (elevated SCR) group of children exhibited globally reduced resting alpha activity, compared to a low arousal group. Likewise, another study comparing eyes-closed and eyes-open conditions in adults revealed that opening the eyes increased SCR, and globally decreased alpha power (Barry et al. 2007). Single administration of caffeine, a well-known psychostimulant, leads to global reductions in alpha power, acceleration of alpha frequency, and increased SCR, relative to placebo (Barry et al. 2005). Elsewhere, it has been reported that a similar single dose of caffeine is associated with a 30 % increase in motor and visual cortex metabolism (Chen & Parrish 2009).

On the other hand, a collection of studies have reported resting EEG abnormalities in pathophysiologies associated with attentional or sensorimotor disorders. Specifically, resting theta and alpha slow-waves are tonically elevated in phenotypes observed in attentional deficit hyperactivity disorder (Snyder & Hall 2006), suggesting lowered cortical arousal. Accordingly, administration of a class of medications known as psychostimulants (e.g. amphetamines) improves behaviour and normalises the EEG spectrum (Clarke et al. 2007). Similarly, reduced delta rhythm amplitude has been found to be a favourable marker of long-term recovery from ischemic cerebral stroke (Cuspineda et al. 2007), correlating with diffusion and perfusion weighted magnetic resonance images of cortical lesions (Finnigan et al. 2004). To date, quantitative EEG

studies have revealed statistical deviations and slowed cortical rhythms in Parkinson's disease (Serizawa et al. 2008), tic-disorder (Leckman et al. 2006) and cerebral palsy (Kułak et al. 2006). Moreover, dystonic involuntary muscle spasms are reported to be specifically associated with increased theta, alpha and low beta (3-18 Hz) rhythms in the basal ganglia (Liu et al. 2008). Latest research also suggests that synchronised rhythms implicated in parkinsonism directly attenuate following deep-brain stimulation therapy (Bronte-Stewart et al. 2009).

Nowadays the EEG's exquisite temporal resolution has been successfully exploited in a host of studies investigating the more short-lived (*phasic*) dynamics of attention and motor performance. During attentional alerting, there occurs an event-related desynchronisation (ERD) in theta, alpha, and beta bands (<30 Hz) (Fan et al. 2007), consistent with the fact that the spontaneous spectral power at these frequencies is inversely correlated with cortical metabolism in frontal and parietal lobes (Tyvaert et al. 2008), which together correspond to the dorsal frontoparietal attentional network (Corbetta et al. 2008). Moreover, selective attention inside the receptive field of stimulus detection strongly reduces alpha (9–11 Hz) synchronization while concomitantly increasing gamma (30-70 Hz) synchronisation (Fries et al. 2008). Gamma synchronisation has recently been put forward as a plausible mechanism for mediating learning and synaptic plasticity (Jensen et al. 2007) given that high frequency oscillations are implicated in many aspects of cortical communication and encoding. Analogous sensory 'bottom-up' activation patterns become more pronounced immediately prior or during motor execution, and may indicate preparatory or task-relevant sensorimotor cortex activation (Neuper et al. 2006). Here, once again, it has been demonstrated that synchronisation of the alpha and low beta bands is inversely correlated with blood-oxygenation of the underlying motor cortex in functional MRI experiments (Oishi et al. 2007). Likewise, spontaneous and localised alpha power inversely predicts the strength of neurotransmission along the corticospinal motor pathway (Sauseng et al. 2009), and has been ascribed a role in regulating cortical *excitability* in visual cortex (Romei et al. 2008). Remarkably, it has also been reported that the shapes of receptive fields in the cat striate cortex are correlated with the general state of the brain as assessed by EEG: where receptive fields are wider during synchronized states and smaller during non-synchronized states (Wörgötter et al. 1998). In summary, brain rhythms may be regarded as pervading almost every aspect of brain function, and their modulation appears to *bias* and temporally coordinate particular sets of neuronal assemblies and functional pathways (Buzsáki & Draguhn 2004).

Neuromodulatory systems

Excepting electrical gap junctions, most communication between neurons in the brain occurs *chemically* via the synapse, whereby neurotransmitter molecules released by the presynaptic neuron diffuse across the synaptic cleft and bind onto the receptors of a postsynaptic neuron. It is not surprising therefore that the brain has harnessed this property to manipulate neural activity on a more global or distributed scale, through a process classically known as *neuromodulation*. The common property of neuromodulatory transmitters, in contrast to simple neurotransmitters (e.g. glutamate or GABA), is that they are usually secreted by a small group of neurons located sub-cortically (brainstem or basal forebrain regions) whose axons diffuse through large areas of the nervous system, and have long-lasting effects on multiple neurons. This enables the nervous system to flexibly tune the level of its overall activity, including that of particular functional and anatomical subsystems. Reviewed below are neurotransmitters which are regarded as acting through *ascending* neuromodulatory systems; despite the different origins and chemical signatures of neuromodulatory systems, they all share reciprocal connections with the frontal cortex, basal ganglia, or parts of the limbic system. Moreover, converging evidence suggests that their effects on downstream targets is functionally similar, insofar as to increase the processing efficacy (or signal-to-noise ratio) of downstream neuronal targets, in order to facilitate a quick and accurate response of the organism to critical environmental situations and/or behaviourally relevant stimuli (Krichmar 2008). Hence, the serotonin (5-HT) system is mainly driven by stress or threat (Millan 2003), the acetylcholine (ACh) system by attentional effort (Baxter M.G. 1999), the dopamine (DA) system by craving and reward (Schultz W. 1997) (Berridge 2004), and the noradrenaline (NA) system by novelty and salience (Yu A.J. 2005). Such neuromodulatory systems are also capable of responding with both tonic and phasic activity (Briand et al. 2007). Tonic mode regulates the overall baseline activity of a neuromodulatory system, but this does not involve bursting. In phasic mode however, the system exhibits short bursts of activity. When the system has reduced tonic activity, the signal-to-noise ratio is low and the animal's behaviour is less purposeful and more distracted. In practice, this type of behaviour may be advantageous in circumstances when the animal may need to explore new actions and creative possibilities. In contrast, during phasic activity *the* signal-to-noise ratio of particular stimuli or actions dramatically increases as the system becomes more attentive and decisive (Aston-Jones G. 2005).

Noradrenaline (NA)

The noradrenergic neurons originate in the brainstem locus coeruleus (LC) nuclei and their terminals project diffusely to almost all regions of the brain, excepting the basal ganglia (Berridge & Waterhouse 2003). There are reciprocal connections between the prefrontal cortex and the LC, and the former provides the strongest cortical input back to the LC neurons (Arnsten & Goldman-Rakic 1984). In particular, the orbitofrontal and anterior cingulate cortices, whose functions are to evaluate cost and reward, project to LC and initiate phasic responses (Aston-Jones 2005). The noradrenergic system is responsive to novel or salient objects in the environment and is generally activated when predictions are violated (e.g. an oddball stimulus) (Yu A.J. 2005). Noradrenaline is reportedly crucial in enhancing the output accuracy of motor actions while adjusting the balance between distractibility and vigilance (Robbins et al. 1998). At reduced levels of tonic LC activity subjects are inattentive, while at very high tonic levels subjects are excessively distracted (Aston-Jones. 2005). Thus, at moderate levels subjects are engaged in a task, respond to task relevant stimuli and perform well. Accordingly, evidence suggests that the relationship between LC phasic and tonic activity is described by a bell-shaped curve, and so an optimal phasic response is manifest only at intermediate levels of tonic activity (Rajkowski et al. 1998). Interestingly, moderate levels of NA upregulate prefrontal activation via high affinity $\alpha 2$ adrenoceptors (Arnsten et al. 1988), while excessive levels of NA release (during severe stress for instance) downregulate prefrontal function via lower affinity $\alpha 1$ receptors (Birnbaum et al. 1999). Thus, it has been suggested that levels of NA also influence whether reflective prefrontal cortical or reflexive posterior cortical systems control our behaviour and cognition (Ramos & Arnsten 2007). While both adrenergic and dopaminergic systems strongly innervate the frontal cortical regions (Briand et al. 2007), other neocortical regions as well as thalamic sensory relay nuclei do not receive dopaminergic input (Moore & Bloom 1978). A large number of studies have demonstrated the role of NA in gating and tuning sensory signals in the thalamus and the sensory cortices (C. W. Berridge & B. D. Waterhouse 2003). For example, it has been shown to sharpen receptive field size in the rat visual cortex (Hurley et al. 2004). Moreover, increasing extracellular NA by drugs or electrostimulation of the LC significantly suppressed spontaneous network activity but left evoked responses to sensory stimulation intact (Foote & Morrison 1987). Previously unresponsive neurons also seemed to be reactivated by an increase in NA, a mechanism that has been referred to as "sensory gating". With respect to the EEG, it was demonstrated that unilateral stimulation of

the LC is sufficient to activate the cortical and hippocampal EEG, whereas bilateral inhibition of the LC was necessary to generate an increase in slow-wave activity (Berridge et al. 1993). Crucially, the bidirectional changes observed in the EEG were always preceded by changes in LC neuronal discharge. Finally, both lesion and pharmacological blockade of LC noradrenergic pathways is known to lead to an increase in motor cortex alpha rhythms (Delagrange et al. 1993). These same rhythms have been observed to be synchronised during passive 'expectant' behaviour in the cat (while waiting for a mouse behind a wall), which desynchronise during attentional alerting (upon seeing the mouse) (Rougeul-Buser & Buser 1997). In humans, in vivo receptor binding studies have suggested that the adrenergic agonist clonidine stimulates alerting processes by modulating the connectivity between brain regions, including the locus coeruleus, that are part of a functional network that mediates attention. Again, the effects of were highly dependent on the baseline level of arousal; if in an eyes closed condition, clonidine reduced the functional interdependence both from frontal cortex to thalamus and in pathways to and from visual cortex, as measured by correlations. However, if clonidine was administered while the subject was engaged in a visual attention task, the effective connectivity between frontal and parietal regions was enhanced, as was the influence of the locus coeruleus on these regions (Coull et al. 1999). This suggests that NA affects global brain processing by promoting functional integration of various brain regions implicated in arousal, rather than exerting local effects within discrete brain regions.

Dopamine (DA)

The dopaminergic system arises from the ventral mesencephalic neurons which are located in two main aggregations: the substantia nigra and ventral tegmental area (VTA). Their axons ascend through the medial forebrain bundle and synapse in the striatum (comprising the nigro-striatal pathway), the basal forebrain, and the neocortex. In primates, the greatest density of dopaminergic fibers occurs in the primary motor cortex, whereas lowest densities are found in the primary visual cortex, and other first-order sensory areas (Lewis et al. 1987). Pharmacological stimulation of the VTA is positively rewarding in animals and results in repetitive self-stimulation (Ikemoto & Wise 2002).This has been reported to release dopamine in the nucleus accumbens of the ventral basal ganglia (Fiorino et al. 1993), a nucleus implicated in addictive behaviours (Niehaus et al. 2009). Cytotoxic lesion of the VTA induces behavioral akinesia (Jones et al. 1973) and leads to reductions of fast EEG activities related to

attentional arousal (Montaron et al. 1982). The neurons of the dopaminergic system fire in both tonic and phasic modes, hence this determines the dynamics of DA release in the prefrontal cortex (Lapish et al. 2007) and striatum where relatively prolonged and frequency-dependent effects can occur (Garris & Wightman 1994), confirming its role as a neuromodulator of these structures (O'Reilly et al. 2002). DA has been observed to regulate neuronal excitability since direct VTA stimulation decreases spontaneous firing of prefrontal pyramidal neurons, through local excitation of interneurons (Lewis & O'Donnell 2000). It has been proposed that co-activation of NMDA glutamate receptors (Wang & O'Donnell 2001) during strong afferent inputs will reactivate the initially silent pyramidal neurons, and owing to lateral-inhibition of neighbouring cells, a winner-takes-all mechanism would predominate (Durstewitz et al. 2000). A phasic release of DA could thus make the prefrontal cortex more reactive to behaviourally relevant stimuli. Analogously DA release in the basal ganglia would enable more effective inhibition of competing motor programs and improve the speed of action selection (Mink 1996). It is interesting to note that Parkinson's disease, which occurs due to depletion of DA in the nigro-striatal pathway, is behaviourally less characterised by motor paralysis per se but rather by the inability to initiate or select certain motor actions (Kropotov & Etlinger 1999). Moreover, children with attention deficit hyperactivity disorder (ADHD) have been found to have genetic mutations in their dopamine transporters (Sharp et al. 2009), whose function is to perform dopamine reuptake at the synapse. Beyond efficient attentional and motor performance, dopamine regulation is also essential during perceptuo-motor learning, where selective striatal DA lesions impaired learning of a serial reaction time task (SRTT), which involves learning a sequence of key presses without conscious awareness (Eckart et al. 2009). Animals in the lesion group showed no decrease in reaction times after repetition, which indicated less automation of sequential behaviour. Neuroimaging studies also report upregulation of the basal ganglia during learning of the SRTT (Rauch et al. 1997; Doyon et al. 1996), where activation of the caudate nucleus is seen in subjects performing the task with a fixed sequence, compared to trials for which locations occur randomly. During positron emission tomography (PET) of subjects playing a video game (Koepp et al. 1998a), performance improvements revealed decreased binding of a radioloabeled DA antagonist, suggesting increased dopamine release in striatum relative to a control condition. This study is compatible with research in animals demonstrating a role for dopamine in stimulus-response learning (Packard & White 1991).

Acetylcholine (ACh)

The brainstem cholinergic system originates from the laterodorsal tegmental and pedunculopontine tegmental nuclei, or LDTg/PPTg. Their ascending fibers run parallel to those of the reticular formation, reaching the thalamus, hypothalamus, and basal forebrain (Jones & Webster 1988). Similar to other neuromodulatory systems, electrostimulation of the LDTg/PPTg complex results in activation of the cortical EEG, partly via the excitation of thalamic neurons (Steriade et al. 1991), where release of ACh is highest during cortical activation (Williams et al. 1994). Cholinergic neurons are most active in wakefulness and REM sleep (Steriade et al. 1990). Surprisingly, lesions of the cholinergic brainstem nuclei do not grossly attenuate cortical activation or waking but produce a selective loss of REM sleep (Jones & Webster 1988). Accordingly a complementary, extra-thalamic, cholinergic pathway exists that stems from the basal forebrain, originating within the medial septal and Meynert nuclei, which diffusely innervate the neocortex (Mesulam et al. 1983), generally exerting an excitatory infuence (McCormick & Bal 1997). Local cholinergic infusions of the thalamic or extra-thalamic pathway indicate that central thalamus and basal forebrain contribute parallel activating pathways which are additive (Dringenberg & Olmstead 2003). In general, ACh has been observed to have an amplifying effect on evoked responses to sensory stimuli visual (Sillito & Kemp 1983), auditory (McKenna et al. 1988) or somatic (Tremblay et al. 1990) domains. In animals a positive correlation has been reported between the spectral power of the faster beta and gamma EEG frequencies and increases in acetylcholine release (Fournier et al. 2004). There is also evidence of tonic and phasic modes of cholinergic discharge (Briand et al. 2007). Firstly, basal forebrain cholinergic neurons are reported to have their bursting activity synchronized with the cortical theta oscillations (4-7 Hz) (Lee et al. 2005). Theta rhythms are frequently modulated in behavioural studies of memory. Selective lesions of the cholinergic basal forebrain impairs short-term memory in rats (Leanza et al. 1996). Ach may regulate encoding via the hippocampal formation (Bland & Oddie 2001), where encoding is higher when stimuli are presented during periods of theta rhythmicity (Griffin et al. 2004). In humans, the amplitude of cortical theta oscillations shortly preceding the onsets of words are higher for later-recalled than for later-forgotten words (Meltzer et al. 2009). Additionally, Ach has been extensively linked to mechanisms mediating executive attention (Sarter et al. 2009). In a placebo controlled study application of scopolamine, a cholinergic antagonist, increased reaction times during a competitive stimulus discrimination task, which was associated with deactivation of the anterior

cingulate cortex, an area anatomically responsible for conflict monitoring (Thienel et al. 2009). Cytotoxic lesions of the cholinergic basal forebrain have been shown to profoundly impair performance of a five-choice serial reaction time task, resulting in increased response latencies and decreased choice accuracy (Muir et al. 1994). Global ACh depletion is a biological marker of Alzheimer's disease (Nordberg 1999), which is characterised by severe impairments of attentional and memory processing (Weintraub et al. 2009). Lastly, ACh has recently been reported to act as a local neurotransmitter in the striatum and the basal ganglia, where it is released by a family of interneurons with smooth dendrites, known as tonically active neurons or TANs. Latest findings suggest that TAN firing is sensitive to stimulus detection, movement control and recognition of a specific context (Apicella 2007). It appears that these interneurons may play a vital part in action selection and learning processes of the striatum as well as behaviourally relevant responses to the environment.

Serotonin (5-HT)

The serotonergic raphe neurons are located in the midline raphe nuclei of the brainstem. 5-HT innervation appears throughout the cortex, amygdala, hippocampus, and ventral part of the striatum (Meneses & Perez-Garcia 2007). The raphe nuclei receive reciprocal projections from the prefrontal cortex and the anterior cingulate cortex (Briand et al. 2007). Electrostimulation of the raphe leads to a behavioral inhibition, akinesia, excessive eating (Jacobs et al. 1974) and sexual behaviour (Foreman et al. 1992). Conversely, dietary depletion of serotonin results in acute insomnia (Jouvet & Pujol 1972), and serotonergic lesions produce aroused wakefulness marked by increased sexual behaviour (Kakeyama et al. 2002). Serotonin secretion by the raphe of is maximal during waking, decreased during deep sleep and minimal during REM (Portas et al. 1998). Specific raphe neurons discharge most in association with repetitive behaviours such as grooming (Jacobs & Fornal 1991). A subpopulation of raphe neurons discharge fire in phase with the hippocampal theta oscillation, the limbic rhythm frequently associated with encoding and memory formation (Kocsis et al. 2006). Recently, investigations have proposed a key role of the prefrontal-raphe feedback loop in the regulation of stress response (Amat et al. 2006). Here, it has been suggested that chronic uncontrollable stress, which can lead to a condition called "learned helplessness", selectively activates the raphe nuclei via the mediation of the prefrontal cortex, leading to a chronic state of anxiety (Maier & Watkins 2005). Paradoxically, serotonin reuptake inhibitors (SSRIs) are given to humans as anxiolytic and anti-depressant drugs (Andersen

et al. 2009); however recent evidence indicates that the immediate, acute effects of SSRI treatment may actually increase anxiety (Sramek et al. 2002). This is in line with evidence that several weeks of SSRI administration is required before antidepressant effects are experienced. The chronic over-expression of synaptic serotonin may act to downregulate (desensitise) the density of post-synaptic 5-HT terminals, whose stimulation by agonists is known to increase anxious behaviour (Van Oekelen et al. 2003). Hence, 5-HT is well placed to regulate optimal performance by modulating emotional and motivational processes which influence cognitive flexibility and impulsivity (Cools et al. 2008). In a standard Go/NoGo task, acute dietary serotonin depletion decreased metabolic activation in the prefrontal cortex, when feedback was given after every response (error monitoring), without changing performance or mood (Evers et al. 2006). In a Go/No-Go task with emotional stimuli, serotonin depletion increased reaction times for happy but not for sad targets (Murphy et al. 2002). On the other hand, increasing extracellular levels 5-HT by intake of citalopram elevated fMRI responses during the NoGo condition in the orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC) and middle temporal gyrus (Del-Ben et al. 2005). In a genetic study that investigated the behavioural effect of serotonin transporter polymorphisms (Fallgatter et al. 2004), it was observed that lower 5-HT reuptake (increased extracellular 5-HT) was associated with greater activation of the anterior cingulate error-monitoring system during a flanker task (Vocat et al. 2008). On the other hand, it has recently been shown that serotonin agonists reduce the ability of rats to tolerate delays in reward (Hadamitzky et al. 2009), consistent with the fact that increased stress or anxiety could be associated with greater impulsivity.

Mechanisms of practice-dependent plasticity

A crucial role for behavioural activation is to facilitate learning, whether it be for the short- or long- term adaptive advantage of the organism. The mechanism of neuroplasticity allows the brain to acquire, store and reproduce specific patterns of behaviour to effectively overcome previously challenging or unexpected situations. The functions of memory, and the nervous system in general, are to essentially predict and prepare for future events based on the organism's acquired experience (Hawkins et al. 2009). Hence, a complementary function for arousal is to encourage an optimal rate of learning, by maximally upregulating the brain's intrinsic mechanisms for neuroplasticity during behaviourally-relevant situations. Investigations of perceptual learning (Karni

& Bertini 1997), or the improvement of perceptual performance as a function of training, have increased our understanding of the neurological mechanisms of this type of skill learning in the developed brain. One striking discovery is that a functionally-relevant degree of plasticity persists in the brain as a result of training, even within first-order sensory and motor cortices. In adults, training on a visual contour detection task over time can results in an improved ability to detect contours, whereby subjects are able to detect contours with fewer line segments (Li et al. 2008). Concomitantly, a correlated enhancement of neuronal responses in primary visual cortex is observed. Moreover, extensive practice on a shape-identification task significantly modified the resting functional connectivity between the visual cortex and frontoparietal areas involved in the control of spatial attention (Lewis et al. 2009). Likewise, these changes varied as a function of performance improvement. Sensorimotor learning has also been reported to lead to an upregulation of particular corticostriatal circuits that persists over time. Lafleur and colleagues (Lafleur et al. 2002) measured changes in cerebral activity before and after practice of a sequence of foot movements which were executed both physically and during motor imagery, and compared them to a perceptual control condition of simply observing the movements passively. Physical execution of the sequence in the early stages of learning produced relative increases in cerebral blood flow in the dorsal premotor cortex, cerebellum, and inferior parietal lobule. Following training, this collection of brain structures ceased to be significantly activated, indicating their involvement in the processing of a novel motor routine. Instead, increased activity was observed in the orbitofrontal and anterior cingulate cortex as well as the striatum, inferring that these regions have a more prominent role in the development of a long-term representation of the motor sequence. An equivalent pattern of activation was seen before and after the motor imagery conditions, which suggests that mental practice recruits a similar set of circuits which are primarily under top-down (attentional) control.

Patients with Huntington's disease, which is characterised by abnormal striatal dopamine transmission, exhibit deficits in perceptuo-motor learning. In the prism adaptation task, where wearing prism goggles adds a systematic shift to visual representations, healthy subjects initially make reaching errors, but with practice, errors decrease. Huntington's patients do not adapt as well as healthy subjects, while patients with Alzheimer's are able to adapt normally despite having a declarative memory disorder (Knowlton 1996). Thus, it appears that motor learning based on perceptual adaptation depends on the basal ganglia, rather than on cortical or temporal lobe regions affected in Alzheimer's disease.

Equally so, during the serial reaction time task, Huntington's patients do not display a difference in reaction time between fixed and random presentation of a sequence (Willingham 1996). On the other hand, patients who have memory deficits (e.g. anterograde amnesia) exhibit normal sequence learning (Nissen et al. 1989). Activation of the striatum while performing the serial reaction time task is reported in a number of neuroimaging studies (Doyon et al. 1996). Distinct activation of the caudate nucleus (a component of the striatum) is seen while healthy subjects perform trials with a fixed compared to a random sequence. Remarkably, activation of the caudate is not observed if participants are verbally told the sequence beforehand and are able to consciously anticipate the location of the upcoming stimulus. In a study aimed at exploring neuronal receptor activation, positron emission tomography (PET) was utilized to measure dopamine release while subjects were playing a video game (Koepp et al. 1998). Compared to a control condition, improvement in performance was associated with decreased binding of radiolabeled dopamine antagonist in the striatum, a sign of increased release of endogenous dopamine. This is compatible with other research in animals demonstrating a role for striatal dopamine in stimulus-response learning (Packard & White 1991).

Generally, it is plausible that the acquisition and consolidation of perceptuo-motor skills is underpinned by the functional plasticity subserving cellular-level processes of neuronal transmission, which are also known to be mediated by neuromodulators. Robust neuromodulation of cortical plasticity was first discovered in the visual cortex, as interventions that blocked noradrenergic transmission disrupted the typical outcome of monocular deprivation (Kasamatsu & Pettigrew 1979). Similar effects where observed for acetylcholine and serotonin (Gu & Singer 1995). Furthermore, the reduced neuroplasticity which occurs in adult cortex as a result of synaptic inhibition (Kirkwood & Bear 1995) may be enhanced by stimulation of noradrenergic, cholinergic, and dopaminergic nuclei innervating the sensorimotor and auditory cortices (Ego-Stengel et al. 2001). Regulation of the number or sensitivity of synaptic receptors might control neuroplasticity through an increase in synaptic transmission which is produced via a mechanism known as long-term potentiation (LTP). Converging evidence indicates that the insertion of dendritic AMPA receptors is one mechanism for the induction of LTP (Malinow & Malenka 2002). This "receptor trafficking" is controlled by intracellular protein kinases which are dependent on the level of a second messenger called cyclic AMP (Lee et al. 2000). In vitro studies demonstrate that dopamine receptor activation stimulates cyclic AMP production, generating a long-term increase in the

synaptic expression of AMPA receptors (Sun et al. 2005). Noradrenaline has been found to activate the intracellular cAMP cascade through beta-noradrenergic receptors, and potentiate population-spike activity in the hippocampus (Harley 2007), facilitating LTP and long-term memory formation (Gelinas et al. 2008). Beta-adrenergic receptor activation also promotes the induction of a late-phase of LTP that involves protein synthesis (Gelinas & Nguyen 2005), which is essential for structural growth of neurons. Likewise, plasticity at hippocampal output synapses has been found to depend on the co-activation of acetylcholine receptors, which can be blocked by scopolamine (Shor et al. 2009). Cortical infusion of the acetylcholine agonist carbachol (or electrostimulation of the basal forebrain) which is paired with visual stimulation results in long-term enhancement of visual evoked potentials in rats. (Kang & Vaucher 2009). Lastly, it has been demonstrated that just after a rat encounters a novel object in a familiar environment, hippocampal responses to stimulation of the perforant pathway are more amplified (Kitchigina et al. 1997). This potentiation does not occur if the rats are pre-treated with propranolol, a noradrenergic antagonist. Later studies also confirmed that the rat locus coeruleus neurons fire in phasic bursts upon its encounter with the novel object (Vankov et al. 1995), resulting in increased hippocampal noradrenaline, thus promoting LTP (Sara 1998). Such evidence directly supports the notion that behavioural arousal is able to facilitate synaptic plasticity, which was first emphasized by S. Kety, who stated that behavioural arousal would induce "...facilitatory changes in all synapses that are currently in a state of excitation" (Kety 1972). The general implication of these collective findings is that neuromodulators serve to facilitate or gate experience-dependent plasticity during behavioral states of learning.

Exploring plasticity with transcranial magnetic stimulation (TMS)

It has been well established that repetitive motor performance and skill learning alter the functional organization of human corticomotor system. In the last decade, transcranial magnetic stimulation (TMS) has helped to demonstrate –noninvasively in humans- that motor practice, skill acquisition and learning are associated with changes in corticospinal excitability, as well as indices of intracortical synaptic transmission. Although TMS is a noninvasive method, it has been physiologically validated by invasive recordings of human and animal corticospinal nerve impulses (Lazzaro et al. 2008). In TMS methodology neuroplastic change is operationally defined as a significant and lasting alteration in the motor evoked potential (MEP), whose amplitude is proportional to

the strength of neurotransmission from motor cortex to muscle, evoked by a magnetic pulse, as depicted in Fig 1.2 below.

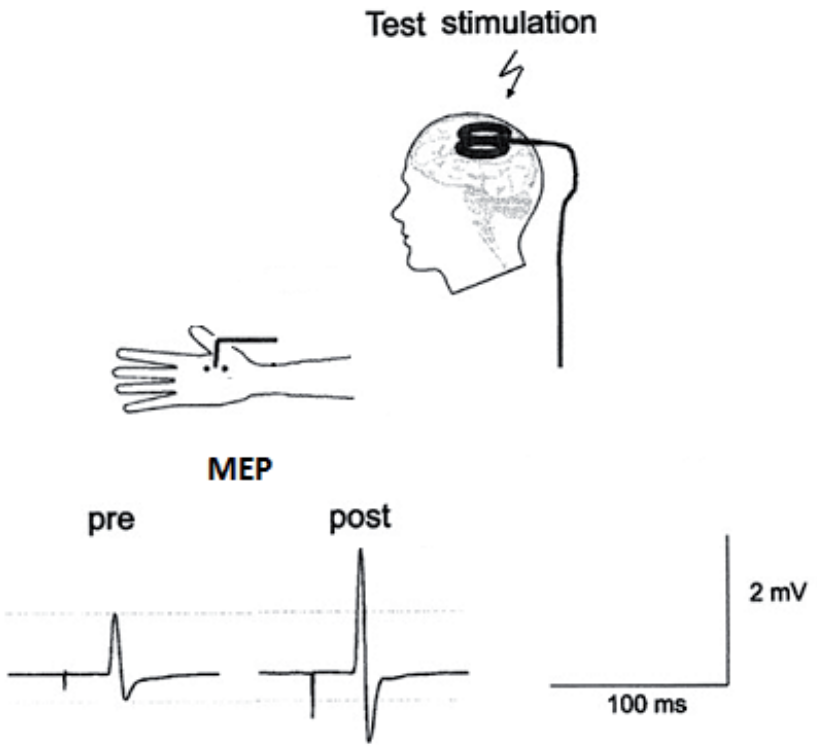

Fig 1.2. A standard 'test' TMS pulse applied over the motor cortex evokes a hand muscle response, which may be accurately recorded by a surface electrode as a motor evoked potential (MEP). Neuroplastic changes may be explored as a result of an experimental intervention, according to the pre-to-post difference of the mean MEP amplitude.

MEPs evoked by single TMS pulses best reflect the overall responsiveness (or excitability) of the trisynaptic corticospinal pathway, whereas those originating from paired pulses enable the discrimination of intracortical synaptic mechanisms (Lazzaro et al. 2008). The most frequently used measures of the latter are intracortical facilitation (ICF) and short intracortical inhibition (SICI), which are sensitive indicators of the relative strength of excitatory (glutamatergic) and inhibitory (GABAergic) neurotransmission, respectively (Ziemann et al. 1996), (Liepert et al. 1997). In general, practice of simple motor tasks produces excitability changes in the primary motor cortex. An enhancement of MEP amplitudes specific to the trained muscle may be observed following a half-hour session of training (Muellbacher et al. 2001). Repetitive motor skill training (for a total of 12 sessions) has been shown to produce MEP increases at rest, compared to strength training which seems to induce decreases in excitability

(Jensen, Marstrand, et al. 2005). Robust changes in intracortical parameters can also be provoked by motor training. Liepert et al. report a hand-muscle specific reduction in SICI (or decrease in GABAergic transmission) following repetitive thumb movements (Liepert et al. 1998). By varying the collection of muscles involved, it was noted that SICI changes only occurred in the muscles active during the task. SICI decreases have been found in leg muscles after skilled training in an ankle movement task, but not after an unskilled task (Perez et al. 2004). On the other hand, ICF (denoting glutamatergic transmission) seems to increase, as observed during training of a repeated wrist movements (Lotze et al. 2003). It has been subsequently observed that application of GABAergic agonists prior to training attenuated both motor performance and motor cortex excitability increases (Bütefisch et al. 2000). Conversely, Ziemann et al. (Ziemann et al. 2001) combined motor practice with ischemic nerve block, a technique which is known to *decrease* GABA-related cortical inhibition. This resulted in an increased MEP and ICF, accompanied by enhancements in the peak acceleration of elbow movements. It has therefore been proposed that the learning of a motor skill, which is associated with dampened GABAergic inhibition, may encourage a strengthening of horizontal motor cortical connections, as has been reported in the rat (Rioult-Pedotti et al. 1998). In line with this hypothesis, GABA agonists (antagonists) have been directly shown to block (facilitate) the induction of LTP in the somatosensory cortex of freely moving rats (Komaki et al. 2007).

In a study investigating the practice of pinch contractions (Muellbacher et al. 2001), behavioural improvements were found to correlate with increases in corticomotor excitability (MEP) in the muscles involved in training. However, although practice-related performance was stable after a one month follow-up, subjects' corticomotor excitabilities had returned to baseline levels. What is more, additional practice of the already over-learned movements did not provoke any changes in excitability. Hence, it is possible that an acute increase in excitability, which is reported by the above TMS studies, acts more like a "catalyst" to facilitate learning, rather than constituting learning itself, which would be reflected by long-term changes in synaptic strengths. It may instead be an indicator of a transient change in membrane excitability, which may also modulate the coupling between neurons. Enhancement in the excitability of neurons in primary motor cortex have been demonstrated during stimulus-response conditioning (Sanes & Donoghue 2000). Therefore one could interpret the increased excitability of neurons to be a reflection of an increased *ability* to learn. In this scenario, an increase in excitability would raise the probability of

neuronal firing, and therefore also increase the coincident firing of neurons which are simultaneously activated by a mutual input or output, thereby enhancing the likelihood of Hebbian modification of synapses (Paulsen & Sejnowski 2000). The latter mechanism may be summarised by the neuroscience maxim: "Neurons that fire together, wire together". According to a more recent model of neuroplasticity (spike-timing dependent plasticity), pre-synaptic followed by post-synaptic spiking has been observed to induce long-term potentiation (LTP), while post-synaptic followed by pre-synaptic spiking causes long-term depression (LTD). This has been the basis for the development of paired associative stimulation (PAS), an innovative protocol in which peripheral nerve stimulation of a muscle of interest is paired with transcranial magnetic stimulation over the respective motor cortical, ensuring almost coincident arrival of both stimuli in the brain (Stefan et al. 2000). It has been demonstrated that PAS can produce reversible plastic changes in corticomotor excitability that last for more than an hour. Dextromethorphan, an NMDA receptor blocker, has been shown to suppress PAS-induced plasticity (Wolters et al. 2003), suggestive of the involvement of spike-timing dependent LTP and LTD-like plasticity in the motor cortex (Stefan et al. 2002). Importantly, Bütefisch et al. (Bütefisch et al. 2000) discovered that dextromethorphan, as well as lorazepam (a GABA agonist), block training-dependent corticomotor excitability changes. Furthermore, it has been shown that scopolamine, an acetylcholine antagonist (Sawaki et al. 2002), and anprazosine, an adrenergic antagonist (Sawaki et al. 2003), both attenuate practice-induced cortical reorganization. Thus the outstanding question is, if learning-related neuroplastic changes can be pharmacologically antagonised, is the reverse also possible?

