The Associative Brain at Work: Evidence from Paired Associative Stimulation Studies in Humans

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ABBREVIATIONS

AD: Alzheimer's dementia; APB: Abductor Pollicis Brevis; AP: anterior-to-posterior; BCM: Bienenstock-Cooper-Munroe; BDNF: Brain Derived Neurotrophic Factor; BCI: brain-computer interface; CPN: common peroneal nerve; cTBS: continuous theta burst stimulation; DBS: deep brain stimulation; ESM: ethosuximide; GABA: γ-aminobutyric acid; HD: Huntington's disease; iTBS intermittent theta burst stimulation; ISI: interstimulus interval; LAI: long-afferent inhibition; LIDs: L-Dopa-induced dyskinesias; LICI: long-interval intracortical inhibition; LTP: long-term potentiation; LTD: long-term depression; M1: primary motor cortex; MCI: mild cognitive impairment; MEP: motor evoked potential; ; MN: median nerve; MS: Multiple Sclerosis; NMDA: N-Methyl-D-aspartate; NDP: nimodipine; PA: posterior-to-anterior; PAS: paired associative stimulation; PD: Parkinson Disease; RMT: resting motor threshold; rTMS: repetitive TMS; S1: primary somatosensory cortex; SEP: somatosensory evoked potential; SICI: short-interval intracortical inhibition; SNP: single nucleotide polymorphism; STDP: spike-timing dependent synaptic plasticity; TA: tibialis anterior; TBS: theta burst stimulation; TDCS: transcranial direct current stimulation; TMS: transcranial magnetic stimulation; VGCC: voltage-gated Ca^{2+}-channels.

INTRODUCTION

Donald Hebb's now-famous rule of synaptic plasticity states: "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased." Although not explicitly stated, the phrase "takes part in firing it" suggests very strongly that there is a close temporal connection between occurrence of the input (A) and the firing of cell B. In other words, the relative timing between synaptic input and post-synaptic activity determines whether there will be a change in the effectiveness of the synapse. Early animal work in the 1980's and 1990's (e.g. Levy and Steward, Neuroscience, 8 (1983), pp. 791–797) confirmed this idea, and showed that in many cases, if synaptic input A preceded discharge of cell B then synaptic strengthening occurred whereas if the order was reversed, the synapse was weakened. The crucial concepts of spike-timing dependent plasticity (STDP) had been born.

It was not before many years later that Stefan and colleagues (2000) published the paper (which contains what must be the most widely reproduced figure in the whole transcranial magnetic stimulation (TMS) literature (see Fig. 1)) on paired associative stimulation (PAS) in humans. Here, they demonstrated for the first time that the excitability of motor cortex could be modulated if they paired somatosensory and TMS inputs in a temporally specific manner. At the time, it seemed to provide a direct link to the basic physiology of cortical neurons that had been so well described in reduced animal preparations, and opened the possibility of testing their behavioral consequences in awake, conscious individuals.

That study sparked a mass of papers on the physiology, pharmacology, pathology and motor effects of PAS which are summarized in detail below. As we will see, a story with a simple beginning has become more complex as time passes. Further sections of the review focus on new protocols of "modified PAS" and possible future application of PAS in neuromorphic circuits designed for brain-computer interface (BCI).

SECTION 1: PHYSIOLOGY OF PAS

PAS represents a non-invasive brain stimulation protocol by which bidirectional changes of neuronal excitability can be induced. In the original protocol one route of stimulation is via somatosensory afferents and the other route via TMS of the motor cortex, but pairings with events converging at other sites of the nervous system and inductions with other stimulation modalities have also generated comparable physiological effects. Repetitive pairings of TMS of the primary motor cortex (M1) conjointly with an afferent input to M1 (such as somatosensory information by peripheral nerve stimulation, e.g. median nerve stimulation (MNS), result in changes of the amplitude of motor evoked potentials (MEP) (Stefan et al., 2000, for review see Müller-Dahlhaus, 2010; Carson and Kennedy, 2013). The direction of changes of MEP amplitudes critically depends on the interval between MNS and TMS. This form of timing dependent plasticity in conscious humans has similarities with STDP as revealed in a variety of model systems (Caporale and Dan, 2008), ranging from cultured neurons (Bi and Poo, 1998) and cortical slice preparations (Magee and Johnston, 1997, Markram et al., 1997) to intact animals (Zhang et al., 1998). These similarities include rapid induction, lasting duration and specificity to the stimulated representation, although the latter property cannot by proven at a microscopic scale using non-invasive stimulation methods. Several lines of evidence suggested that the site of action of PAS-induced plasticity is at the level of the cortex (Müller-Dahlhaus et al., 2010; Carson and Kennedy, 2013). Interstimulus intervals (ISIs) in the order of 20-25 ms led to a lasting enhancement of MEP amplitudes, whereas ISIs of around 10ms (PAS_{10}) result in depression (Wolters et al., 2003; Weise et al., 2013). This has been suggested to reflect the sequence of events induced at the level of the M1 (Wolters et al., 2003, 2005).

In the original version of PAS, the interval between MNS and TMS was 25ms (PAS_{25}). The first component (N20) of the median nerve somatosensory-evoked potential (MN-SEP) typically arrives in the primary somatosensory cortex (S1) at around 20 ms (Allison et al., 1991). Taking into

account some additional milliseconds for the MNS signal to be relayed from S1 to M1, the afferent signal evoked by MNS may arrive in M1 shortly before transsynaptic excitation of corticospinal neurons by the TMS pulse. PAS also increased cortical excitability when the interval between afferent pulse and magnetic stimulation of the M1 is only 21.5 ms (Weise et al., 2006). In a series of experiments, Hamada and colleagues showed that different physiological mechanisms underlie both excitability-enhancing PAS-variants. If the cerebellum was treated with either anodal or cathodal direct current stimulation simultaneously with the PAS intervention, PAS_{25}-induced plasticity was blocked, whereas $PAS_{21.5}$ was still able to enhance corticospinal excitability (Hamada et al., 2012). Subsequently, cerebellar-dependent and cerebellar-independent PAS were shown to be related to different types of motor learning (Hamada et al., 2014). By changing the direction of the induced current in M1, Hamada and colleagues (2014) activated two independent sets of synaptic inputs to corticospinal neurons. Excitability changes produced by repetitive activation of anterior to-posteriorly directed current (AP inputs) conjointly with afferent stimulation depended on cerebellar activity (PAS_{25}) and selectively altered model-based motor learning as tested in a visuomotor gain adaptation task. In contrast, the changes observed with repetitive stimulation of posterior-to-anteriorly directed current (PA inputs) conjointly with afferent stimulation ($PAS_{21.5}$) were independent of cerebellar activity and specifically modulated model-free learning as indexed by motor improvement in a ballistic acceleration task. The findings by Hamada and co-workers (2012, 2014) indicate that at least some of the regular PAS_{25} effect may involve a trans-cerebellar route. However, it remains unclear why conditioning the cerebellum with both anodal and cathodal direct current produced the same blocking effect on PAS_{25}-induced plasticity. Popa and co-workers (2013) showed that conditioning the cerebellum with intermittent theta burst stimulation (iTBS) subsequently blocked PAS_{25}-induced plasticity, whereas PAS_{25}-induced plasticity was facilitated, and lost its spatial specificity, after conditioning with continuous, presumably cerebellar excitability depressant TBS. Facilitation of PAS after continuous TBS (cTBS) is not readily reconciled with the results obtained by Hamada (2012), since cerebellar cTBS and direct current stimulation have

induced oppositely directed changes. Together these findings indicate that the notion of a singular afferent route to the M1 driving PAS-related plasticity is probably wrong; it also suggests that simple models of the effects of TDCS and TBS on motor cortex may not be valid when translated to the different anatomy of the cerebellum. The data point to cerebellar contribution to the canonical PAS response, yet its nature remains to be further clarified.

According to an influential theory, long-term potentiation/depression (LTP/LTD) of glutamatergic synapses is induced by the magnitude, and perhaps the speed, of Ca^{2+} surge in the postsynaptic cell (Lisman, 1989). There are at least three mechanisms by which postsynaptic [Ca^{2+}] is increased: Upon near-synchronous stimulation, Ca^{2+} ions may enter the postsynaptic cell through (i) N-Methyl-D-Aspartate (NMDA)-receptors or (ii) by voltage-dependent Ca^{2+}-channels. Ca^{2+} may also increase (iii) as a consequence of release from intracellular Ca^{2+}-stores. An important component of the canonical STDP is the participation of back-propagating action potentials which travel from the neuron's soma or from the proximal dendrite back into the dendritic tree (Feldman, 2012). Back-propagation provides an important dendritic signal which interacts with incoming signals at the dendritic tree. PAS-induced plasticity clearly represents a system level response toward a stimulation protocol whose components each engage neuronal ensembles, not single neuronal cells or even compartments of neurons. Although a macroscopic response, relatively simple models that are built on principles of STDP and Ca^{2+}-dependent plasticity at the level of glutamatergic synapses successfully capture several of its essential properties (Fung and Robinson, 2013). While PAS-induced plasticity shares certain properties with STDP of glutamatergic synapses important differences remain and similarity must not be taken as identity and caution must be applied when comparing system-level findings with cellular mechanisms (Müller-Dahlhaus et al., 2010; Carson and Kennedy, 2013).