II. NEUROMODULATORY INTERVENTIONS

"EXOGENOUS" NEUROMODULATION

Pharmacological effects

One of the first studies on the effects of drugs on learning was published by Karl Lashley (Lashley 1917) in 1917, who discovered that every-day administration of strychnine (a blocker of the inhibitory chlorine channel) to rats just before training on a maze enhanced their performance relative to controls, as revealed by reduced overall errors on consecutive days. A modern, and more comprehensive equivalent may be found in a study on humans by Meintzschel and Ziemman (Meintzschel & Ziemann 2006), who investigated the effects of prior-intake of NA, DA, Ach agonists as well as antagonists on practice-dependent motor learning in healthy subjects in a placebo-controlled, randomized, double-blind crossover design. Motor learning was evaluated by the directional accuracy of isolated thumb movements induced by TMS stimulation. All three neuromodulatory system agonists (NA: methylphenidate, DA: cabergoline, ACh: tacrine) were shown to boost practice-dependent motor learning, whereas the antagonists reduced it (NA: prazosin, DA: haloperidol, ACh: biperiden). Moreover, enhancements of learning under NA and Ach were positively correlated with increases in corticomotor excitability of the relevant muscle, as tested by the motor evoked potential (MEP) amplitude. A collection of modern studies report comparable effects. The noradrenergic reuptake inhibitor (reboxetine) was observed to improve acquisition of a motor skill involving rapid elbow flexion whilst provoking MEP increases, both of which were absent following control motor performance of an over-learned finger sequence (Plewnia et al. 2004). This would suggest that reboxetine does not boost performance per se but rather facilitates training effects during the acquisition of a more complex routine. However, Wang (Wang et al. 2009) specifically measured the behavioral effects of a single dose of the reboxetine on the one-off performance of tasks with differing motor complexity and perceptuo-motor demands. The authors observed that reboxetine had a discrepant effect on visuomotor performance depending on the task. Simple and repetitive motor movements such as index finger tapping and rapid pointing were not affected by reboxetine, while tasks involving greater visuomotor dexterity such as joystick control and 3-dimensional hand–object interactions demonstrated reliable gains in motor performance compared to placebo. Notably, the improvements in

movement speed did not compromise movement accuracy, since error rates were the same between the reboxetine and placebo conditions. In a follow-up fMRI study by the same laboratory (Grefkes et al. 2009), it was demonstrated that, compared to placebo, the enhanced performance seen in the joystick control task under reboxetine was linked to increased activation of frontal, parietal, and visual cortices. Moreover, analyses of functional connectivity revealed that the metabolic coupling between these areas was amplified. Specifically, both frontal and parietal cortex exercised a greater influence on sensory areas, including primary visual and motor cortex.

There has also been interest in using neuromodulators to boost motor recovery following cortical or subcortical damage. Animal experiments have revealed that the positive effects of pharmacological intervention on functional recovery require that motor re-training is applied within the window of activity of the drug (Feeney et al. 1982). To evaluate the potential role of neuromodulators in enhancing motor recovery on a beam-walking task, investigators injected extracellular noradrenaline, dopamine, or placebo in rats one day after unilateral lesion of sensorimotor cortex (Boyeson & Feeney 1990). Here, noradrenaline proved to be the necessary agent in accelerating motor recovery, since pharmacological blockage of noradrenaline synthesis but coupled with dopamine application failed to facilitate recovery. This suggests a more prominent role for NA compared to DA (which is its chemical precursor) in functional recovery after cortical sensorimotor injury. However, a recent double-blind, placebo-controlled trial reported enhanced procedural motor learning (finger tapping plus SRT reaction time) in chronic stroke patients during a single session of exposure to the dopaminergic precursor Levodopa (Rösser et al. 2008). During two counterbalanced fMRI examinations, stroke patients performed an active motor task or a passive one conducted by the investigator, with their impaired hand. Compared to a placebo condition, oral administration of fluoxetine (a serotonin reuptake inhibitor) was found to significantly enhance motor performance of the active motor task, and was moreover associated with an increased activation of the ipsilesional primary motor cortex (Pariente et al. 2001). Lastly, boosting cerebral acetylcholine in Alzheimer's patients is known to improve declarative memory and learning impairments caused by cholinergic deficits (Pepeu & Giovannini 2009). Animal studies have shown that chronic infusion of nicotine (a cholinergic agonist) in rats improves recall in a maze task commonly used to test spatial working memory (Levin et al. 1998).

There are a number of caveats, however, with respect to the effectiveness of neuromodulators to improve learning and performance. Firstly, effects critically

depend on optimal dosages. For example, a dose of nicotine equivalent to that of smokers enhances learning in mice (Gould & Lommock 2003) yet much higher doses disrupt contextual fear learning (Gould & Wehner 1999). Similarly, dopamine has been shown to impair tactile acuity (on a two-point discrimination of a stimulated finger) in humans at high doses but not low doses (Bliem et al. 2007). It has therefore been proposed that the action of many neuromodulators follows a bell shaped curve, first formalised by Yerkes and Dodson (Yerkes 1908). More recently, using the paired associative stimulation (PAS) paradigm on the motor cortex (which does not involve any active movements), Monte-Silva et al. (Monte-Silva et al. 2009) discovered that plasticity changes in MEP followed an inverted U-shape according to the dosage of a D2 receptor agonist. The second caveat regards possible interaction effects between different neuromodulatory systems. Single neuromodulators may be necessary but not sufficient to improve performance. Amphetamine, a mainly noradrenergic agonist (Rothman et al. 2001), has a positive effect on impulsivity in the rat which is compromised by depletion of the serotonergic system (Winstanley et al. 2003). Moreover, the brain's neuromodulatory network is highly intertwined and this may give rise to complex interactions between subsystems. Several studies report that serotonin acts through multiple 5-HT receptors, which are able to indirectly influence dopaminergic activity in all major pathways (Alex & Pehek 2007). Direct infusion of a serotonin antagonist into the rat prefrontal cortex is also accompanied by a strong attenuation of prefrontal dopamine levels (Mukhina 2009). Also, the memory boost observed following cholinergic infusions of the caudate nucleus is prevented by concomitant lesion of the nigro-striatal dopamine pathway, inferring a co-dependence between acetylcholine-dopamine systems in striatal memory processes (White 1997). On the other hand the application of some agents has an inhibitory or antagonistic effect on learning. The GABAergic agonist lorazepam has been shown to decrease training-dependent performance of thumb movements (Bütefisch et al. 2000). This is consistent with the fact that GABAergic agonists (antagonists) decrease (increase) LTP in somatosensory cortex (Komaki et al. 2007).

Repetitive transcranial magnetic stimulation (rTMS)

Magnetic stimulation was initially developed as a tool for nerve excitation of muscles and the peripheral nervous system. The inventors then revealed its potential to stimulate the brain transcranially in a noninvasive and painless way (Barker et al. 1985). During TMS, an alternating electric current runs

through a large coil of wire, creating a brief but focussed magnetic field with a surface areas that depends on the shape of the coil (Hallett 2007). The evoked magnetic field penetrates the skin and bone of the skull, and induces current only within the conducting neuronal axons of the cortex, causing them to fire action potentials. Repetitive TMS works by applying multiple single pulses rapidly in succession (with a frequency typically ranging between 0.5-20 Hz). It has been shown that this method can produce changes in motor cortical excitability that outlast the period of stimulation (Chen et al. 1997); It is moreover possible to induce bidirectional cortical excitability changes depending on the frequency of stimulation, by producing an inhibition ($\leq$ 1Hz) or a facilitation ($>$1 Hz) of cortical function (Chen et al. 1997). Generally speaking, low-frequency rTMS (1 Hz) decreases the excitability of targeted cortical regions, while high-frequency rTMS (20 Hz) has the opposite effect (Gangitano et al. 2002). Although the precise neuronal mechanisms behind the long-lasting effects of TMS are still unknown, they have been likened to the classic phenomena of long-term potentiation (LTP) and depression (LTD) observed in the *brain* after repeated activation of synaptic pathways. rTMS exposure can result in persistent effects on NMDA binding sites up to a day after stimulation (Kole et al. 1999). It is also likely that, as is the case with LTP, endogenous neuromodulators and neurotransmitters may have mediating role in the observed plasticity effects, which could have an important therapeutic value. A number of studies report in situ evidence of rTMS effects by using ex vivo or in vivo techniques in the rat. rTMS has been shown to induce a dopamine increase in the striatum (Keck et al. 2002), as well as serotonin release in the frontal cortex (Kanno et al. 2003). The former result has been replicated noninvasively in human subjects with the help of PET neuroimaging methods, whereby a selective release of dopamine in the striatum was observed following high frequency rTMS of primary motor cortex (Strafella et al. 2003) and dorsolateral prefrontal cortex (Strafella et al. 2001). It was therefore logical to examine whether high frequency rTMS could facilitate motor learning by inducing excitability increases in primary motor cortex, a structure known to be implicated in the acquisition of motor routines (Plautz et al. 2000; Nudo et al. 1996). It was subsequently revealed that high frequency rTMS of primary motor cortex during training of contralateral sequential finger movements enhanced sequential key presses accuracy and reaction time (Kim et al. 2004), relative to sham stimulation. As with many pharmacological interventions above, it was noted that such effects could also be dependent on the complexity of the task. Thus, 5-Hz rTMS failed to enhance performance of a simple but rapid index-

finger abduction task (Agostino et al. 2007), whereas more complex sequential motor tasks could be improved (Kim et al. 2004).

On the other hand, another approach consists of applying low frequency (inhibitory) rTMS to the motor cortex which is ipsilateral to the side of training, in light of the observation of "interhemispheric rivalry" caused by transcallosal inhibitory connections (Netz 1999). This leads to increases in motor cortical excitability of the opposite (contralateral) motor cortex, which may accordingly result in improvements in motor sequence learning of the ipsilateral hand without affecting performance of the contralateral hand (Kobayashi et al. 2004). In an attempt to examine more comprehensively the cortical areas upregulated by rTMS (Yoo, You, et al. 2008) participant were asked to perform a sequential finger motor task inside an fMRI scanner immediately following 10 Hz rTMS applied over their primary motor cortex. The investigators found that enhanced motor performance was correlated with significant blood flow enhancements in the basal ganglia, superior frontal gyrus, presupplementary motor area, medial temporal lobe, inferior parietal lobe, and cerebellum compared with sham-stimulated participants. In an extended study investigating offline (long-term) practice effects, subjects performed a daily continuous tracking task which was preceded either by excitatory (5 Hz), inhibitory (1 Hz) or sham rTMS of dorsal premotor cortex. Motor consolidation was then measured by a delayed retention test of repeated and random movement sequences. Excitatory rTMS was found to improve motor memory consolidation and off-line learning as evidenced by lower overall errors at retention, in contrast to the inhibitory and sham groups who showed slightly worse tracking error at retention as compared to the end of practice (Boyd & Linsdell 2009).

The recently developed methods of EEG-TMS co-registration have opened a new window of understanding on the effects of TMS on the parallel activity of cortical oscillations. In a very recent study (Hamidi et al. 2009) high frequency rTMS was given to the superior parietal lobule while participants performed a visual working memory task for locations or shapes. Here, it was found that the improvement and impairment of task accuracy between subjects was associated with the individual effect rTMS had on the amplitude of alpha rhythm of the parietal EEG. On the whole, evoked decreases (increases) in alpha power lead to improvement (impairments) in performance. This is consistent with a separate finding that rTMS perturbation of parietal cortex pre-stimulus alpha desynchronisation leads to errors in visual identification (Capotosto et al. 2009) and supports a causal role for EEG oscillations in regulating the dorsal frontoparietal network during visuospatial attention.

Lastly, the impact of high frequency rTMS over the left dorsolateral prefrontal cortex (DLPFC) on central executive performance of a Stroop task was also investigated in healthy subjects. Compared to sham stimulation, reaction times significantly decreased on both incongruent and congruent trials pointing to a facilitation of processing speed and action selection, while mood remained unchanged. The data moreover reiterate the central role of the left DLPFC in the top-down control of attentional performance (Vanderhasselt et al. 2006).

Transcranial direct-current stimulation (tDCS)

The first investigations involving invasive brain stimulation occurred almost 50 years ago when researchers applied weak direct currents directly to the exposed cortices of animals (Bindman et al. 1964). It was observed that such currents were able to exert a direct influence on the spontaneous discharge and evoked responses of neurons (Purpura & McMurtry 1965). Modern tDCS devices give rise to similar neurophysiological effects that were described in those first experiments, albeit they have been designed to do so noninvasively and through the skull (Priori 2003). Conveniently, low-voltage direct currents (by way of simple scalp electrodes) are able to fully penetrate the skull and reach the underlying cortical tissues. These spreading currents are able to alter neuronal trans-membrane potentials non-focally (Miranda et al. 2006), and depending on their polarity modulate the excitabilities and firing rates of neurons. As with rTMS, longer application of tDCS can alter cortical function for periods that outlast the duration of stimulation. Thus 15 minutes of tDCS can lead to neuroplastic changes that last up to 90 minutes (Nitsche & Paulus 2001). The direction of the underlying cortical excitability change is largely controlled by the polarity of the overlying electrode. Anodal (positive charge) and cathodal (negative charge) stimulation respectively increase and decrease cortical excitability, as tested by TMS-evoked MEP amplitudes (Nitsche & Paulus 2000). According to an fMRI experiment which assessed online hand grasping movements, 20 min of prior anodal tDCS significantly amplified the activation of underlying primary sensorimotor cortex compared to sham (Jang et al. 2009). In contrast, cathodal tDCS has been shown to increase the power in the slow-wave delta and theta bands of the EEG (Ardolino et al. 2005). Moreover, Antal (Antal, Varga, et al. 2004) observed that cathodal stimulation significantly decreased while anodal stimulation slightly increased the faster beta and gamma frequency powers of underlying cortical oscillations.

Evidence suggests that the most likely mechanism with which tDCS modulates neuronal excitabilities is through the opening of voltage-gated ion channels; prolonged ion exchange may result in modification of the resting membrane threshold (Ardolino et al. 2005), leaving neurons in a hyper- or hypo-excited state. In addition, synaptic plasticity may also have a role in tDCS effects, as findings from several pharmacological studies seem to suggest. Sodium and calcium channel blockers have been found to directly block the excitability increases induced during anodal tDCS over the motor cortex (Nitsche et al. 2003). The direct excitability enhancements were not eliminated by the independent application of a NMDA receptor antagonist, but in this case long-term plasticity effects were prevented. Therefore, it has been proposed that the cortical excitability shift is firstly produced by alterations of voltage-gated ion channel conductances, whose long-term effect is then maintained by synaptic, NMDA-dependent changes. This explanation is in line with findings that d-cycloserine, an NMDA-agonist, prolongs the duration of motor cortical excitability enhancements after anodal tDCS (Nitsche et al. 2004). A latest study utilizing magnetic resonance spectroscopy reports that anodal tDCS induces only reductions of GABA, whereas cathodal stimulation also reduces glutamate levels (Stagg et al. 2009).

To summarize, excitatory (anodal) tDCS applied over primary motor cortex during motor training has been found increase the accuracy of key presses in a sequential finger movement task; this effect was absent with cathodal tDCS (Vines et al. 2006); Moreover, anodal tDCS produced transient performance enhancements in a visuomotor coordination task (Antal, Nitsche, et al. 2004). The same protocol reduced reaction times in the ubiquitous serial-reaction time task, but only during fixed sequence relative to random trials (Nitsche et al. 2003). Moreover, it is reported to enhance dexterity in the Jebsen-Taylor hand function test (JTT) in healthy subjects (Boggio et al. 2006). Although this is an examination typically used in stroke research (where individual tasks are timed, such as picking up small objects), subjects were left to reach a stable level of JTT performance before tDCS was given. This therefore suggests performance improvements beyond levels achievable under normal conditions. Lastly, anodal tDCS over primary sensorimotor cortex increased detection accuracy in a tactile discrimination task of grating orientations. There was a transient (40 min) enhancement of performance in this task with the contralateral (but not ipsilateral) finger, compared to a sham condition (Ragert et al. 2008).

Since the studies above only explored the effects of noninvasive stimulation within a single session, the influence of tDCS or rTMS over long-term plasticity

and retention is still relatively unknown. However in a latest study conducted in 2009, Reis (Reis et al. 2009) examined the impact of tDCS on the online (within-session) and offline (between-session) components of motor skill learning, using a sequential visual isometric pinch task, which is sufficiently challenging to ensure performance improvements over at least 5 sessions of training. Greater task difficulty allows a more valid comparison to real life skills, which seldom take only a day to acquire. Skill measures were based on positive shifts in the task's speed–accuracy trade-off curve. Subjects received anodal tDCS over the primary motor cortex before each practice session which was repeated over 5 consecutive days. Anodal tDCS enhanced online learning (but this was limited only to first exposure on day 1) as well as offline learning, which continued throughout the remaining 4 sessions. On average, performance at the beginning of day n + 1 was better than at the end of day n, and this accounted for the positive offline tDCS improvement over the control group. Importantly, the cumulative skill level remained enhanced in the tDCS group at 3-months, given that the rate of forgetting across the follow-up period was similar between the sham and tDCS conditions.

Caveats

It should be noted that the reported effects represent averages across subjects, and that there exists significant inter-individual variability as well as intra-individual variability depending on the timing and context of stimulation. Interindividual variability has been ascribed to be probably a result of genetic differences. For example, the degree of plasticity induced in the motor cortex by both rTMS and tDCS was observed to be dependent on a polymorphism of a gene associated with brain-derived neurotrophic factor (BDNF) (Cheeran et al. 2008), a protein which is involved in regulating synaptic plasticity as well as encouraging the growth and differentiation of new neurons and synapses (Kuczewski et al. 2009). Likewise, age seems to play a key role, with older adults (>50 years) demonstrating weaker responses following paired-associative stimulation (Müller-Dahlhaus et al. 2008). Remarkably, intra-individual variation appears to be equally, if not more, pronounced (Fratello et al. 2006). A host of studies report evidence of what is referred to as "homeostatic plasticity". Here, the history of prior learning (plasticity induction) in the brain inversely impacts on the degree of subsequent plastic changes of the same polarity. Hence prior increases in synaptic strength (e.g. LTP) are more likely to be accompanied by decreases in synaptic strength later on if the same learning paradigm is repeated (Müller et al. 2007). This appears to be the consequence of physiological and/

or computational ceiling pressures which occur naturally in synapses, the molecular mechanism of which is still under investigation (Abraham 2008). Hence in many cases excitatory brain stimulation may effectively give rise to opposite (depressed) effects on MEP amplitude or motor learning performance (Jung & Ziemann 2009), if prior activities of synaptic pathways have caused them to become more saturated in one direction (and vice versa). For instance, high frequency stimulation enhanced (impaired) tactile spatial discrimination if it was preceded by LTD-like (LTP-like) induction of plasticity in somatosensory cortex (Bliem et al. 2008). Practically this also implies that if the cortex has experienced a recent period of learning, further learning of the same type or direction will be more difficult to engender. This has also raised a renewed interest for the role of sleep and its effect on learning and consolidation of long-term skills (which requires repeated practice on separate days).

Accidental seizures are the most serious adverse events reported with TMS to date. Seizures have resulted from both single-pulse TMS, usually at high stimulus intensities, and high-frequency rTMS (Rossi et al. 2009).

"ENDOGENOUS" NEUROMODULATION

Neurofeedback

Neurofeedback (NFB) is a special case of brain-computer interface technology (BCI), which is utilised to record, process, and translate real-time information of a person's brain activity by means of a computer. In so-called "open-loop" applications, specific patterns of brain activity can be recognised by a computer and used to help interact with the environment independent of the body's conventional mode of output, which is motor. This is the basis of modern interventions which enable completely paralysed patients to control a cursor on the computer screen in order to communicate (Birbaumer et al. 2006). On the other hand, in a closed-loop or "neuro feedback" design, a sensory description of the brain activity itself is fed-back to the user, thereby enabling learned and volitional control of the neural substrate(s) being represented (Fetz 2007). Put more simply, a NFB interface acts as a virtual "mirror" to real neuronal activities occurring within the brain, thereby enabling a person to gain effective control over them. This process of self-regulation has been historically attributed to learning through "operant conditioning", while an alternative framework can be found in control theory (Marken 2009). Interestingly Lutzenberger and colleagues

(Lutzenberger et al. 1980) showed that patients with extended prefrontal lobe lesions were unable to learn NFB control despite intact intellectual functioning. This seems to implicate the frontal lobes in the initial learning of NFB control. Although the precise mechanisms of these learned control processes are still unknown, NFB may be defined as operating within a fully *closed* loop, that is to say, without the introduction of external agents or forces. It may therefore be considered as fully "endogenous". Hence NFB may be functionally distinguished from the aforementioned pharmacological and electromagnetic interventions on the basis that the nervous system does not receive any extrinsic input or support, but must do the work in and of itself to produce changes. This may prove to be an important feature for biological systems with dynamic equilibria such as the brain, which manifest states of withdrawal, tolerance, and adaptation (Poulos & Cappell 1991). Currently, either EEG (Delorme & Makeig 2003) or fMRI (DeCharms 2007) recording is most frequently used to provide real-time information of brain activity, while functional near-infrared spectroscopy (fNIRS) is in the development stage (Sorger et al. 2009). Crucially, a host of investigations have provided validation and evidence for successful regulation of select cortical activities and oscillations via NFB (DeCharms 2007), (Birbaumer et al. 2006), (Delorme & Makeig 2003), including the activity of single neurons (Fetz 2007).

EEG-based neurofeedback

The EEG is typically recorded at the scalp surface, and represents the moment-to-moment electrical activity of the cerebral cortex. The EEG is produced by the summation of synaptic currents that arise on the dendrites and cell bodies of millions of cortical pyramidal cells that are primarily located a few centimetres below the scalp surface. It is generally accepted that the scalp EEG reflects synchronous changes of dendritic (post-synaptic) ionic currents from a large number of cortical neurons underneath the recording electrode (Niedermayer & Lopes Da Silva 1999). The EEG neuronal patterns can be dynamically linked to SPECT/fMRI metabolic activities, which are measures of blood flow (Oishi et al. 2007). Glucose regulation and restoration of ionic concentrations occur several seconds after electrical impulses and synaptic activity, and therefore, blood flow changes are secondary to the nearly instantaneous electrical activity that gives rise to the high temporal resolution of the EEG (John et al. 1977). The EEG may therefore be considered a unique non-invasive indicator of coordinated *synaptic* activity across cortical networks (Niedermayer & Lopes Da Silva 1999). Crucially, it has been widely observed that synaptic transmission

as well as plasticity exhibit *frequency* dependence (Markram et al. 1999) –a variable which can be directly exploited and controlled during the application of EEG-based neurofeedback. It was Kamiya who first demonstrated that control of human EEG rhythms can be successfully learned with the aid of a NFB loop more than 40 years ago (Nowlis & Kamiya 1970; Kamiya 1968). In this case real-time information of alpha rhythm activity was provided to users via auditory feedback. Those who were able to enhance spontaneous alpha reported mental states reflecting relaxation and "letting go". Around the same time, another important discovery was made. In cats, Sterman and colleagues demonstrated for the first time that natural entrainment of EEG rhythms via operant conditioning could alter the long-term susceptibility to drug-induced motor seizures (Sterman 1969). The union of these two historic discoveries: the feasible control of human EEG rhythms with neurofeedback –on the one hand, and long-term induction of brain plasticity by direct EEG entrainment– on the other, paved the way for a novel scientific approach towards modulating human brain function in health and disease. Although its course has been protracted and mostly met with scepticism, the recent advent of larger controlled studies and meta-analyses vouch for a closer look at NFB research, especially in the treatment of epilepsy (Tan et al. 2009), attentional-deficit hyperactivity disorder (Arns et al. 2009) and autism (Coben et al. 2009). The mechanism of how the apparent entrainment of the EEG induces a long-term impression on brain activity is still unclear. Converging evidence suggests that maintaining the cortex in a persistent oscillatory pattern with NFB effectively "conditions" the neuronal circuits to produce this same pattern with a higher probability in the future (Cho et al. 2008; Gevensleben et al. 2009; Sterman et al. 1970). Akin to general learning processes such as skill or language acquisition, neurofeedback usually requires repeated applications of individual 'training' sessions of about 30-60 minutes each, occurring on separate days and spread out over weeks or months depending on the person's response. The neuronal mechanisms through which this training effect occurs still remains to be elucidated, but it may be theoretically explained by evidence that the magnitude of an EEG oscillation increases with the number of neurons/synapses giving rise to it (Niedermayer & Lopes Da Silva 1999), combined with the Hebbian principle that "neurons that fire together, wire together". Consequently, during amplified or 'synchronised' oscillations, the population(s) of neurons which are coherently involved in generating an oscillatory pattern would further strengthen the connections between themselves, thus making it easier for this population pattern to emerge once again in the future. Conversely, maintaining a group of neurons in a

prolonged desynchronised state would weaken the correlated firing of their synapses and attenuate the connections that give rise to synchronisation. These concepts have recently been mathematically elaborated in silico with a neural network model of Hebbian learning (Tass & Majtanik 2006) and verified in vivo by desynchronising electrostimulation of hippocampal circuits (Tass et al. 2009).

Caveats

Learning to enhance particular EEG rhythms through neurofeedback may in many cases lead to unpredictable effects on the distributed cortical EEG spectrum. For example, training to raise theta (4-8 Hz) over alpha (8-12 Hz) amplitudes at parietal sites was associated with a post-training reduction of beta (14-18 Hz) activity in the prefrontal cortex after repeated sessions (Egner et al. 2004). It is should therefore be borne in mind that neocortical dynamics, which are additionally regulated via thalamocortical interactions, are complex and that modulation of a self-organising system such as the brain cannot preclude the possibility of some unaccounted for downstream effects. However, this inevitably holds true for almost all interventions which deal with the brain and its panoply of networks.

Optimising performance with neurofeedback

The close relationship between modulation of the nervous system, neuromodulators and associated changes in the EEG has been extensively covered in the previous sections. It is therefore pertinent to review the NFB literature which is relevant to the enhancement of optimal performance. The large part of neurofeedback research to date has concentrated on improving cognitive functioning, such as attentional skills. The first conducted study of this type investigated NFB regulation of the theta rhythm and its impact on the execution of a simulated radar monitoring task, and was published in the journal *Science* (Beatty et al. 1974). Based on previous observations that drowsiness and decreases in arousal commonly result in elevations of theta power, the investigators randomised subjects to two groups: one whose aim was to decrease the ratio of theta (3–7Hz) amplitude relative to the rest of the EEG spectrum (3-30 Hz), and the other to increase this ratio. The NFB training for both groups was contingent on the EEG activity of the left parietal-occipital area and consisted of a 60-min practice session. The subjects subsequently performed the radar task for 120 min whilst concurrently attempting to control their theta

in the designated direction with NFB. The main findings demonstrated that the theta suppression group exhibited the highest rate of detection which was furthermore associated with a decreased NFB theta ratio during performance. However, no difference in performance was evident between groups when EEG feedback was given for an hour before, but not during, the radar monitoring task. The latter effect may initially suggest that for NFB training to have an infuence on performance it would need to be executed concomitantly with the cognitive task. However this experiment consisted of only one hour of exposure to NFB, which may have been insufficient to significantly induce cumulative plastic changes in the brain.

Motivated by research revealing the efficacy of NFB in improving the symptoms impulsivity in attentional-deficit disorder in children (Lubar et al. 1995), Egner & Gruzelier recently explored the potential long-term effects of a similar approach in healthy subjects (Egner & Gruzelier 2004). In this case, subjects were allocated to three protocol groups: the first two consisted of elevating either the primary motor cortex low beta rhythm ("sensorimotor rhythm" or SMR: 12-25 Hz) or beta1 rhythm (15-18 Hz), whilst simultaneously suppressing the flanking theta (4-7 Hz) and high beta (22-30 Hz) frequencies. The third was an active-control group engaged in the Alexander technique. The groups were tested on the performance of two tests of sustained attention: the well-known Test of Variables of Attention (TOVA) and an auditory divided attention task. They were also assessed on target evoked potential amplitudes in a sensory attention paradigm (auditory oddball). Assessments were given prior and subsequent to a once-weekly NFB schedule consisting of a total of 10 sessions of 15 min each. The authors reported a protocol-specific effect for the SMR group which was associated with an increased perceptual sensitivity index (which expresses a ratio of hit rate to false alarm rate, derived from signal detection theory), and reduced omission errors and reaction time variability. Beta1 training was associated with faster reaction times and increased target evoked potential amplitudes (indicating a more concerted neuronal response), whereas no changes were evident in the control group. These findings validated a previous study demonstrating EEG correlated improvements on attentional variables when the SMR and beta1 protocols were interleaved (Egner & Gruzelier 2001). In a subsequent study by Vernon et al. the same 'SMR-Theta' protocol (for a total of eight sessions) was demonstrated to lead to significant improvement in cued recall performance on a computerised working memory task, and to some extent showed improved accuracy of focused attentional processing using a 2-sequence continuous performance task (Vernon et al.

2003). These changes were not found in the control group whose EEG feedback was contingent to increase theta amplitude.

Furthermore, 10 sessions of specific enhancement of motor cortex SMR (without concomitant theta suppression) has recently been shown to be conducive to positive changes in sleep parameters (increased number of sleep spindles and a reduction in sleep onset). Importantly, the average within-session increase in SMR was subsequently associated with an enhancement in retrieval score on a declarative learning task after a 90 min nap (Hoedlmoser et al. 2008). Once again, there was an absence of effect in the control group which received feedback contingent on a random selection of EEG frequencies. The direct link between SMR (low beta) rhythms and their impact on cognitive performance is still unclear. Invasive recordings of these rhythms in animals have identified a neurophysiological substrate responsible for their emergence. They seem to occur during awake but immobile behaviour, and are associated with the bursting of thalamic ventrobasal neurons, hyper-polarization of relay cells and attenuation of conduction of somatosensory information to cortex (Sterman 1969). More recently, human studies have shown that low beta rhythms are produced during inhibition of a prepared movement in the Go-NoGo task, occurring focally in the motor cortex around 300 ms after the presentation of the NoGo stimulus (Zhang et al. 2008). Moreover, the power of both alpha and beta rhythms in motor cortex has been observed to be negatively correlated with underlying cortical blood flow oxygenation/metabolism (Ritter et al. 2009). In the only fMRI study to date which explored the after-effects of EEG neurofeedback, 15 children with ADHD received NFB for a total 40 sessions, at three training sessions per-week (Lévesque et al. 2006). The first 20 sessions consisted of concomitant SMR enhancement and theta suppression, while the last 20 of beta1 enhancement and theta suppression. Neuroimaging during the conflict condition on a Stroop task revealed a significant post-intervention upregulation of metabolic activity in anterior cingulate cortex and in the basal ganglia (caudate nucleus and substantia nigra) compared to a control group. This is respectively consistent with NFB modulation of regions anatomically responsible for attentional and motor processing.

Meanwhile, another NFB approach that has received considerable attention is the so called ‘Alpha-Theta’ protocol, which is performed in a relaxed, eyes closed state with auditory feedback. Here, the aim is to facilitate a progressive decrease in arousal by first promoting alpha rhythms through a pleasant sound (e.g. running brook). As the person reaches a deeper state of deactivation theta rhythms start to emerge and these are subsequently

encouraged by the reward of a more relaxing sound (e.g. ocean waves). The aim is to keep the subject in the theta state for as long as possible, as this slow-wave has been linked to hypnagogia, reduced anxiety and long-range functional connectivity between cortical regions (Gruzelier 2009). This protocol was first observed to be beneficial as an adjunct treatment of alcoholism (Peniston & Kulkosky 1989) and posttraumatic stress disorder (Moore 2005). The main performance enhancing effect of this NFB protocol has been found in the field of artistry. Musical performance was assessed by Egner and Gruzelier in 2003 when conservatoire students were randomised to one of the following groups: SMR, beta1, alpha-theta, mental-skills training, physical exercise, or Alexander technique (Egner & Gruzelier 2003). Expert judges' ratings revealed that the alpha-theta protocol selectively produced robust post-training performance improvements, while all other groups did not demonstrate any significant changes. Mean alpha-theta group improvements ranged between 13.5% and 17% on evaluation scores for ''musicality,'' ''stylistic accuracy,'' ''interpretative imagination,'' and ''overall quality''. Subsequently, Raymond and colleagues discovered positive effects of alpha-theta training on dance performance (Raymond, Sajid, et al. 2005). Neurofeedback training significantly improved scores on the 'Timing' subscale, whereas 'Technique' was enhanced by heart-rate variability biofeedback training. No reliable changes were evident for the no-treatment control group. Furthermore, in a separate study specifically aimed at investigating personality and mood, 9 sessions of alpha-theta caused participants to feel significantly more energetic, composed, agreeable, elevated and confident than did sham neurofeedback, when measured with the Profile of Mood States (POMS) questionnaire (Raymond, Varney, et al. 2005).

III. AIMS

It is now possible to draw several conclusions from the literature that has been covered:

(i) The efficacy of learning and performance varies across different states of behaviour and central nervous system activity.

(ii) These states have neurobiological signatures, and they can be regulated by neuromodulatory subsystems.

(iii) The neuromodulatory systems may themselves be up- or down- regulated exogenously (e.g. pharmacologically, rTMS, tDCS) or endogenously (e.g. behavioral activation, neurofeedback).

It is also apparent from the review of non invasive brain stimulation studies that it is possible (at least temporarily) to boost perceptuo-motor learning and/or performance. This improvement has been consequently linked to the modulation of endogenous neurophysiological substrates, which are anatomically reflected in the levels of certain chemical neurotransmitters and functional activities, including blood oxygenation (BOLD) and neuronal oscillation (EEG). The neurofeedback literature, on the other hand, has provided evidence in equivalent domains. NFB has been successfully used to improve cognitive and behavioural performance in clinical settings as well as in the healthy population, which is associated with reports of anatomically-specific functional changes in fMRI activation (Lévesque et al. 2006) and EEG rhythms (Fernández et al. 2007; Cannon et al. 2007). However, to the best of the author's knowledge, no studies exist to date which have specifically investigated the potential impact of NFB on perceptuo-motor skills.

Study 1 – Optimising microsurgical skills with neurofeedback

The hypothesis that neurofeedback may optimize perceptuo-motor skill can be traced to previous reports of improved attention and motor impulsivity (Egner & Gruzelier 2001; Egner & Gruzelier 2004) for the SMR-Theta protocol, and improved timing (Raymond, Sajid, et al. 2005) and stylistic accuracy (Egner & Gruzelier 2003) in artistic performance for the Alpha-Theta protocol. The

former protocol has also been observed to improve memory recall following sleep modulation (Hoedlmoser et al. 2008), an important element in offline motor sequence learning (Fischer et al. 2002). Moreover the Alpha-Theta protocol has been shown to reduce anxiety (Moore 2005), a dimension that may prove crucial in performing a skill under pressure. Hence, it would be potentially fruitful to explore if either of these two 'classic' protocols could modulate learning and performance of a perceptuo-motor skill. By virtue of the fact that NFB intervention usually requires multiple sessions spread over weeks, the learning of a complex skill that requires both online plus offline acquisition would seem to be the most appropriate. One sector of medical and socioeconomic importance where development of perceptuo-motor skills is paramount is surgery. As a subspecialty, microsurgical skills, which are implemented for example in ophthalmic (eye) surgery, represent the upper ranks in fine precision hand-finger manoeuvres and ambidexterity (Gogate 2009). Moreover, microsurgical operations are achieved while the surgeon is viewing through a microscope, requiring a considerable level of visuomotor adaptation and training (Benjamin 2005). Therefore ophthalmic microsurgery would be an excellent paradigm with which to test the hypothesised beneficial effects of NFB on motor performance and training. In this case, junior eye surgeons who were already taking part in the standard National Health Service surgical training curriculum were randomised to three groups: SMR-Theta, Alpha-Theta, and a wait-list control group. The approximate number of surgeons in each group was estimated to be approximately n = 10. Each NFB group received 8 sessions of NFB in total, at a biweekly frequency spread over a 2-3 month period of standardised surgical training. Surgeons were assessed before (baseline) and immediately after this period for intra/inter-group differences in performance. The performance of several standardised surgical tasks were evaluated in the speed and accuracy domains, via measures of time for the former and by expert judges' ratings of masked video recordings for the latter. In order to maintain a controlled environment the assessments were conducted on an artificial eye in a "surgical skills" training room.

Study 2 – Direct effects of neurofeedback on motor cortical plasticity

In comparison with the much larger amount of studies demonstrating long-lasting clinical and behavioural effects of NFB, very few investigations have been carried out to date on the mechanisms and neurophysiological substrates of EEG-based NFB other than EEG measures. A consensus of TMS literature purports significant and durable changes in brain plasticity following noninvasive brain stimulation techniques such as rTMS and tDCS (Wagner et al. 2007) linked to improved performance in the human cortico-motoneuronal system. Critically, the SMR-Theta protocol has been observed to lead to long-term fMRI alterations in the striatum (Lévesque et al. 2006) while NFB regulation of slow-cortical electrical potentials is also known to be able to modulate basal ganglia and premotor cortex fMRI activation (Birbaumer et al. 2006). Thus, in a second study, it could be appropriate to probe the extent of the effects of NFB on the corticomotor system with TMS methodology. This may ultimately enable more direct comparisons of effect size with other noninvasive stimulation techniques. Online neurofeedback regulation of selective motor cortex activities has been documented in EEG (Delorme & Makeig 2003) as well as fMRI (Yoo, Lee, et al. 2008) measures. Most importantly however, there has been no demonstration to date of a chronologically *direct* neuroplastic effect following NFB. That is, of a robust and durable change in neurophysiological function immediately after a single session of NFB. This is possibly because NFB neuroplasticity effects are assumed to cumulate gradually over time (usually >8 sessions) and are seemingly regarded as too weak to be tangible across a single session. However, both rTMS and tDCS display consistent and long-lasting changes in corticomotor excitability after single sessions, and if NFB is to be seen as an efficacious tool it would be useful if it could potentially demonstrate some influence on TMS parameters. In order to disentangle more easily the effects of particular bandwidths on corticomotor excitability, it would be preferable to adhere to exploring the NFB effect of discrete EEG rhythms separately. Given the legacy of the inhibitory SMR (12-15 Hz) rhythm in NFB applications, it may be worthwhile investigating whether entrainment of this rhythm during a single session (30 min) has any subsequent and lasting (up to 20 min) impression on the standard TMS measures of corticospinal excitability, short intracortical inhibition, and intracortical facilitation. Reliable changes in the latter two parameters will serve to substantiate whether the observed effects are expressed intracortically (Lazzaro et al. 2008). On the other hand, an additional protocol of interest may be alpha (8-12 Hz) rhythm desynchronisation, which could

be useful in hypothetically producing an opposing and excitatory response in motor cortex according to the EEG literature (Rossini et al. 1991). The estimated subject number for each protocol group was approximately n=12, based on previous TMS studies of cerebral plasticity (Ziemann et al. 2008).

Study 3 – Facilitating motor learning with one session of neurofeedback

Lastly, and depending on the neurophysiological effect of NFB on the TMS measures of the second experiment, one should be able formulate a NFB protocol that could be successful in enhancing online (i.e. within-session) performance and learning of a standardised motor task. The serial reaction time task (SRTT) has proven a practical paradigm to assess implicit perceptuo-motor learning, which is a form of procedural motor learning where skill improves over multiple trials without the subject's conscious awareness of a repeating sequence (Robertson 2007). The SRTT has been consistently used to explore perceptuo-motor performance following noninvasive brain stimulation (Nitsche et al. 2003; Terney et al. 2008). Once again, this would enable direct comparisons of NFB effects with other exogenous approaches. In light of previous research, it appears that protocols that lead to excitability increases of the primary motor cortex most consistently engender improvements in the SRTT of the contralateral hand. It was hypothesized that alpha rhythm desynchronisation would be associated with increased motor cortex excitability, given the inverse relationship between MEP amplitude and alpha power (Sauseng et al. 2009). Hence the aim consisted of activating the right primary motor cortex with a single session of alpha suppression NFB (30 min) beforehand, in order to facilitate subsequent implicit learning of the SRTT (12 key presses) with the non-dominant hand. On another occasion (1 week apart), the same subject was tested on a different sequence without prior NFB, as part of a control condition. The experiment consisted of a counterbalanced design, and the estimated number of subjects required for this experiment was n=10.

IV. EXPERIMENTS

Study 1: Optimising microsurgical skills with neurofeedback

Introduction

Neurofeedback has assumed a role in performance enhancement of healthy individuals within fields as diverse as cognition, sport and artistry (Gruzelier & Egner 2005). In particular recent studies report significant improvements in attention (Egner & Gruzelier 2004; Egner & Gruzelier 2001), memory (Vernon et al. 2003), mental rotation (Hanslmayr et al. 2005), mood (Raymond, Varney, et al. 2005), dance (Raymond, Sajid, et al. 2005) and musical ability (Egner & Gruzelier 2003). Neurofeedback skill enhancement in the novel area of microsurgery has not been investigated to date, while vital function of surgery in medicine cannot be overestimated. The set of skills required to undertake microsurgical procedures includes many of the cognitive and sensorimotor skills which neurofeedback has been shown to enhance. The demands on those undergoing surgical training are considerable and often stressful (Gibson et al. 2005). There may also exist time pressures on those seeking to acquire surgical skills and the availability of expert trainers is often at a premium. To this end there is investment in developing and evaluating procedures to enhance surgical training and performance such as virtual reality (Larsen et al. 2009), motion tracking (Ezra et al. 2009) and cognitive training (Van Herzeele et al. 2008). In this study, we examine the effect of two distinct neurofeedback protocols on the acquisition of microsurgical skills by a group of trainee ophthalmic surgeons.

The first protocol, commonly referred to as Alpha-Theta (AT), aims to raise theta (5–8 Hz) over alpha (8–11 Hz) activity levels during a wakeful eyes-closed condition in order to induce a deep relaxation state, given the association between theta activity and meditative states (Aftanas & Golocheikine 2001) plus wakefulness-to-sleep transition (Broughton & Hasan 1995). It has been especially employed as a complementary therapy in post-traumatic stress disorder (PTSD) (Moore 2005), alcoholism (Peniston & Kulkosky 1989), and has been shown to ease anxiety (Moore 2005; Raymond et al. 2005), as well as enhance artistic ability (Gruzelier et al. 2006). Hence this type of training may benefit stamina via its relaxation effect, and boost morale by enhancing positive

mood through its putative action on the limbic emotion system (Gruzelier 2009).

The second protocol, known as SMR-Theta (SMR), aims to elevate 'Sensorimotor Rhythm' [SMR] (12-15 Hz) while concurrently suppressing theta activity, and has been shown to reduce the threshold of epileptic seizures (Sterman & Egner 2006) and symptoms of Attention Deficit Hyperactivity Disorder (ADHD) (Lubar 1991). From a theoretical perspective this protocol appears to increase generic brain arousal, since it can also enhance attentional performance in healthy subjects (Egner & Gruzelier 2001). On the other hand, it also serves to reinforce inhibitory functions, such as those implicated in thalamic sensorimotor gating (Sterman 1996) and genesis of sleep spindles (Fuentealba et al. 2005). Most importantly, a growing body of research points to a possible relationship between SMR rhythm and long term potentiation (LTP), widely regarded as the main mechanism behind long term memory. For example, stimulating bursts of oscillations in this frequency range induce long-term modifications on excitatory neocortical synapses (Rosanova & Ulrich 2005). Moreover, 7-14 Hz spindling has also been proposed to 'open molecular gates of plasticity' (Sejnowski & Destexhe 2000), by activating Ca2+ currents prior to transition to stage 1 sleep. This role in facilitating sensorimotor control and learning has clear implications for surgical performance.

In brief, ophthalmic surgery, by virtue of the scale at which surgery is undertaken and the extreme adverse consequence of error, provides an ideal model with which to evaluate the potential benefits of neurofeedback. Surgical performance in a skills laboratory (Anastakis et al. 1999a) was assessed by means of two principal measures, surgical time and technique, representing the main critical dimensions in surgical proficiency: pace and accuracy (Szalay et al. 2000). The pre-post intervention assessment consisted of four microsurgical sub-tasks, each a simulation of part of a cataract operation using a model eye (Anastakis et al. 1999). Our initial hypothesis was that neurofeedback training would beneficially modify measures of time and accuracy in these tasks, with the aim of enhancing individual surgical skills (scheduled within the context of standardized and ongoing medical training) by modulating general cerebral function towards more 'efficacious' neural information processing appropriate to both the execution, as well as the retention, of fine sensorimotor manoeuvres.

Materials and Methods

Study Design

The participants were 22 eye surgeons (10 males, 12 females; mean age 33.5, SD 5.12) from the Western Eye Hospital, London, UK. They volunteered to participate and did not receive any monetary reward. The subjects were allocated at random to one of 2 training groups: SMR-Theta neurofeedback (n=10) or Alpha-Theta neurofeedback (n=10). Both groups underwent 8 half hour sessions of training, using the relevant protocol, over a period of 2-3 months. A randomly selected subset of all subjects was assigned to a third group, a wait-list 'control' group (n=8), in order to test for effects of practice and time. These subjects completed an additional assessment which occurred about three months prior to the start of training. Subsequently, they undertook the same experimental procedure as their respective training group. Two of the wait-list subjects did not complete their neurofeedback training, so only their control assessments were included in the analysis.

A number of tests were used to examine the effect of the different neurofeedback protocols on surgical performance and behavioral attention. Prior to and after the training program subjects completed the following tests. Firstly they completed a self-report state measure of mood (Profile of Mood States and Spielberger's Anxiety Index). They then performed a multiple-task surgical assessment on an artificial eye. Finally they completed the Attention Network Test, a 20 min psychometric test administered on computer. The surgical performance test consisted of four tasks to be completed in the following order: sideport, phaco wound, capsulorrhexis, and suture knot. Surgical performances were recorded on digital video, then scored by two expert judges. Both judges were consultant ophthalmic surgeons as well as qualified teachers, and were blind to individual identity, group membership and performance order. They rated the discrete surgical tasks individually, with the same score template, consisting of binary scores (1 or 0) for every condition fulfilled or unfulfilled, respectively.

Surgical Assessment

The surgical performance assessment consisted of four sub-tasks, each a simulation of part of a cataract operation using a model eye and completed in the following order: 'sideport incision', 'phaco wound', 'capsulorrhexis' and

'suture'. Current ophthalmic surgical practice involves extra manipulation of the eye through a small self-sealing wound in the cornea ('sideport incision'). Removal of the cataractous lens is carried out by ('phaco') emulsification using minimally invasive ultrasound energy transmitted via a probe inserted through a self-sealing corneal wound ('phaco wound'). Prior to phacoemulsification a round hole is made in the front coating of the lens ('capsulorrhexis). A stitch ('suture') is sometimes used for extra wound security at the end of the operation. These simulated surgical procedures were performed in standardized conditions. Digital videos of the complete surgical procedure were recorded in magnification via the microsurgical lens. These were analysed digitally and 3 objective measures were computed. The *overall* time denoted the start to finish time. This was subdivided into the *task* time and *pause* time, the former being defined as time spent in contact with the eye (with the instrument), whereas the latter as the time spent between tasks in preparation. Taken as a whole, the computed measures always obeyed the following formula: *overall* time = total *task* time + total *pause* time. On the other hand, Surgical Technique was scored independently by each of the 2 judges after a preliminary calibration session with a series of "test" videos. Next, each judge would evaluate the whole randomised set of microsurgical performance videos, where subject, group identity, and presentation order were kept anonymous. The score template comprised of a total possible score of 54 criteria, rated in a yes/no (1/0) binary method e.g. correct angle of blade parallel to iris. The template had structured subsections corresponding to the 4 tasks of sideport, phaco wound, capsulorrhexis, and suture knot. The total score was expressed as a percentage, out of 54 points.

Neurofeedback apparatus

EEG signals were registered using a Procomp+ differential amplifier (Thought Technology Ltd, Montreal, QC), neurofeedback training was carried out with Neurocybernetics EEG Biofeedback software (Encino, CA). The EEG was sampled at 160 Hz by the A/D converter in the Procomp+ and bandpass filtered by the Neurocybernetics EEGer software to extract high beta (22-30 Hz), SMR (12-15 Hz), alpha (8-11 Hz) and theta (4-7 Hz) components, with a smoothing time constant of 0.5 seconds. A low pass filter was additionally used at 50 Hz.

SMR training

Training began with a 3-min baseline period during which the EEG-band amplitudes were recorded at rest with eyes open, in the absence of feedback. This baseline was then used as the initial criterion for the contingent feedback that followed. This consisted of eight 3-min periods, each consisting of 170 s of feedback, with 10 s breaks in between. Band amplitude values are transformed online into geometrical visual feedback representations, displayed on a 15" computer monitor. Operant contingencies were such that rewards (or 'points') were gained whenever the subject increased SMR band activity without concurrent increases in theta and high beta band activity. The subjects were seated in a comfortable chair about 1.5 m from the monitor and they were instructed to simply let the feedback process guide them into learning how to maximize their point score. The feedback thresholds were automatically reset during each break period to maintain a constant level of reinforcement. The reward band threshold was set at 0.8 times its baseline average, while the high beta and theta inhibit thresholds were set at 1.2 times their baseline average. All neurofeedback EEG was recorded from Cz, with reference and ground electrodes placed on either earlobe, while impedance was kept below 10 kΩ using an impedance checker.

Alpha-Theta training

The alpha-theta protocol involved only auditory feedback with eyes closed. A 3-min eyes-closed baseline was first recorded in the absence of feedback; this was then used to set initial alpha and theta band thresholds. Subsequently, eyes-closed auditory feedback was engaged for a continuous 27 minutes. Both alpha and theta band related sounds acted as rewards and were intended to induce relaxation. Alpha activity was represented by a 'babbling brook' background sound and theta by an 'ocean waves' sound, the latter was set to have a higher priority over the former when both reward conditions were met. The operant contingencies were by this means intended to induce higher theta-to-alpha ratios under waking conditions. Trains of suprathreshold alpha and theta activity elicited a high and low pitch gong sound respectively to feedback bursts of high alpha and theta activity. Subjects wore a set of headphones and relaxed in a comfortable reclining chair. They were instructed to relax deeply in order to achieve an increase in the amount of theta sound representation, but to avoid falling asleep. During the course of the session the experimenter aimed to

maintain alpha and theta reward band values within a range of minimally 30% to maximally 65% of time above threshold. The EEG was recorded from Pz, with reference and ground electrodes placed on either earlobe, and impedance kept below 10kΩ.

Sustained attention measures

A paradigm named The Attentional Networks Test (ANT) (Fan et al. 2002) was used to simultaneously evaluate the efficiency and correlation between the three putative independent attentional networks of alertness, conflict, and orienting. The experiment, performed via computer, is a combination of spatial cueing and a flanker task. The subject is presented a row of 5 horizontal arrows and is required to report as quickly as possible the direction (left or right) of the centre arrow (the target) by pressing a corresponding key. To introduce a conflict factor, the target is flanked by four side arrows, which can be either in the same direction as that of the target (congruent condition), or in the opposite direction (incongruent condition). To introduce an orienting factor, the stimulus row is presented at two different locations, either above a fixation point or below it. To introduce an alerting factor, the row is preceded by a cue (cue condition) or not (no-cue condition). In addition, when there is a cue, it is presented at the centre fixation location (centre-cue condition) or at the locations where the stimulus row is to appear (orienting-cue condition). The subject's reaction time for each trial (RT) is recorded, and the efficiencies of the three attentional networks are measured as follows: Alerting efficiency = RT(no-cue) – RT(centre-cue), Orienting efficiency = RT(centre-cue) – RT(orienting-cue), Conflict efficiency = RT(incongruent) – RT(congruent).

Data analysis

The IIR (Infinite Impulse Response) bandpass filtered EEG-signal sampled at 160 Hz was converted by EEGer (Neurocybernetics, Encino, CA) to peak-peak voltages and exported to a summary file. The data was averaged over artefact-free epochs of 1 s for the respective bands of theta (4-7 Hz), alpha (8-11 Hz), SMR (12-15 Hz) and high beta (22-30 Hz). The amplitude values in these bands were used for statistical analysis of absolute changes in spectral EEG. In order to investigate the relations between individual neurofeedback protocols and changes in performance, learning-indices for each protocol were calculated. It was not possible to ensure that the time of day for training remained constant across the sessions for each participant, and any comparisons made between

sessions could potentially introduce confounding factors resulting from changes in emotional state, arousal, amount of sleep and time between EEG acquisition and food intake (Fishbein et al. 1990). Hence, following Lubar et al. (Lubar et al. 1995) successful neurofeedback learning was defined by an increase in the *training ratio*, or the ratio of activity in the training frequency relative to the inhibitory frequencies. For the Alpha-Theta and SMR groups respectively, this was expressed by theta divided by alpha activity, or t/a ratio, and a SMR/theta ratio, or SMR divided by theta activity. Two additional indices of neurofeedback learning were calculated for each protocol, a *within-session* learning coefficient (the regression between the training ratio of each 3-min period and the number of periods) and an *across-session* coefficient (the regression between the within-session coefficient and the session number) to establish relationships of EEG learning across time.

Statistical analysis

Continuous objective measures, such as time and EEG, were regarded as parametric, whereas discrete subjective measures, such as mood and judges' ratings, were regarded as non-parametric. Pre- versus post-training effects were assessed by a TIME x GROUP (2 x 2) repeated measures ANOVA on the two experimental groups for parametric surgical time measures. Exploratory paired t-tests or Wilcoxon tests were respectively carried out on parametric time and non-parametric technique scores in order to examine pre-post changes in each group. For groups where significant performance effects were detected, the relation between the learning index of each neurofeedback protocol and the performance change score (subtracting post-training from pre-training values) was analyzed by means of regression analysis. Lastly, performers' mean EEG training ratios were also compared via a median split of 'top' versus 'bottom' performance change scores.

Mood measures

The Profile of Mood States (POMS) (Lorr et al. 1981) questionnaire was used to assess pre-performance mood levels on a five-point Likert scale. Pre- and post-training scores assessed possible changes in mood as a result of training. This questionnaire has subscales of: composed–anxious, agreeable–hostile, elevated–depressed, confident–unsure, energetic–tired and clearheaded–confused. A positive score on each subscale is proportional to feelings of 'negative mood' on the axis. For instance, a positive score on the composed-anxious subscale

denotes anxious feelings, a negative one feeling composed etc. In addition, subjects completed the Spielberger's State & Trait Anxiety Inventory (Kellner & Uhlenhuth 1991). The questions have a four-point Likert scale and are divided in two sections, with separate scores of *state* and *trait* anxiety, defined as anxiety felt at the moment and in the past week, respectively.

Results

Test-retest intervals

Figure 2.1 summarizes the number of days elapsed between pre- and post-training assessments, or test-retest interval, for the 3 protocol groups. One-way ANOVA reported no statistically significant differences between SMR and AT groups ($F(1,18)=0.01$, $p=0.92$).

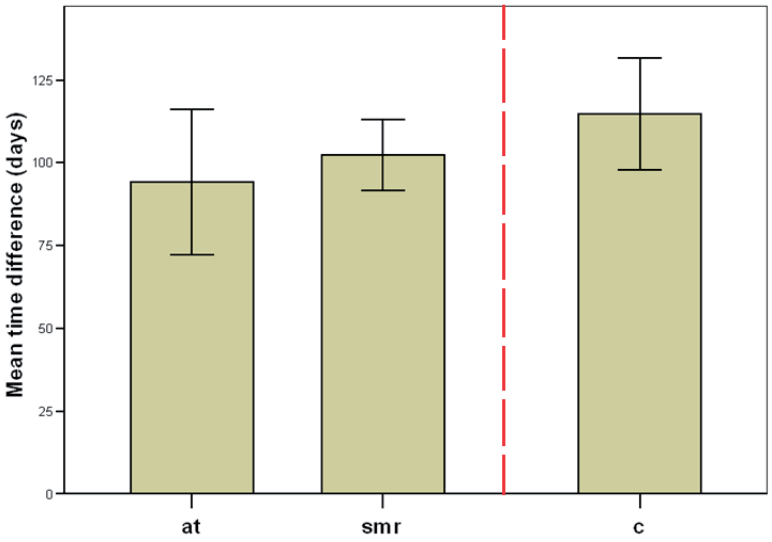

Fig 2.1. Test-retest intervals for AT and SMR groups. Wait-list control assessments C are illustrated for qualitative comparison.

Attention Network Test (ANT)

One-way ANOVAs on the initial scores of all ANT variables indicated no differences between SMR and AT groups prior to training. As can be seen from Table 1.1, hypothesized trends for all groups were only confirmed for decreases in RT, with the control group effect proving largest on a paired t-test ($t_9=9.936$, $p<0.01$). Response accuracy increased for the control as well as SMR groups, and decreased for the AT group, yet none of the paired t-test values were statistically reliable. Time 1 measures were subtracted from Time 2 measures to give an effective post-training change for the efficiency of the

three attentional networks, as shown in Fig 2.2. All groups demonstrated an increase in alertness, while expected changes in the AT training group were manifest in efficiency increases in orienting, and to a smaller extent conflict; however, paired t-tests did not reveal any significant changes. Surprisingly, a decrease approaching significance was found for orienting (t_9=2.21, p=0.055) in the SMR-group, followed by marginally significant decreases in conflict for SMR (t_9=1.86, p=0.096) and control (t_9=1.93, p=0.090) groups.

Group	Efficiency	Time 1		Time 2	
		Mean	SD	Mean	SD
SMR	alert (ms)	33.8	14.1	36.9	19.6
n=10	orient (ms)	29.8	13.8	22.5	7.4
	conflict (ms)	99.4	28.3	84.7	23.6
	RT (ms)	545.0	38.6	544.7	49.9
	accuracy (%)	97.8	1.7	98.0	1.1
AT	alert (ms)	32.6	22.0	42.0	17.7
n=10	orient (ms)	28.8	16.0	33.2	14.2
	conflict (ms)	74.5	17.4	76.0	10.9
	RT (ms)	511.4	41.7	507.2	43.7
	accuracy (%)	98.4	1.4	95.5	8.3
control	alert (ms)	28.5	18.0	36.9	18.3
n=8	orient (ms)	28.9	21.6	26.3	14.5
	conflict (ms)	86.8	21.8	68.6	16.3
	RT (ms)	524.8	30.5	495.1	31.6
	accuracy (%)	94.6	12.0	98.1	1.3

Table 1.1 Means and standard deviations on all ANT measures in each protocol condition before and after training.

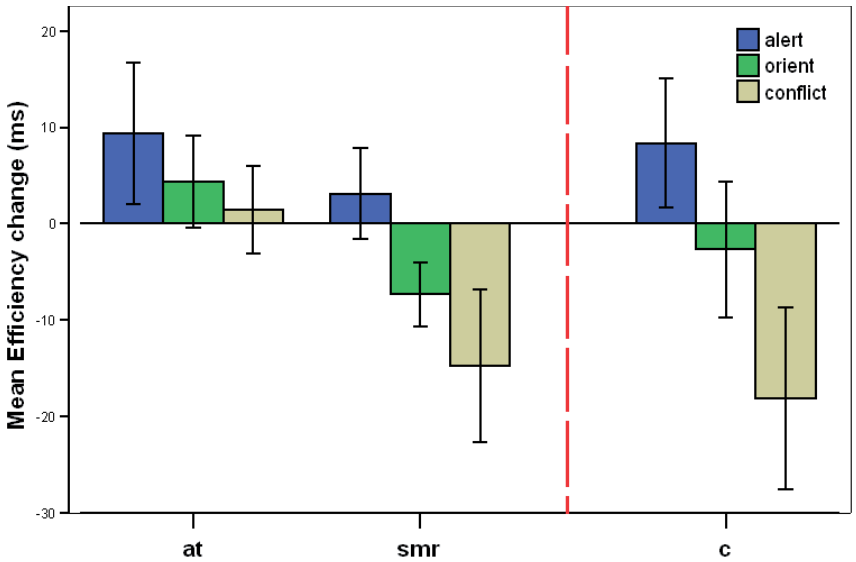

Fig. 2.2 Attention Network Test post-training changes in mean conflict and RT for SMR and AT groups. Wait-list control assessments C are illustrated for qualitative comparison.

Neurofeedback Learning

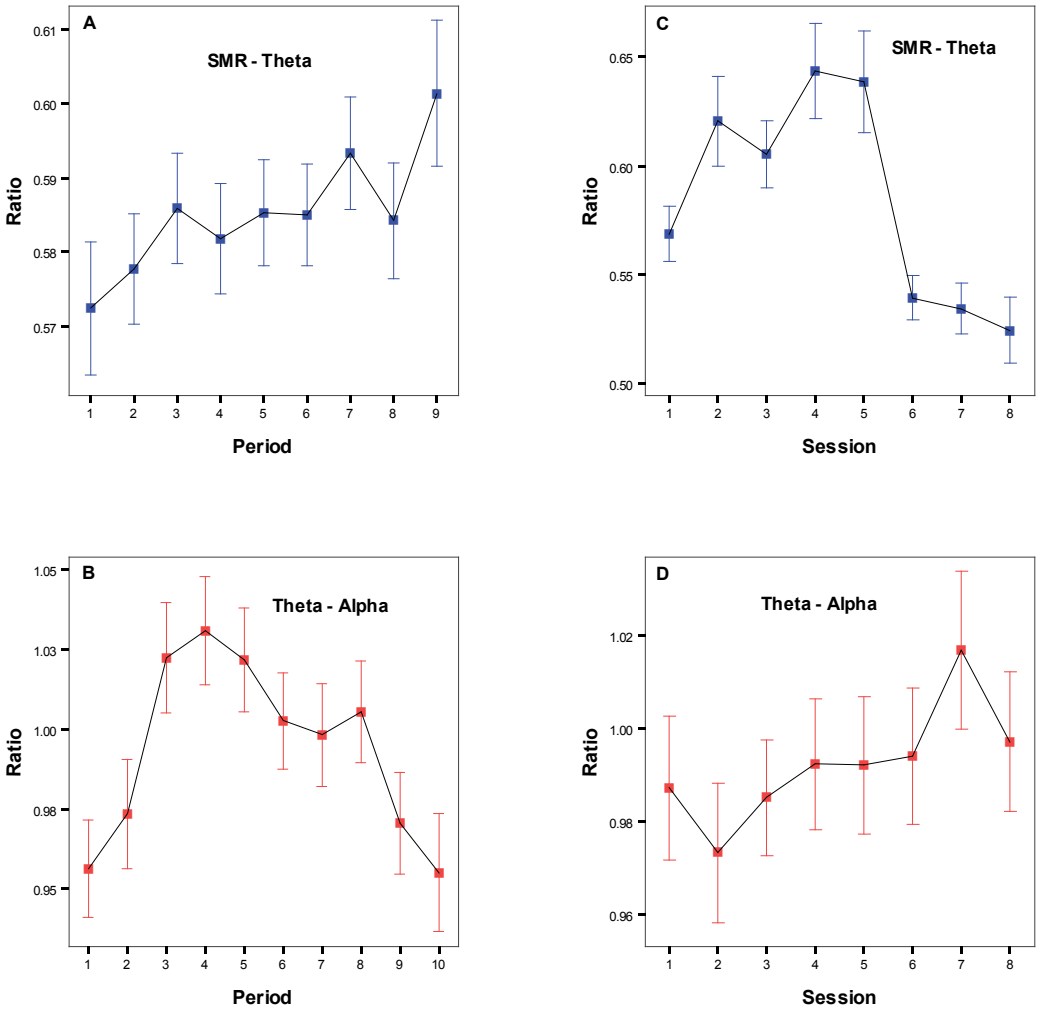

Fig. 2.3 *Left panel:* Mean ratio of SMR/theta (**A**) and theta/alpha (**B**) amplitude, across training *periods*. *Right panel:* Mean ratio of SMR/theta (**C**) and theta/alpha (**D**) amplitude, across training *sessions*.

For the two training groups, mean training ratio amplitudes for each of the periods collapsed across the eight training sessions are shown in Fig 2.3A and 2.3B. Mean SMR-group ratios exhibited a training-related increase from period 1 (baseline) to period 9 (0.57 and 0.60 respectively), and were highly significant (paired t_{71}=-3.44, $p<0.001$). The AT-group demonstrated elevated training ratios reliably from baseline up to and until period 8, reaching maximal levels during period 4 (0.96 and 1.03, paired t_{77}= 3.96, $p<0.001$), followed by a gradual decline to baseline in the last 2 periods.

As can be seen from Fig 2.3C and 2.3D, the mean session ratio increased from session 1 for both groups, reaching peaks at session 4 (0.569 and 0.644 respectively, paired t_{83}=-3.84, $p<0.001$) for the SMR-group and session 7 (0.988 and 1.03, paired t_{83}=-3.66, $p<0.001$) for the AT-group. It is possible that the rapid drop in SMR-group training ratio in the last 3 sessions reflected a reduction in subjects' motivation following mastery.

Surgical Performance Time

One-way ANOVAs on SMR and AT groups for initial values of *overall* time ($F(1,18)=0.46$, $p=0.51$), *task* time ($F(1,18)=0.54$, $p=0.47$), and *pause* time ($F(1,18)=0.05$, $p=0.83$) values showed no significant differences between groups prior to training. A TIME x GROUP repeated measures ANOVA revealed a single omnibus effect for *task* time ($F(1,18)=8.34$, $p=0.01$), without significant interaction ($F(1,18)=1.69$, $p=0.21$). Fig 2.4A confirms the hypothesized reduction in *overall* performance time for both training groups, with very marginal significance for the AT-group (one tailed $t_9=1.37$, $p=0.10$) and SMR-group (one tailed $t_9=1.51$, $p=0.083$), compared to control (one tailed $t_7=0.21$, $p=0.42$). This is further reflected in reductions in mean *task* time for the SMR-group (8:41 and 6:24, 26%), the AT-group (7:16 and 6:24, 12%) and the control (7:12 and 7:04, 2%), statistically most reliable for the SMR-group ($t_9=2.80$, $p=0.021$), while remaining insignificant for the AT-group ($t_9=1.20$, $p=0.26$) and control ($t_7=0.13$, $p=0.90$), as seen in Fig 2.4B. The mean *pause* time changes altered the least significantly, as depicted in Fig 2.4C, with a reduction for the AT ($t_9=0.71$, $p=0.50$) and control ($t_7=0.37$, $p=0.72$) groups, although interestingly, it increased for the SMR-group (t_9=-0.61, $p=0.56$), albeit unreliably.