Excitability enhancing PAS did not alter γ-aminobutyric acid (GABA)A-ergic inhibition in M1 (Stefan et al., 2002), as indexed by short-interval paired-pulse TMS (Kujirai et al., 1993). Thus, LTP-like PAS effects do not arise from long-term disinhibition of the M1 – at least as far as testable

by paired-pulse TMS. Experiments showed that both the excitability facilitating PAS_{25}-protocol (Elahi, 2012) and the excitability depressant PAS_{10}- protocol (Weise et al., 2013) are blocked by applying a subthreshold magnetic pulse 2 or 3ms before the principal TMS pulse, even when the strength of the latter was adjusted to generate a MEP of similar amplitude to that with the unconditioned magnetic pulse. These experiments, therefore, not only provided indirect evidence for the location of PAS-induced changes in superficial cortical layers, but also for its eminent inhibitory control. However, as phasic GABA-Aergic intracortical inhibition can be tested by double-pulse TMS at 3 ms, the influence of tonic GABA-B related inhibition is less clear. The fact that neural elements involved in generating late I-waves appear predominantly modulated by PAS (Di Lazzaro et al., 2010) has important implications: The degree to which such elements are recruited by TMS should be predictive of the propensity of PAS to induce plasticity. Indeed, there is indirect evidence that variation in response to PAS is influenced by which interneuron networks are recruited by the TMS pulse (Murase et al., 2015).

Direct recordings of descending corticospinal activity after PAS

The physiological basis of PAS-induced plasticity has been characterized by evaluating directly the effects of this protocol of stimulation on corticospinal activity evoked by single pulse transcranial magnetic stimulation. A single TMS pulse to the M1 evokes activity in corticospinal fibers that can be recorded directly in conscious humans through electrodes implanted into the epidural space at the high cervical level for the relief of pain (Di Lazzaro and Rothwell, 2014). Such recordings have shown that depending on the stimulus intensity and orientation of the induced current in M1, multiple cortical circuits can be activated by TMS (Di Lazzaro and Rothwell, 2014). A TMS inducing a PA current in the brain evokes a high frequency discharge (around 650 Hz) of a population of cortical pyramidal neurons (Di Lazzaro and Rothwell, 2014) (Figure 2). In analogy with experimental studies in animals, it has been proposed that this high-frequency discharge originates from the activation of the axons of cortical interneurons projecting upon the corticospinal

cells. Because of their indirect origin these waves were termed I-waves (Amassian et al., 1987, Di Lazzaro and Rothwell, 2014). Beyond this clear oscillatory activity, a more complex descending activity can be recorded at epidural level when the direction of the induced current in the brain is changed to an AP direction. With AP stimulation, the threshold for stimulation increases and the latency of the MEP, particularly in the contracting muscle, is delayed by 2-3 ms when compared to PA stimulation (Sakai et al., 1997) (Hamada et al., 2013). The corresponding activity at epidural level is represented by volleys with later peak latencies and/or longer durations than those seen after PA stimulation and, at lower intensities, no clear epidural activity can be identified with this form of magnetic stimulation even in the presence of a clear muscle response (Di Lazzaro et al., 2001) (Figure 2). This less synchronized activity evoked by low intensity AP stimulation might not take origin from the circuits producing the high-frequency I-waves but might be produced by a different source of interneuronal inputs to corticospinal cells with a lower propensity to oscillatory synchronous discharge or a lower frequency discharge (Figure 2).

Comparison of the epidural activity recorded using different orientations of the induced current in the brain thus suggests that TMS can activate different populations of cortico-cortical axons that provide inputs to corticospinal cells: 1) a population of cortical interneurons producing high-frequency and highly synchronized discharge of corticospinal cells (I-waves) preferentially activated by PA stimulation. This circuit is probably represented by oscillatory interneurons projecting to the corticospinal cells; 2) a population of cortical interneurons producing poorly synchronized discharge of corticospinal cells activated in isolation by low-intensity AP stimulation. This circuit might be composed of interneurons with less pronounced oscillatory properties or a lower frequency of oscillation. However, a selective activation of these circuits takes place only with a specific orientation of the induced current in the brain and only within a limited range of stimulus intensities. At higher intensities, both circuits might be activated even though the epidural activity produced by the high frequency oscillatory circuit is predominant and tends to obscure the remaining activities. A model exists explaining I-waves by the characteristics of the branching of

the dendritic tree (Rusu et al., 2014) which in conjunction with the assumption of horizontally oriented pyramidal tract (PT) cells in the anterior wall of M1 (Laakso et al., 2014) may explain AP and PA differences on the basis of the horizontal orientation of the motor cortex.

Epidural recordings before and after PAS showed that different PAS protocols might have differential effects on specific cortical circuits even though the effects on MEPs are indistinguishable. Both, $PAS_{21.5}$ and PAS_{25} produce MEP facilitation. However, the effects on epidural activity are completely different (Figure 2). While after PAS_{25} the MEP enhancement is paralleled by an enhancement in the amplitude and number of the I-waves, after $PAS_{21.5}$ there is no change in these waves, thus suggesting that for this protocol it is the activity of the non-oscillatory interneuronal circuit that might be enhanced and thus, the extra activity is not recognizable at epidural level (Hamada et al., 2014). Thus, the circuits facilitated by $PAS_{21.5}$ could be the same circuits that are preferentially activated by low-intensity AP stimulation. As mentioned above, several studies also suggest that the mechanisms of the PAS_{25} and $PAS_{21.5}$ aftereffects are not physiologically identical and that they involve plasticity in two separate cortical circuits (Hamada et al., 2012) (Hamada et al., 2014). The reasons for the differential effects of PAS_{25} and $PAS_{21.5}$ on the excitability of oscillatory and non-oscillatory cortical circuits are currently unknown.

Pharmacology of PAS

A large number of studies have provided relevant insight into the pharmacology of PAS by investigating changes in responses to PAS after acute or chronic administration of various drugs acting on the central nervous system. Most of the relevant findings coming from pharmacological studies are summarized in Table 1.

Determinants of individual differences in sensitivity to PAS

Several studies have consistently shown that the efficacy of PAS_{25} to induce LTP-like plasticity in human M1 varies considerably in the normal population with a substantial portion of non-

responders showing either no change or an opposite than expected effect on corticospinal excitability (Müller-Dahlhaus et al., 2008; Kriváneková et al., 2011; López-Alonso et al., 2014; Vallence et al., 2013). Some variability might be accounted for by differences in the repetition rate, duration, or other variables of the PAS protocol. Sale et al. (2007) found a short PAS_{25} protocol (i.e., 132 paired stimuli at 0.2 Hz) to be more effective that a long PAS_{25} protocol (i.e., 90 paired stimuli at 0.05 Hz) in inducing LTP-like changes in corticomotor excitability, and this difference in efficacy was reproduced in the same group of subjects in a second PAS session. As described in detail above, PAS-induced LTP-like plasticity involves two separate time-dependent mechanisms. One central finding was that concurrent anodal TDCS of the cerebellum blocked the effect of PAS_{25} but not $PAS_{21.5}$ (Hamada et al., 2012). A more recent study showed that PAS_{25} and $PAS_{21.5}$ were mutually inhibitory when being intermingled (Strigaro et al., 2014). This raises the possibility that intra- and inter-individual differences in responsiveness to PAS might be due to differences in the concurrent activation of PAS_{25} and $PAS_{21.5}$ related mechanisms.

The substantial inter-subject variability of PAS effects on corticospinal excitability might reflect stable "trait-related" differences in individual responsiveness to the plasticity-inducing effects of PAS. The relevance of genetic factors was examined in a twin study in which the ability of PAS_{25} to evoke a LTP-like increase in corticospinal excitability was compared in pairs of monozygotic (MZ) and dizygotic (DZ) twins (Missitzi et al., 2011). In 9 MZ twin-pairs, intra-pair differences in baseline-normalized MEP amplitudes was half of intra-pair differences found in 12 DZ twin-pairs, resulting in an estimated heritability of 0.68. Although the study sample was small, the twin study suggests a substantial genetic influence determining inter-individual variability in the response to PAS interventions. Another study examined the influence of a common single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene (Cheeran et al., 2008). In nine individuals with a Val66Met genotype, PAS_{25} induced LTP-like plasticity, but not in nine matched individuals with a Val66Val genotype (Cheeran et al., 2008; Missitzi et al., 2011). Genetic factors might be associated with neuroanatomical differences in the corticospinal

motor system which might determine the individual responsiveness to PAS. A T1-weighted magnetic resonance imaging (MRI) study revealed a positive relationship between the cortical thickness of the targeted sensorimotor cortex and the efficacy of PAS_{25} to induce LTP-like corticomotor plasticity (Conde et al., 2012). Individuals with a strong LTP-like after-effect had thicker gray matter in the stimulated sensorimotor cortex, accounting for approximately 50% of the inter-individual variance (Conde et al., 2012). Taken together, these studies suggest that there might be individuals who are "responders" or "non-responders" depending on genetic, anatomical or other traits.

In addition to stable trait-like variables, a range of time-variant state-related variables can rapidly alter the individual responsiveness to PAS, turning "responders" into "non-responders" or flipping the sign of PAS-induced plasticity from a LTP-like to LTD-like plasticity or vice versa. This state-dependent variation of individual responsiveness to PAS might substantially contribute to inter-subject response variability (Ziemann and Siebner, 2015). Some of these state variables might change the responsiveness to PAS over long time scales of months or years such as a reduced responsiveness to PAS in older individuals (Müller-Dahlhaus et al., 2008).