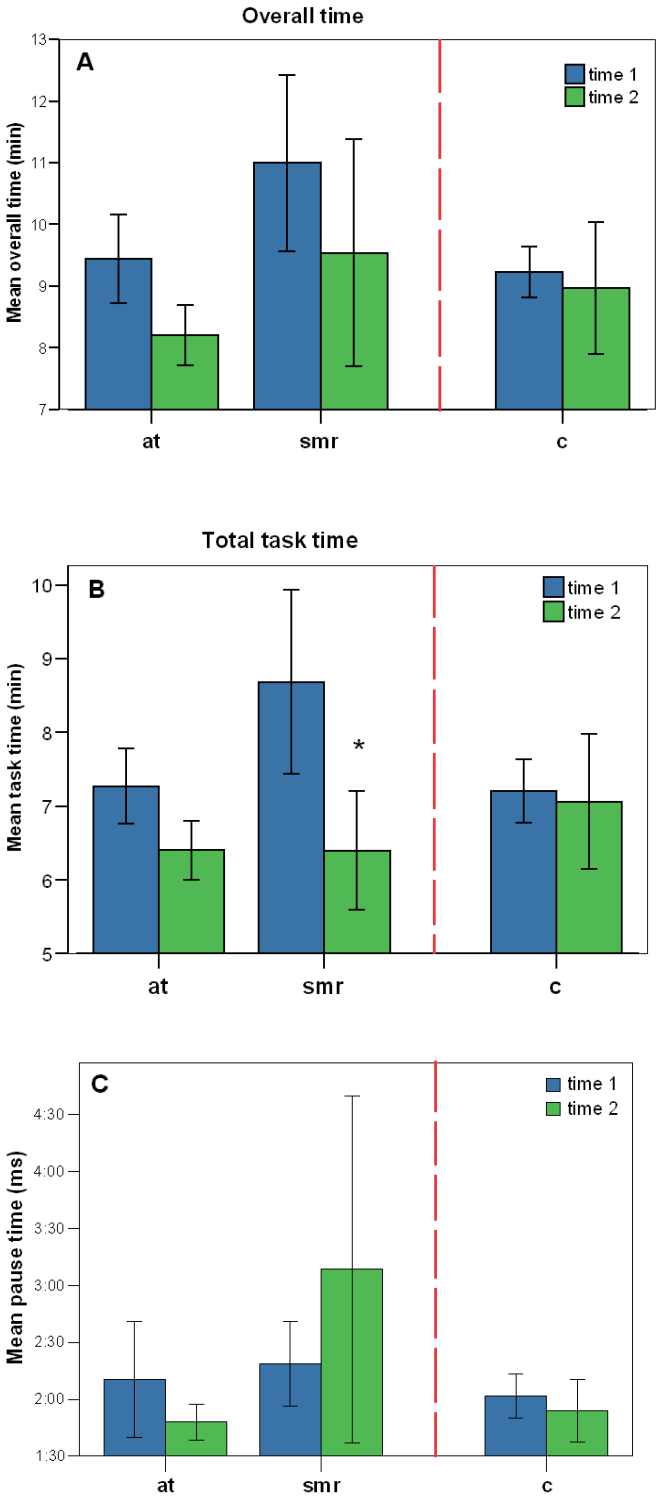

Fig. 2.4 Mean duration for overall performance time (**A**), total task time (**B**) and total pause time (**C**), for AT and SMR experimental groups before (time 1) and after (time 2) training. Wait-list control assessments C are illustrated for qualitative comparison. Asterisks denote a significant paired t-test difference ($p<0.05$) between time 1 and time 2.

Finally, repeated measure ANOVAs on the discrete surgical task times of SMR and AT groups disclosed a single main effect for TIME in the *knot* task ($F(1,18)=5.03$, $p=0.04$), without a significant interaction. However, exploratory paired t-tests disclosed that only the SMR-group exhibited a significant decrease in the duration of the knot task from time 1 to time 2 ($t_9=2.26$, $p=0.05$), as can be seen in Fig 2.5. A similar, although insignificant, trend was found for the knot task in the AT-group ($t_9=0.85$, $p=0.42$), as well as in the sideport task in all groups.

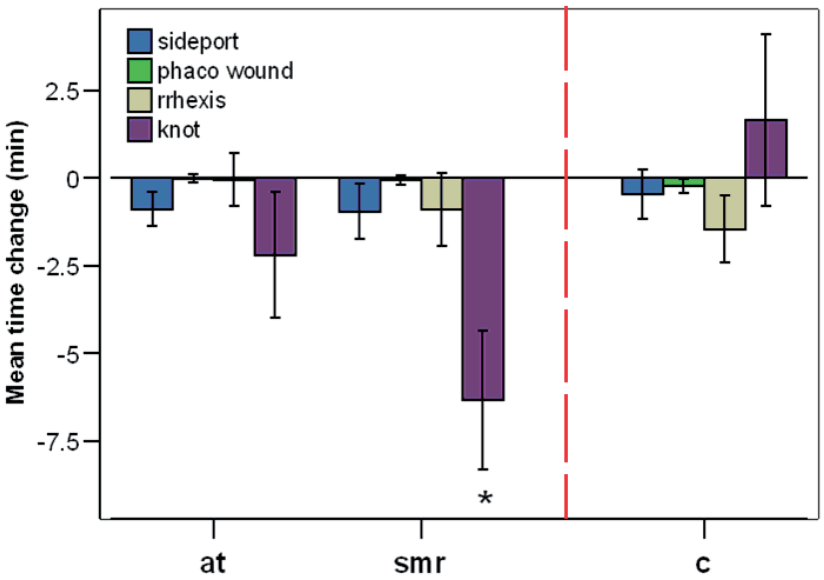

Fig. 2.5 Post-training mean time change for discrete surgical tasks for AT and SMR groups. Wait-list control assessments C are illustrated for qualitative comparison. Asterisks denote a significant difference ($p<0.05$) between time 1 and time 2.

Surgical Technique

The non-parametric Kruskall-Wallis test found no significant differences between the judges' initial mean scores of SMR and AT groups (chi–square=0.01, p=0.940). Wilcoxon tests were conducted on related samples to highlight pre-post technique changes within each protocol. As seen in Fig. 2.6 the AT-group overall score increased as hypothesized from 82.3% to 84.0%, although the difference proved unreliable (z_{10}=-0.92, p=0.358). The SMR-group showed the largest positive change from an overall score of 79.6% to 83.7%, and as such proved significant (z_{10}= -2.1, p=0.038). The least distinction was seen for the control, demonstrating a statistically insignificant (z_8=0.0, n.s.) reduction from 81.8% to 81.6%.

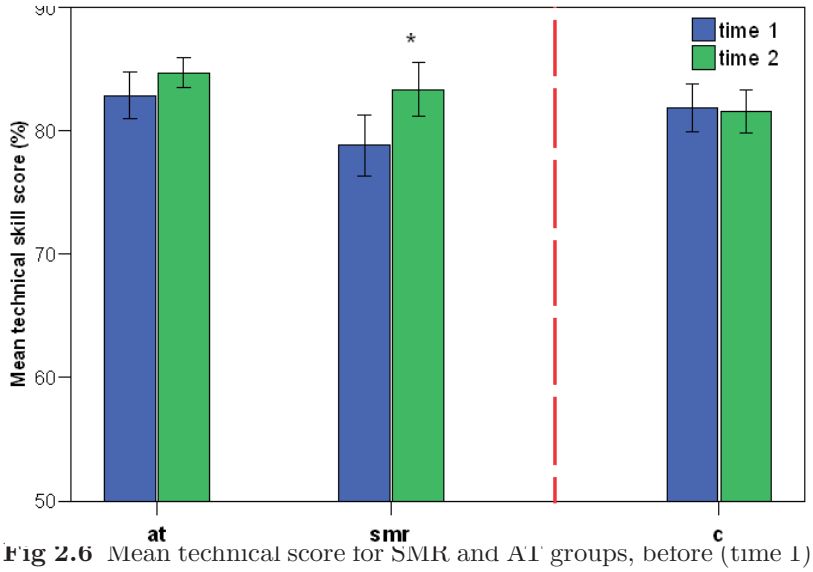

Fig 2.6 Mean technical score for SMR and AT groups, before (time 1) and after (time 2) training. Wait-list control assessments C are illustrated for qualitative comparison. Asterisks denote a significant difference ($p<0.05$) between time 1 and time 2.

Fig 2.7 shows separate percentage score changes for each discrete surgical task. Although the AT protocol exhibits positive changes for all tasks, the considerable standard error on the bars did not yield a statistically robust outcome. However, a marked as well as significant increase of 6 % was established on the knot task for the SMR-group (z_{10}=-2.38, p=0.018). All other changes remained statistically negligible.

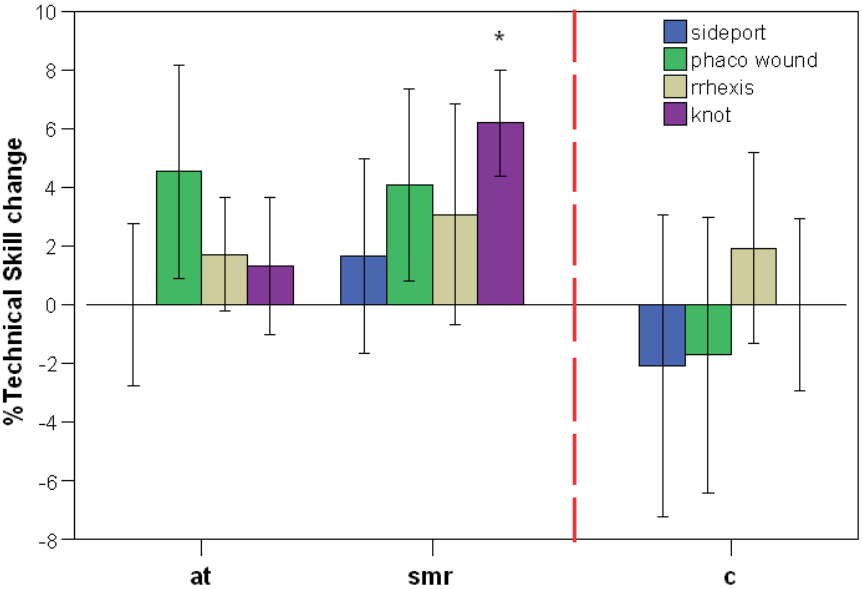

Fig 2.7 Post-training technical score change in discrete surgical tasks for SMR and AT groups. Wait-list control assessments C are illustrated for qualitative comparison. Asterisks denote a significant paired t-test difference ($p<0.05$) between time 1 and time 2.

An inter-rater reliability analysis was conducted on the technique scores of all randomised videos evaluated by the two judges. For the *overall* technique score, the average measure intraclass correlation coefficient equated to ICC_{55}=0.63 and ICC_{19}=0.85, respectively for all videos and SMR-group only videos. Non-parametric analysis yielded a Kendall Concordance Coefficient of W=0.48 and W=0.76, respectively. The correlation between subjective and objective performance measures was also investigated. Positive changes in overall technique were coupled to reductions in total task time for the SMR-group (Spearman rho=-0.70, p=0.036), and add to their validity.

Neurofeedback vs. surgical performance relationships

For the SMR-group, neither significant nor marginally significant correlations were obtained between neurofeedback learning indices and mean change in task time or overall technique. Nevertheless, it was found that successful within-session SMR-training was associated with an increase in total pause time (r=0.584, p=0.077). Incorporating the fact that pause time was additionally negatively correlated with task time (r=-0.251), a significant partial correlation between within-session learning and pause time was obtained (r=0.703, p=0.035), as an effective index of their relationship. Successful within-session AT training correlated significantly with overall technique (r=0.638, p=0.047). In addition, across-session AT training marginally correlated with overall performance time (r=-0.523, one tailed p=0.060).

Lastly, an added association between training ratio and surgical performance was explored; the SMR group was median split into two equal halves of 5 subjects each: the top five subjects with greatest reductions in objective surgical *task* time were labelled *high* improvers**,** whereas the bottom half were labelled *low* improvers**.** Mean training SMR/theta ratios were then computed for each subgroup collapsing the first (1-4) and second half (5-8) of total sessions (Fig 2.8). A strong interaction was obtained highlighting higher mean SMR-Theta ratio in the last 4 sessions for *high* compared to *low* improvers ($F(1,77)=7.4$, $p<0.01$). This falloff in learning ratio in low improvers was further explored by examining absolute EEG bands separately. As shown in Fig 2.8, there was an interaction between Group x Theta amplitude change ($F(1,79)=5.9$, p=0.017) whereby the theta amplitude significantly increased in the low improvers in the second half of sessions (0.60, SD 1.2) compared with a non-significant decrease in high improvers (-0.48, SD 2.5). Of relevance to the falloff in training in low improvers, there was also a significantly greater number of days (8.5 to 4.8, d=0.76) elapsed between the latter half of training

sessions of low versus high improvers (unpaired t_{34}=-2.2, p=0.035); implying that the longer the intersession interval, the poorer the learning in the direction of training goals.

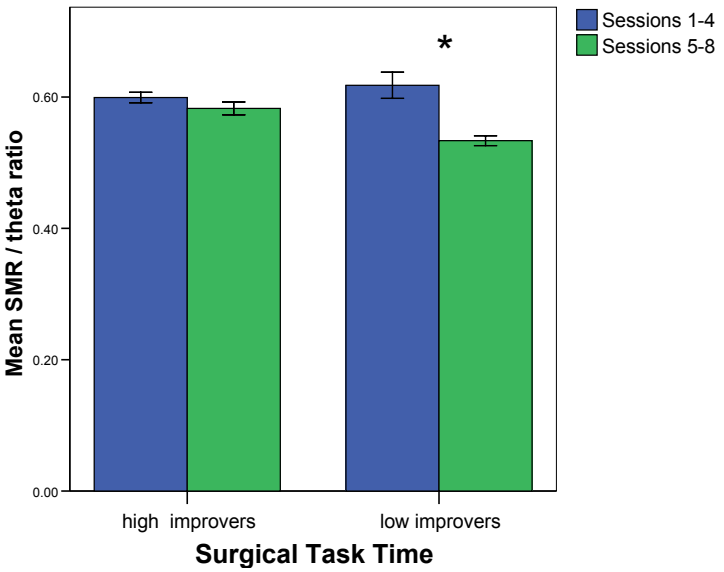

Fig 2.8 SMR-theta ratio for high vs low improvers in *task* time

Similarly, a reliable change was evident for the AT group, when median split according to *technique* (Fig 2.9). *High* improvers increased their training ratio across the first 4 sessions compared to last 4 sessions considerably more than *low* improvers (interaction F(1,96)=-5.2, p=0.025).

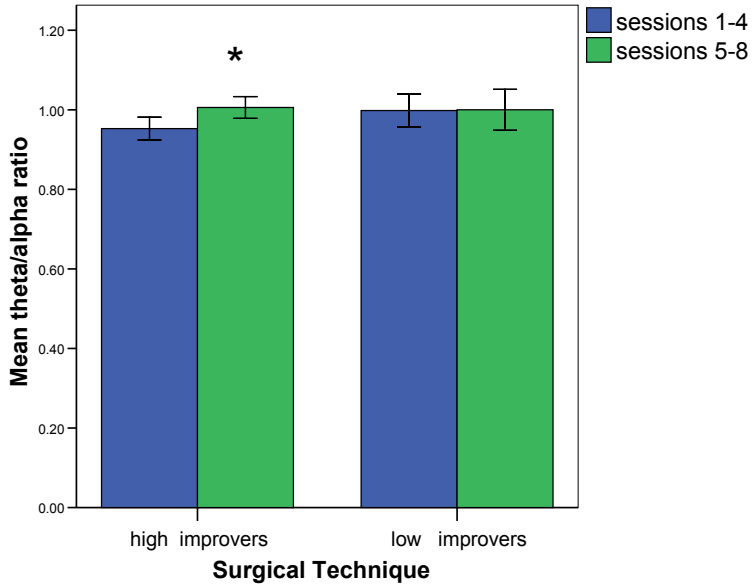

Fig 2.9 Theta/alpha ratio for high vs low improvers in *technique* score

Profile of Mood States (POMS)

Group	Variables	Time 1		Time 2	
		Mean	SD	Mean	SD
SMR	Tension	-6.0	6.3	-8.9	5.6
n=10	Depression	3.6	11.3	1.1	3.3
	Anger	-2.3	6.6	-3.0	4.5
	Vigor	14.4	7.5	13.9	6.9
	Fatigue	4.3	4.3	4.4	4.9
	Confusion	-6.6	7.9	-8.9	6.4
	TOT	7.4	22.7	-1.3	17.6
AT	Tension	-6.4	4.6	-6.0	7.3
n=10	Depression	0.6	4.2	0.0	6.3
	Anger	-5.6	5.2	-4.0	6.0
	Vigor	16.1	7.1	16.3	5.2
	Fatigue	3.9	5.2	3.4	5.4
	Confusion	-9.3	5.6	-7.3	4.6
	TOT	-0.8	12.9	2.4	22.9
control	Tension	-4.0	7.0	-4.6	6.4
n=8	Depression	1.9	9.6	4.9	10.4
	Anger	-1.6	4.6	-0.9	6.6
	Vigor	11.6	8.2	13.0	8.0
	Fatigue	3.1	7.4	3.6	4.9
	Confusion	-4.6	6.1	-6.0	6.7
	TOT	6.4	25.4	10.0	22.8

Table 2. Means and standard deviations of all POMS scores in each experimental condition, before and after training.

One-way ANOVAs on all POMS variables showed no initial differences between groups. Table 2 and Fig. 2.10 show that the expected trends in training groups were only confirmed for the SMR-group, which showed reductions in scores on all but one (fatigue) POMS subscale, reflecting a total score change (7.4 and -1.3) in the direction of more 'positive' mood. The largest subscale difference appeared for tension (-6 and -8.9). The AT-group, in spite of very minor reductions in fatigue and depression, showed a small increase in total score (-0.8 and 2.4) in the direction of more 'negative' mood change. A similar total trend featured in the control group. However, because of the large variance and small group size none of the changes reached paired t-test significance.

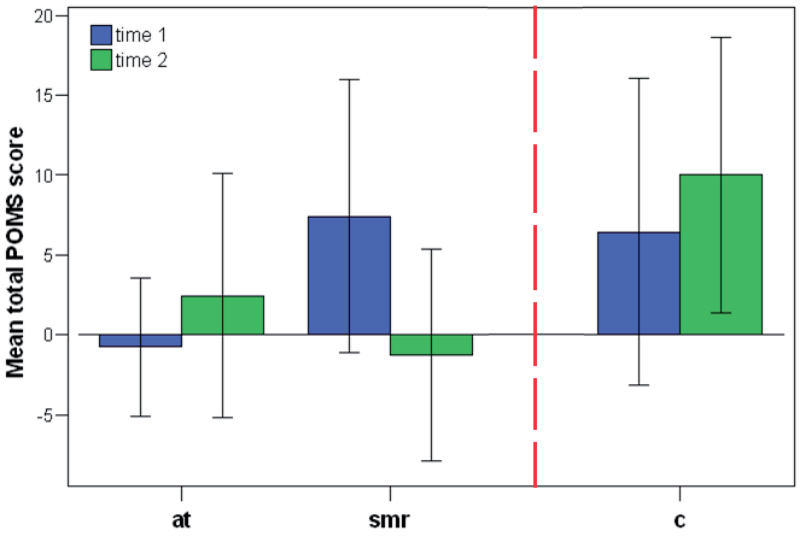

Fig 2.10 Mean POMS scores for each for SMR and AT groups, before (time 1) and after (time 2) training. Wait-list control assessments C are illustrated for qualitative comparison.

Spielberger's State Anxiety Inventory

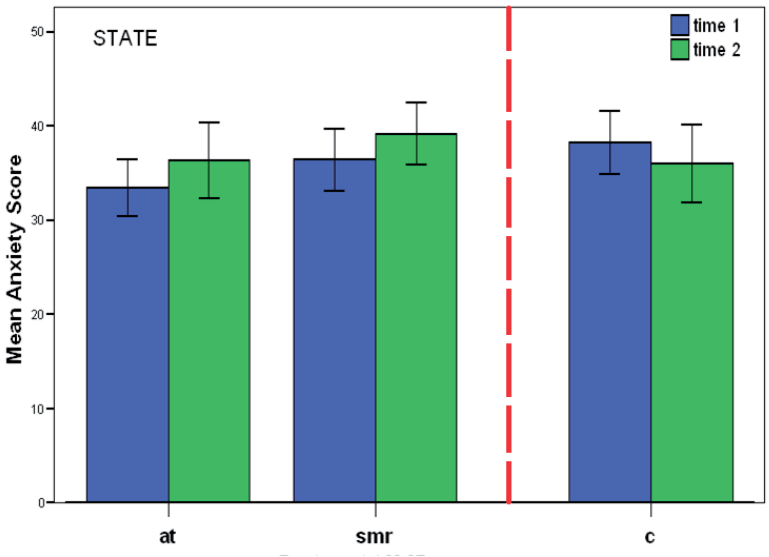

Fig 2.11. Mean *state* anxiety for SMR and AT groups, before (time 1) and after (time 2) training. Wait-list control assessments C are illustrated for qualitative comparison.

No significant differences were detected for either state or trait variables between groups at time 1. Fig 2.11 shows state anxiety increased at time 2 for SMR (36.4 to 39.1) and AT (33.4 to 36.3) groups while on the other hand it decreased for control (38.3 to 36.0) assessments. As seen in Fig 2.12, trait anxiety decreased for both SMR (41.9 to 37.4, 11%) and control (41.6 to 39.1, 6%) assessments, remaining relatively unaffected for AT (36.4 to 37.1, up 2%).

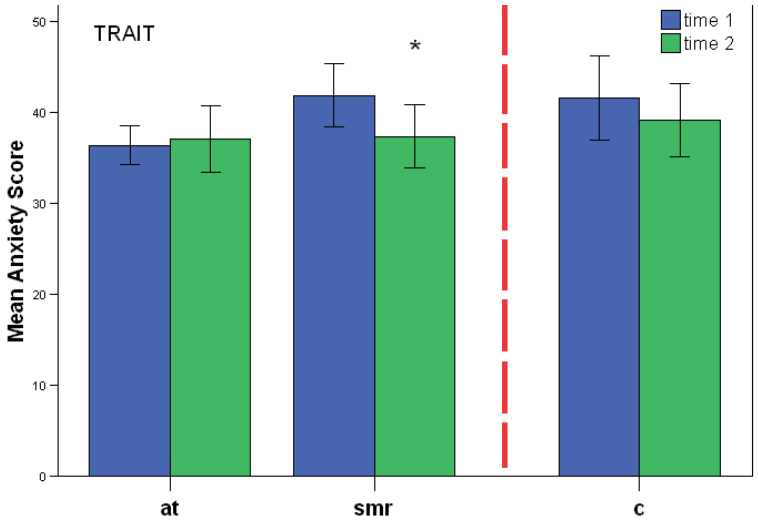

Fig 2.12 Mean *trait* anxiety for SMR and AT groups, before (time 1) and after (time 2) training. Wait-list control assessments C are illustrated for qualitative comparison.

Related sample Wilcoxon tests on all groups revealed one statistically significant change: the reduction in trait anxiety for the SMR group (z_8=-2.38, p=0.017) compared to control. The relation between anxiety score changes and neurofeedback training was additionally investigated. As seen in Fig 2.13, two reasonably reliable effects were discovered: a correlation between *state* anxiety change and AT within-session learning (r=-0.66, p=0.053), and more importantly an interaction of high vs low improvers in *trait* anxiety and SMR training ratio (F (1,86)=3.87, p=0.052).

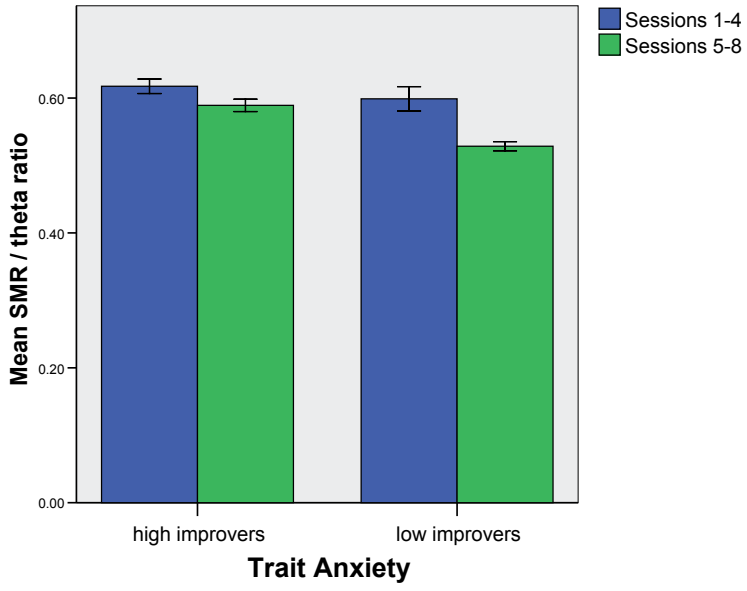

Fig 2.13 SMR ratio for high vs low improvers in *trait* anxiety

Discussion

Evidence of voluntary EEG self-regulation, firstly for the SMR protocol, is supported by mean within session increases in SMR and concomitant decreases in theta activity, and a mean between session increase in the SMR/theta ratio across five sessions, followed by a decline to baseline (Fig 2.3). On average, alpha/theta training showed within session increases in the theta-alpha ratio (Egner et al. 2002), which remained significant up until the 24th minute. However, there was a tailing off in the last 5 minutes, somewhat unexpectedly and out of line with previous training outcomes, possibly resulting from the relatively long session duration, which exceeded the conventional 15 minutes. Notably, there was a significant correlation in theta-alpha ratio between sessions, an encouraging result not achieved in our previous studies (Egner et al. 2002).

To the best of our knowledge, the behavioural data are the first to suggest that neurofeedback training may be utilised to improve micro-surgical performance, as denoted by relative improvements in performance and task time, whilst enhancing technique as compared to wait-list control assessments. Pre-to-post exploratory analyses of surgeons participating in SMR training revealed significantly lower overall task times by approx. 25% (Fig 2.4), while a concomitant enhancement in technique was observed by approx. 5% (Fig 2.6). The increase in pause time for this group was not hypothesised, and although statistically insignificant, correlated reliably with a decrease in overall performance time as well as task time. Hence, the subjects showing highest improvements in task speed also displayed increases in preparation time during the same performance. Interestingly, the explanation for this result could be argued in two ways: either it was due to changes related to strategy, or it owes a causal relation to protocol-specific effects. When we consider that the parallel yet contrasting AT and control protocol findings did not reveal explicit changes in pause time, it is tempting to ascribe the cause to SMR neurofeedback. The reliability of the effects with this protocol is strengthened further by the finding that those participants who showed the greater improvement in time on task were also those who showed increased maintenance of the SMR/theta ratio (Fig 2.8) as well as a lower number of days between neurofeedback training sessions. Another possibility may have been a loss of motivation or interest in *low* improvers towards the second half of neurofeedback training. Nonetheless, the first and second interpretations are not necessarily exclusive of each other, and might act in combination. Hence, a congruent account would argue that protocol-specific effects in some way 'facilitated' a change to occur in strategy, by inducing a relaxed re-centring process during pauses followed by stronger focus

throughout task time. Substantial evidence of changes in the pre-performance mood levels for this group, in anxiety and tension for instance (Fig 2.10 and 2.12), hint at the feasibility of such a mechanism. Interestingly, although raised state anxiety levels in both training groups might refer to increased pressure preceding the final performance, exploratory analyses indicated that only the SMR group exhibited significant reductions of trait anxiety levels, of circa 10% (Fig 2.12), which were closely related to training efficacy (Fig 2.13). Seeing as less time is spent on task and therefore in direct contact with the eye itself, its exposure to mechanical stresses is reduced, and this could noticeably improve operation recovery. In practice, within-group analyses on the SMR group revealed that this is reflected by considerable improvement in speed and technique on the knot task (Fig 2.5 and 2.7), which surgeons generally took longest to complete and seemed to experience most difficulty with. Our results thus remain in line with previous research on trained enhancement of SMR activity as a method for reducing impulsiveness/ hyperactivity (Lubar & Shouse 1976), as well as for enhancing attention more generally (Egner & Gruzelier 2001). Moreover, they are also compatible with recent reports that elevated SMR/sigma activity predicts performance improvements on procedural motor tasks and may be related to consolidation of motor learning following sleep (Fogel & Smith 2006). In light of the previously cited studies linking SMR, sleep spindle activity, and synaptic plasticity, it is possible that daytime SMR neurofeedback (depending on its sequence relative to the surgical training schedule) may have similarly aided the priming as well as the preservation of new synaptic connections before they were consolidated during the night's sleep. This would be in line with reports that motor sequence learning increases sleep spindles in post-training sleep (Morin et al. 2008) and that sleep spindle (13-15 Hz) activity correlates with sleep-dependent improvement in visuomotor performance (Tamaki et al. 2008).

Notwithstanding, the SMR-Theta protocol also required the suppression of theta (4-7 Hz) amplitudes, whose training reduction while significant for the group as a whole, in later sessions became differentially elevated in the low improvers. Decrease in cortical theta power has been reported during activation of the attentional alerting network (Fan et al. 2007), found to predict better reaction time performance (Besserve et al. 2008a), and interpreted as a stronger inhibition of long-term memory networks aiding the processing of external stimuli. Moreover, desynchronisation of cortical slow waves, which include the theta range, is an indicator of increased cortical activation, elicited for instance by stimulation of the cholinergic or noradrenergic systems (Dringenberg &

Vanderwolf 1998). An attractive and tentative explanation might combine the latter finding with the large body of evidence that pharmacological activation of these neuromodulatory systems leads to robust enhancement of LTP and practice-dependent motor learning (Ziemann et al. 2006).

On the other hand, the same distinctions that gave salience to the SMR-group results, weaken the impression of the AT-group findings, mainly because of their qualitative similarity in trend to the control assessments for all three surgical time measures: overall time, task time and pause time, reaching marginal significance for overall time change. Nonetheless, significant associations between training ratio and improvement in surgical technique, by exploratory correlation and median-split ANOVA analyses, suggest a likely connection between them (Fig 2.9). An added finding, consistent with our recent studies, is that within-session training significantly correlated with changes in pre-performance state anxiety. It should also be noted that average AT sessions showed a gradual decline in the training ratio after 10 minutes or so, and could well be regarded as unrepresentative of optimal AT training (Egner et al. 2002).

Of the hypothesized attentional network effects of the SMR and AT protocols, expected efficiency increases in alerting were confirmed for both training groups, although these were insignificant and qualitatively mirrored the effects of the control assessments; likewise for SMR and control reductions in conflict efficiency. The most significant change obtained was a reduction in orienting for the SMR-group. It should be noted that a negligible reduction featured in the control group and the absence of a TIME x GROUP interaction suggests this result should be interpreted with caution. Nevertheless there is the possibility that SMR enhancement of more 'focussed' attention differentially impacted on this network, perhaps via the reputed trade-off linking cognitively driven top-down (focus) and stimulus driven bottom-up (orienting) processes (Mayer et al. 2004).

One major methodological limitation of the study concerns the strength of the control protocol and the wait-list design, as subjects used for the control and training protocol were the same. In other words, the post-assessments of the control group subjects were also the pre-assessments of the neurofeedback group subjects. Hence, a repeated measures ANOVA on all groups was not performed given the lack of independent observation between experimental conditions (a mixture of the same as well as different subjects between experimental conditions). This has primarily had the effect of precluding quantitative statistical analyses between all three protocol groups, as well as leaving only qualitative comparisons with the control assessments possible. With regard to

the issue of possible practice effects the training change was analysed strictly between back-to-back assessments (2 and 3), so all differences occurring during the control period were discounted by default. Meanwhile, surplus analyses for changes between first and final assessments (1 and 3) on all variables did not produce any disparate conclusions. Lastly, qualitative test-retest interval times indicated comparable if not greater elapsed time among control compared to training assessments, and substantially weaken the argument for effects owing to time.

The limited statistical findings of the study should also be acknowledged. Firstly, the total inter-rater reliability of 0.64 is not high enough to establish an explicit conclusion regarding effects on technique for all 3 groups. In contrast, the one significant effect, obtained for the SMR protocol, demonstrated a good reliability of 0.84, indicating a clearly positive effect for this group. Secondly, given the small group sizes as well as fluctuating workload and biorhythm of National Health Service doctors, it is difficult to rule out variability in test-retest consistency or control for surgical experience gain outside, yet during the study. In this respect, ANOVAs on surgical times yielded no interactions between experimental protocols. These could be clarified in future with independent control and experimental groups consisting of greater numbers of subjects. In addition, while comparing two intervention conditions to a no-intervention control group, the issue of therapist contact or 'placebo' effects may be raised. However, in light of the qualitatively different impact of the two interventions on performance, it seems unlikely that these effects should account entirely for the observed outcome. On the other hand, important variability occurred in training session regularity between subjects, and call into question optimal group training efficacies, which may have potentially produced greater improvements.

In conclusion, this is the first study to report preliminary evidence for performance enhancement in microsurgical procedure by means of EEG biofeedback training. More specifically, uncorrected pre-to-post comparisons suggest that SMR/theta training is associated with the greatest improvements in surgical technique, as well as an average 25% reduction in contact time with the eye, which may thereby serve to alleviate post-operation recovery. In light of the fact that no statistically significant interaction effects were either present between the SMR and AT groups, nor possible to evaluate quantitatively with respect to the control group, the present findings may be regarded as exploratory, and their replication is therefore warranted in a larger study with independent experimental and control groups.

Study 2: Direct effects of neurofeedback on motor cortical plasticity

Introduction

Most NFB involves multiple sessions repeated on at least a weekly basis, and whose effects generally accumulate over time, reputedly as a result of neuroplasticity (for peak performance about 10 sessions, for clinical application > 30, (Hanslmayr et al. 2005; Lévesque et al. 2006; Doehnert et al. 2008)). Over the years numerous studies have demonstrated behavioural as well as neurophysiological alteration after *long-term* NFB training, such as improvement in attention and cognitive performance and their accompanying EEG/ERP changes. (Egner & Gruzelier 2004; Gruzelier et al. 2006). However, to date and to the best of the author's knowledge, no work exists or provides evidence for a causal and more direct temporal relationship between self-regulation of brain activity and concomitant short-term change in synaptic plasticity, or its mechanisms. This could possibly be due to the belief that the modulatory effect(s) that follow a discrete session of neurofeedback are too fine to be detected immediately thereafter, or alternatively, occur at some later stage, for example during sleep. However as is common for all learning paradigms, NFB training occurs within a temporally distinct period or 'session', and if it is ever to claim the grail of inducing lasting neuroplastic changes (and thus be taken seriously as a non-invasive tool for brain stimulation such as rTMS and tDCS (Wagner et al. 2007), a stronger association is clearly warranted between a single training session and the putative plasticity, if any, it engenders.

Nowadays, the study of neuroplasticity in the intact (and awake) human brain has been made possible with the advent of transcranial magnetic stimulation (TMS). Here, evidence of neuroplastic change may be demonstrated noninvasively by an altered neurotransmission of the corticomotor projection to the hand, a method that has been physiologically validated by invasive recordings of human and animal corticospinal nerve impulses (Lazzaro et al. 2008). Although neuroplasticity appears to be functionally active through diverse cellular processes in the central nervous system (Nelson & Turrigiano 2008), in TMS methodology it is operationally defined as a significant and lasting change in the motor evoked potential (MEP), whose amplitude is representative of the strength of neurotransmission from motor cortex to muscle, evoked by a magnetic pulse. A growing body of evidence (Lazzaro et al. 2008) indicates that MEPs from a single TMS pulse best reflect the overall responsiveness of

the corticospinal pathway, or corticospinal excitability (CSE), whereas those originating from paired pulses (with interstimulus intervals of milliseconds) enable the discrimination of intracortical mechanisms, such as short intracortical inhibition (SICI) and facilitation (ICF), which are modulated by transynaptic neurotransmission (Ziemann 2004).

Our initial hypothesis was that NFB-induced alpha (8-12 Hz) rhythm desynchronisation, generally considered a marker of cortical activation (Neuper, Wörtz, & Pfurtscheller, 2006), would enhance both corticospinal excitability and intracortical facilitation, while effecting a reduction in intracortical inhibition. Conversely, low beta ("SMR", 12-15 Hz) synchronisation, which has been associated with cortical deactivation (Oishi et al. 2007), sleep spindles (Sterman 1996) and GABAergic function (Jensen, Goel, et al. 2005), was expected to induce an opposite corticospinal and intracortical pattern. Although endogenous oscillations have thus far been implicated in many 'ongoing' functions such as binding and attention (Schroeder & Lakatos 2009), explicit evidence is still scarce on their role, if any, in neuroplasticity (Axmacher et al. 2006; Axmacher, Mormann, Fernández, Elger, & Fell, 2006). We postulated that, in line with previous stimulation research, the more pronounced as well as persistent the oscillatory patterns would prove during NFB, the more substantial and long-lasting (plastic) would turn out to be their after-effects.

Materials and Methods

Participants

24 healthy participants (12 women, age: 31 $\pm$ 5 years), all with normal or corrected-to-normal visual acuity participated in the experiment. All were recruited via the participants' database of the Department of Psychology of University London and were *naive* to the neurofeedback protocols used in this study. Experimental procedures were approved by the local ethics committee and in accordance with the Declaration of Helsinki.

Study design

Subjects were randomly allocated to 2 protocol groups for a single 30-min NFB session: alpha suppression ($n = 12$) or low beta enhancement ($n = 12$). For the purpose of testing hypotheses concerning protocol-specific effects on target EEG frequency components, subjects underwent resting EEG recordings for 3-min

immediately before and after their NFB training session. In order to test the hypotheses concerning the protocol-specific effects on corticospinal excitability (CSE), TMS motor evoked potential (MEP) responses were collected before (pre) and twice after (post 1, post 2) each NFB session, consecutively at right and left hand muscles.

Neurofeedback apparatus and EEG recording

EEG signals were recorded using a NeXus-10 DC-coupled EEG amplifier using a 24-bit A-D converter (MindMedia, the Netherlands), and visual NFB training was carried out with the accompanying Biotrace+ software interface on an Intel DualCore computer with a 15" screen. The EEG used for feedback was sampled at 256 Hz with Ag/Cl electrodes at the right FDI cortical representation/'hot spot' (approx. C3) referenced to the contralateral mastoid. The scalp area was carefully scrubbed with NuPrep abrasive gel, followed by application of Ten20 electrode paste. The ground electrode was placed on the right arm. The signal was IIR bandpass filtered to extract alpha (8-12 Hz) and low beta (12-15) amplitudes (μV peak-peak) respectively with an epoch size of 0.5 seconds. In the same way, EEG was co-registered at the left FDI representation (approx. C4) referenced to its contralateral mastoid. IIR digital filtered (Butterworth 3rd order) EEG amplitude data of each band (delta (1-4 Hz), theta (4-7Hz), alpha (8-12 Hz), low beta (12-15 Hz), beta (15-25 Hz), high beta (25-40 Hz), low gamma (40-60 Hz), and high gamma (60-120 Hz) were then exported at 32 samples/second and voltage-threshold artifacted for ocular, head movement and EMG contamination. Outlying data points were rejected at >3 standard deviations using histogram analysis. Moreover, the Fast Fourier Transform (FFT) of raw (256 samples/sec) data was used in the calculation of *mean frequency* for each band. Averages of all measures were computed offline for 3 minute epochs each defined as a training 'period'. Resting baselines consisted of feedback-free pre and post neurofeedback EEG measurement in the eyes open condition. Periods 1-10 consisted of neurofeedback training.

Neurofeedback training procedures

The ALPHA group aimed to suppress absolute alpha (8-12 Hz) amplitude while the BETA group aimed to elevate absolute low beta amplitude (12-15 Hz). Accordingly, reward thresholds were set to be either 30% of the time above or below the initial alpha or low beta mean amplitude (baseline) respectively. The first baseline was recorded during a 3-min eyes open EEG recording at rest

immediately before the start of feedback, and the second 3-min immediately after the end of training. Subjects were given no explicit verbal instructions and were told to be guided by the feedback process instead. This was achieved via a collection of different visual displays/games whose control reflected the modulation of the trained EEG amplitude. Both protocols employed the same series of five Biotrace+ software games, which were played in a random order for approximately 6 minutes each (mandala, space invaders, mazeman, bugz, puzzles). In the case of the low beta down protocol a supplementary inhibit was coupled to excess mastoid and EMG activity to ensure low beta reward was not artifact driven.

Neurofeedback data analyses

The degree of NFB-mediated EEG change for each subject was estimated by the *ratio* of EEG amplitudes between the neurofeedback EEG and the initial baseline EEG. This was calculated for each of the 10 training periods, and designated as change in the *training EEG*. Additionally, any pre-to-post change in the resting EEG following training was expressed by the ratio of the second divided by the first mean baseline amplitude, and designated as change in the *resting EEG*.

Transcranial magnetic stimulation: procedure and apparatus

Fig 3.1 Scheme of the study. R FDI = trained left hemisphere, L FDI = untrained right hemisphere.

The course of the experiment is shown in Fig 3.1, which was used to test the impact of NFB training on corticomotor measures of corticospinal excitability (CSE), short intracortical inhibition (SICI), and intracortical facilitation (ICF). TMS parameters (CSE, SICI, and ICF) were measured before (pre) and twice after NFB (post 1 and post 2). In random order, 78 TMS responses were measured, which required approximately 6 minutes per hemisphere. We evaluated the TMS parameters of both hemispheres, first left (trained) and then right (untrained) hemisphere, to investigate hemispheric effects of NFB.

The post 1 measurement was performed circa 3-15 minutes after NFB training, and post 2 after 15-27 minutes. Well established standard TMS paradigms were used to measure the corticospinal and intracortical parameters (Lazzaro et al. 2008). All measurements were carried out with two monophasic Magstim 200 magnetic stimulators (Magstim, Whitland, UK), which were connected with a "Y-cable" to a 70 mm figure-of-eight coil. We determined the 'hot spot' of the first dorsal interosseous muscles (FDI) for each hemisphere separately. The coil was placed flat on the skull with the handle pointing backward and rotated about 45° away from the midline. Resting motor threshold (RMT) intensity was defined as the lowest stimulator output intensity capable of inducing motor evoked potentials (MEPs) of at least 50 µV peak-to-peak amplitude in the FDI muscle in at least half of 10 trials. Active motor threshold (AMT) was defined as the intensity needed to evoke an MEP of about 200 mV during a 5-10% maximum voluntary contraction. Corticospinal excitability (CSE) was quantified by the amplitude of the motor evoked potential (MEP) elicited by a single test TMS pulse. The test pulse intensity was set to yield an average MEP amplitude of 1 mV at baseline (pre), and was kept constant throughout the experiment. Short latency intracortical inhibition and intracortical facilitation (SICI and ICF) were evaluated using the paired pulse protocol developed by Kujirai et al (Kujirai et al. 1993). In random trials the test pulse was preceded by a sub-threshold conditioning pulse (80% AMT) with an interstimulus interval (ISI) of 2, 3, 10 or 12 ms. The test response was suppressed (SICI) at ISI = 3ms; whereas facilitation occurred at ISI = 10 and 12ms (ICF = mean of both time points). A run consisted of 78 stimuli given at approximately 0.25 Hz. 48 paired-pulse (12 for each ISI) and 30 single-pulse MEPs were recorded. Single-pulse MEP amplitudes were normalised as post 1 divided by pre , and post 2 divided by pre, respectively. For SICI and ICF the amplitude of the conditioned response was expressed as a percent of the amplitude of the test response alone. Ratios < 1 indicate inhibition, whereas ratios > 1 indicate facilitation.

Electromyographic measures and analysis

Surface electromyographic (EMG) recordings were made using a belly-tendon montage with Ag/AgCl-plated surface electrodes (9 mm diameter). Raw EMG signal was amplified and filtered using Digitimer D150 amplifiers (Digitimer Ltd., Welwyn Garden City, Herts., UK), with a time constant of 3 ms and a low-pass filter of 3 kHz. Signals were recorded via a CED 1401 laboratory interface (Cambridge Electronic Design Ltd., Cambridge, UK) and stored on a PC for later analysis using a sampling rate of 5 kHz.

Statistical analyses

Pre- versus post NFB-training effects were assessed by a GROUP x HEMISPHERE x TIME (2 x 2 x 3) repeated measures ANOVA on the two experimental groups for changes in the TMS measures. Exploratory pre- versus post-training outcome of TMS (MEP, SICI, ICF) and EEG parameters (resting baseline) were then determined with paired t-tests for each protocol group. A correlation analysis was subsequently performed for EEG training/baseline variable change vs. change in TMS parameters. With regards to the weighted least squares (WLS) regression analyses, the reciprocal variances of the EEG time samples of interest were used as each subject's coefficients.

Results

One-Way ANOVAs did not disclose any statistically significant differences ($p<0.05$) between protocol groups neither for age nor baseline measures of EEG band power (delta to high gamma), or TMS measures (RMT, single-pulse MEP, 3 ms SICI, and ICF) in either the trained or untrained hemispheres.

NFB training dynamic

Mean alpha and low beta amplitude during each 3-min period of the neurofeedback training session is depicted in Fig 3.2 A and B, for the ALPHA and BETA groups respectively for each hemisphere. Mean ALPHA-group amplitude for the trained hemisphere exhibited a general decrease from resting baseline (9.08) to period 10 (8.50), with a minimum at 15-18 minutes, or period 6 (7.93, $t_{11}=4.0$, $p=0.002$), in line with training direction, and largely paralleled by the contralateral hemisphere. Paired t-test comparisons of baseline with period means revealed a significant reduction ($p<0.05$) for all periods except periods 2, 8, and 10. For the BETA-group, whose aim on the other hand was to increase low beta, mean amplitude became statistically higher than baseline (5.95) uniquely between 24-27 minutes, or period 9 (6.62, $t_{11}=-2.4$, $p=0.034$). No significant increases were observed in the contralateral hemisphere.

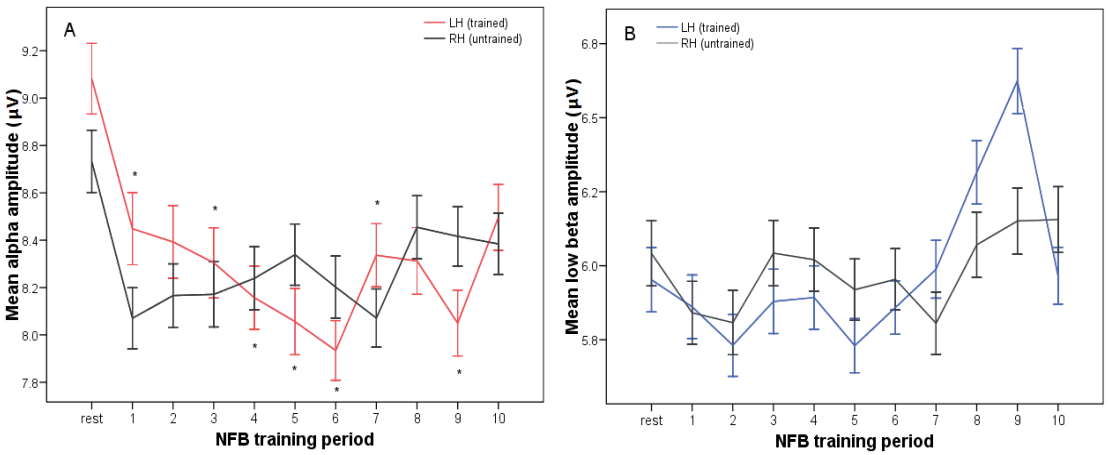

Fig 3.2 Time-course of the mean training EEG amplitudes for **A**) ALPHA and **B**) BETA groups, during a session of neurofeedback. Asterisks denote periods significantly different from baseline. Error bars represent 95 CI.

Across periods, within-subject EEG amplitude correlations between theta, alpha, low beta, and high beta EEG band pairs during training were consistently positive at the $p<0.01$ level, within a range of $0.5 < r < 0.9$. In other words, amplitude increases/decreases in all EEG bands' <25 Hz covaried in parallel with each other. Furthermore, for the ALPHA group, high gamma mean frequency (60-120 Hz) was *inversely* correlated with alpha amplitude during training ($r= -0.25$, $p<0.01$). No significant online associations were detected between EEG bands and direct current (DC) shifts, although the latter exhibited a negative correlation with period number ($r= -0.31$, $p<0.01$) in the ALPHA group.

TMS main effects

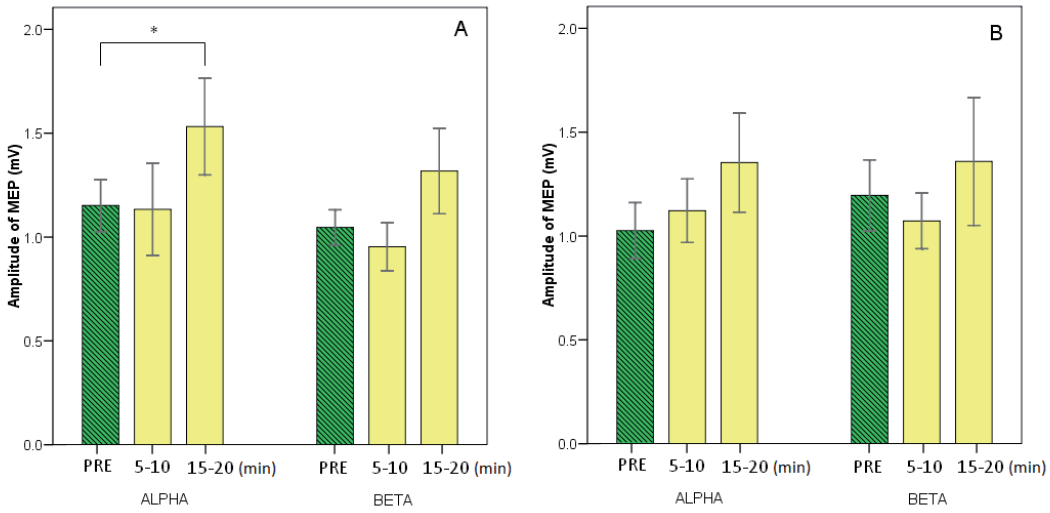

Fig 3.3 Mean corticospinal excitability (CSE) of **A**) trained (left) hemisphere, and **B**) untrained (right) hemisphere following the ALPHA and BETA protocols at times post 1 and 2. Error bars represent SEM.

A GROUP x HEM x TIME (2 x 2 x 3) repeated measures ANOVA revealed a main TIME effect of significance for CSE ($F(2,44) = 7.55$, $p < 0.01$). Furthermore, there was a significant TIME X HEM interaction effect for SICI ($F(2,44) = 4.35$, $p = 0.02$), while no other main or interaction effects proved significant. Post-hoc, exploratory t-tests disclosed no significant pre-post differences for the untrained hemisphere in CSE (Fig 3.3B), SICI (Fig 3.4B) nor ICF. Fig 3.3A depicts the mean effect of alpha suppression NFB on CSE in the trained hemisphere. Here, MEP amplitudes were significantly increased at post 2 compared to pre (130%, t_{11}=-2.6, p=0.025), or circa 20 min after termination of NFB training. For the untrained hemisphere a similar albeit non-significant increase in MEP amplitudes was found post 2 (135%, t_{11}=-1.691, p=0.12). Interestingly, no facilitatory effects were found just after (<10 min) NFB in the trained hemisphere (post 1), while an intermediate enhancement of 115% became manifest at around 10 minutes in the untrained hemisphere (Fig 3.3B, post 1, n.s.). A reliable trained hemisphere within-subject correlation between testing order (pre, post 1, post 2) and MEP amplitude was also observed (r=0.43, p <0.01). As seen in Fig 3.4A, we found a significant and sustained decrease of intracortical inhibition (SICI 3 ms) at post 1 and post 2 uniquely in the trained hemisphere (post 1: 174%, t_{11}=-3.5, p<0.01; post 2: 165%, t_{11}= -2.6, p=0.023). No other intracortical parameters were significantly altered following ALPHA protocol training. As can be seen in Fig. 3.3, no significant differences in CSE were found following low beta enhancement, although an initial decrease followed by increase was seen in both hemispheres at post 1 and post 2. Likewise for the BETA protocol, no significant changes in SICI were observed in the trained (Fig 3.4A) or untrained hemisphere (Fig 3.4B).

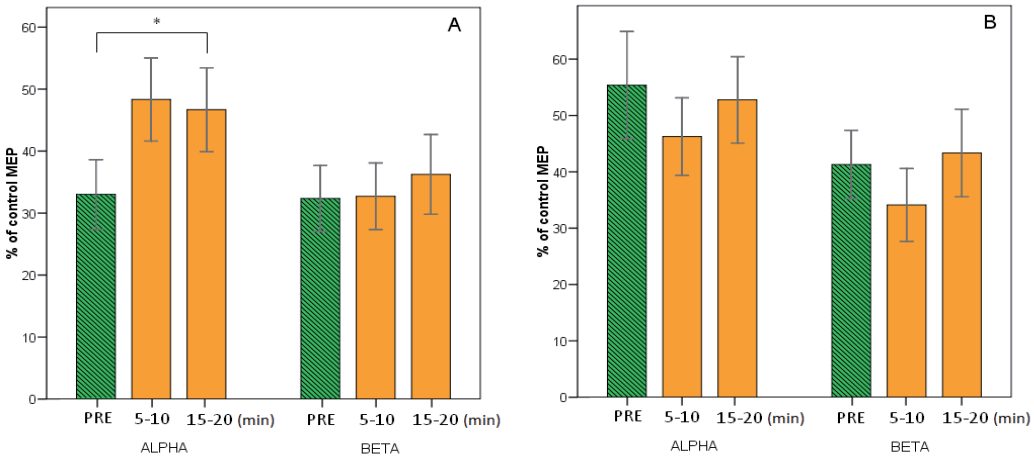

Fig 3.4 Mean short intracortical inhibition (SICI) of **A**) trained (left) hemisphere, and **B**) untrained (right) hemisphere following ALPHA and BETA protocols at times post 1 and 2. Higher values signify lower SICI (disinhibition). Error bars represent SEM.

TMS-EEG relationships

Corticospinal excitability (CSE)

Effective NFB training for each subject was defined by a training coefficient, or the Pearson correlation between the period number (1 to 10) and its corresponding mean EEG amplitude (alpha and low beta amplitude, for ALPHA and BETA groups respectively). This has previously (Gruzelier & Egner 2005) proven a good estimator of the temporal consistency of either an increase or a decrease in the training EEG amplitude from baseline, which can be expressed in the range of -1 (steady decrease) and +1 (steady increase).

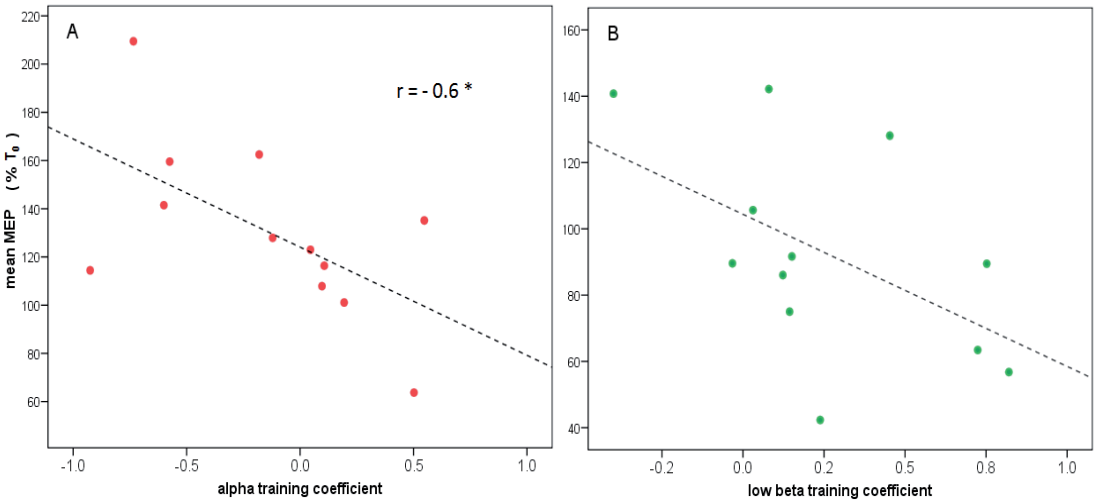

Fig 3.5 Scatter plots of subjects' (n=12) training coefficients *vs* mean MEP change for **A**) ALPHA group at post 2 and **B**) BETA group at post 1

As depicted in Fig 3.5A, a scatter plot of alpha training coefficient versus post 2 MEP amplitude for the ALPHA group revealed a significant negative correlation (r=-0.59, p=0.044), meaning that in general greater temporal consistency of alpha decrease from baseline is associated with greater increase in corticospinal excitability. Moreover, a parallel *positive* correlation was observed between high gamma mean frequency (60-120 Hz) training coefficient and MEP post 2 (r=0.62, p=0.031). No significant correlations were evident at post 1 (r=-0.32, n.s.). For the BETA protocol (Fig 3.5B), the correlation between reliable low beta synchronisation and direction of MEP change was similarly negative at post 1, albeit less robust (r=-0.53, p=0.08; weighted least-squares (WLS) regression r=-0.62, p=0.03). This relationship was absent at post 2 (r=-0.25, n.s.). Regarding the relation between TMS changes and absolute EEG parameters, firstly, no reliable relationships were evident between MEP change and absolute EEG amplitudes in any band, during any period of the

neurofeedback session. However, when the EEG amplitudes were normalised as a percentage of their 3-min baseline value at rest, strong associations appeared, signalling that a change in the EEG was closely coupled to a change in MEP. Fig 3.6 illustrates the Pearson cross-correlation value between the post 2 MEP amplitude (outcome variable) and normalised alpha amplitude of each period (predictor variable) during neurofeedback in the ALPHA group. As anticipated, we observed mainly negative correlations between alpha power and MEP increase, however there was a gradual trend of increasing significance from the beginning of the session that reached a maximum at around the middle of the session, during periods 6 (r=-0.61, p=0.35) and 7 (r=-0.63, p=0.30), or between 15-21 minutes of neurofeedback. Interestingly, period 6 also coincided with the minimum alpha amplitude during training (see Fig 3.2A).

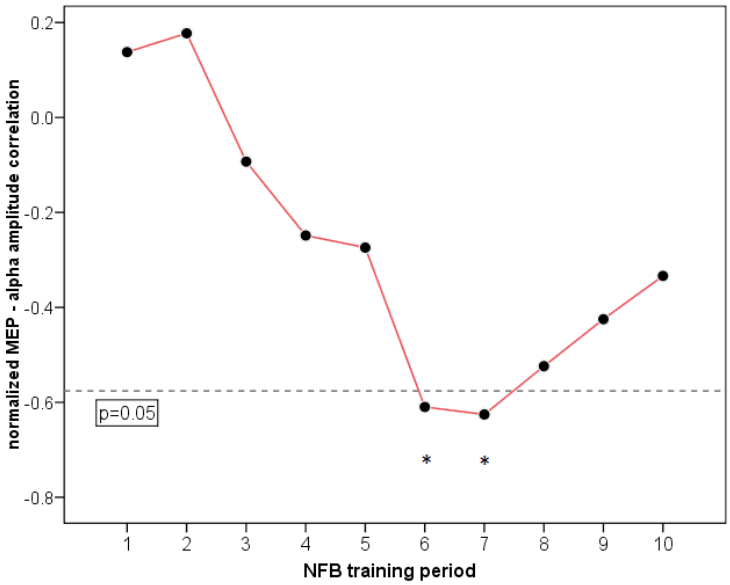

Fig 3.6 Post 2 MEP (%pre) vs. alpha amplitude (%pre) correlations, for all ALPHA-group periods

The EEG amplitude ratio of the post-neurofeedback resting baseline and the pre-baseline proved to be another successful predictor of post 2 MEP change in all bands investigated below *high* beta (delta: r=-0.64, p=0.03; theta: r=-0.7, p=0.012; alpha: r=-0.71, p=0.01; low beta: r=-0.62, p=0.03), suggesting that the more suppressed the slower EEG amplitudes were after NFB training the greater the enhancement of the MEP 20 minutes later. This also appeared to be positively the case for resting change in the high gamma mean frequency (r=0.53, p=0.07). Lastly, during periods 7, 8, 9 correlations remained significantly positive ($r > 0.6$, $p<0.05$) and predicted resting alpha amplitude change from *training* alpha amplitudes.

As seen in Fig 3.7, the overall implication is that a three-way significant association was thus established between core changes in training EEG, resting EEG and corticospinal excitability.

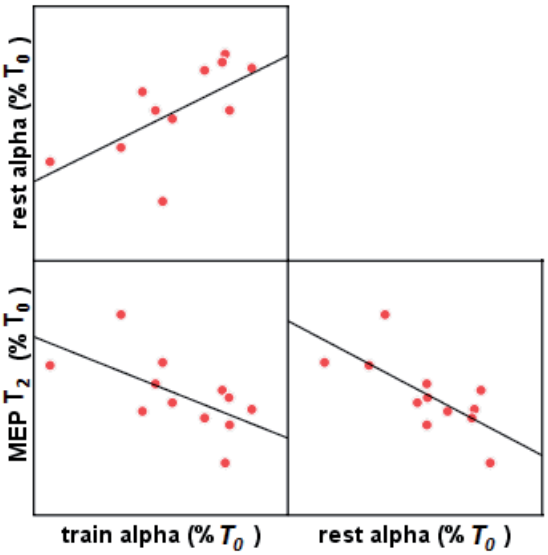

Fig 3.7 Matrix plot of training alpha (period 7 %pre), resting alpha (%pre), MEP (post 2 %pre) amplitudes. All correlations were significant at r > |0.6|, p<0.05

Analogous analyses were performed on the BETA group for relationships between single-pulse MEP and low beta amplitudes, disclosing a significant association similar to that found with ALPHA between resting low beta change and post 1 MEP (WLS r=-0.58, p=0.050) as well as a borderline correlation between training period 6 and post 1 MEP (WLS r=-0.52, p=0.08). Low beta amplitude during period 6 was in turn also tightly correlated with its subsequent change at rest (WLS r=0.67, p=0.02), mirroring closely but less reliably, the three-way relationship reported for the ALPHA group. No significant associations were observed between MEP and the remaining EEG bands in the BETA group (e.g. resting alpha vs MEP post 1: WLS r=-0.17, p=0.60)

SICI / ICF

For the ALPHA group, there was significant positive correlation (r=0.58, p=0.05) between alpha training coefficient and 3ms SICI (%pre) change at post 1, suggesting that it was the weakest performers that had the greatest reductions in SICI. However relatively robust correlations were discovered for the DC training coefficient and SICI post 1 (r=-0.6, p=0.04), SICI post 2 (r=-0.53, p=0.07) and ICF post 2 (r=0.79, p<0.01). Moreover ICF post 2 (but not post 1) change was inversely proportional with SICI at post 1 (r=0.63, p=0.03) and post 2 (r=0.72, p<0.01), suggesting that SICI decreases may

have preceded ICF increases. No significant links were apparent for the BETA group, however marginal negative associations were observed between ICF at post 1 and low beta training coefficient (r=-0.51, p=0.09) and resting low beta amplitude change(r=-0.52, p=0.08). Resting alpha amplitude (in the BETA group) was uncorrelated (r=0.14, p=0.67).

Discussion

In summary, exploratory analyses revealed that sustained neurofeedback-mediated EEG changes in the ALPHA group (Fig. 3.2A) resulted in a reliable (>20 min) overall increase in CSE (130%) (Fig 3.3A) and decrease in SICI (174%) (Fig 3.4A), when compared to the non-significant longer-lasting changes in the underperforming BETA group (Fig. 3.3B and 3.4B). On the other hand, these results are tempered by the absence of a reliable interaction for a GROUP x TIME effect, indicating that the hypothesis of a significant difference between experimental groups cannot be confidently asserted. Nevertheless, correlation analyses revealed robust relationships between the historical activity of certain brain rhythms during neurofeedback and the resultant change in corticospinal excitability(15). Specifically during NFB, alpha (8-12 Hz) desynchronisation (Fig 3.5A) coupled with increased mean frequencies of high gamma rhythms (60-120 Hz) was tightly correlated with LTP-like (>20 min) enhancement of single-pulse MEPs. In contrast, NFB low beta (12-15 Hz) synchronisation was correlated with short term (>5 min) reductions of CSE (Fig 3.5B). Thirdly, in both groups, *resting* EEG amplitude change was predicted by neurofeedback EEG, and was a *predictor of* later MEP amplitudes (Fig 3.7).

In this experiment, the longer-term neuroplastic effects following alpha desynchronisation are unlikely to be consequences of basic changes in psychological arousal after NFB, as the within-subject MEP data denote a significant positive correlation between amplitude and elapsed time following training, while the reverse would be otherwise expected (the BETA group did not demonstrate similar changes, reducing the likelihood of a placebo effect). Bearing in mind that neuroplastic induction may have begun during NFB (Fig 3.6), such a progressive dynamic could be suggestive of a time course involving cellular cascades known to occur during early LTP (Cooke & Bliss 2006). In contrast, *short term potentiation* amplitudes are markedly extinguished by 15-20 min (Schulz & Fitzgibbons 1997). A reduction in alpha band power has commonly been found to be associated with increased cortical excitability (Sauseng et al. 2009), cortical metabolism (Oishi et al. 2007), attention (Fries

et al. 2008) and behavioural activation (Rougeul-Buser & Buser 1997). In this study a negative correlation between low-end frequencies (esp. alpha) and high gamma mean frequencies during NFB was also detected, as well as a positive correlation between the latter and single-pulse MEP increase. It is supported by recent reports linking high frequency oscillations (HFO) or higher gamma activity with learning (Ponomarenko et al. 2008) and attention (Fries et al. 2008), as well as with increased BOLD activity (Niessing et al. 2005), neuronal depolarisation and firing rate (Grenier et al. 2001). Moreover, the ALPHA group reduction in intracortical inhibition (SICI) at post 1 and 2 may be attributed to a decrease in cortical GABAergic transmission (Hallett 2007). This could possibly be the system's intrinsic reaction in order to further facilitate plasticity, as previous reports have found an antagonistic relationship between inhibitory and excitatory transmission on motor plasticity and LTP (Bütefisch et al. 2000; Komaki et al. 2007). At present, the release of endogenous neuromodulators cannot be confirmed as an interacting mechanism for the observed effects. One candidate may be noradrenaline (NA), which is released during attentive behaviour (Berridge & Waterhouse 2003) and has been reported to enhance LTP (Harley 1987), desynchronise alpha rhythms (Rougeul-Buser & Buser 1997), and both increase CSE and decrease SICI concomitantly (Ziemann 2004).

As low beta entrainment was suboptimal (Fig 3.2B), it is possible that it was associated with an inappropriate training approach in some subjects which was perhaps more desynchronising than synchronising, hence the increased corticospinal excitability observed later on. This is supported by the negative correlations between low beta training and MEP (Fig 3.5B), which remain in line with findings that low beta synchronisation is associated with motor-cortical deactivation (Oishi et al. 2007) and inhibition (Zhang et al. 2008).

It is tempting to compare the average effect size(s) in this study with those of existing noninvasive brain stimulation (NIBS) protocols used to induce neuroplasticity. Repetitive magnetic (Ziemann et al. 2008) and direct current (Nitsche & Paulus 2001) stimulation investigations report average CSE and SICI changes of around 150%, which is comparable to the range we observed following alpha desynchronisation. Remarkably, this may indicate that regardless of whether endogenous or exogenous techniques are used, they appear to appeal to a common neural substrate, which is intrinsic to the brain. Crucially however, numerous NIBS protocols induce after-effects that last for periods up to an hour. Therefore a question of scientific and therapeutic importance is, how long can endogenously-driven effects last?

Another intriguing question is whether the observed plasticity effects are a direct consequence of longer-term changes to the dynamics of 'resting' or spontaneous rhythms (Sauseng et al. 2009), and associated thalamo-cortical networks (Thut & Miniussi 2009; Steriade & Timofeev 2003). This seems a tempting account in light of the significant three-way correlations between amplitude changes in training EEG, resting EEG, and MEP. Moreover, *post hoc* structural equation modelling results point to an indirect effect of NFB (via the resting EEG) on single-pulse MEP. If ultimately confirmed, it would suggest that the brain indeed 'shapes itself' (Rudrauf et al. 2003), whereby its past activity (history) may determine or bias its future state (of processing) (Silvanto et al. 2008), and so in perpetuum. In this case, the concept of a 'background' or stable state would cease to be informative, as it would be continually in flux and shaped by present activity. A caveat to the points raised above is that during some forms of exogenous stimulation, EEG rhythms are inconsistently modulated (Thut & Miniussi 2009), while mid-range frequencies (around alpha or theta) have been reported to have contrasting neuroplastic effects (Ziemann et al. 2008). We hope that future studies will elucidate these complex relationships further, and speculate that both endogenous and exogenous stimulation may preferentially activate distinct functional networks or pathways.

The novel finding that SICI (ICF) was positively (negatively) correlated with slow shifts in DC potential are compatible with the established view that slow cortical negativities are a marker of increased excitability and/or cortical disinhibition (Niedermayer & Lopes Da Silva 1999). As this was for the ALPHA group only, this relationship awaits replication, and endorses the online/offline use of TMS full-band EEG co-registration. The apparent lack of correlation of paired-pulse or DC measures with oscillatory EEG in this study is especially noteworthy. The latter effect has been documented previously and may suggest physiologically separate mechanisms of action (Kotchoubey et al. 1999). We have to acknowledge that our recording conditions were suboptimal, as we did not additionally short-circuit the skin(Vanhatalo et al. 2005); although random fluctuations of skin/sweat voltages would be an unlikely account for the compatible SICI/ICF correlations.