Other state-dependent variables act on very short time scales leading to relatively abrupt changes in responsiveness to PAS. The magnitude as well as the focus of attention at the time of PAS is an important state-dependent determinant of PAS efficacy (Stefan et al., 2004; Kampke et al., 2012). Several studies found a positive association between the individual responsiveness to the LTP-inducing effects of PAS and alertness (Mainberger et al., 2013; Kloeppel et al., 2016) or focused attention (Stefan et al., 2004). Intrinsic circadian fluctuations in responsiveness to PAS may also play an important role (Sale et al., 2007). It was recommended to conduct PAS studies at a fixed time of day, preferably in the afternoon, because PAS given in the afternoon was found to be more effective and more reproducible than PAS applied in the morning (Sale et al., 2007). As discussed above, neuropharmacological factors also play an important role in defining the individual responsiveness to PAS.

Another important mechanism that can acutely alter individual responsiveness to PAS is metaplasticity (Siebner et al., 2014; Karabanov et al., 2015). Using PAS, homeostatic regulation of PAS-induced plasticity has been shown in the motor and sensory cortex (Müller et al., 2007, Bliem et al., 2008; Pötter-Nerger et al., 2012). For PAS of M1, the LTP-like effects of a SEP-latency adjusted PAS_{25} protocol can be influenced by a preceding PAS session. The priming effects revealed a homeostatic pattern, confirming a sliding threshold for LTP/LTD induction in human M1 (Müller et al., 2007). The "normal" LTP-inducing effects of PAS_{25} were enhanced by a preceding LTD-inducing PAS_{10} session, whereas a preceding LTP-inducing PAS_{25} session decreased LTP induction of the primed PAS intervention (Müller et al., 2007). Homeostatic regulation of PAS-induced corticospinal plasticity was also demonstrated with a priming session of low- (1Hz) or high-frequency (5Hz) rTMS to ipsilateral dorsal premotor cortex (Pötter-Nerger et al., 2012). In both studies, those individuals with the strongest LTP-like or LTD-like response in the priming session also showed the strongest homeostatic response, flipping the PAS effect into the opposite direction. In other words, good initial responders were those who showed an attenuated or opposite "plasticity" response to the second PAS intervention. It needs to be mentioned that the priming effects of two consecutive PAS protocols are complex and critically depend on the interval between the two PAS protocols, involving homeostatic or non-homeostatic effects (Müller-Dahlhaus et al., 2015).

The level of motor activity preceding PAS can also alter the efficacy of a subsequent PAS protocol, occluding (Lepage et al., 2013) or enhancing (Mang et al., 2014) the potential of PAS to induce LTP-like plasticity. For instance, 20 minutes of aerobic exercise (i.e., 20-min high-intensity cycling) facilitated the LTP-like response to PAS_{25} (Mang et al., 2014). PAS_{25} was also found to be more effective in inducing LTP-like plasticity in the corticospinal system in physically active individuals relative to sedentary individuals (Cirillo et al., 2009). Yet there appears to be no clear link between inter-individual differences in PAS responsiveness and individual motor learning abilities as tested with well-established tasks probing serial reaction time learning, visuomotor

adaptation, or sequential visual isometric pinch force control (López-Alonso et al., 2015). The functional interactions between motor training and PAS effects on corticospinal excitability speak to overlapping mechanisms behind the neuroplastic changes induced by PAS of M1 and motor learning, but the large intra- and inter-individual variability of PAS-induced plasticity render it difficult to establish associations between neuroplastic responses to PAS and motor learning (Vallence et al., 2013).

The rapid changeability of the individual PAS effects in response to training, a preceding PAS session, or drug manipulations questions the rationale behind grouping individuals into "responders" or "non-responders" to PAS, as even strong initial responders might become non-responders depending on their recent "history" of neural activity and plasticity. Within-subject variations in responsiveness to PAS and other brain stimulation protocols may also explain why no significant correlations were found between the individual LTP-like responses to PAS or TBS (Vallence et al., 2013), the individual responses to PAS of sensory or motor cortex (Kriváneková et al., 2011), or between individual LTP-like responses to PAS and motor learning (Vallence et al., 2013) [López-Alonso et al. 2015]. The existing data strongly suggest that test-retest reliability should be assessed when splitting participants into so-called "responders" and "non-responders".

In view of the complex relationships between a given PAS protocol and the individual's tendency to express LTP- or LTD-like plasticity, researchers have explored the relationship between the excitability profile of M1 at pre-intervention baseline and the responsiveness to PAS. An early study suggested that corticomotor excitability as measured with single-pulse TMS at baseline determined PAS efficacy (Müller-Dahlhaus et al., 2008), while two studies found no relation between the baseline MEP response to single-pulse TMS and the individual responsiveness to PAS (Sale et al., 2007; Labruna et al., 2015). Two studies suggested that the strength of short-interval intracortical inhibition (SICI) at baseline may influence the LTP-like effects of PAS_{25} (López-Alonso et al., 2014; Murase et al., 2015). However, López-Alonso et al. (2014) demonstrated that low SICI was associated with an LTP-like response, while Murase et al. (2015)

showed that LTP-responders had stronger SICI. The inconsistency might be due to the different techniques use in the two studies (López-Alonso et al., 2014; Murase et al., 2015). The ability of TMS to target late I-wave activity was proposed as explanation for the putative link between SICI and PAS efficacy (Murase et al., 2015). SICI is associated with a reduction of late I-wave activity (Di Lazzaro et al., 1998). Moreover, the LTP-like effect of PAS_{25} is associated with a lasting increase in late I-waves (Di Lazzaro et al., 2009). Therefore, it was argued that the ability of single-pulse TMS to effectively recruit late I-waves will result in strong SICI and a high sensitivity to the LTP-inducing effects of PAS_{25} (Murase et al., 2015). However, the predictive power of baseline SICI was only 10% (López-Alonso et al., 2014) and another study found no relation between the strength of SICI and PAS efficacy (Strube et al., 2015). One study showed that stronger short-latency afferent inhibition (SAI) correlated with weaker PAS effects, accounting for about 40% of the inter-individual variability in PAS response. These findings suggest that simultaneous activation of GABA-A receptor mediated by SAI during PAS influences the direction and magnitude of PAS-induced plasticity contributing also to inter-individual variability (Cash et al., 2016).

Metaplasticity between PAS and another NIBS protocol

Metaplasticity means that the threshold for activity-dependent synaptic plasticity is dynamic, and changes as a function of the integrated prior activity of the postsynaptic neuron (Abraham, 2008, Abraham and Bear, 1996). The term homeostatic metaplasticity refers to a conservative principle of stabilizing synaptic weights in neuronal networks while maintaining the capacity for synaptic plasticity. This has been formalized in the influential Bienenstock-Cooper-Munro (BCM) theory of bidirectional synaptic plasticity (Bienenstock et al., 1982): the threshold for induction of LTP over LTD is not stable but varies as a function of the integrated postsynaptic activity: it decreases with low levels of previous postsynaptic activity, favoring LTP induction, and vice versa with high levels of previous postsynaptic activity, favoring LTD induction. As a consequence, this sliding LTP threshold safeguards neurons and networks to stay within a physiological synaptic

modification range, and to prevent runaway plasticity.

Müller and colleagues were the first to investigate metaplasticity at the level of human M1 using PAS protocols. They studied PAS_{25} preceded by either the same PAS_{25} protocol, or by PAS_{10}. The LTP-like MEP increase induced by PAS_{25} in a control condition was occluded by priming with PAS_{25}, but showed a trend towards enhancement when primed by the PAS_{10} protocol (Müller et al., 2007). In addition, the effects on MEP amplitude induced by primed PAS_{25} inversely correlated with those induced by priming PAS (Müller et al., 2007). Because the two subsequent PAS protocols likely activated the same or at least overlapping neuronal circuits, it was concluded that 'homosynaptic-like' homeostatic metaplasticity in accord with the BCM theory caused the observed interactions between two subsequent PAS protocols. In another study, PAS_{25} or PAS_{10} were primed by short-train (150 pulses) cTBS150 that is subthreshold for inducing an LTD-like decrease of MEP amplitude (Huang et al., 2010). CTBS150 resulted in enhancement of subsequent PAS_{25}-induced MEP increase and switched PAS_{10}-induced MEP depression to MEP increase (Ni et al., 2014). These findings are fully in agreement with homeostatic metaplasticity and show, in addition, that the priming is not required to induce overt plasticity itself for its metaplastic interaction with a subsequent plasticity protocol.

Another study investigated the effects of priming PAS by low-frequency (1 Hz) or high-frequency (5 Hz) rTMS applied to the dorsal premotor cortex (Pötter-Nerger et al., 2009). 1 Hz rTMS priming switched a PAS_{10}-induced MEP decrease to an increase while, conversely, 5 Hz rTMS priming switched a PAS_{25}-induced MEP increase to a decrease (Pötter-Nerger et al., 2009). These data demonstrate that the interaction of convergent but separate inputs to the M1, in this case activated by priming of the dorsal premotor cortex and by PAS, is fully consistent with the BCM theory of 'heterosynaptic' homeostatic metaplasticity.

It has been shown that cTBS of the lateral cerebellum decreases MEP amplitude while iTBS increases MEP amplitude (Koch et al., 2008). In agreement with homeostatic metaplasticity, priming of the cerebellum with cTBS resulted in enhancement of PAS_{25}-induced MEP increase,

whereas priming of the cerebellum with iTBS led to occlusion of PAS_{25}-induced LTP-like plasticity (Popa et al., 2013). Of note, the same TBS priming protocols showed no significant interaction with LTP-like plasticity induced by iTBS of M1 (Popa et al., 2013). The authors concluded that cerebellar priming effects occurred through modulation of somatosensory processing at the level of the dentate nucleus or thalamus, thus interfering with the somatosensory pathways activated by PAS (Wolters et al., 2005), but not iTBS of M1.