Overall our results remain consistent with classic evidence from both cellular and non-invasive studies detailing that very high frequency stimulation usually induces synaptic potentiation whereas lower frequencies may engender synaptic depression (Cooke & Bliss 2006). The discovery of spike-timing dependent plasticity (STDP) (Markram et al. 1997) has recently overshadowed

interest in frequency-dependent forms of synaptic plasticity (Markram et al. 1999). It is commonly established that the EEG per se is generated by the summed electrical fluctuations of EPSPs (Niedermayer & Lopes Da Silva 1999), and so may potentially be a close correlate of changes in synaptic transmission frequency or dendritic activity/spiking (Williams et al. 2007). Higher frequencies could reflect denser temporal incidence of EPSPs and hence greater influx of calcium (a trigger of LTP) through voltage-gated ion channels (Na^{+}, Ca^{2+}). Intracellularly, Cam Kinase II has also been found to be particularly sensitive to the *frequency* of calcium oscillations (De Koninck 1998). Moreover, a recent study observed that zero net-current extracellular high-frequency stimulation in cultured neurons gave rise to an overall depolarization of the cell membrane (Schoen & Fromherz 2008), which could hypothetically lower activation thresholds for voltage-gated ion channels. However, in our study we did not observe significant changes in the resting motor threshold (considered to reflect changes in membrane excitability), making a case for a transynaptic effect more likely. On the whole, the cited work above, as well as the activity-dependent relationships observed in this study, vouch for the very probable involvement of network oscillations in the mediation of synaptic plasticity (Steriade & Timofeev 2003). Latest findings that appear to support this role includes plasticity-inducing stimulations based on slow-wave sleep, sleep spindle (Rosanova & Ulrich 2005) and theta (Huang et al. 2005) endogenous rhythms.

In light of the initial neurophysiological evidence presented in this study, a repetitive alpha suppression protocol could theoretically be of significant therapeutic value in clinical cases where the pathophysiology consists of poor corticospinal activation and/or increased inhibition; in a motor disorder such as stroke for example. Moreover, as other methods of neuromodulation are reported to facilitate motor learning by inducing increases in cortical excitability (Ziemann et al. 2008), this protocol may be potentially useful in enhancing practice-dependent motor performance in healthy subjects. Hence, this hypothesis will be the object of investigation in the following experiment. Lastly, whilst additionally supporting previous clinical applications of neurofeedback (Heinrich et al. 2007), a similar NFB approach aimed at cortical activation may eventually prove to be appropriate for brain disorders exhibiting above-normal slow wave EEG power, such as attention deficit hyperactivity disorder (ADHD) (Lubar 1991), traumatic brain injury (Thatcher 2000), and depression (Korb et al. 2008).

Study 3: Facilitating motor learning with one session of neurofeedback

Introduction

The serial reaction-time task (SRTT) was originally developed by Nissen & Bullemer (Nissen & Bullemer 1987) in order to investigate implicit memory, that is, learning which is not based on the conscious recall of information. This type of learning is most often present during the acquisition of motor procedures, hence it is also termed *procedural memory*. During the serial reaction-time task participants are asked to press the key underneath a stimulus appearing within a series of locations on a computer screen (e.g. an asterisk in one of four fixed locations). Crucially, the appearance of the stimulus occurs in a 'pseudorandom order', or within a fixed sequence of considerable length that is usually not identified by the subject. After repeated exposure the subject's reaction times to the locations decreases across consecutive training blocks, but nonetheless increases to pre-training levels when a switch occurs from the fixed sequence to a truly random appearance of stimuli. During both execution and subsequent recall, participants are generally unaware of either the fixed or random nature of the sequence that was presented to them. Recent work has shown that implicit sequence learning can occur strictly perceptually, when the SRTT is altered to eliminate motor responses (Dennis et al. 2006). Without motor responses, participants can still learn the regularities present within the perceptual domain, and therefore learn the sequence perceptually. Hence, the SRTT combines both perceptual and motor learning components.

The simple nature and application of the SRTT has made it a convenient choice for examining the impact of various interventions on perceptuo-motor performance and learning. Nitsche et al. (Nitsche et al. 2003) first explored the impact of raising motor cortex excitability with anodal tDCS on SRTT learning, based on previous observations that the motor cortex transiently exhibits an increase in excitability during learning of sequential finger movements (Pascual-Leone et al. 1994). The results of the tDCS experiment were striking: online tDCS applied during the course of the experiment (15 min) decreased reaction times in a shorter number of trials of the fixed sequence, as well as overall reaction time in the random sequence, when compared to sham (Nitsche et al. 2003). Local stimulation of the primary motor cortex resulted in increased performance, whereas that of premotor and medial prefrontal cortices had no impact. Thus the effects were anatomically and protocol (anodal vs cathodal)

specific. Based on this prospect and neurobiological evidence, the principal aim of the present experiment was to assess whether NFB-mediated enhancement of primary motor cortex excitability would engender similar advantages in healthy subjects in comparison to a no-treatment condition. Specifically, preceding results point to the feasibility of increasing motor cortex excitability for a period of at least 20 minutes following a single session of NFB desynchronisation of alpha (8-12 Hz) rhythms. This protocol also appears to reduce short-interval intracortical inhibition, or SICI, a TMS measure which is inversely associated with successful motor learning (Teo et al. 2009). Crucially, the 20 min post-intervention temporal window overlaps with the time needed to complete the SRTT, which is appropriate to assess any direct improvements in perceptuo-motor learning. Moreover, in order to enable direct comparisons of effect size between endogenous and exogenous neuromodulation methods, the SRTT parameters (block and sequence length, etc.) were kept as closely as possible to the original experiment with tDCS (Nitsche et al. 2003).

Materials and Methods

Experimental Design

In total, 10 healthy subjects (age: 35.7, SD: 12.7, right handed, 6 female) participated in this experiment. Each subject performed the SRTT task (lasting approx. 20 min) on two different days in a counterbalanced design denoting 2 experimental conditions. The first condition consisted of receiving a 30 min NFB session immediately *before* performance of the SRTT task with the left hand. The NFB protocol was set-up to suppress alpha (8-12 Hz) amplitude at right motor cortex (electrode site C4). Thus it paralleled the protocol used in the last study which demonstrated increased corticomotor excitabilities. The second condition was a control assessment consisting of only SRTT performance without prior NFB, in order to discriminate whether the NFB intervention has any beneficial effects over a strictly 'no-treatment' condition, which may be useful in information for medical or neurorehabilitation settings. The conditions were separate at least a week apart and consisted of two entirely different motor sequences in order to control for any possible practice or plasticity effects.

Serial reaction time task (SRTT)

Subjects were seated in front of a 15" computer screen at eye level and a keyboard. They were instructed to independently press a series of four keys ('C','G', 'H', and 'M') with a different finger of the right hand (index finger for 'C', middle finger for 'G', ring finger for 'H', and little finger for 'M'). An asterisk appeared in one of 4 positions that were horizontally spaced on a computer screen and permanently marked by white dots. The subjects were told to press the key corresponding to the horizontal location of the active asterisk as quickly and accurately as possible. After a button was pushed, the asterisk disappeared and reappeared 500ms later in a new location, independent of a correct or incorrect response. The experiment consisted of 8 blocks of 120 trials each. In blocks 1 and 6, the sequence of asterisks followed a random order, and asterisks were presented equally frequently in each position and never in the same position in two consecutive trials. In all other remaining blocks (2–5 and 7-8), an identical 12-key sequence of asterisk positions was repeated 10 times (e.g. abadbcdacbdc). Participants were not told about the repeating sequence at any point in the experiment. After the experiment however, they were asked whether they were aware of any repeating pattern, and if so, to write it down. The experiment was conducted in a counterbalanced within-subject design. Hence 2 different versions of the 12-key sequence were presented to each subject on separate occasions (a week apart), in order to prevent potential interference effects from prior learning.

Apparatus and EEG analysis

EEG signals were recorded using a NeXus-10 DC-coupled EEG amplifier using a 24-bit A-D converter (MindMedia, the Netherlands), and visual NFB training was carried out with the accompanying Biotrace+ software interface on an Intel DualCore computer with a 15" screen. The EEG used for feedback was sampled at 256 Hz with Ag/Cl electrodes at the right primary motor cortex (electrode site C4) referenced to the contralateral mastoid. The scalp area was carefully scrubbed with NuPrep abrasive gel, followed by application of Ten20 electrode paste. The ground electrode was placed on the right arm. The signal was IIR bandpass filtered to extract alpha (8-12 Hz) amplitude (µV peak-peak) with an epoch size of 0.5 seconds. Reward thresholds were set to be 30% of the time above the initial alpha mean amplitude (baseline). The first baseline was recorded during a 3-min eyes open EEG recording at rest immediately before the start of feedback, and the second 3-min immediately after the end

of training. Subjects were given no explicit verbal instructions and were told to be guided by the feedback process instead. This was achieved via a collection of different visual displays/games whose control reflected the modulation of the trained EEG amplitude. This consisted of five Biotrace+ software games, which were played in a random order for approximately 6 minutes each (mandala, space invaders, mazeman, bugz, puzzles).

Data analysis

In each SRTT trial, reaction time (RT) was recorded from the appearance of the asterisk until the first button was pushed by the subject. Mean RT was calculated for each subject for each block of trials of a given experimental condition (NFB vs control). Response times of less than 200 ms or more than 3000 ms were automatically discarded, or those that were above 3 standard deviations of the individual subject's mean response time. In addition, the standard deviation of subject RT's in every block was calculated as an index of variability of response. Lastly, an error rate (ER) was calculated to assess the number of incorrect responses in each block and experimental condition. Statistical analyses were conducted for the absolute values of RT, standard deviation of RT, and ER with a within-subject repeated measures ANOVA (CONDITION x BLOCK; 2 x 8). Post-hoc paired sample Student's t-tests (two-tailed) were performed on RT, ER, and standard deviations between blocks to explore learning effects. Additionally, since RT differences between blocks 5 (fixed sequence) and 6 (random sequence) represent a relative measure of procedural learning, a within-subject repeated measures ANOVA (CONDITION x BLOCK; 2 x 2) was performed to test for an interaction between the NFB and control condition. Thus, a confirmed interaction indicates a significant difference exists between factor combinations.

Results

Out of the 10 subjects, only one noted there may have been a repeating sequence after the experiment. However, she was unable to explicitly recall the sequence when asked to write it down. T-tests revealed no significant differences in overall RT's between the two different sequences, or experimental condition order.

Mean reaction time (RT)

A within-subject repeated measures ANOVA (CONDITION x BLOCK; 2 x 8) disclosed a marginally significant main effect for CONDITION ($F(1, 9)=3.7$, $p=0.08$), indicating that there was perhaps a trend for a lower overall RT for the neurofeedback (521 ms) vs control (555 ms) conditions. A significant main effect for BLOCK ($F(7, 63)=2.2$, $p=0.05$) points to a decrease in RT across blocks, where overall RT for random blocks 1 and 6 was 560 and 551 ms, respectively. Overall RT for fixed sequence blocks 2, 3, 4, 5, 7 and 8 was 536, 524, 538, 531, 536, and 529 ms, respectively. On the other hand, a significant interaction effect ($F(7, 63)=2.7$, $p=0.02$) was observed for CONDITION x BLOCK. This suggests a quantitative difference between the dynamic reduction of RTs across blocks of the neurofeedback and control conditions. As depicted in Fig 4.1A, the NFB intervention appears to induce a more rapid decrease in RT especially in the early fixed sequence blocks 2, 3, 4 and 5; exploratory analyses using Fisher's LSD (Least Significant Difference) paired t-tests indicated significantly reduced RTs between NFB vs control conditions in block 2 ($t_9=2.4$, $p=0.04$), block 3 ($t_9=3.2$, $p=0.01$), block 4 ($t_9=2.3$, $p=0.05$), and 5 ($t_9=3.6$, $p< 0.01$), as shown by asterisks in Fig 4.1A.

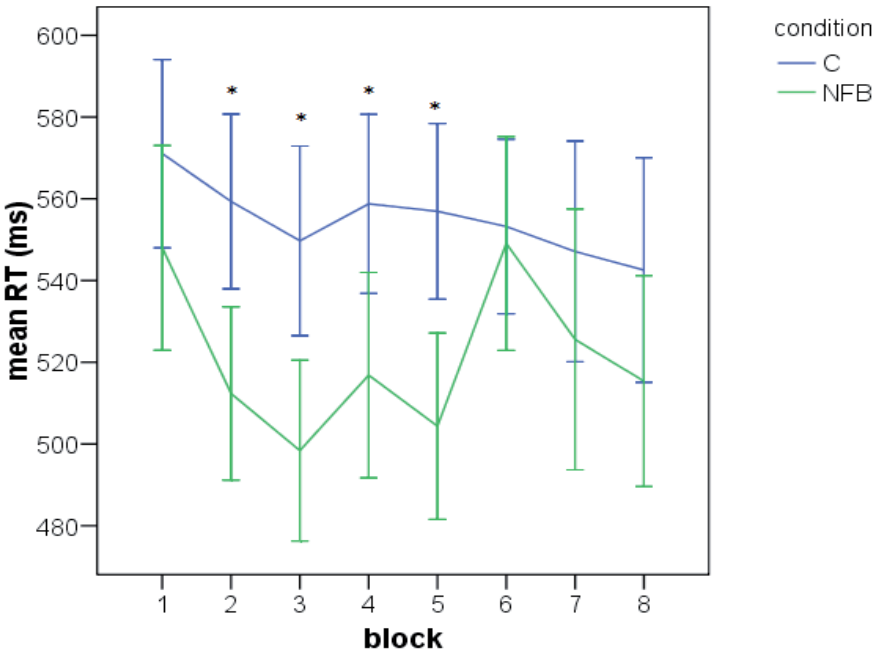

Fig 4.1A Serial-reaction time task *absolute* response time (RT) across 8 blocks for the neurofeedback (NFB) and control (C) conditions. The key-stroke sequence was random during blocks 1 and 6, and fixed during blocks 2, 3, 4, 5, 7, 8. Asterisks indicate blocks with significant differences between NFB vs control conditions. Error bars represent SEM.

A separate analysis between fixed (block 5) and random blocks (block 6) via a 2 x 2 ANOVA (CONDITION x BLOCK) revealed a reliable interaction ($F(1,9)=8.5$, $p=0.02$), with an insignificant main effect for CONDITION ($F(1,9)=2.8$, $p=0.13$) and a significant main effect for BLOCK ($F(1, 9)= 16.6$, $p<0.01$). To rule out that small a priori stimulation RT group differences -which may have been due to baseline-driven RT differences influencing the results systematically independent of the implicit learning process– a second analysis was performed following the approach of *Nitsche et al.* (Nitsche et al. 2003). Here, normalised RTs were calculated by dividing values from blocks 2–8 by block 1, as shown in Fig 4.1B. An ANOVA across all blocks mirrored the results obtained with the absolute RTs: an insignificant main effect for CONDITION ($F(7, 63)=1.5$, n.s.), and a significant effect for BLOCK ($F(7, 63)=2.2$, $p=0.05$) as well as the CONDITION x BLOCK interaction ($F(7, 63)=3.0$, $p < 0.01$). Furthermore, following normalisation, exploratory analyses using uncorrected paired t-tests indicated no statistically reliable differences of RTs between NFB vs control blocks (all blocks $p>0.05$): block 2 ($t_9=1.9$, $p=0.08$), block 3 ($t_9=2.2$, $p=0.06$), block 4 ($t_9=2.2$, $p=0.06$), and block 5 ($t_9=2.1$, $p=0.06$). On the other hand, a 2 x 2 ANOVA (CONDITION x BLOCK) between fixed (block 5) and random block (block 6) revealed an insignificant main effect for CONDITION ($F(1, 9)=0.4$, n.s.) and a significant main effect for BLOCK ($F(1, 9)=18.0$, $p< 0.01$) and a reliable interaction ($F(1, 9)=9.8$, $p=0.01$).

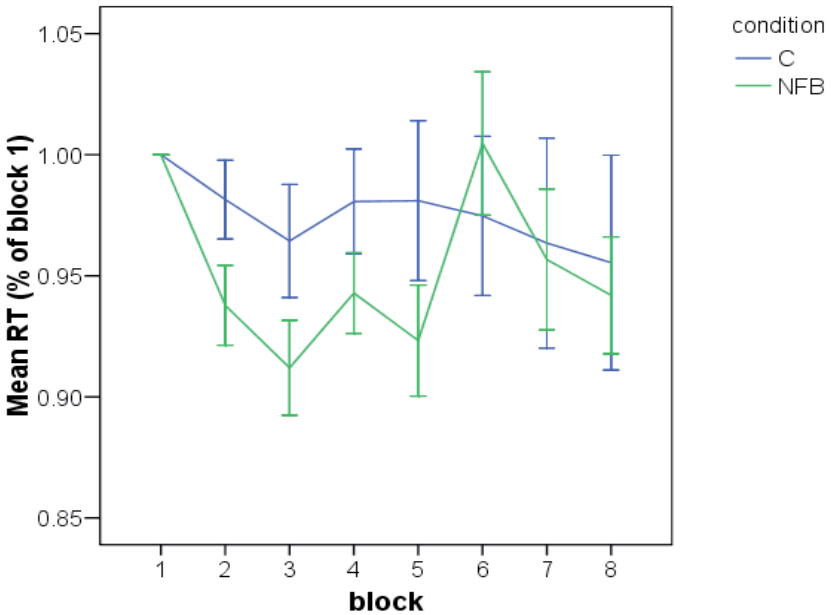

Fig 4.1B Serial-reaction time task *normalised* response time (RT) across 8 blocks for the neurofeedback (NFB) and control (C) conditions. The key-stroke sequence was random during blocks 1 and 6, and fixed during blocks 2, 3, 4, 5, 7, 8. Error bars represent SEM.

Mean error rate (ER)

Analogous analyses were conducted for mean error rates within each block. As can be seen in Fig. 4.2, mean error rates between neurofeedback and control conditions did not appear to differ substantially. This was corroborated by a lack of a significant interaction effect ($F(7, 63)=1.8$, $p=0.1$) in a within-subject repeated measures ANOVA (CONDITION x BLOCK; 2 x 8). Moreover, we observed an insignificant main effect for CONDITION ($F(1, 9)=0.9$, n.s.) and a significant main effect for BLOCK ($F(7, 63)=2.2$, $p=0.05$), indicating a trend for increasing errors across blocks, perhaps due to fatigue. No NFB blocks were significantly different from the control condition after Bonferroni corrected paired t-tests.

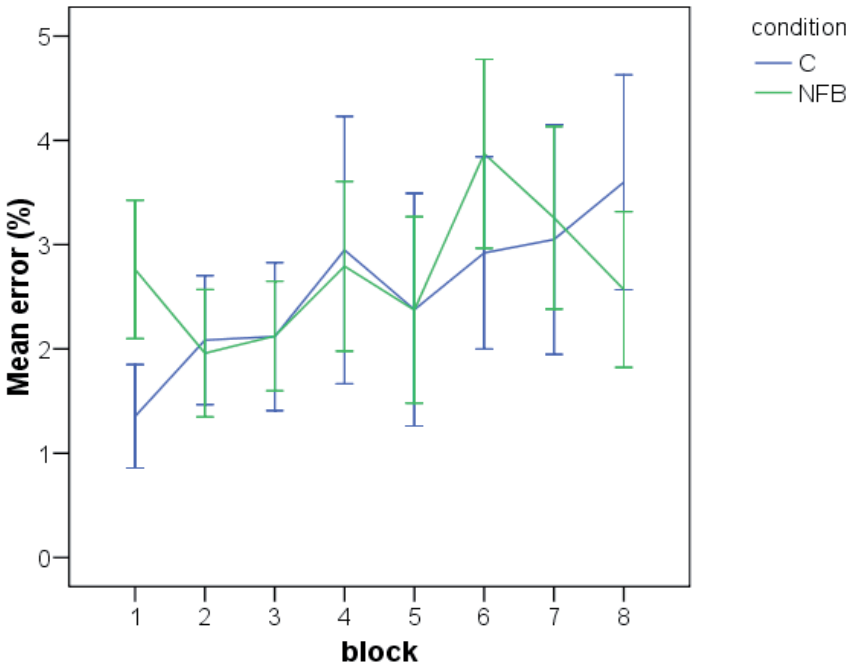

Fig 4.2 Serial-reaction time task error rate (%) across blocks for the neurofeedback (NFB) and control (C) conditions. The key-stroke sequence was random during blocks 1 and 6, and fixed during blocks 2, 3, 4, 5, 7, 8. Error bars represent 1 standard error of the mean (SEM).

Variability of reaction times

Within-subject repeated measures ANOVA analyses were conducted for the variability, or standard deviation (SD) of reaction times within each block. The standard deviation of reaction times between neurofeedback and control conditions did not appear to differ substantially between conditions, as evidenced

by a lack of a significant main effect neither for BLOCK ($F(7, 63)=2.0$, $p=0.14$), nor CONDITION x BLOCK interaction ($F(7, 63)=0.4$, n.s.). As can be observed from Fig 4.3, the main effect for CONDITION ($F(1, 9)=0.06$, n.s.) was also insignificant. In accordance with this, Bonferroni corrected paired t-tests did not reveal any significantly different NFB blocks from control blocks.

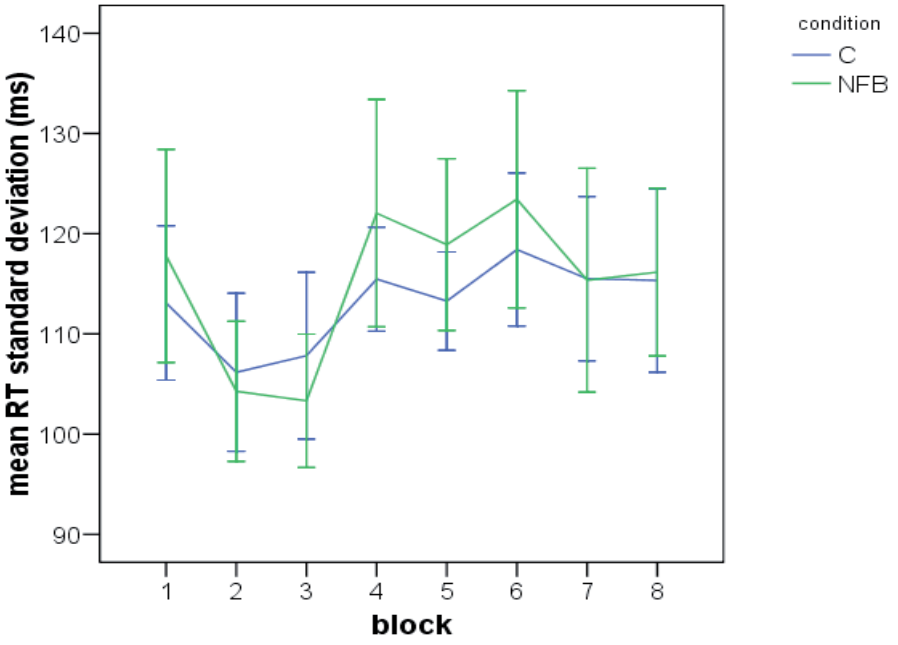

Fig 4.3. SRTT response time variability across blocks for the neurofeedback (NFB) and control (C) conditions. The key-stroke sequence was random during blocks 1 and 6, and fixed during blocks 2, 3, 4, 5, 7, 8. Error bars represent 1 standard error of the mean (SEM).

Discussion

Overall, our findings demonstrate that a single neurofeedback (NFB) session may be directly used to facilitate the early acquisition and de novo performance of a procedural perceptuo-motor task. In comparison to a counterbalanced condition without NFB, the same participants who had NFB immediately prior to SRTT performance exhibited a significantly faster reduction of reaction times across blocks. This occurred in the absence of explicit awareness of a repeating sequence, which may be considered as evidence of enhanced implicit learning. Importantly, baseline reaction time (block 1) between NFB and control conditions was not significant, and no significant differences were observed between the normalised times of the initial fixed sequence block (block 2); hence the results cannot be simply explained by a simple reduction in response latency. This is also supported by the observation of an interaction between

experimental conditions for fixed (block 5) vs. random (block 6) sequences. As can be seen from Fig 4.1, mean reaction time of the fixed sequence (block 5) was more diminished for the NFB condition, but increased again during the random block 6. This observation would be difficult to attribute to an unspecific and general reduction of reaction time produced by NFB. Finally, no significant differences were observed between conditions in error rate (Fig 4.2) or reaction time variability (Fig 4.3), such that performance after NFB could not be accounted for by a speed–accuracy trade-off, where faster reaction times (higher speed) are sometimes paralleled by more mistakes (less accuracy).

The choice to evaluate the perceptuo-motor performance of the left hand was made in view of evidence from other non-invasive brain stimulation interventions which report larger improvements for the non-dominant versus dominant hand (Boggio et al. 2006; Vines et al. 2008). In accordance with this, transcallosal inhibition is reported to be asymmetric, with stronger inhibitory projections originating in the dominant hemisphere (Netz et al. 1995). The findings are nevertheless consistent with the notion that short-term enhancement of primary motor cortex excitability, here by alpha-band desynchronisation NFB (previously found to enhance corticospinal excitability and reduce intracortical inhibition for at least 20 minutes), may subsequently lead to more efficacious motor learning. Effects of improved SRTT performance have also been demonstrated after excitability-enhancing direct current stimulation (tDCS) (Nitsche et al. 2003) of the contralateral motor cortex in healthy subjects. Conversely, inhibitory 1Hz rTMS had a detrimental effect on motor learning in a study by another group (Muellbacher et al. 2002). Importantly, modulated performance of the SRTT can be extrapolated to and may have direct implications for rehabilitation in pathophysiology. Hence, chronic stroke patients that received anodal tDCS on the affected motor cortex report demonstrate enhancement in SRTT performance (Fregni et al. 2005). The same protocol has crucially been shown to improve execution of the Jebsen-Taylor Hand Function Test (JTT) (Hummel et al. 2005), a widely used, well validated test for functional motor assessment that reflects activities of daily living. Likewise, the dopamine precursor Levodopa is able to induce a significant boost in SRTT performance of stroke patients (Rösser et al. 2008). Hence, the possibility of similarly combining NFB intervention with usual rehabilitative treatments may be a promising way to improve the outcome of neurorehabilitation in real-life scenarios.

It is interesting to note that another non-invasive intervention, tDCS stimulation, must be applied *during* the motor task itself in order to cause

improvements in learning (Nitsche et al. 2003). Accordingly, excitatory tDCS given just before the SRTT does not lead to performance enhancements. This effect has been interpreted as resulting from a putative 'homeostatic' effect i.e. prior potentiation of synaptic strengths by excitation reduces the subsequent capacity to learn. On the other hand, the effects of NFB appear to run contrary to similar mechanisms as evidenced by the current results. It is likely therefore that the mode of action differs between these two methods. Specifically, it has been shown that cortical plasticity changes that outlast tDCS stimulation are NMDA-receptor dependent (Nitsche et al. 2003). This could theoretically explain the homeostatic effect, given this central role of this receptor in synaptic potentiation (Cooke & Bliss 2006). On the other hand, while both tDCS and NFB share excitability increases reflected in amplified MEPs, NFB may not *in and of itself* induce synaptic potentiation. Rather, similar to what has been reported with neuromodulatory transmitters (Meintzschel & Ziemann 2006), it may act to prime or catalyse the neural substrate towards more efficient learning, once it occurs. Given that the current NFB protocol also decreases SICI, this is consistent with experimental observations that a prior decrease of GABAergic intracortical inhibition (induced by ischemic nerve block) subsequently boosts practice-dependent plasticity (Ziemann et al. 2001). Hence, a parsimonious explanation may be that sustained NFB gives rise to a cumulative release of endogenous neuromodulators (e.g. noradrenaline, dopamine) which then modulate cortical excitability and practice-dependent plasticity over a broader temporal window of activity.

Although NFB impacts EEG oscillations which directly reflect cortical activities, it is not implausible that this may be indirectly accompanied by the added modulation of subcortical inputs and outputs of the primary motor cortex, the most prominent of which is the basal ganglia. The neuro-anatomical correlates of successful SRTT performance implicate the basal ganglia as a key structure that seems to be necessary as well as sufficient for procedural learning. Firstly, patients with basal ganglia disorders such as Parkinson's (Muslimovic et al. 2007) and Huntington's (Willingham 1996) show impaired learning and performance of the SRTT. Secondly, selective lesions of the striatum in rats do not lead to pronounced motor deficits but rather decrease response accuracy and slow reaction times in the SRTT compared to a control group (Eckart et al. 2009). Human neuroimaging studies also report striatal activation when subjects are performing the SRTT with a fixed compared to a random sequence (Doyon et al. 1996; Rauch et al. 1997). Additionally, striatal activation was absent when subjects were explicitly told the sequence beforehand, and occurred only in the

frontal cortex (Doyon et al. 1996). This is in line with a recent study describing skill improvements on the SRTT following inhibitory rTMS of prefrontal cortex in humans (Galea et al. 2009), and supportive of an interference effect between consolidation of declarative (explicit) and procedural (implicit) processing in the brain. However, the EEG of other cortical locations was not recorded in the present study, thus one cannot rule out that secondary motor areas, such as the supplementary motor area (SMA) and premotor area (PMA), were not concurrently activated during NFB. In addition, converging evidence suggests that dopamine is crucial for motor sequence learning and synaptic plasticity in primary motor cortex (Molina-Luna et al. 2009; Eckart et al. 2009), hence the possibility exists that NFB may have upregulated dopaminergic tone in the motor cortex and/or basal ganglia, in a similar way to what has been observed following other non-invasive brain stimulation techniques such as rTMS (Keck et al. 2002).

Lastly, it is necessary to acknowledge the principal methodological limitations of this pilot study. Firstly, the control condition cannot be realistically regarded as placebo-controlled. Sham-neurofeedback (by giving false feedback from a previous EEG recording) is usually easy to implement but in many cases leads to heterogeneous and interfering results. This is because the participant either becomes aware of or struggles with the lack of control of the NFB interface. Passivity or frustration may therefore have a highly variable and inconsistent impact on brain excitability. Future studies could avoid this problem by using other forms of biofeedback for the control condition (such as heart rate variability or EMG). Alternatively, to confirm that the NFB effect is anatomically-specific, the EEG could be fed-back from a different cortical site, such as the temporal cortex. Nevertheless, the relatively robust effect observed in this study, which may be directly compared to similar findings obtained with tDCS (Nitsche et al. 2003), argues for an unlikely case of a placebo effect.

V. CONCLUSION

General discussion

It is now possible to evaluate the experimental results in relation to the main goals of the thesis. The findings of the first study suggest that the application of at least one neurofeedback protocol (SMR-Theta) may facilitate the acquisition of complex perceptuo-motor skills, which in this case are present in microsurgical techniques. Such enhancement was associated with a significant increase in surgical accuracy and a concomitant decrease in time on task. However, a statistical comparison between neurofeedback groups could not confirm the effect's specificity due to an insignificant Protocol x Group interaction, and the comparisons with the control assessments, although encouraging, remained qualitative. On the other hand, exploratory analyses revealed the positive effects were most related to trainees that maintained the highest neurofeedback session frequency and training efficacy as evidenced by directed changes of their EEG spectra. Specifically, performance improvement appeared to be most linked to neurofeedback learning ratios and long-term reductions in slow-wave theta amplitude. This same protocol has previously been shown to improve attentional performance in healthy (Egner & Gruzelier 2004) as well as clinical populations, such as ADHD (Lévesque et al. 2006). Interestingly, children with ADHD exhibit elevated levels of theta rhythms which normalise with medication (Clarke et al. 2007) as well as after neurofeedback (Gevensleben et al. 2009). Hence, in the present study, neurofeedback may have influenced perceptuo-motor skills by modulating attentional networks. In support of this, theta suppression has been shown to improve detection performance in a radar monitoring task (Beatty et al. 1974) and general cognitive performance (Besserve et al. 2008). A complementary hypothesis is based on evidence that pharmacological (Sebban et al. 1999) and electrical (Ardolino et al. 2005) activation of the cortex reduces slow-wave rhythms (incl. theta), and therefore theta decreases in motor cortex may reflect an upregulation of underlying neuronal excitability, which occurs during motor learning (Perez et al. 2004) and its facilitation (Ziemann et al. 2001). This seems particularly compatible with the results of this thesis's second study which demonstrates a reliable correlation between suppression of a broad range of slow-wave frequencies (1-15 Hz) (esp. alpha, but also theta) and an increase in corticomotor excitability.

Owing to the special sensitivity of TMS methods, the correlative findings of the second study argue for a more direct and causal relationship between within-session neurofeedback training and post-session cortical neuromodulatory changes in healthy humans. Remarkably, as little as 30 minutes of neurofeedback training is able to induce mean changes in corticospinal excitability and decreases in intracortical inhibition of up to 200% (the maximum recorded in one subject was 210%). It has been shown that these changes are tightly correlated to the intra-session neurofeedback training dynamic, and last for at least 20 minutes, which may be considered a long-term modification in neurotransmission (Schulz & Fitzgibbons 1997). Moreover, a structural equation model suggested that the resting (spontaneous) state of EEG rhythms acts as a mediator between the neurofeedback session and the subsequent activity-dependent changes observed in the TMS parameters. The present data suggest that short-term plastic changes of the spontaneous (baseline) EEG that occur following a session of neurofeedback are directly proportional to the within-session modulation of the EEG. Hence, what may be likened to a "memory foam" effect, repetitive application of neurofeedback training over multiple sessions is hypothesised to modify the resting EEG in the direction imposed by the neurofeedback protocol. This mechanism is particularly supported by recent studies that reveal directed alterations of long-term EEG power following neurofeedback (Cho et al. 2008; Hoedlmoser et al. 2008; Gevensleben et al. 2009). Importantly, such spectral changes appear to be strongly correlated with improvements in cognitive performance (Hoedlmoser et al. 2008) and clinical scores of behaviour (Gevensleben et al. 2009). In this respect, the findings of the second study offer a preliminary basis for the 'missing link' between the historically reported benefits of repeated neurofeedback sessions and direct validation of neuroplastic change after an individual session of training. According to the three criteria of temporal dynamic, magnitude, and persistence, self-regulation of the EEG could potentially be considered as a valuable and atypical addition to the arsenal of non-invasive brain stimulation methods, distinguished by the fact that it is functionally endogenous.

Lastly, based on evidence that one session of neurofeedback is sufficient to induce persistent changes in cortical function from the second study, it was hypothesised that this could impact positively on the learning curve of a procedural perceptuo-motor task. Indeed this was demonstrated to be the case with the finding of improved reaction times for the non-dominant hand relative to a no-intervention control condition. This is therefore supportive of the view proposed in the *Introduction* that the intrinsic, self-induced regulation

of particular neural substrates (here primary motor cortex) is capable of influencing and optimising the behavioural performance of the organism as a whole. Thus, in conclusion, neurofeedback may be regarded as a simple yet effective tool with which to "harness" the endogenous mechanisms that remain native to the organism and which have developed to serve it intelligently over the course of evolution. Critically, biological maladaptation is a common trait in nature and it may be potentially viable, via neurofeedback, to stimulate and thus readjust certain dormant or compensatory neurobiological processes which could promote functional recovery in cases of cerebral pathophysiology.

Methodological limitations and future directions

Firstly, owing to the difficulty of acquiring sufficient numbers of surgeons for study 1, its experimental design incorporated a mixture of overlapping control and neurofeedback group assessments. This prevented a direct quantitative comparison between experimental and control groups. Given that the comparisons to the control protocol were only qualitative, no statistical conclusions could be made to rule out that the neurofeedback intervention was a case of placebo.

Moreover, as the post-hoc analyses were exploratory this lessens their statistical import, and runs the risk of increasing the type I error (rejecting the null hypothesis of no significant differences between neurofeedback groups, when it is actually true). These aspects could be minimised in future studies by firstly using larger samples of surgeons, and secondly by making sure either all of them complete control assessments (within-group design) or by dedicating a wholly independent group of controls (between-group design). Moreover, it would also be useful to record more accurately each individual's prior surgical experience, for example the number of simulated or real operations conducted in theatre, so as to ensure control over different levels of experience by using this as a covariate (the present work gauged experience in years, only). The study of complex perceptuo-motor skills such as surgical procedures could also be improved by using more accurate methods to estimate task velocity and error. Modern surgical virtual reality simulators (Larsen et al. 2009) used for training surgeons would be an ideal apparatus with which to test individual performance, as various parameters relating to instrument and microscope handling, surgical efficiency and tissue treatment are recorded digitally by the system. The optimal frequency and total number of sessions of neurofeedback

training should also be manipulated in order to arrive at maximising learning effects and minimising time spent outside of theatre.

With regard to plastic changes following a single session of neurofeedback, the second study would certainly benefit from the inclusion of a sham-control group, in place of the low-beta group which served as an active-control group and which did not demonstrate significant unidirectional changes. Here the lack of a clear interaction and post-hoc exploratory analyses again undermined the specificity of the neurofeedback protocol effect, as the post-intervention differences may have resulted from individual (and hence, group) differences in attending to the neurofeedback stimuli. Alternatively, if two active experimental groups are to be used, it should be ensured that most participants have been trained sufficiently enough to be able to induce a reliable change in the EEG (in study 2, only the alpha protocol was found to do so in naïve participants). From the theoretical point of view, it may be especially interesting to explore the temporal limit of the after-effects. This will enable more direct comparisons of effect size and duration with other non-invasive brain stimulation technologies. Moreover, by applying antagonists of particular neuromodulators it may be possible to determine whether neurofeedback is directly associated with their release, similarly to what has already been demonstrated with rTMS and tDCS. The possible limitations of EEG entrainment should also be explored, given that some frequencies and cortical locations may require multiple sessions of NFB training, as evidenced for the SMR rhythm in the second study. Accordingly, the use of whole-head (multi-channel) EEG recording in the future may reveal more comprehensive changes of brain rhythms across the whole cortical mantle, and thereby localise other cortical regions which may be indirectly affected via neurofeedback. Likewise, fMRI neuroimaging during EEG neurofeedback may be able to uncover the cortico-subcortical networks which are up- or down-regulated with respect to particular protocols. Lastly, with regard to perceptuo-motor skills, one crucial step would involve investigating whether the positive findings can be generalised to motor pathophysiologies, which may result in improved recovery times following stroke or traumatic head injury for example, both of which are associated with abnormal EEG activity (Finnigan et al. 2007; Thatcher 2000). Hence, a potential direction may consist of exploring whether one or multiple sessions of neurofeedback impact motor learning of the affected limb, and if this is associated with changes in TMS or EEG measures compared to placebo. Other lesser known disorders include cerebral palsy (Kułak et al. 2006) and focal dystonias (Kristeva et al. 2005).

Closing remarks

More than 40 years ago Lomo (Lomo 1966) reported on what he termed "frequency potentiation" of excitatory synaptic activity by electrical stimulation of hippocampal neurons, the first example of long-term potentiation (LTP), a classic phenomenon of synaptic plasticity. Later, LTP was found to be more effective when modelled on electrical patterns inherent to the structure being potentiated (Larson & Lynch 1986). Nowadays the growing application of noninvasive brain stimulation devices such as TMS and tDCS enable the study of neuroplasticity in the intact human brain (Ziemann et al. 2008). Likewise, the modern trend has been towards more physiologically-based patterns of stimulation, such as theta-burst (Huang et al. 2005) and random noise (Terney et al. 2008). However, modern exogenous brain stimulation methods such as transcranial magnetic stimulation (TMS) and direct current stimulation (tDCS) induce plasticity by electro-magnetic fields that are by definition still artificial i.e. the driving forces they produce may not necessarily be natural or intrinsic to the brain. In contrast, EEG neurofeedback enables the brain to regulate its own oscillationsi *in vivo*, and allows them to operate organically across cortical networks. Moreover, the inherent problem faced by many behavioural manipulations of the EEG is the difficulty of dissociating stimulus-dependent versus stimulus-independent oscillations. However during neurofeedback subjects are exposed to the same feedback stimuli; hence their entrained EEG differences may be considered as resulting minimally from exogenous factors, and rather represent the modulation of endogenous or 'stimulus-independent' brain states. As a consequence, EEG neurofeedback may be a promising tool for more organic investigations into the mechanism and functional intersection of neuronal oscillations, neuromodulators, synaptic plasticity and homeostasis. After a history of scepticism for more than 40 years since the discovery of neurofeedback (Kamiya et al. 1969, Sterman et al. 1969), small, haphazard but nevertheless important steps have been made towards establishing this method as worthy of more scientific attention. Systematic research is therefore warranted in this wide-ranging technique still poorly understood as to its underlying neurophysiological mode of action (Sterman 1996). In light of the astonishing plasticity displayed by the human brain (Pascual-Leone et al. 2005), the prospect that such a tool could nonetheless offer is important and urgent enough to motivate future investigations so as to establish the true extent of its impact on normal and pathological brain function. The fruits of such an inquiry could potentially lead to a remarkably safe, non-invasive and above all natural approach for directing neuroplastic change.

REFERENCES

Abraham, W.C., 2008. Metaplasticity: tuning synapses and networks for plasticity. *Nature Reviews Neuroscience*, 9(5), 387.

Aftanas, L.I. & Golocheikine, S.A., 2001. Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. *Neuroscience Letters*, 310(1), 57-60.

Agostino, R. et al., 2007. Effects of 5 Hz subthreshold magnetic stimulation of primary motor cortex on fast finger movements in normal subjects. *Experimental brain research*, 180(1), 105-11.

Alex, K.D. & Pehek, E.A., 2007. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacology & Therapeutics*, 113(2), 296-320.

Amat, J. et al., 2006. Previous experience with behavioral control over stress blocks the behavioral and dorsal raphe nucleus activating effects of later uncontrollable stress: role of the ventral medial prefrontal cortex. *The Journal of Neuroscience*, 26(51), 13264-72.

Anastakis, D.J. et al., 1999. Assessment of technical skills transfer from the bench training model to the human model. *American Journal of Surgery*, 177(2), 167-70.

Andersen, J. et al., 2009. Recent advances in the understanding of the interaction of antidepressant drugs with serotonin and norepinephrine transporters. *Chemical Communications*, (25), 3677-92.

Antal, A. et al., 2004. Direct current stimulation over V5 enhances visuomotor coordination by improving motion perception in humans. *Journal of Cognitive Neuroscience*, 16(4), 521-7.

Antal, A. et al., 2004. Oscillatory brain activity and transcranial direct current stimulation in humans. *Neuroreport*, 15(8), 1307-10.

Apicella, P., 2007. Leading tonically active neurons of the striatum from reward detection to context recognition. *Trends in Neurosciences*, 30(6), 299-306.

Ardolino, G. et al., 2005. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *The Journal of Physiology*, 568(Pt 2), 653-63.

Arns, M. et al., 2009. Efficacy of neurofeedback treatment in ADHD: the effects on inattention, impulsivity and hyperactivity: a meta-analysis. *Clinical EEG and Neuroscience*, 40(3), 180-9.

Arnsten, A. & Goldman-Rakic, P., 1984. Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. *Brain Research*, 306, 9-18.

Arnsten, A.F., Cai, J.X. & Goldman-Rakic, P.S., 1988. The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes. *The Journal of Neuroscience*, 8(11), 4287-98.

Aston-Jones G., C.J., 2005. An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, 28, 403-450.

Atkeson, C.G., 1989. Learning arm kinematics and dynamics. *Annual Review of Neuroscience*, 12, 157-83.

Axmacher, N. et al., 2006. Memory formation by neuronal synchronization. *Brain Research Reviews*, 52(1), 170-82.

Barker, A.T., Jalinous, R. & Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. *Lancet*, 1(8437), 1106-7.

Barry, R.J. et al., 2007. EEG differences between eyes-closed and eyes-open resting conditions. *Clinical Neurophysiology*, 118(12), 2765-73.

Barry, R.J. et al., 2005. Caffeine effects on resting-state arousal. *Clinical Neurophysiology*, 116(11), 2693-700.

Barry, R.J. et al., 2004. EEG differences in children as a function of resting-state arousal level. *Clinical Neurophysiology*, 115(2), 402-8.

Baxter M.G., C.A., 1999. Cognitive functions of the basal forebrain. *Current Opinion in Neurobiology*, 9, 178-183.

Beatty, J. et al., 1974. Operant control of occipital theta rhythm affects performance in a radar monitoring task. *Science*, 183(127), 871-3.

Benjamin, L., 2005. Selection, teaching and training in ophthalmology. *Clinical & Experimental Ophthalmology*, 33(5), 524-30.

Bergan, J.F. et al., 2005. Hunting increases adaptive auditory map plasticity in adult barn owls. *The Journal of Neuroscience*, 25(42), 9816-20.

Berridge, K.C., 2004. Motivation concepts in behavioral neuroscience. *Physiology and Behavior*, 81, 179-209.

Berridge, C.W. & Waterhouse, B., 2003. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, 42(1), 33-84.

Berridge, C.W. et al., 1993. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. *Neuroscience*, 55(2), 381-93.

Besserve, M. et al., 2008. Prediction of performance level during a cognitive task from ongoing EEG oscillatory activities. *Clinical Neurophysiology*, 119(4), 897-908.

Bindman, L.J., Lippold, O.C. & Redfearn, J.W., 1964. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *The Journal of Physiology*, 172, 369-82.

Birbaumer, N. et al., 2006. Physiological regulation of thinking: brain-computer interface (BCI) research. *Progress in Brain Research*, 159, 369-91.

Birnbaum, S. et al., 1999. A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex. *Biological Psychiatry*, 46(9), 1266-74.

Bland, B.H. & Oddie, S.D., 2001. Theta band oscillation and synchrony in the hippocampal formation and associated structures: the case for its role in sensorimotor integration. *Behavioural Brain Research*, 127(1-2), 119-36.

Bliem, B. et al., 2007. Dopaminergic influences on changes in human tactile acuity induced by tactile coactivation. *Experimental brain research*, 181(1), 131-7.

Bliem, B. et al., 2008. Homeostatic metaplasticity in the human somatosensory cortex. *Journal of Cognitive Neuroscience*, 20(8), 1517-28.

Boggio, P.S. et al., 2006. Enhancement of non-dominant hand motor function by anodal transcranial direct current stimulation. *Neuroscience Letters*, 404(1-2), 232-6.

Boyd, L.A. & Linsdell, M.A., 2009. Excitatory repetitive transcranial magnetic stimulation to left dorsal premotor cortex enhances motor consolidation of new skills. *BMC Neuroscience*, 10, 72.

Boyeson, M.G. & Feeney, D.M., 1990. Intraventricular norepinephrine facilitates motor recovery following sensorimotor cortex injury. *Pharmacology, Biochemistry, and Behavior*, 35(3), 497-501.

Briand, L.A. et al., 2007. Modulators in concert for cognition: Modulator interactions in the prefrontal cortex. *Progress in Neurobiology*, 83, 69-91.

Broadbent, D.E., 1965. Information processing in the nervous system. *Science*, 150(695), 457-62.

Bronte-Stewart, H. et al., 2009. The STN beta-band profile in Parkinson's disease is stationary and shows prolonged attenuation after deep brain stimulation. *Experimental Neurology*, 215(1), 20-8.

Broughton, R. & Hasan, J., 1995. Quantitative topographic electroencephalographic mapping during drowsiness and sleep onset. *Journal of Clinical Neurophysiology*, 12(4), 372-86.

Buzsáki, G. & Draguhn, A., 2004. Neuronal oscillations in cortical networks. *Science*, 304(5679), 1926-9.

Bütefisch, C.M. et al., 2000. Mechanisms of use-dependent plasticity in the human motor cortex. *Proceedings of the National Academy of Sciences of the United States of America*, 97(7), 3661-5.

Cannon, R. et al., 2007. The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. *The International Journal of Neuroscience*, 117(3), 337-57.

Capotosto, P. et al., 2009. Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *The Journal of Neuroscience*, 29(18), 5863-72.

Cechetto, D. & Saper, C., 1990. Role of the cerebral cortex in autonomic function. In L. A. & S. K. *Central Regulation of Autonomic Functions*. Oxford: Oxford Univ. Press, pp. 208-223.

Cheeran, B. et al., 2008. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *The Journal of Physiology*, 586(Pt 23), 5717-25.

Chen, R. et al., 1997. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*, 48(5), 1398-403.

Chen, Y. & Parrish, T.B., 2009. Caffeine dose effect on activation-induced BOLD and CBF responses. *NeuroImage*, 46(3), 577-83.

Cho, M.K. et al., 2008. Alpha neurofeedback improves the maintaining ability of alpha activity. *Neuroreport*, 19(3), 315-7.

Christie, M.J., 1973. Electrodermal activity and the stress response. A review. *Acta medica Polona*, 14(4), 343-55.

Clarke, A.R. et al., 2007. Effects of stimulant medications on the EEG of girls with Attention-Deficit/Hyperactivity Disorder. *Clinical Neurophysiology*, 118(12), 2700-8.

Coben, R., Linden, M. & Myers, T.E., 2009. Neurofeedback for Autistic Spectrum Disorder: A Review of the Literature. *Applied Psychophysiology and Biofeedback*.

Cohen, M.X. et al., 2009. Neuroelectric signatures of reward learning and decision-making in the human nucleus accumbens. *Neuropsychopharmacology*, 34(7), 1649-58.

Cooke, S.F. & Bliss, T.V., 2006. Plasticity in the human central nervous system. *Brain*, 129(Pt 7), 1659-73.

Cools, R., Roberts, A.C. & Robbins, T.W., 2008. Serotoninergic regulation of emotional and behavioural control processes. *Trends in Cognitive Sciences*, 12(1), 31-40.

Corbetta, M. & Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, 3(3), 201-15.

Corbetta, M., Patel, G. & Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. *Neuron*, 58(3), 306-24.

Coull, J.T. et al., 1999. Noradrenergically mediated plasticity in a human attentional neuronal network. *NeuroImage*, 10(6), 705-15.

Critchley, H.D. et al., 2002. Volitional control of autonomic arousal: a functional magnetic resonance study. *NeuroImage*, 16(4), 909-19.

Critchley, H.D., 2002. Electrodermal responses: what happens in the brain. *The Neuroscientist*, 8(2), 132-42.

Cuspineda, E. et al., 2007. QEEG prognostic value in acute stroke. *Clinical EEG and Neuroscience*, 38(3), 155-60.

De Koninck, P., 1998. Sensitivity of CaM Kinase II to the Frequency of Ca2+ Oscillations. *Science*, 279(5348), 227-230.

DeCharms, R.C., 2007. Reading and controlling human brain activation using real-time functional magnetic resonance imaging. *Trends in Cognitive Sciences*, 11(11), 473-81.

Deiber, M.P. et al., 1997. Frontal and parietal networks for conditional motor learning: a positron emission tomography study. *Journal of Neurophysiology*, 78(2), 977-91.

Del-Ben, C.M. et al., 2005. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. *Neuropsychopharmacology*, 30(9), 1724-34.

Delagrange, P. et al., 1993. Effects of locus coeruleus lesions on vigilance and attentive behaviour in cat. *Behavioural Brain Research*, 53(1-2), 155-65.

Delorme, A. & Makeig, S., 2003. EEG changes accompanying learned regulation of 12-Hz EEG activity. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 11(2), 133-7.

Denes, G. et al., 1982. Unilateral spatial neglect and recovery from hemiplegia: a follow-up study. *Brain*, 105 (Pt 3), 543-52.

Dennis, N.A., Howard, J.H. & Howard, D.V., 2006. Implicit sequence learning without motor sequencing in young and old adults. *Experimental Brain Research*, 175(1), 153-64.

Doehnert, M. et al., 2008. Slow cortical potential neurofeedback in attention deficit hyperactivity disorder: is there neurophysiological evidence for specific effects? *Journal of Neurophysiology*, 115(10), 1445-56.

Dolan, R.J., 2007. The human amygdala and orbital prefrontal cortex in behavioural regulation. *Philosophical Transactions of the Royal Society of London. Series B*, 362(1481), 787-99.

Doyon, J. et al., 1996. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. *The European Journal of Neuroscience*, 8(4), 637-48.

Dringenberg, H.C. & Olmstead, M.C., 2003. Integrated contributions of basal forebrain and thalamus to neocortical activation elicited by pedunculopontine tegmental stimulation in urethane-anesthetized rats. *Neuroscience*, 119(3), 839-53.

Dringenberg, H.C. & Vanderwolf, C.H., 1998. Involvement of direct and indirect pathways in electrocorticographic activation. *Neuroscience and Biobehavioral Reviews*, 22(2), 243-57.

Durstewitz, D., Seamans, J.K. & Sejnowski, T.J., 2000. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. *Journal of Neurophysiology*, 83(3), 1733-50.

Eckart, M.T. et al., 2009. 6-Hydroxydopamine Lesions in the Rat Neostriatum Impair Sequential Learning in a Serial Reaction Time Task. *Neurotoxicity Research*.

Egner, T., Zech, T.F. & Gruzelier, J.H., 2004. The effects of neurofeedback training on the spectral topography of the electroencephalogram. *Clinical Neurophysiology*, 115(11), 2452-60.

Egner, T. & Gruzelier, J.H., 2004. EEG biofeedback of low beta band components: frequency-specific effects on variables of attention and event-related brain potentials. *Clinical Neurophysiology*, 115(1), 131-9.

Egner, T. & Gruzelier, J.H., 2003. Ecological validity of neurofeedback: modulation of slow wave EEG enhances musical performance. *Neuroreport*, 14(9), 1221-4.

Egner, T. & Gruzelier, J.H., 2001. Learned self-regulation of EEG frequency components affects attention and event-related brain potentials in humans. *Neuroreport*, 12(18), 4155-9.

Egner, T., Strawson, E. & Gruzelier, J., 2002. EEG signature and phenomenology of alpha/ theta neurofeedback training versus mock feedback. *Applied Psychophysiology and Biofeedback*, 27(4), 261–270.

Ego-Stengel, V. et al., 2001. Acetylcholine-dependent induction and expression of functional plasticity in the barrel cortex of the adult rat. *Journal of Neurophysiology*, 86(1), 422-37.

Evers, E.A. et al., 2006. The effect of acute tryptophan depletion on the BOLD response during performance monitoring and response inhibition in healthy male volunteers. *Psychopharmacology*, 187(2), 200-8.

Ezra, D.G. et al., 2009. Skills acquisition and assessment after a microsurgical skills course for ophthalmology residents. *Ophthalmology*, 116(2), 257-62.

Fallgatter, A.J. et al., 2004. Allelic variation of serotonin transporter function modulates the brain electrical response for error processing. *Neuropsychopharmacology*, 29(8), 1506-11.

Fan, J. et al., 2007. The relation of brain oscillations to attentional networks. *The Journal of Neuroscience*, 27(23), 6197-206.

Fan, J. et al., 2002. Testing the efficiency and independence of attentional networks. *The Journal of Cognitive Neuroscience*, 14(3), 340-7.

Feeney, D.M., Gonzalez, A. & Law, W.A., 1982. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science*, 217(4562), 855-7.

Fernández, T. et al., 2007. Changes in EEG current sources induced by neurofeedback in learning disabled children. An exploratory study. *Applied Psychophysiology and Biofeedback*, 32(3-4), 169-83.

Fetz, E.E., 2007. Volitional control of neural activity: implications for brain-computer interfaces. *The Journal of Physiology*, 579(Pt 3), 571-9.

Finnigan, S.P. et al., 2007. Quantitative EEG indices of sub-acute ischaemic stroke correlate with clinical outcomes. *Clinical Neurophysiology*, 118(11), 2525-32.

Finnigan, S.P. et al., 2004. Correlation of quantitative EEG in acute ischemic stroke with 30-day NIHSS score: comparison with diffusion and perfusion MRI. *Stroke*, 35(4), 899-903.

Fiorino, D.F. et al., 1993. Electrical stimulation of reward sites in the ventral tegmental area increases dopamine transmission in the nucleus accumbens of the rat. *Behavioural Brain Research*, 55(2), 131-41.

Fischer, S. et al., 2002. Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences of the United States of America*, 99(18), 11987-91.

Fishbein, D.H., Thatcher, R.W. & Cantor, D.S., 1990. Ingestion of carbohydrates varying in complexity produce differential brain responses. *Clinical EEG (electroencephalography)*, 21(1), 5-11.

Fogel, S.M. & Smith, C.T., 2006. Learning-dependent changes in sleep spindles and Stage 2 sleep. *Journal of Sleep Research*, 15(3), 250-5.

Foote, S.L. & Morrison, J.H., 1987. Extrathalamic modulation of cortical function. *Annual Review of Neuroscience*, 10, 67-95.

Foreman, M.M., Hall, J.L. & Love, R.L., 1992. Effects of fenfluramine and para-chloroamphetamine on sexual behavior of male rats. *Psychopharmacology*, 107(2-3), 327-30.

Fournier, G.N. et al., 2004. Cortical acetylcholine release and electroencephalogram activation evoked by ionotropic glutamate receptor agonists in the rat basal forebrain. *Neuroscience*, 123(3), 785-92.

Fratello, F. et al., 2006. Modulation of corticospinal excitability by paired associative stimulation: reproducibility of effects and intraindividual reliability. *Clinical Neurophysiology*, 117(12), 2667-74.

Freedman, L.W. et al., 1994. The relationship of sweat gland count to electrodermal activity. *Psychophysiology*, 31(2), 196-200.

Fregni, F. et al., 2005. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport*, 16(14), 1551-5.

French, J.D. & Magoun, H.W., 1952. Effects of chronic lesions in central cephalic brain stem of monkeys. *Archives of Neurology and Psychiatry*, 68(5), 591-604.

Fries, P. et al., 2008. The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. *The Journal of Neuroscience*, 28(18), 4823-35.

Frohman, L.A., 1983. CNS peptides and glucoregulation. *Annual Review of Physiology*, 45, 95-107.

Fuentealba, P. et al., 2005. Membrane bistability in thalamic reticular neurons during spindle oscillations. *Journal of Neurophysiology*, 93(1), 294-304.

Fuster, J.M., 1958. Effects of stimulation of brain stem on tachistoscopic perception. *Science*, 127(3290), 150.

Galea, J.M. et al., 2009. Disruption of the Dorsolateral Prefrontal Cortex Facilitates the Consolidation of Procedural Skills. *Journal of Cognitive Neuroscience*, May 4. [Ep.

Gamer, M. et al., 2008. Combining physiological measures in the detection of concealed information. *Physiology & Behavior*, 95(3), 333-40.

Gangitano, M. et al., 2002. Modulation of input-output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex. *Clinical Neurophysiology*, 113(8), 1249-57.

Garris, P.A. & Wightman, R.M., 1994. Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an in vivo voltammetric study. *The Journal of Neuroscience*, 14(1), 442-50.

Gelinas, J.N. et al., 2008. Beta-adrenergic receptor activation during distinct patterns of stimulation critically modulates the PKA-dependence of LTP in the mouse hippocampus. *Learning & Memory*, 15(5), 281-9.

Gelinas, J.N. & Nguyen, P.V., 2005. Beta-adrenergic receptor activation facilitates induction of a protein synthesis-dependent late phase of long-term potentiation. *The Journal of Neuroscience*, 25(13), 3294-303.

Gevensleben, H. et al., 2009. Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. *International Journal of Psychophysiology*, 74(2), 149-57.

Gibson, A. et al., 2005. The first cut is the deepest: basic surgical training in ophthalmology. *Eye*, 19(12), 1264-70.

Gogate, P.M., 2009. Small incision cataract surgery: Complications and mini-review. *Indian journal of Ophthalmology*, 57(1), 45-9.

Gould, T.J. & Lommock, J.A., 2003. Nicotine enhances contextual fear conditioning and ameliorates ethanol-induced deficits in contextual fear conditioning. *Behavioral Neuroscience*, 117(6), 1276-82.

Gould, T.J. & Wehner, J.M., 1999. Nicotine enhancement of contextual fear conditioning. *Behavioural Brain Research*, 102(1-2), 31-9.

Grefkes, C. et al., 2009. Noradrenergic Modulation of Cortical Networks Engaged in Visuomotor Processing. *Cerebral Cortex*, 20(4), 783-797

Grenier, F., Timofeev, I. & Steriade, M., 2001. Focal synchronization of ripples (80-200 Hz) in neocortex and their neuronal correlates. *Journal of Neurophysiology*, 86(4), 1884-98.

Griffin, A.L. et al., 2004. Theta-contingent trial presentation accelerates learning rate and enhances hippocampal plasticity during trace eyeblink conditioning. *Behavioral Neuroscience*, 118(2), 403-11.

Gross, A. et al., 2004. Clozapine-induced QEEG changes correlate with clinical response in schizophrenic patients: a prospective, longitudinal study. *Pharmacopsychiatry*, 37(3), 119-22.

Gruzelier, J., 2009. A theory of alpha/theta neurofeedback, creative performance enhancement, long distance functional connectivity and psychological integration. *Cognitive Processing*, 10 Suppl 1, 101-9.

Gruzelier, J. & Egner, T., 2005. Critical validation studies of neurofeedback. *Child and Adolescent Psychiatric Clinics of North America*, 14(1), 83-104, vi.

Gruzelier, J., Egner, T. & Vernon, D., 2006. Validating the efficacy of neurofeedback for optimising performance. *Progress in Brain Research*, 159, 421-31.

Gu, Q. & Singer, W., 1995. Involvement of serotonin in developmental plasticity of kitten visual cortex. *The European Journal of Neuroscience*, 7(6), 1146-53.

Hadamitzky, M. et al., 2009. Effects of acute systemic administration of serotonin2A/C receptor ligands in a delay-based decision-making task in rats. *Behavioural Pharmacology*, 20(5-6), 415-23.

Hallett, M., 2007. Transcranial magnetic stimulation: a primer. *Neuron*, 55(2), 187-99.

Halsband, U. & Freund, H.J., 1993. Motor learning. *Current Opinion in Neurobiology*, 3(6), 940-9.

Hamidi, M. et al., 2009. Repetitive Transcranial Magnetic Stimulation Affects behavior by Biasing Endogenous Cortical Oscillations. *Frontiers in Integrative Neuroscience*, 3, 14.

Hanslmayr, S. et al., 2005. Increasing Individual Upper Alpha Power by Neurofeedback Improves Cognitive Performance in Human Subjects. *Applied Psychophysiology and Biofeedback*, 30(1), 1-10.

Harley, C.W., 2007. Norepinephrine and the dentate gyrus. *Progress in Brain Research*, 163, 299-318.

Harley, C.W., 1987. A role for norepinephrine in arousal, emotion and learning?: limbic modulation by norepinephrine and the Kety hypothesis. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, 11(4), 419-58.

Hawkins, J., George, D. & Niemasik, J., 2009. Sequence memory for prediction, inference and behaviour. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 364(1521), 1203-9.

Heinrich, H., Gevensleben, H. & Strehl, U., 2007. Annotation: neurofeedback - train your brain to train behaviour. *Journal of Child Psychology and Psychiatry*, 48(1), 3-16.

Hillyard, S.A., Vogel, E.K. & Luck, S.J., 1998. Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London. Series B*, 353(1373), 1257-70.

Hoedlmoser, K. et al., 2008. Instrumental conditioning of human sensorimotor rhythm (12-15 Hz) and its impact on sleep as well as declarative learning. *Sleep*, 31(10), 1401-8.

Huang, Y. et al., 2005. Theta burst stimulation of the human motor cortex. *Neuron*, 45(2), 201-6.

Hummel, F. et al., 2005. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*, 128(Pt 3), 490-9.

Hurley, L.M., Devilbiss, D.M. & Waterhouse, B.D., 2004. A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. *Current Opinion in Neurobiology*, 14(4), 488-95.

Ikemoto, S. & Wise, R.A., 2002. Rewarding effects of the cholinergic agents carbachol and neostigmine in the posterior ventral tegmental area. *The Journal of Neuroscience*, 22(22), 9895-904.

Jacobs, B.L. & Fornal, C.A., 1991. Activity of brain serotonergic neurons in the behaving animal. *Pharmacological Reviews*, 43(4), 563-78.

Jacobs, B.L., Wise, W.D. & Taylor, K.M., 1974. Differential behavioral and neurochemical effects following lesions of the dorsal or median raphe nuclei in rats. *Brain Research*, 79(3), 353-61.

Jang, S.H. et al., 2009. The effect of transcranial direct current stimulation on the cortical activation by motor task in the human brain: an fMRI study. *Neuroscience Letters*, 460(2), 117-20.

Jasper, H.H. & Droogleever-Fortuyn, J., 1948. Thalamo-cortical systems and the electrical activity of the brain. *Federation Proceedings*, 7(1 Pt 1), 61.

Jensen, J.L., Marstrand, P.C. & Nielsen, J.B., 2005. Motor skill training and strength training are associated with different plastic changes in the central nervous system. *Journal of Applied Physiology*, 99(4), 1558-68.

Jensen, O., Kaiser, J. & Lachaux, J., 2007. Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences*, 30(7), 317-24.

Jensen, O. et al., 2005. On the human sensorimotor-cortex beta rhythm: sources and modeling. *NeuroImage*, 26(2), 347-55.

John, E.R. et al., 1977. Neurometrics. *Science*, 196(4297), 1393-410.

Jones, B.E. & Webster, H.H., 1988. Neurotoxic lesions of the dorsolateral pontomesencephalic tegmentum-cholinergic cell area in the cat. I. Effects upon the cholinergic innervation of the brain. *Brain Research*, 451(1-2), 13-32.

Jones, B.E. et al., 1973. The effect of lesions of catecholamine-containing neurons upon monoamine content of the brain and EEG and behavioral waking in the cat. *Brain Research*, 58(1), 157-77.

Jouvet, M. & Pujol, J.F., 1972. [Role of monoamines in the regulation of alertness. Neurophysiological and biochemical study]. *Revue Neurologique*, 127(1), 115-38.

Jueptner, M. & Weiller, C., 1998. A review of differences between basal ganglia and cerebellar control of movements as revealed by functional imaging studies. *Brain*, 121 (Pt 8), 1437-49.

Jung, P. & Ziemann, U., 2009. Homeostatic and nonhomeostatic modulation of learning in human motor cortex. *The Journal of Neuroscience*, 29(17), 5597-604.

Jung, S.H. et al., 2008. Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. *Clinical Neurophysiology*, 119(1), 71-9.

Kakeyama, M. et al., 2002. Decrease of serotonin and metabolite in the forebrain and facilitation of lordosis by dorsal raphe nucleus lesions in male rats. *Endocrine Journal*, 49(5), 573-9.

Kamiya, J., Callaway, E. & Yeager, C., 1969. Visual evoked responses in subjects trained to control alpha rhythms. *Psychophysiology*, 5, 683-695.

Kamiya, J., 1968. Conscious control of brain waves. *Psychology Today*, 1, 57-60.

Kang, J.I. & Vaucher, E., 2009. Cholinergic pairing with visual activation results in long-term enhancement of visual evoked potentials. *PloS One*, 4(6), e5995.

Kanno, M. et al., 2003. Effects of acute repetitive transcranial magnetic stimulation on extracellular serotonin concentration in the rat prefrontal cortex. *Journal of Pharmacological Sciences*, 93(4), 451-7.

Karni, A. & Bertini, G., 1997. Learning perceptual skills: behavioral probes into adult cortical plasticity. *Current Opinion in Neurobiology*, 7(4), 530-5.

Kasamatsu, T. & Pettigrew, J.D., 1979. Preservation of binocularity after monocular deprivation in the striate cortex of kittens treated with 6-hydroxydopamine. *The Journal of Comparative Neurology*, 185(1), 139-61.

Kastner, S. et al., 1999. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron*, 22(4), 751-61.

Keck, M.E. et al., 2002. Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. *Neuropharmacology*, 43(1), 101-9.

Kellner, R. & Uhlenhuth, E.H., 1991. The rating and self-rating of anxiety. *The British journal of psychiatry. Supplement*, (12), 15-22.

Kety, S.S., 1972. The possible role of the adrenergic systems of the cortex in learning. *Research publications - Association for Research in Nervous and Mental Disease*, 50, 376-89.