PAS applied to S1 can induce LTP-like increase or LTD-like decrease in excitability as measured by the mean amplitude of the early somatosensory evoked potentials. The direction of excitability change depends on the interval between peripheral nerve stimulation and single-pulse TMS of the contralateral somatosensory cortex, similar to PAS-induced STDP in M1 (Wolters et al., 2005). When primed by PAS_{25} subsequent peripheral high-frequency electrical stimulation resulted in a decrease of SEP amplitude, but in an SEP increase when primed by PAS_{10} (Bliem et al., 2008). This study demonstrated that homeostatic metaplasticity operates as a general principle of regulating plasticity across different areas of human cerebral cortex.

Under certain conditions, it might be desirable to non-homeostatically augment synaptic plasticity to enhance LTP-/LTD-dependent processes in the brain, such as during learning. In this vein, it was demonstrated that the interaction of two subsequent identical PAS_{25} protocols is highly time-dependent: At a PAS1-PAS2 interval of 10 min, PAS2 increased the duration of the PAS1-induced LTP-like MEP increase, at an interval of 30 min, PAS2 increased the magnitude and duration of the PAS1-induced LTP-like MEP increase, while at intervals of 60 min and 180 min, PAS2 had no additional effect on MEP size (Müller-Dahlhaus et al., 2015). These findings support evidence from basic research (Peineau et al., 2007) that LTP can be augmented if induction protocols are optimally spaced (by about 30 min), while homeostatic metaplasticity occurs at intervals >60min.

In another study, priming of short-duration PAS_{25} by short-duration (7 min) anodal TDCS enhanced LTP-like plasticity, while priming with short-duration cathodal TDCS switched this LTP-

like plasticity to LTD-like plasticity (Nitsche et al., 2007). The authors speculated that these non-homeostatic metaplasticity effects could be explained if TDCS and PAS activate distinct neuronal circuits without significant physiological interaction. The resulting change of MEP amplitude would then be reflected by a summation of independent effects of the priming TDCS protocol and the subsequent PAS LTP protocol.

Priming of PAS_{25} and PAS_{10} with very low-frequency (0.1 Hz) rTMS resulted in occlusion of both, LTP-like and LTD-like plasticity (Delvendahl et al., 2010). Therefore, these data were not fully in accord with homeostatic metaplasticity according to the BCM theory. While 0.1Hz rTMS did not change MEP amplitude when given alone, it increased SICI and long-interval intracortical inhibition (LICI), i.e., paired-pulse TMS markers of GABA-A-ergic and GABA-B-ergic inhibition, respectively (Delvendahl et al., 2010). The authors concluded that this increase in cortical inhibition was responsible for the general occlusion of subsequent induction of LTP- and LTD-like plasticity by PAS, in accordance with previous studies that have demonstrated a critical role of the level of inhibition in slices of rat motor cortex (Castro-Alamancos et al., 1995, Hess et al., 1996). Similarly, at the systems level of human M1, GABAergic drugs suppressed PAS-induced LTP- and LTD-like plasticity (Fuhl et al., 2015, Heidegger et al., 2010, Lücke et al., 2014, McDonnell et al., 2007).

Interactions between PAS and motor learning

Basic studies provided compelling evidence that learning is an LTP-dependent process (Sanes and Donoghue, 2000). In rat motor cortex, less LTP but more LTD could be induced if that motor cortex was engaged in recent motor skill learning compared with a non-training condition (Rioult-Pedotti et al., 1998, Rioult-Pedotti et al., 2000). The authors interpreted this reduced probability for LTP induction after motor skill learning as a means to maintain synaptic weights within a physiological synaptic modification range. If motor learning strengthens the same synapses that are also involved in LTP induction, then the observed interactions follow homeostatic metaplasticity according to the BCM theory. At the systems level of the human M1, practice of fastest possible

thumb abductions resulted in learning, defined by an increase in maximum peak acceleration of the practiced movements, and prevented subsequent PAS_{25}-induced MEP increase in a thumb muscle but enhanced subsequent PAS_{10}-induced MEP decrease (Ziemann et al., 2004). These findings in accord with the BCM theory of homeostatic metaplasticity were subsequently confirmed by others (Avanzino et al., 2015, Elahi et al., 2014, Rosenkranz et al., 2007, Stefan et al., 2006).

Homeostatic metaplasticity may also apply when motor practice follows PAS-induced plasticity. In support of this idea, PAS_{10}-induced LTD-like plasticity enhanced subsequent learning of fastest possible thumb abduction movements, whereas PAS_{25}-induced LTP-like plasticity decreased it (Jung and Ziemann, 2009). Notably, this homeostatic interaction was observed only if PAS and motor practice were separated by a delay of 90 min, similar to the time-dependency of homeostatic metaplasticity when testing the interactions of two PAS protocols (see above). In contrast, a delay of 0min resulted in enhancement of learning by priming with both, PAS_{10} and PAS_{25} (Jung and Ziemann, 2009). In summary, these findings could open up the opportunity to enhance learning processes by priming with PAS, for instance during motor rehabilitation of stroke patients. However, more evidence is needed, as others could not confirm a significant interaction between PAS and subsequent motor skill learning (Elahi et al., 2014).

Interactions between PAS and motor learning in pathology

Finally, testing the interaction between PAS and motor learning can be utilized to investigate for abnormalities of metaplasticity in neurological disorders. Training of fastest possible thumb abductions without priming resulted in similar learning, i.e. an increase in the peak acceleration of the trained movement, in patients with task-dependent focal hand dystonia (writer's cramp) and healthy controls (Kang et al., 2011). In the healthy control group, PAS_{25} priming suppressed subsequent motor learning and PAS_{10} enhanced it, in accord with homeostatic metaplasticity. In contrast, the writer's cramp group exhibited absent PAS_{25} and PAS_{10} priming effects on subsequent motor learning (Kang et al., 2011). The extent of failure to reduce motor learning by priming with

PAS_{10} in the writer's cramp patients directly correlated with clinical severity of their dystonia (Kang et al., 2011). These data corroborate the notion that deficient homeostatic metaplasticity of practice-dependent plasticity plays a significant role in the pathophysiology of writer's cramp (Quartarone et al., 2005).

SECTION 2: PAS IN MOVEMENT DISORDERS AND OTHER NEUROPSYCHIATRIC CONDITIONS

Parkinson's Disease (PD)

In Parkinson's disease (PD), most studies that used $PAS_{21.5}$ (Morgante et al. 2006) or PAS_{25} (Ueki et al. 2006; Schwingenschuh et al. 2010; Kacar et al. 2013) found decreased LTP-like plasticity when PD patients were studied off medication. Dopaminergic medication restored the LTP-like plasticity (Ueki et al. 2006) but only in patients without levodopa-induced dyskinesia (LID) and not in patients with LID (Morgante et al. 2006). However, different results have also been reported. A study found exaggerated response to PAS_{25} with greater spread to non-targeted muscles in PD patients off medication compared to controls, and the response normalized with dopaminergic medication (Bagnato et al. 2006). The responses in PD patients off medication in that study resemble the results reported for dystonia (Quartarone et al. 2003; Weise et al. 2006). Another study used "rapid" (5 Hz) PAS_{25} and found no difference in plasticity responses between PD patients with LID in both on and off mediation states compared to age-matched controls, but plasticity responses were weak in all the groups studied (Kishore et al. 2014).

Most studies tested PD patients on chronic dopaminergic medications, which may influence plasticity response. One study showed that drug naive PD patients had similar reduction in LTP-like effect as patients on chronic dopaminergic medications who had similar severity of PD (Kacar et al. 2013). Studies in early PD patients with longitudinal follow up are a useful way to assess the nature of changes in cortical plasticity in PD. Early, drug naive PD patients had decreased response to

PAS_{25} on the more affected side but had exaggerated response on the less affected side, which may represent compensation (Kojovic et al. 2012). Over 12 months follow-up, the asymmetry in PAS response decreased and this correlated with reduction in asymmetry of UPDRS scores, which may reflect reduction in compensatory mechanisms with disease progression (Kojovic et al. 2015). There has been considerable interest on the role of the cerebellum in PD, particularly its involvement in LID. Interestingly, inhibitory cTBS of the cerebellum increased the PAS_{25} response in dyskinetic PD patients but not in age-matched controls (Kishore et al. 2014).

Since there is no prominent cortical pathology in non-demented PD patients, most investigators considered that the alterations in cortical plasticity measured by PAS in PD are likely due to changes in basal ganglia - cortical projections. Therefore, how deep brain stimulation (DBS) of the basal ganglia affects cortical plasticity was tested in a group of dyskinetic PD patients treated with subthalamic nucleus (STN) deep brain stimulation (DBS) (Kim et al. 2015). The response to $PAS_{21.5}$ was impaired in both on and off medication states with the stimulators turned off, consistent with the results of a previous study in PD patients without DBS (Morgante et al. 2006). Turning the stimulators on in the off medication state had no effect but in the medication on state with stimulator turned on, there was restoration of cortical plasticity (Kim et al. 2015). This study showed that alteration of basal ganglia output with DBS can modulate cortical plasticity, and is consistent with the hypothesis that alterations in cortical plasticity are related to changes in cortical-basal ganglia connections. However, it is not known whether a background of chronic STN DBS is required to restore the cortical plasticity and whether the DBS at another target such as the internal globus pallidus has similar effects.