Kim, Y. et al., 2004. Facilitative effect of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. *Neuroscience Letters*, 367(2), 181-5.

Kirkwood, A. & Bear, M.F., 1995. Elementary forms of synaptic plasticity in the visual cortex. *Biological Research*, 28(1), 73-80.

Kitchigina, V. et al., 1997. Novelty-elicited, noradrenaline-dependent enhancement of excitability in the dentate gyrus. *The European Journal of Neuroscience*, 9(1), 41-7.

Knowlton B.J., S.N., 1996. Dissociations within nondeclarative memory in Huntington's disease. *Neuropsychology*, 10, 538-548.

Kobayashi, M. et al., 2004. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology*, 62(1), 91-8.

Kocsis, B. et al., 2006. Serotonergic neuron diversity: identification of raphe neurons with discharges time-locked to the hippocampal theta rhythm. *Proceedings of the National Academy of Sciences of the United States of America*, 103(4), 1059-64.

Koepp, M.J. et al., 1998. Evidence for striatal dopamine release during a video game. *Nature*, 393(6682), 266-8.

Kole, M.H. et al., 1999. Changes in 5-HT1A and NMDA binding sites by a single rapid transcranial magnetic stimulation procedure in rats. *Brain Research*, 826(2), 309-12.

Komaki, A. et al., 2007. Effects of GABAergic inhibition on neocortical long-term potentiation in the chronically prepared rat. *Neuroscience Letters*, 422(3), 181-6.

Korb, A.S. et al., 2008. Brain electrical source differences between depressed subjects and healthy controls. *Brain Topography*, 21(2), 138-46.

Kotchoubey, B. et al., 1999. Changes in EEG power spectra during biofeedback of slow cortical potentials in epilepsy. *Applied Psychophysiology and Biofeedback*, 24(4), 213-33.

Krichmar, J.L., 2008. The Neuromodulatory System: A Framework for Survival and Adaptive Behavior in a Challenging World. *Adaptive Behavior*, 16(6), 385-399.

Kristeva, R. et al., 2005. Electroencephalographic spectral power in writer's cramp patients: evidence for motor cortex malfunctioning during the cramp. *NeuroImage*, 27(3), 706-14.

Kropotov, J.D. & Etlinger, S.C., 1999. Selection of actions in the basal ganglia-thalamocortical circuits: review and model. *International Journal of Psychophysiology*, 31(3), 197-217.

Kuczewski, N. et al., 2009. Activity-dependent dendritic release of BDNF and biological consequences. *Molecular Neurobiology*, 39(1), 37-49.

Kujirai, T. et al., 1993. Corticocortical inhibition in human motor cortex. *The Journal of Physiology*, 471, 501-19.

Kułak, W. et al., 2006. Neurophysiologic and neuroimaging studies of brain plasticity in children with spastic cerebral palsy. *Experimental Neurology*, 198(1), 4-11.

Lafleur, M.F. et al., 2002. Motor learning produces parallel dynamic functional changes during the execution and imagination of sequential foot movements. *NeuroImage*, 16(1), 142-57.

Lapish, C.C. et al., 2007. The ability of the mesocortical dopamine system to operate in distinct temporal modes. *Psychopharmacology*, 191(3), 609-25.

Larsen, C.R. et al., 2009. Effect of virtual reality training on laparoscopic surgery: randomised controlled trial. *British Medical Journal*, 338, b1802.

Larson, J. & Lynch, G., 1986. Induction of synaptic potentiation in hippocampus by patterned stimulation involves two events. *Science*, 232, 985-988.

Lashley, K., 1917. The Effects of Strychnine and Caffeine Upon the Rate of Learning. *Psychobiology*, 1(2), 141-169.

Lazzaro, V.D., Ziemann, U. & Lemon, R.N., 2008. State of the art: Physiology of transcranial motor cortex stimulation. *Brain Stimulation*, 1(4), 345-362.

Leanza, G. et al., 1996. Selective immunolesioning of the basal forebrain cholinergic system disrupts short-term memory in rats. *The European Journal of Neuroscience*, 8(7), 1535-44.

Leckman, J.F. et al., 2006. Annotation: Tourette syndrome: a relentless drumbeat--driven by misguided brain oscillations. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 47(6), 537-50.

Lee, H.K. et al., 2000. Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. *Nature*, 405(6789), 955-9.

Lee, M.G. et al., 2005. Cholinergic basal forebrain neurons burst with theta during waking and paradoxical sleep. *The Journal of Neuroscience*, 25(17), 4365-9.

Levin, E.D. et al., 1998. Nicotine-dizocilpine interactions and working and reference memory performance of rats in the radial-arm maze. *Pharmacology, Biochemistry, and Behavior*, 61(3), 335-40.

Lewis, B.L. & O'Donnell, P., 2000. Ventral tegmental area afferents to the prefrontal cortex maintain membrane potential 'up' states in pyramidal neurons via D(1) dopamine receptors. *Cerebral Cortex*, 10(12), 1168-75.

Lewis, C.M. et al., 2009. From the Cover: Learning sculpts the spontaneous activity of the resting human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 106(41), 17558-63.

Lewis, D.A. et al., 1987. The distribution of tyrosine hydroxylase-immunoreactive fibers in primate neocortex is widespread but regionally specific. *The Journal of Neuroscience*, 7(1), 279-90.

Li, W., Piëch, V. & Gilbert, C.D., 2008. Learning to link visual contours. *Neuron*, 57(3), 442-51.

Liepert, J. et al., 1998. Task-dependent changes of intracortical inhibition. *Experimental Brain Research*, 118(3), 421-6.

Liepert, J. et al., 1997. The glutamate antagonist riluzole suppresses intracortical facilitation. *Journal of Neural Transmission*, 104(11-12), 1207-14.

Lindsley, D.B. et al., 1950. Behavioral and EEG changes following chronic brain stem lesions in the cat. *Electroencephalography and Clinical Neurophysiology*, 2(4), 483-98.

Liu, X. et al., 2008. The sensory and motor representation of synchronized oscillations in the globus pallidus in patients with primary dystonia. *Brain*, 131(Pt 6), 1562-73.

Lomo, T., 1966. Frequency potentiation of excitatory synaptic activity in the dentate area of the hippocampal formation. *Acta Physiologica Scandinavia*, 68(Suppl. 277), 128.

Lorr, M. et al., 1981. Profile of mood states. *Journal of Clinical Psychiatry*, 60, 89-95.

Lotze, M. et al., 2003. Motor learning elicited by voluntary drive. *Brain*, 126(Pt 4), 866-72.

Lubar, J.F. et al., 1995. Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. *Biofeedback and Self-Regulation*, 20(1), 83-99.

Lubar, J.F., 1991. Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. *Biofeedback and Self-Regulation*, 16(3), 201-225.

Lubar, J.F. & Shouse, M.N., 1976. EEG and behavioral changes in a hyperkinetic child concurrent with training of the sensorimotor rhythm (SMR): a preliminary report. *Biofeedback and Self-regulation*, 1(3), 293-306.

Lutzenberger, W. et al., 1980. Self-regulation of slow cortical potentials in normal subjects and patients with frontal lobe lesions. *Progress in Brain Research*, 54, 427-30.

Lévesque, J., Beauregard, M. & Mensour, B., 2006. Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. *Neuroscience letters*, 394(3), 216-21.

Maier, S.F. & Watkins, L.R., 2005. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin, and corticotropin-releasing factor. *Neuroscience and Biobehavioral Reviews*, 29(4-5), 829-41.

Malinow, R. & Malenka, R.C., 2002. AMPA receptor trafficking and synaptic plasticity. *Annual Review of Neuroscience*, 25, 103-26.

Marken, R.S., 2009. You say you had a revolution: Methodological foundations of closed-loop psychology. *Review of General Psychology*, 13(2), 137-145.

Markram, H. et al., 1999. Frequency-Dependent Synaptic Transmission in the Neocortex. In M. Baudry, L. Davis, & R. Thompson *Advances in Synaptic Plasticity*. MIT press.

Markram, H. et al., 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*, 275(5297), 213-5.

Mayer, A.R. et al., 2004. Neural networks underlying endogenous and exogenous visual-spatial orienting. *NeuroImage*, 23(2), 534-41.

McCormick, D.A. & Bal, T., 1997. Sleep and arousal: thalamocortical mechanisms. *Annual Review of Neuroscience*, 20, 185-215.

McKenna, T.M. et al., 1988. Muscarinic agonists modulate spontaneous and evoked unit discharge in auditory cortex of cat. *Synapse*, 2(1), 54-68.

Meintzschel, F. & Ziemann, U., 2006. Modification of practice-dependent plasticity in human motor cortex by neuromodulators. *Cerebral Cortex*, 16(8), 1106-15.

Meltzer, J.A., Fonzo, G.A. & Constable, R.T., 2009. Transverse patterning dissociates human EEG theta power and hippocampal BOLD activation. *Psychophysiology*, 46(1), 153-62.

Meneses, A. & Perez-Garcia, G., 2007. 5-HT(1A) receptors and memory. *Neuroscience and Biobehavioral Reviews*, 31(5), 705-27.

Mesulam, M.M. et al., 1983. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience*, 10(4), 1185-201.

Millan, M.J., 2003. The neurobiology and control of anxious states. *Progress in Neurobiology*, 70, 83-244.

Mink, J.W., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. *Progress in Neurobiology*, 50(4), 381-425.

Miranda, P.C., Lomarev, M. & Hallett, M., 2006. Modeling the current distribution during transcranial direct current stimulation. *Clinical Neurophysiology*, 117(7), 1623-9.

Molina-Luna, K. et al., 2009. Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PloS One*, 4(9), e7082.

Montaron, M.F. et al., 1982. Ventral mesencephalic tegmentum (VMT) controls electrocortical beta rhythms and associated attentive behaviour in the cat. *Behavioural Brain Research*, 6(2), 129-45.

Monte-Silva, K. et al., 2009. Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and nonfocal plasticity in humans. *The Journal of Neuroscience*, 29(19), 6124-31.

Moore, N.C., 2005. The Neurotherapy of Anxiety Disorders. *Journal of Adult Development*, 12(2-3), 147-154.

Moore, R.Y. & Bloom, F.E., 1978. Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. *Annual Review of Neuroscience*, 1, 129-69.

Morin, A. et al., 2008. Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. *Sleep*, 31(8), 1149-56.

Moruzzi, G. & Magoun, H.W., 1949. Brain stem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology*, 1(4), 455-73.

Muellbacher, W. et al., 2002. Early consolidation in human primary motor cortex. *Nature*, 415(6872), 640-4.

Muellbacher, W. et al., 2001. Role of the human motor cortex in rapid motor learning. *Experimental Brain Research*, 136(4), 431-8.

Muir, J.L., Everitt, B.J. & Robbins, T.W., 1994. AMPA-induced excitotoxic lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function. *The Journal of Neuroscience*, 14(4), 2313-26.

Mukhina, E.A., 2009. [Experience with simultaneous cataract extraction and trabeculectomy]. *Vestnik Oftalmologii*, (2), 35-7.

Murphy, F.C. et al., 2002. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology*, 163(1), 42-53.

Muslimovic, D. et al., 2007. Motor procedural learning in Parkinson's disease. *Brain*, 130(Pt 11), 2887-97.

Müller, J.F. et al., 2007. Homeostatic plasticity in human motor cortex demonstrated by two consecutive sessions of paired associative stimulation. *The European Journal of Neuroscience*, 25(11), 3461-8.

Müller-Dahlhaus, J.F. et al., 2008. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental Brain Research,* 187(3), 467-75.

Neiss, R., 1988. Reconceptualizing arousal: psychobiological states in motor performance. *Psychological Bulletin*, 103(3), 345-66.

Nelson, S.B. & Turrigiano, G.G., 2008. Strength through diversity. *Neuron*, 60(3), 477-82.

Netz, J., 1999. Asymmetry in transcallosal inhibition. *Electroencephalography and Clinical Neurophysiology. Supplement*, 51, 137-44.

Netz, J., Ziemann, U. & Hömberg, V., 1995. Hemispheric asymmetry of transcallosal inhibition in man. *Experimental Brain Research*, 104(3), 527-33.

Neuper, C., Wörtz, M. & Pfurtscheller, G., 2006. ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Progress in Brain Research*, 159, 211-22.

Niedermayer, E. & Lopes Da Silva, F., 1999. *Electroencephalography: Basic Principles, Clinical Applications and Related Fields.* Fourth., Williams & Wilkins.

Niehaus, J.L., Cruz-Bermudez, N.D. & Kauer, J.A., 2009. Plasticity of addiction: a mesolimbic dopamine short-circuit? *The American Journal on Addictions*, 18(4), 259-71.

Niessing, J. et al., 2005. Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science*, 309(5736), 948-51.

Nissen, M.J., Willingham, D. & Hartman, M., 1989. Explicit and implicit remembering: when is learning preserved in amnesia? *Neuropsychologia*, 27(3), 341-52.

Nissen, M.J. & Bullemer, P., 1987. Attentional requirements of learning: Evidence from performance measures. *Cognitive Psychology*, 19, 1-32.

Nitsche, M.A. et al., 2004. Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology*, 29(8), 1573-8.

Nitsche, M.A. et al., 2003. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of Cognitive Neuroscience*, 15(4), 619-26.

Nitsche, M.A. et al., 2003. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, 553(Pt 1), 293-301.

Nitsche, M.A. & Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, 57(10), 1899-901.

Nitsche, M.A. & Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, 527 Pt 3, 633-9.

Nordberg, A., 1999. PET studies and cholinergic therapy in Alzheimer's disease. *Revue Neurologique*, 155 Suppl, S53-63.

Nowlis, D.P. & Kamiya, J., 1970. The control of electroencephalographic alpha rhythms through auditory feedback and the associated mental activity. *Psychophysiology*, 6(4), 476-84.

Nudo, R.J. et al., 1996. Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *The Journal of Neuroscience*, 16(2), 785-807.

O'Connor, D.H. et al., 2002. Attention modulates responses in the human lateral geniculate nucleus. *Nature Neuroscience*, 5(11), 1203-9.

O'Reilly, R.C. et al., 2002. Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control. *Cerebral Cortex*, 12(3), 246-57.

Oishi, N. et al., 2007. Neural correlates of regional EEG power change. *NeuroImage*, 36(4), 1301-12.

Packard, M.G. & White, N.M., 1991. Dissociation of hippocampus and caudate nucleus memory systems by posttraining intracerebral injection of dopamine agonists. *Behavioral neuroscience*, 105(2), 295-306.

Paisley, A.C. & Summerlee, A.J., 1984. Relationships between behavioural states and activity of the cerebral cortex. *Progress in Neurobiology*, 22(2), 155-84.

Pariente, J. et al., 2001. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. *Annals of Neurology*, 50(6), 718-29.

Pascual-Leone, A. et al., 2005. the Plastic Human Brain Cortex. *Annual Review of Neuroscience*, 28(1), 377-401.

Pascual-Leone, A., Grafman, J. & Hallett, M., 1994. Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science*, 263(5151), 1287-9.

Paulsen, O. & Sejnowski, T.J., 2000. Natural patterns of activity and long-term synaptic plasticity. *Current Opinion in Neurobiology*, 10(2), 172-9.

Peniston, E.G. & Kulkosky, P.J., 1989. Alpha-theta brainwave training and beta-endorphin levels in alcoholics. *Alcoholism, Clinical and Experimental Research*, 13(2), 271-9.

Pepeu, G. & Giovannini, M.G., 2009. Cholinesterase inhibitors and beyond. *Current Alzheimer Research*, 6(2), 86-96.

Perez, M.A. et al., 2004. Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Experimental Brain Research*, 159(2), 197-205.

Peterson, B.S. et al., 1999. An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Biological Psychology*, 45(10), 1237-58.

Plautz, E.J., Milliken, G.W. & Nudo, R.J., 2000. Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiology of Learning and Memory*, 74(1), 27-55.

Plewnia, C. et al., 2004. Improved motor skill acquisition after selective stimulation of central norepinephrine. *Neurology*, 62(11), 2124-6.

Ponomarenko, A.A. et al., 2008. Frequency of network synchronization in the hippocampus marks learning. *The European Journal of Neuroscience*, 27(11), 3035-42.

Portas, C.M. et al., 1998. On-line detection of extracellular levels of serotonin in dorsal raphe nucleus and frontal cortex over the sleep/wake cycle in the freely moving rat. *Neuroscience*, 83(3), 807-14.

Poulos, C.X. & Cappell, H., 1991. Homeostatic theory of drug tolerance: a general model of physiological adaptation. *Psychological Review*, 98(3), 390-408.

Priori, A., 2003. Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, 114(4), 589-95.

Purpura, D.P. & McMurtry, J.G., 1965. Intracellular activities and evoked potential changes during polarization of motor cortex. *Journal of Neurophysiology*, 28, 166-85.

Ragert, P. et al., 2008. Improvement of spatial tactile acuity by transcranial direct current stimulation. *Clinical Neurophysiology*, 119(4), 805-11.

Rajkowski, J. et al., 1998. State-related activity, reactivity of locus ceruleus neurons in behaving monkeys. *Advances in Pharmacology*, 42, 740-4.

Ramos, B.P. & Arnsten, A.F., 2007. Adrenergic pharmacology and cognition: focus on the prefrontal cortex. *Pharmacology & Therapeutics*, 113(3), 523-36.

Rauch, S.L. et al., 1997. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping*, 5(2), 124-32.

Raymond, J. et al., 2005. Biofeedback and Dance Performance: A Preliminary Investigation. *Applied Psychophysiology and Biofeedback*, 30(1), 65-73.

Raymond, J. et al., 2005. The effects of alpha/theta neurofeedback on personality and mood. *Brain Research. Cognitive Brain Research*, 23(2-3), 287-92.

Reis, J. et al., 2009. Noninvasive cortical stimulation enhances motor skill acquisition over multiple days through an effect on consolidation. *Proceedings of the National Academy of Sciences of the United States of America*, 106(5), 1590-5.

Rioult-Pedotti, M.S. et al., 1998. Strengthening of horizontal cortical connections following skill learning. *Nature Neuroscience*, 1(3), 230-4.

Ritter, P., Moosmann, M. & Villringer, A., 2009. Rolandic alpha and beta EEG rhythms' strengths are inversely related to fMRI-BOLD signal in primary somatosensory and motor cortex. *Human Brain Mapping*, 30(4), 1168-87.

Robbins, T.W. et al., 1998. Neural systems underlying arousal and attention. Implications for drug abuse. *Annals of the New York Academy of Sciences*, 846, 222-37.

Robertson, E.M., 2007. The serial reaction time task: implicit motor skill learning? *The Journal of Neuroscience*, 27(38), 10073-5.

Romei, V. et al., 2008. Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. *Cerebral Cortex*, 18(9), 2010-8.

Rosanova, M. & Ulrich, D., 2005. Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. *The Journal of Neuroscience*, 25(41), 9398-405.

Rossi, S. et al., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*.

Rossini, P.M. et al., 1991. Brain excitability and electroencephalographic activation: non-invasive evaluation in healthy humans via transcranial magnetic stimulation. *Brain Research*, 567(1), 111-9.

Rothman, R.B. et al., 2001. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*, 39(1), 32-41.

Rougeul-Buser, A. & Buser, P., 1997. Rhythms in the alpha band in cats and their behavioural correlates. *International Journal of Psychophysiology*, 26(1-3), 191-203.

Rudrauf, D. et al., 2003. From autopoiesis to neurophenomenology: Francisco Varela's exploration of the biophysics of being. *Biological Research*, 36(1), 27-65.

Rösser, N. et al., 2008. Levodopa improves procedural motor learning in chronic stroke patients. *Archives of Physical Medicine and Rehabilitation*, 89(9), 1633-41.

Sanes, J.N. & Donoghue, J.P., 2000. Plasticity and primary motor cortex. *Annual Review of Neuroscience*, 23, 393-415.

Sara, S.J., 1998. Learning by neurones: role of attention, reinforcement and behaviour. *Comptes rendus de l'Académie des sciences. Série III, Sciences de la vie*, 321(2-3), 193-8.

Sarter, M., Parikh, V. & Howe, W.M., 2009. nAChR agonist-induced cognition enhancement: integration of cognitive and neuronal mechanisms. *Biochemical Pharmacology*, 78(7), 658-67.

Sauseng, P. et al., 2009. Spontaneous locally restricted EEG alpha activity determines cortical excitability in the motor cortex. *Neuropsychologia*, 47(1), 284-8.

Sawaki, L. et al., 2002. Cholinergic influences on use-dependent plasticity. *Journal of Neurophysiology*, 87(1), 166-71.

Sawaki, L. et al., 2003. Effect of an alpha(1)-adrenergic blocker on plasticity elicited by motor training. *Experimental Brain Research*, 148(4), 504-8.

Schoen, I. & Fromherz, P., 2008. Extracellular stimulation of mammalian neurons through repetitive activation of Na+ channels by weak capacitive currents on a silicon chip. *Journal of Neurophysiology*, 100(1), 346-57.

Schroeder, C.E. & Lakatos, P., 2009. Low-frequency neuronal oscillations as instruments of sensory selection. *Trends in Neurosciences*, 32(1), 9-18.

Schultz W., D.P., 1997. A neural substrate of prediction and reward. *Science*, 275, 1593-1599.

Schulz, P.E. & Fitzgibbons, J.C., 1997. Differing mechanisms of expression for short- and long-term potentiation. *Journal of Neurophysiology*, 78(1), 321-34.

Sebban, C. et al., 1999. Changes in EEG spectral power in the prefrontal cortex of conscious rats elicited by drugs interacting with dopaminergic and noradrenergic transmission. *British Journal of Pharmacology*, 128(5), 1045-54.

Sejnowski, T.J. & Destexhe, A., 2000. Why do we sleep? *Brain Research*, 886(1-2), 208-223.

Serences, J.T. et al., 2005. Coordination of voluntary and stimulus-driven attentional control in human cortex. *Psychological Science*, 16(2), 114-22.

Serizawa, K. et al., 2008. Comparison of quantitative EEGs between Parkinson disease and age-adjusted normal controls. *Journal of Clinical Neurophysiology*, 25(6), 361-6.

Sharp, S.I., McQuillin, A. & Gurling, H.M., 2009. Genetics of attention-deficit hyperactivity disorder (ADHD). *Neuropharmacology*.

Shin, A.C., Zheng, H. & Berthoud, H., 2009. An expanded view of energy homeostasis: neural integration of metabolic, cognitive, and emotional drives to eat. *Physiology & Behavior*, 97(5), 572-80.

Shor, O.L., Fidzinski, P. & Behr, J., 2009. Muscarinic acetylcholine receptors and voltage-gated calcium channels contribute to bidirectional synaptic plasticity at CA1-subiculum synapses. *Neuroscience Letters*, 449(3), 220-3.

Shulman, G.L. et al., 1997. Top-down modulation of early sensory cortex. *Cerebral cortex*, 7(3), 193-206.

Sillito, A.M. & Kemp, J.A., 1983. Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Research*, 289(1-2), 143-55.

Silvanto, J., Muggleton, N. & Walsh, V., 2008. State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Sciences*, 12(12), 447-54.

Smith, A.T., Singh, K.D. & Greenlee, M.W., 2000. Attentional suppression of activity in the human visual cortex. *Neuroreport*, 11(2), 271-7.

Snyder, S.M. & Hall, J.R., 2006. A meta-analysis of quantitative EEG power associated with attention-deficit hyperactivity disorder. *Journal of Clinical Neurophysiology*, 23(5), 440-55.

Sorger, B. et al., 2009. Another kind of 'BOLD Response': answering multiple-choice questions via online decoded single-trial brain signals. *Progress in Brain Research*, 177, 275-92.

Sramek, J.J., Zarotsky, V. & Cutler, N.R., 2002. Generalised anxiety disorder: treatment options. *Drugs*, 62(11), 1635-48.

Stagg, C.J. et al., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *The Journal of Neuroscience*, 29(16), 5202-6.

Stefan, K., Wycislo, M. & Classen, J., 2004. Modulation of associative human motor cortical plasticity by attention. *Journal of Neurophysiology*, 92(1), 66-72.

Stefan, K. et al., 2000. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*, 123 Pt 3, 572-84.

Stefan, K. et al., 2002. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. *The Journal of Physiology*, 543(Pt 2), 699-708.

Steriade, M. & Timofeev, I., 2003. Neuronal plasticity in thalamocortical networks during sleep and waking oscillations. *Neuron*, 37(4), 563-76.

Steriade, M., McCormick, D.A. & Sejnowski, T.J., 1993. Thalamocortical oscillations in the sleeping and aroused brain. *Science*, 262(5134), 679-85.

Steriade, M. et al., 1991. Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proceedings of the National Academy of Sciences of the United States of America*, 88(10), 4396-400.

Steriade, M. et al., 1990. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation processes in thalamocortical systems. *The Journal of Neuroscience*, 10(8), 2541-59.

Sterman, M.B. & Egner, T., 2006. Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied Psychophysiology and Biofeedback*, 31(1), 21-35.

Sterman, M.B., 1996. Physiological origins and functional correlates of EEG rhythmic activities: implications for self-regulation. *Biofeedback and Self-Regulation*, 21(1), 3-33.

Sterman, M.B., Howe, R.C. & Macdonald, L.R., 1970. Facilitation of spindle-burst sleep by conditioning of electroencephalographic activity while awake. *Science*, 167(921), 1146-8.

Sterman M.B., Wyrwicka W., Howe R.,1969. Behavioral and neurophysiological studies of the sensorimotor rhythm in the cat. *Electroencephalography and Clinical Neurophysiology*, 27, 678-679.

Strafella, A.P. et al., 2001. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *The Journal of Neuroscience*, 21(15), RC157.

Strafella, A.P. et al., 2003. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain*, 126(Pt 12), 2609-15.

Sun, X., Zhao, Y. & Wolf, M.E., 2005. Dopamine receptor stimulation modulates AMPA receptor synaptic insertion in prefrontal cortex neurons. *The Journal of Neuroscience*, 25(32), 7342-51.

Szalay, D. et al., 2000. Using operative outcome to assess technical skill. *American Journal of Surgery*, 180(3), 234-7.

Tamaki, M. et al., 2008. Fast sleep spindle (13-15 hz) activity correlates with sleep-dependent improvement in visuomotor performance. *Sleep*, 31(2), 204-11.

Tan, G. et al., 2009. Meta-analysis of EEG biofeedback in treating epilepsy. *Clinical EEG and Neuroscience*, 40(3), 173-9.

Tass, P.A. et al., 2009. Long-lasting desynchronization in rat hippocampal slice induced by coordinated reset stimulation. *Physical Review*, 80(1 Pt 1), 011902.

Tass, P.A. & Majtanik, M., 2006. Long-term anti-kindling effects of desynchronizing brain stimulation: a theoretical study. *Biological Cybernetics*, 94(1), 58-66.

Teff, K.L., 2008. Visceral nerves: vagal and sympathetic innervation. *JPEN*, 32(5), 569-71.

Teo, J.T. et al., 2009. Differing effects of intracortical circuits on plasticity. *Experimental Brain Research*, 193(4), 555-63.

Terney, D. et al., 2008. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *The Journal of Neuroscience*, 28(52), 14147-55.

Thatcher, R.W., 2000. EEG operant conditioning (biofeedback) and traumatic brain injury. *Clinical EEG (electroencephalography)*, 31(1), 38-44.

Thienel, R. et al., 2009. Muscarinic antagonist effects on executive control of attention. *The International Journal of Neuropsychopharmacology*, 12(10), 1307-17.

Thut, G. & Miniussi, C., 2009. New insights into rhythmic brain activity from TMS-EEG studies. *Trends in Cognitive Sciences*, 13(4), 182-9.

Tremblay, N., Warren, R.A. & Dykes, R.W., 1990. Electrophysiological studies of acetylcholine and the role of the basal forebrain in the somatosensory cortex of the cat. II. Cortical neurons excited by somatic stimuli. *Journal of Neurophysiology*, 64(4), 1212-22.

Tyvaert, L. et al., 2008. Effects of fluctuating physiological rhythms during prolonged EEG-fMRI studies. *Clinical Neurophysiology*, 119(12), 2762-74.

Uhlhaas, P.J. & Singer, W., 2006. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*, 52(1), 155-68.

Ursin H., E.H., 2004. The cognitive activation theory of stress. *Psychoneuroendocrinology*, 29, 567-592.

Vaez, M., Hashemi, E. & Jalali, S., 2008. Arousal and Activation in a Sport Shooting Task. *Applied Sciences*, 4(6), 824-829.

Van Herzeele, I. et al., 2008. Cognitive training improves clinically relevant outcomes during simulated endovascular procedures. *Journal of Vascular Surgery*, 48(5), 1223-30, 1230.e1.

Van Oekelen, D., Luyten, W.H. & Leysen, J.E., 2003. 5-HT2A and 5-HT2C receptors and their atypical regulation properties. *Life Sciences*, 72(22), 2429-49.

Vanderhasselt, M. et al., 2006. The influence of rTMS over the left dorsolateral prefrontal cortex on Stroop task performance. *Experimental Brain Research*, 169(2), 279-82.

Vanhatalo, S., Voipio, J. & Kaila, K., 2005. Full-band EEG (FbEEG): an emerging standard in electroencephalography. *Clinical Neurophysiology*, 116(1), 1-8.

Vankov, A., Hervé-Minvielle, A. & Sara, S.J., 1995. Response to novelty and its rapid habituation in locus coeruleus neurons of the freely exploring rat. *The European Journal of Neuroscience*, 7(6), 1180-7.

Vernon, D. et al., 2003. The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *International Journal of Psychophysiology*, 47(1), 75-85.

Vines, B.W., Nair, D. & Schlaug, G., 2008. Modulating activity in the motor cortex affects performance for the two hands differently depending upon which hemisphere is stimulated. *The European Journal of Neuroscience*, 28(8), 1667-73.

Vines, B.W., Nair, D.G. & Schlaug, G., 2006. Contralateral and ipsilateral motor effects after transcranial direct current stimulation. *Neuroreport*, 17(6), 671-4.

Vocat, R., Pourtois, G. & Vuilleumier, P., 2008. Unavoidable errors: a spatio-temporal analysis of time-course and neural sources of evoked potentials associated with error processing in a speeded task. *Neuropsychologia*, 46(10), 2545-55.

Wachtel, P.L., 1968. Anxiety, attention, and coping with threat. *Journal of Abnormal Psychology*, 73(2), 137-43.

Wager, T.D., Jonides, J. & Reading, S., 2004. Neuroimaging studies of shifting attention: a meta-analysis. *NeuroImage*, 22(4), 1679-93.

Wagner, T., Valero-Cabre, A. & Pascual-Leone, A., 2007. Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering*, 9, 527-65.

Wang, J. & O'Donnell, P., 2001. D(1) dopamine receptors potentiate nmda-mediated excitability increase in layer V prefrontal cortical pyramidal neurons. *Cerebral Cortex*, 11(5), 452-62.

Wang, L.E. et al., 2009. Noradrenergic stimulation and motor performance: differential effects of reboxetine on movement kinematics and visuomotor abilities in healthy human subjects. *Neuropsychologia*, 47(5), 1302-12.

Weintraub, S. et al., 2009. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. *Alzheimer Disease and Associated Disorders*, 23(2), 91-101.

Werk, C.M. et al., 2006. Long-term depression in the sensorimotor cortex induced by repeated delivery of 10 Hz trains in vivo. *Neuroscience*, 140(1), 13-20.

White, N.M., 1997. Mnemonic functions of the basal ganglia. *Current Opinion in Neurobiology*, 7(2), 164-9.

Wickens, C.D. & Kessel, C., 1980. Processing resource demands of failure detection in dynamic systems. *Journal of Experimental psychology. Human perception and performance*, 6(3), 564-77.

Williams, J.A. et al., 1994. State-dependent release of acetylcholine in rat thalamus measured by in vivo microdialysis. *The Journal of Neuroscience*, 14(9), 5236-42.

Williams, S.R., Wozny, C. & Mitchell, S.J., 2007. The back and forth of dendritic plasticity. *Neuron*, 56(6), 947-53.

Willingham D.B., K.W., 1996. Motor skills have diverse neural bases: Spared and impaired skill acquisition in Huntington's disease. *Neuropsychology*, 10, 315-321.

Winstanley, C.A. et al., 2003. Global 5-HT depletion attenuates the ability of amphetamine to decrease impulsive choice on a delay-discounting task in rats. *Psychopharmacology*, 170(3), 320-31.

Wolters, A. et al., 2003. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *Journal of Neurophysiology*, 89(5), 2339-45.

Wörgötter, F. et al., 1998. State-dependent receptive-field restructuring in the visual cortex. *Nature*, 396(6707), 165-8.

Yerkes, R.M. & Dodson, J.D. (1908). The relation of strength of stimulus to rapidity of habit formation. *Journal of Comparative Neurology and Psychology*, 18, 459-482.

Yoo, S. et al., 2008. Neurofeedback fMRI-mediated learning and consolidation of regional brain activation during motor imagery. *International Journal of Imaging Systems and Technology*, 18(1), 69-78.

Yoo, W. et al., 2008. High frequency rTMS modulation of the sensorimotor networks: behavioral changes and fMRI correlates. *NeuroImage*, 39(4), 1886-95.

Yu A.J., D.P., 2005. Uncertainty, neuromodulation, and attention. *Neuron*, 46, 681-692.

Zhang, Y. et al., 2008. Response preparation and inhibition: The role of the cortical sensorimotor beta rhythm. *Neuroscience*, 156(1), 238-246.

Ziemann, U. et al., 2008. Consensus: Motor cortex plasticity protocols. *Brain Stimulation*, 1(3), 164-182.

Ziemann, U. et al., 2006. Pharmacological modulation of plasticity in the human motor cortex. *Neurorehabilitation and Neural Repair*, 20(2), 243-51.

Ziemann, U., 2004. TMS and drugs. *Clinical Neurophysiology*, 115(8), 1717-29.

Ziemann, U. et al., 2001. Modulation of practice-dependent plasticity in human motor cortex. *Brain*, 124(Pt 6), 1171-81.

Ziemann, U., Rothwell, J.C. & Ridding, M.C., 1996. Interaction between intracortical inhibition and facilitation in human motor cortex. *The Journal of Physiology*, 496, Pt 3, 873-81.