In summary, cortical plasticity induced by PAS appears to be decreased in PD patients off medication and is partially restored in some patients on medication. However, some studies showed different findings. These may be related the small number of subjects tested in most studies and to the complex interactions between patients and technical factors that differed between studies and could influence the plasticity response. The patient factors include different stages of PD, history of

medical or surgical treatment, less affected versus more affected sides, presence of LID or tremor. The technical factors of PAS include the timing between MNS and TMS ($PAS_{21.5}$ vs. PAS_{25}), the repetition rate of PAS, the number of paired stimuli used to induce plasticity, muscle activation before, during and after plasticity induction, attention, time of day and the variability of PAS response. Nevertheless, PAS studies in PD patients have provided evidence of reduced cortical plasticity in PD with greater impairment in patients with LID, and increased plasticity as a compensatory mechanism in early PD. Cortical plasticity is influenced by the basal ganglia and modulation of cortical plasticity may be involved in mediating the effects of DBS.

Dystonia

By using PAS, it was demonstrated that the both LTP and LTD like facilitatory-inhibitory effects on TMS-evoked MEPs recorded from the target muscle were enhanced in patients with focal hand dystonia (FHD) (Quartarone et al., 2003; Weise et al., 2006). A relevant feature of PAS-induced associative plasticity in healthy controls is that the after effects are largely confined to the cortical target representation receiving a dual congruent input (Stefan et al., 2000). This input specificity is lost in FHD, where PAS induces cortical excitability changes also in the nearby muscle representations (Quartarone et al., 2003, 2008; Weise et al., 2006: Belvisi et al., 2013). The loss of spatial specificity of PAS induced after effects, is probably related to the abnormalities of neuronal inhibition identified previously both in the motor and somatosensory system in dystonic patients (Quartarone et al., 2009; Quartarone and Hallett, 2013). The abnormalities of sensory-motor plasticity represent an endophenotypic trait of dystonia as they are not confined to the neural circuits affected by dystonia but generalize across the entire sensory-motor system (Quartarone et al., 2008). In contrast, patients with psychogenic dystonia had normal facilitation in APB and, as expected from the usual topographic organization of PAS, absent facilitation in first dorsal interosseous (FDI) (Quartarone et al., 2009). However, different results have also been reported. In a study conducted on 15 patients with writing dystonia the authors found the effects of PAS are

highly variable and they conclude that that enhanced plasticity should not be considered a dystonic fingerprint, because the direction of response can vary, and there is overlap between patient and healthy data (Sadnicka et al., 2014).

PAS can also modulate inhibitory motor circuits producing a lasting decrease of long afferent inhibition (LAI) and LICI in the motor representation of the targeted or trained muscle in normal volunteers (Russmann et al., 2009). In the same set of experiments the authors demonstrated that a motor learning task induce the same modulation of LAI and LICI (Russmann et al., 2009). Patients with focal dystonia have an abnormal modulation of LAI and LICI after PAS or motor learning that might indicate a maladaptive plasticity, which may underlie the difficulty that they have to learn a new sensorimotor task (Meunier et al., 2012). An abnormal PAS_{25} LTP-like plasticity has been reported in patients with generalized DYT1 dystonia prior to surgery.

DBS to the internal globus pallidus can be a very powerful treatment for dystonia (Coubes et al., 2000) and recent long-term results demonstrate that benefits are maintained after more than 10 years (Cif et al., 2010). An intriguing point is that, in contrast to the almost immediate effects of DBS on the majority of symptoms in Parkinson's disease, it may take several months to achieve maximum clinical benefit in patients with dystonia (Yianni et al., 2003; Vidailhet et al., 2005). In this fascinating field of research PAS studies have been very useful for testing cortical plasticity at baseline and after DBS stimulation. Immediately after DBS treatment PAS response was reduced on average compared with to healthy controls (Tisch et al., 2007) and tended to recover toward normal levels at 6 months (Ruge et al., 2011). The reduction of PAS response after DBS resembles the pattern seen in bradykinetic patients with PD (Morgante et al., 2006) and may be one factor contributing to potential parkinsonian side effects after long-term DBS in dystonic patients. The effects of DBS on PAS-induced plasticity did not correlate significantly with the changes in clinical scores (Ruge et al., 2011). This finding can be explained considering that enhanced plasticity does not induce per se the dystonic symptoms but causes inappropriate association between sensorimotor inputs and outputs, that ultimately lead to excess of involuntary movements (Quartarone and

Hallett, 2013). Interestingly the larger the response to the PAS protocol the more likely were patients able to maintain the clinical improvement obtained after long-term DBS. This apparently contradictory effect could be explained considering that patients who have the 'highest plasticity' can better restore a normal motor repertoire after long term DBS. This paradoxical effect might also explain why patients with the most stable memories (and the highest PAS response after years of DBS) are the ones who experience the least decline in clinical symptoms when turning off DBS. Finally it should be considered that the amount of PAS-induced plasticity after several years of DBS is related to the parameters of stimulation. The current drain can be calculated from the combination of stimulation parameters (pulse height, duration and frequency) used for DBS and the impedance (see Kuncel and Grill, 2004). A good response to PAS is also associated with low levels of DBS current drain. If this link is causal, then it may be possible in the near future, based on PAS findings, to adjust stimulus parameters to maximize long-term clinical effects (Ruge et al., 2011).

An extremely pronounced enhancement of PAS was also demonstrated in Costello syndrome (CS) (Dileone et al., 2010) a rare multiple congenital anomaly disorder caused by mutations in the HRAS protooncogene and characterized by mental retardation (Costello, 1977) and generalized dystonia (Dileone et al., 2012). In CS patients the increase of MEP amplitude after PAS is four times larger compared to that observed in age-matched healthy subjects, CS patients also have a loss of PAS topographical specificity (Dileone et al., 2010). Interestingly, PAS enhancement is paralleled by an impairment of another form of LTP-like phenomenon produced by intermittent theta burst stimulation of the motor cortex, suggesting that HRAS-dependent signaling pathways have a differential influence on different protocols inducing plasticity in human brain (Dileone et al., 2016). The pronounced abnormality of PAS in CS patients suggests a possible role of HRAS in LTP-like mechanisms involved in PAS.

Huntington's disease and Gilles de la Tourette Syndrome

Studies using the PAS technique in HD have detected abnormalities in M1 long-term plasticity.

PAS is considered to be a form of STDP, as PAS-induced LTP/LTD-like phenomena can be elicited in M1 by repetitive activation of specific sensorimotor circuits within a restricted time window. The fact that MEPs remain unchanged after PAS in patients with HD suggests that M1 LTP-like plasticity, as tested by PAS, is reduced in Huntington's disease (HD) (Crupi et al., 2008). These findings are in keeping with a number of data from experimental models of early HD that demonstrate abnormal plasticity also in the early phase of the disease (Mazarakis et al., 2005; Milnerwood et al., 2006; Crupi et al., 2008). It is therefore likely that mechanisms of long-term plasticity in cortical motor areas are impaired in patients with HD, which might in turn contribute to the pathophysiology of this motor disorder. It is, however, difficult to ascertain whether altered plasticity is a primary or secondary phenomenon in HD. One hypothesis is that changes in M1 plasticity in patients with early-phase HD reflect altered thalamo-cortical inputs to M1 (DeLong and Wichmann, 2007). An alternative hypothesis is that the abnormal plasticity observed in M1 in patients with HD reflects early compensatory mechanisms adopted by the motor system to improve motor output control.

Although the pathophysiology of Gilles de la Tourette (GTS) is still unclear, recent studies have suggested that altered plasticity in M1 contributes to the pathophysiology of this disease. This hypothesis came from the observation that patients with GTS had abnormal responses to iTBS/cTBS (Suppa et al. 2011, 2014; Wu et al. 2012) and PAS (Brandt et al. 2014; Martín-Rodríguez et al. 2015). Brandt and colleagues (2014) found reduced responses to PAS in adult patients with GTS. By contrast, Martin-Rodriguez et al. (2015) demonstrated abnormally increased responses to PAS in adult patients with GTS. This inconsistency might arise from the different clinical features of the patients enrolled in the previous studies, since Martin-Rodriguez and coll. (2015) specifically investigated adult patients with severe GTS.

PAS in other neuropsychiatric conditions

Besides studies in patients with movement disorders, a number of authors have examined responses

to PAS in patients with various neuropsychiatric conditions. The main findings coming from these PAS studies are summarized in **Table 2**.

SECTION 3: MODIFIED PAS PROTOCOLS

An increasing number of modified PAS protocols have been designed and assessed in healthy subjects and in patients with various neurological disorders. Most of the modified PAS protocols share neurophysiological features including associativity, timing-dependent directionality, topographical specificity, state dependence and, finally, duration of the after-effects (30-60 min). Some of the modified PAS protocols implied the application of PAS to M1 cortico-spinal neurons controlling the lower limb (Stinear and Hornby, 2005; Prior and Stinear, 2006; Mrachacz-Kersting et al., 2007), while others were based on rapid-rate stimuli (Quartarone et al., 2006; Srivanitchapoom et al., 2016). Several PAS protocols have been designed to induce LTP- and LTD-like plasticity specifically in the primary sensory cortex (S1) (Wolters et al., 2005) or in the spinal cord (Taylor and Martin, 2009; Cortes et al., 2011; Leukel et al., 2012), whereas other implied afferent sensory inputs to M1 other than those used in the original PAS protocol including nociceptive, proprioceptive, visual and acoustic stimuli (Schecklmann et al., 2011; Suppa et al., 2013, 2015a, 2015b, 2016; Naro et al., 2015a, 2015b; Edwards et al., 2014; Sowman et al., 2014). By using a rather different experimental approach, several authors have designed new PAS protocols based on afferent volleys to M1 driven by other cortical areas including the contralateral M1 (Rizzo et al., 2009, 2011; Kogenemaru et al., 2009), the ventral premotor cortex (PMv) (Buch et al., 2011), the supplementary motor area (SMA) (Arai et al., 2011) and the posterior parietal cortex (PPC) (Koch et al., 2013; Veniero et al., 2013; Chao et al., 2015) as well as subcortical structures such as the cerebellum (Lu et al., 2012) and specific basal ganglia nuclei (Udupa et al., 2016). Finally, several new PAS protocols required associativity between exogenous and

endogenous activation of M1 (Thabit et al., 2010; Mrachacz-Kersting et al., 2012; Jochumsen et al., 2016).

PAS targeting the primary motor leg area

Two early studies assessed a new PAS protocol targeting the M1 hot spot for the lower limb in healthy subjects (Stinear and Hornby, 2005; Prior and Stinear, 2006). The authors delivered TMS over the tibialis anterior (TA) muscle motor hotspot (120 stimuli at intensity for eliciting about 0.5 mV MEPs), paired with electric peripheral stimulation of the common peroneal nerve (CPN) at 0.2 Hz (10 min of stimulation), during treadmill walking. ISIs between TMS and CPN stimulation have been individualized for each participant (MEP latency + 5 ms; range: 35-42 ms). The authors found that when TMS was given after the estimated arrival time in M1 of the afferent sensory volley, MEPs increased, whereas when TMS was delivered prior the estimated arrival time, MEPs decreased in amplitude (Stinear and Hornby, 2005; Prior and Stinear, 2006). In a further study, Mrachacz-Kersting et al. (2007) again delivered TMS over the TA muscle M1 hotspot (360 stimuli at 120% resting motor threshold (RMT)) paired with electric peripheral stimulation of the CPN at 0.2 Hz (30 min of stimulation). The authors found that PAS at 45, 50 and 55 ms ISIs increased MEPs suggesting LTP-like plasticity, whereas PAS at 40 ms decreased MEPs suggesting LTD-like plasticity in M1 (Mrachacz-Kersting et al., 2007).

Rapid-rate PAS of the primary motor hand area

A number of authors have designed and assessed the effect of modified PAS protocols characterized by rapid repetition (5Hz) or paired stimulation and a sub-threshold intensity of the TMS stimulus. Quartarone et al. (2006) reported a rapid-rate PAS protocol consisting of TMS over M1 (600 stimuli at 90% active motor threshold (AMT)), paired with electric median nerve stimuli at 5 Hz (2 min of stimulation). The authors showed that rapid-rate PAS_{25} induced significant facilitation of MEPs, whereas PAS_{10} it did not (Quartarone et al., 2006). Recently, Srivanitchapoom

et al. (2016) demonstrated that 1 minute of rapid-rate PAS_{10} delivered at lower frequency (0.25 Hz) and at 80% AMT, significantly decreased MEP amplitude.

Wolters and coll. (2005) designed a PAS protocol able to elicit LTP- and LTD-like plasticity specifically in S1. PAS employed TMS over S1 (180 stimuli at 0.1 Hz and 150% of RMT) coupled with MNS at an ISI equaling the individual MN-SEP N20 latency. They found that PAS increased the MN-SEP P25 amplitude. More recently, Tsang et al. (2014) reported a rapid-rate PAS protocol in which TMS targeted S1 (600 stimuli at 5 Hz and 70% of RMT) coupled with preceding MNS at an ISI equaling the individual MN-SEP N20 - 2.5 ms. This rapid-rate PAS protocol increased S1 excitability, as reflected by reduced paired pulse inhibition (PPI) and by a trend for increased MN-SEP N20 and P25 amplitudes. This rapid-rate sensory PAS protocol also increased M1 excitability as demonstrated by significant MEP facilitation (Tsang et al., 2014).

PAS protocols acting at the spinal cord level

Besides the previous studies of Meunier et al. (2007) and Lamy et al. (2010) demonstrating that the original PAS protocol modifies also spinal excitability (as reflected by changes in the H-reflex), several studies have designed new PAS protocols able to elicit LTP- and LTD-like plasticity specifically in spinal circuits. The first study from Taylor and Martin (2009) reported a new protocol employing electric peripheral stimulation of the brachial plexus able to elicit antidromic motor axon activation timed to coincide at the alpha-motor neuron with descending volleys induced by cervicomedullar stimulation (cervical MEPs – cMEPs, in the biceps brachii muscle). The authors applied TMS (50 stimuli at intensity for eliciting 1mV MEPs) paired at 0.1 Hz with electric stimuli at various ISIs (about 8 min of stimulation). The authors found that PAS at 3 ms ISI increased cMEPs, whereas PAS at -13 and +22 ms ISIs decreased cMEPs from the biceps brachialis muscle, demonstrating LTP- and LTD-like plasticity in spinal circuits (Taylor and Martin, 2009). Later, Cortes and coll. (2011) designed a protocol consisting of TMS given over the M1 hot spot for the soleus muscle (90 stimuli at 80% RMT) paired with electric stimulation of posterior tibial nerve

(TN) able to elicit H-reflex from soleus muscle, at 0.1 Hz (15 min of stimulation). When electric TN stimulation was given 20 ms after the TMS pulse, the H-reflex amplitude increased significantly, suggesting LTP-like plasticity in the spinal cord. Finally, Leukel et al. (2012) applied TMS over M1 hot spot of the soleus muscle (360 stimuli at 100% RMT) paired with electric TN stimulation, at 0.2 Hz and -1 ms ISI (30 min of stimulation). Again, the H-reflex amplitude from the soleus muscle increased suggesting LTP-like plasticity in the spinal cord (Leukel et al., 2012; Bunday and Perez, 2012).

PAS protocols with other afferent sensory volleys to M1

In healthy subjects, a modified PAS protocol has been designed combining TMS over M1 with activation of the nociceptive system achieved by laser pulses given over the skin (Nd:YAP laser pulse, wave length: 1.34 μm, pulse width: 2-20 ms, maximum energy: 7 J). In more details, Laser-PAS consisted of TMS pulses (60 stimuli, intensity for 1 mV MEPs) at 0.1 Hz, each TMS pulse following a single laser stimulus delivered at an ISI of laser evoked potentials (LEPs) N1 component latency + 50 ms (Laser-PAS50) (10 min of stimulation) (Suppa et al., 2013). The after-effects induced by Laser-PAS50 are thought to reflect LTP-like plasticity arising from pain-motor integration processes (Suppa et al., 2013). A recent study showed that differently from healthy subjects, patients with PD have reduced responses to Laser-PAS50 when off and on therapy. In addition, patients with PD reporting chronic pain in the same upper limb investigated with Laser-PAS50, had greater abnormalities compared with patients without pain or those reporting pain in other body regions (Suppa et al., 2016, personal communication). Overall these observations suggest that chronic pain, a common non-motor symptom in PD, further degrades LTP-like plasticity in M1 in patients with PD, through mechanisms of abnormal pain-motor integration (Suppa et al., 2016, personal communication). A further application of Laser-PAS50 has been reported in a relatively small cohort of post-anoxic subjects with unresponsive wakefulness syndrome (UWS) (Naro et al., 2015a). Laser-PAS50 induced significant MEP changes in some of

the UWS cohort suggesting that pain-motor integration processes still operate in these patients (Naro et al., 2015a).

Edwards et al. (2014) assessed the effect of TMS over M1 (400 stimuli, 120% RMT) associated with passive movements (cyclic pattern of wrist extension and flexion through a range of 90º) achieved by a robotic device, at 1 Hz. When TMS was triggered by the robotic device to coincide with the lengthening phase and in the mid of flexion to extension wrist position, MEPs from FCR muscle decreased in amplitude (Edwards et al., 2014). The authors suggested that passive movements changed afferent proprioceptive volleys driven by muscle spindles at spinal and cortical level and in turn led to LTD-like plasticity in M1 (Edwards et al., 2014).

A previous study in healthy subjects reported a new PAS protocol employing TMS over M1 coupled with visual evoked potentials (VEP) (Suppa et al., 2015a). In this protocol termed visual-PAS (V-PAS), hemifield VEPs have been elicited by pattern-reversal visual stimuli (half screen with black-and-white checks changing phase at 1 Hz; individual check visual angle 30′; field size 24°; luminance contrast 80%). V-PAS consisted of 600 VEPs elicited at 1 Hz frequency and each VEP preceded a TMS pulse over M1 (intensity for eliciting 1 mV MEPs) at ISIs ranging from VEP' P100 peak latency + 40-140 ms (10 min of stimulation) (Suppa et al., 2015a). The V-PAS-induced after-effects depended on the specific ISI used and ranged from inhibition (ISI 40 ms) to no change (ISIs 60-80 and 140 ms), and finally to facilitation of MEPs (ISIs 100-120 ms) (Suppa et al., 2015a). A further V-PAS study applied in a cohort of patients with idiopathic generalized epilepsy (IGE), manifesting or non-manifesting the photoparoxysmal response (PPR), demonstrated that compared to healthy subjects, patients with PPR had abnormally increased responses to V-PAS_{100}, a finding not present in patients with IGE but without PPR. Overall these findings suggested that altered LTP- and LTD-like plasticity induced by visuo-motor integration processes contribute to the pathophysiology of PPR (Suppa et al., 2015b).

Two previous studies reported protocols designed with TMS over M1 paired with acoustic stimuli. Schecklmann and coll. (2011) coupled TMS over the auditory cortex (200 stimuli, 100%

RMT) with monoaural acoustic stimuli (4kHz, 400 ms, 60 dB) able to elicit long-latency acoustic evoked potentials (AEPs), at 45 and 10 ms ISIs, and at 0.1 Hz (33 min of stimulation). Both protocols (PAS at 10 and 45 ms ISIs) decreased AEPs' N1-P2 complex suggesting LTD-like plasticity in the auditory cortex. More recently, Sowman et al. (2014) coupled TMS over M1 (200 stimuli, at 120% RMT) with acoustic cues consisting of brief vocalizations ("Hey"), delivered at 80 dB, with 4-5 sec of ISI (less than 30 min of stimulation). Following PAS, MEPs increased in amplitude suggesting LTP-like plasticity in M1, due to audio-motor integration processes (Sowman et al., 2014). Naro and coll. (2015b) paired TMS over M1 (600 stimuli at 90% RMT, 3 blocks of 200 pulses in 40 sec, 10 sec of intertrain interval) with a transauricular electric stimulation of the acoustic nerve (500 Hz sine tone) able to elicit long-latency AEPs, at 5Hz, in patients with chronic disorders of consciousness. PAS increased MEPs in patients with minimally conscious state (MCS) but not in those with UWS in whom the audio-motor integration was prominently affected (Naro et al., 2015b).

PAS protocols with afferent volleys to M1 driven by other cortical structures

Three previous studies have assessed the after-effects of PAS protocols combining bi-hemispherical M1 stimulation at specific ISIs (Rizzo et al., 2009, 2011; Kogenemaru et al., 2009). In the studies of Rizzo et al. (2009, 2011), PAS employed TMS pulses (90 stimuli, intensity for eliciting 1 mV MEPs) delivered bi-hemispherically (M1 and contralateral M1 - cM1) at 0.05 Hz and 8 ms ISI. PAS induced significant MEP facilitation suggesting LTP-like plasticity in the target M1. In the study of Kogenemaru and coll. (2009), PAS employed TMS (180 stimuli at 120% RMT) at 0.1 Hz and 5-25 ms ISIs. PAS at 15 ms ISI increased MEPs suggesting LTP-like plasticity in the target M1. These effects are probably mediated through transcallosal motor fibers.

A single study by Buch et al. (2011) examined the after-effects induced by TMS over the PMv (90 stimuli at 110% RMT) paired at 8 ms ISI with ipsilateral M1 stimulation (intensity for eliciting 1 mV MEPs), at 0.1 Hz (15 min of stimulation). The direction of the after-effects reflected

the sequential order of the two stimuli: PMv-to-M1 stimulation elicited increased-amplitude MEPs, suggesting LTP-like plasticity, whereas the opposite order (M1-to-PMv) led to decreased-amplitude MEPs, suggesting LTD-like plasticity in M1, due to PMv-to-M1 functional connectivity (Buch et al., 2011).

Another study by Arai et al. (2011) applied a protocol with TMS given over the SMA (3 blocks of 50 stimuli, less than 10 min each, at 140% AMT) paired with near simultaneous bilateral or a single unilateral M1 stimulation (intensity for 1 mV MEPs), at 8 ms ISI, and at 0.1 Hz (15 min of stimulation). Again, the direction of the aftereffects reflected the order of the two stimuli as well as the specific ISI used: SMA-to-M1 stimulation at 6 ms ISI elicited increased-amplitude MEPs suggesting LTP-like plasticity, whereas the opposite order (M1-to-SMA) at 15 ms ISI led to decreased-amplitude MEP, suggesting LTD-like plasticity in M1 due to SMA-to-M1 effective connectivity (Arai et al., 2011).

A number of studies have reported the after-effects of several protocols coupling TMS of the PPC and ipsilateral M1. Koch et al. (2013) and Veniero et al. (2013) described a protocol based on TMS delivered over the PPC (100 stimuli at 90% RMT) and ipsilateral M1 (intensity for eliciting 1 mV MEPs), at 5 ms ISI, and at 0.2 Hz (about 8 min of stimulation). Again, the direction of the after-effects reflected the order of the two stimuli: PPC-to-M1 decreased MEPs suggesting LTD-like plasticity, whereas M1-to-PPC elicited MEP facilitation suggesting LTP-like plasticity (Koch et al., 2013; Veniero et al., 2013), possibly related to motor cortex orientation (Sommer et al., 2013). The direction of the aftereffects reverted when the coil orientation (over M1) changed from PA to AP: PPC-to-M1 PAS with AP orientation increased rather than decrease MEP amplitudes (Koch et al., 2013; Veniero et al., 2013). More recently, Chao et al. (2015) demonstrated that a similar protocol combining TMS over PPC (180 stimuli at 90% RMT) and over the ipsilateral M1 (intensity for eliciting 1 mV MEPs), at 0.2 Hz (15 min of stimulation) and 8 ms ISI, also increased MEP amplitude suggesting LTP-like plasticity in M1, presumably due to PPC-to-M1 effective connectivity.

PAS protocols with afferent volleys to M1 driven by subcortical structures

Lu et al. (2012) reported aftereffects induced by a new PAS protocol combining TMS over the cerebellum (120 stimuli at 95% AMT) and over the contralateral M1 (intensity for eliciting 1 mV MEPs) delivered at 2, 6 and 10 ms ISIs, and at 0.25 Hz (8 min of stimulation). Cerebellar PAS at 2 ms ISI increased MEP amplitude suggesting LTP-like plasticity, whereas, PAS at 6 and 10 ms ISIs decreased MEP amplitude suggesting LTD-like plasticity, through activation of cerebello-thalamic projections to M1 (Lu et al., 2012).

Another PAS approach was based on pairing basal ganglia nuclei and M1 stimulations. In an elegant study in patients with PD, Udupa and coll. (2016) assessed the effect of PAS involving stimulation of the subthalamic nucleus (STN) with deep brain stimulation (DBS) electrodes (180 stimuli; pulse width: 60µs; voltage: 1.5-4.0 V) and TMS over M1 (intensity for eliciting 1 mV MEPs), at 0.1 Hz and at 3 or 23 ms ISIs (30 min of stimulation) (Udupa et al. 2016). The specific ISIs used in this protocol have been set according to previous observations of Kuriakose et al. (2010) who demonstrated that in patients with PD, a single STN-DBS pulse transiently increases M1 excitability at about 3 ms, probably through antidromic activation of the hyperdirect cortical-STN pathway, and at about 23 ms likely through orthodromic activation of the basal ganglia thalamo-cortical pathway. Udupa et al. (2016) found that STN-cortical PAS at both ISIs (3 and 23 ms) increased cortical excitability in patients with PD suggesting LTP-like plasticity in M1. Thus, M1 plasticity can be induced by pairing of basal ganglia and cortical stimuli at appropriate intervals. While the precise mechanisms of action of STN-DBS are not known (Udupa and Chen 2015), these studies showed that STN-DBS could induce and modulate cortical plasticity.

PAS protocols requiring endogenous activation of M1

Thabit et al. (2010) first designed and assessed a new PAS protocol implying TMS delivered over M1 (240 stimuli at 120% RMT) during the reaction time of a simple reaction time task implying

ballistic thumb abduction movements, at 0.2 Hz (20 min of stimulation). The rationale was to elicit plasticity mechanisms in M1 by delivering TMS immediately before movement onset and thus during the expected endogenous activation of M1. The authors found that TMS delivered at 50 ms before or 100 ms after movement onset significantly increased MEPs suggesting LTP-like plasticity in M1 (Thabit et al., 2010). Although movement related cortical potentials (MRCP) were not recorded, it was hypothesized that LTP-like plasticity occurred because neural elements in M1 activated by TMS overlapped, at least in part, with those generating the late motor component of MRCP. However, Thabit et al. (2010) did not clarify the specific MRCP subcomponent related to the self-triggered movements (Suppa and Papazachariadis, 2013).

Mrachacz-Kersting and coll. (2012) designed a new protocol not requiring TMS but rather implying electric stimulation of the common peroneal nerve (CPN) (2 sets of 25 trials each with 50 stimuli every 10-12 sec) and endogenous activation of M1 during contingent negative variation (CNV). In the experiment designed by Mrachacz-Kersting et al. (2012), after the "go" signal, participants were asked to imagine a ballistic ankle dorsiflexion, to hold the imagined voluntary contraction for 2 sec and then to release the imagined contraction. When the CPN-induced afferent volley was timed to arrive during the late phase of CNV (the CNV mean peak negativity), compared to baseline, MEPs from the TA muscle (used to probe plasticity) increased significantly suggesting LTP-like plasticity in M1 (Mrachacz-Kersting et al., 2012). Jochumsen et al. (2016) extended the previous findings of Mrachacz-Kersting et al. (2012) and designed a protocol coupling endogenous activation of M1, during CNV, induced by imagined dorsiflexion of the ankle joint, and electric stimulation of the TN (supplying the antagonist soleus muscle). When the afferent volley from electric TN stimulation reached the sensorimotor cortex, at the onset of CNV, compared to baseline, MEPs from the TA muscle (heterotopic muscle) decreased, suggesting LTD-like plasticity in M1 (Jochumsen et al., 2016). Mrachacz-Kersting et al. (2012) and Jochumsen et al. (2016) did not apply TMS in their PAS protocols. Thus, the exact location where associativity occurred remains rather unclear. Hence, it is difficult to clarify whether the associativity demonstrated by the

authors (Mrachacz-Kersting et al., 2012; Jochumsen et al., 2016) reflected intrinsic M1 activity or rather enhanced functional connectivity between M1 and non-primary areas (Suppa and Papazachariadis, 2013). However, the interesting studies of Mrachacz-Kersting et al. (2012) and Jochumsen et al. (2016) have provided new advances in the experimental design and possible application of PAS protocols in humans. The various PAS protocols reported here may in the future help to develop new experimental approaches able to induce LTP- and LTD-like plasticity in M1 through brain computer interface (BCI) technologies to improve motor disabilities or the capability to interact with the environment in patients with severe neurological disorders.

SECTION 4: PROSPECTS IN NEUROMORPHIC CIRCUITS

The discussion so far provided ample illustration of the observed temporally causal nature of PAS, that very intuitively led to the assumption that STDP at the single synapse level could provide a natural conceptual setting for the observed phenomenology in PAS studies. However, the spatial and temporal scale at which PAS operates makes it plausible to assume that whole synaptic populations are involved, possibly heterogeneous in the relevant time scales and "synaptic rules"; rather, it has become increasingly clear that STDP is one aspect of a multi-faceted long-term synaptic plasticity phenomenology, discovered to be significantly more complex than initially believed (Shouval et al., 2010). At the same time, there is mounting interest in the development of microelectronic devices coupled in real-time to the nervous tissue, to build hybrid systems for neuroprosthetics (whereby a lost or impaired function is recovered) or BCI (by which physiological brain activity is decoded to drive an artificial device). In these contexts, it is increasingly recognized that endowing the artificial component of the hybrid system with adaptive and plastic properties would greatly expand their potential and applicability in real-life situations. It is then just a natural step to try and incorporate available models of synaptic plasticity to underpin the desired adaptive

behavior of neuroprosthetic or BCI systems; the involved strategies for closed-loop, real-time hybrid system, and the associated development of "neuromorphic" chips, also have potential to possibly augment PAS, endowing them with adaptive capabilities. In the PAS domain, such options just begin to be considered (Royter et al., 2016; Sabathiel et al., 2016); in the following, to provide a hint at available methodologies to make progress towards closed-loop, adaptive PAS systems, we first briefly touch upon the present status of implementable synaptic plasticity models, and next give few examples of neuromorphic electronic synaptic implementations and hybrid closed-loop systems.

Since the early '90, several experiments provided evidence that the sign and magnitude of long-term synaptic modifications can be determined by the relative timing of the pre- and post-synaptic spikes (Bi and Poo, 1998; Levy and Steward, 1983; Markram et al., 1997; Sjöström et al., 2001); the synapse is potentiated (or depressed) when the pre-synaptic spike precedes (or follows) a post-synaptic spike within a time window of 10-20 ms. The ensuing synaptic plasticity model was termed STDP (Song et al., 2000). The implications of STDP at the network level were extensively investigated (Babadi and Abbott, 2010; Song and Abbott, 2001; Song et al., 2000), as well as the possible computational role of STDP (e.g. Gerstner et al., 1996; Gutig and Sompolinsky, 2006; Legenstein et al., 2005). However, accumulating experimental evidence gradually revealed a richer picture: plasticity may depend on neuron type and connections; it occurs in multiple and concurrent forms, including rate-dependent, voltage-dependent and spike-timing-dependent; it can be homosynaptic or heterosynaptic, not to mention short-term plasticity and homeostatic synaptic mechanisms. Theoretical work acknowledged such complexity by developing models flexible enough to encompass multiple factors of synaptic plasticity (e.g. Graupner and Brunel, 2012), where STDP can be recovered as a special case of a more general synaptic rule, and their effects at the network level (Zenke et al., 2015). These developments had impact on the quest for microelectronic counterparts of neuronal networks with plastic synapses, frequently termed "neuromorphic" after C. Mead over two decades ago (Mead, 1989).

Broadly speaking, neuromorphic devices can be either chips in which dedicated electronic microcircuits mimic the dynamics of single neurons and synapses, often exploiting the analog electronic features of the silicon substrate or, more in general, special-purpose hardware providing low-power and real-time implementations of models supposedly adequate for mimicking the input-output properties of a neural structure at the appropriate scale of interest. Neuromorphic design seems in principle a reasonable option to build biomimetic devices acting as "equal partners" of nervous tissue that they could be directly interfaced to (Liu, 2015; Azghadi et al., 2014). In the following, we briefly mention few examples illustrating both non-trivial computational tasks that neuromorphic networks can perform thanks to synaptic plasticity, and a model-based approach to hybrid systems for closed-loop neuroprosthetics.

Associative memory (the ability to retrieve memorized information from partial clues) was the conceptual setting in which early attractor neural network models were developed (Amit, 1992), wherein simple forms of Hebbian plasticity underpinned selective associative memory for a prescribed set of stimuli classes. In a series of works, we implemented neuromorphic chips of spiking neurons and synapses endowed with a form of spike-driven Hebbian plasticity suggested inFusi et al. (2000) and Brader et al., 2007.We were able to first show(Giulioni et al., 2009) that the neuromorphic network could learn to classify correlated artificial stimuli; we demonstrated in (Giulioni et al., 2011) robust associative memory states in the neuromorphic network, and we were able to parallel, in the chip operation, the theoretical knowledge on the repertoire of memory states, and on the role of noise; finally, in(Giulioni et al., 2015) we showed that a memory-related synaptic structure could be autonomously generated in a 'naturalistic' condition wherevisual stimuli coming from a 'silicon retina' (Lichtsteiner et al., 2008) were repeatedly used as input to the neuromorphic network: Hebbian plasticity built associative representations of the visual stimuli with no supervision.

In the domain of bio-hybrid systems, closed-loop neuroprostheses, bidirectionally interfaced with the brain, have begun to emerge, offering the prospect of substituting damaged or impaired

brain structures; among many recent works, we mention a recent summary of control strategy in this context given in Wright et al. (2016). Boi et al. (2016) illustrate the use of a neuromorphic learning system for BCI and the recent volume by El Hady et al. (2016) offers an up-to-date overview. In Hogri et al. (2015), we provided a proof-of-concept of a neuro-inspired model-based approach to neuroprostheses. A neuromorphic chip was designed and fabricated (Bamford et al., 2012) to implement real-time processing of neural signals, and a synaptic plasticity rule relevant in the cerebellum; the chip was interfaced with cerebellar input and output nuclei in real time, to reproduce cerebellum-dependent learning of classical conditioning of the eye-blink response in anesthetized rats. The core of the chip was a field-programmable mixed-signal array specialized for neural signal processing and neural modeling. The programmable system was based on the intimate mixing of switched capacitor analogue techniques with low speed digital computation. Paired conditioned and unconditioned stimuli were repeatedly presented to an anaesthetized rat and recordings were taken simultaneously from two pre-cerebellar nuclei. These paired stimuli were detected in real time from multi-channel data recorded from the anesthetized rat. The occurrence and relative timing of the detected events elicited on-chip synaptic plasticity, resulting in turn in learning to deliver a well-timed trigger for conditioned eye-blink response; also, repetition of unpaired trials led to the extinction of the conditioned response trigger, compatible with known features of natural cerebellar learning. Such a model-based approach does not require prior system identification, allowing for de novo experience-based learning in the brain-chip hybrid, with interesting advantages (and limitations) compared to existing parametric ‘‘black box’’ models, that are open to further investigation. In the above examples, the neuromorphic approach was instantiated in its most ambitious form, whereby a direct correspondence is established between the chip’s circuital components and the theoretical models of single neurons and synapses. Such ambition also brings limitations, of course, and these may be relevant when it comes to inserting the neuromorphic chip in a loop including multiple and complex brain structures, as it would be the case for closed-loop PAS that involves TMS of the cortex.

An approach based on neuromorphic neural networks could in the long term provide biomimetic components of adaptable and flexible closed-loop systems, much superior to any ad hoc "lumped" solutions based on the implementation of an input-output relationship of interest; however, waiting for technology (and theory) to provide support for very large-scale, adaptive neuromorphic networks on chip, solutions can be delivered by specialized hardware lumping in one biomimetic device complex input-output properties. Examples of such a "lumped" approach are provided by (Berger, 2012) and (Hampson, 2012). In the first example, a neuroprosthesis aims to restore in a rat the ability to form new memories, which is typically lost after damage to the hippocampus; the artificial component of the prosthesis is a biomimetic nonlinear model that predicts the spatio-temporal output activity of the hippocampus region CA1, based on inputs recorded pre-synaptically to CA1. In the second example, a nonlinear model analogous to the one demonstrated in (Berger, 2012) extracted and characterized layer-dependent firing patterns recorded from multiple minicolumns in the prefrontal cortex of non-human primates during a working memory task; this allowed the layer-specific substitution of task-related neuron firing patterns with electrical stimulation in the same recording regions at the time of target selection; besides improving normal task performance, such stimulation regained performance when applied following pharmacological lesion disrupting decision making in the same task.

It is also noteworthy that as early as 2006 (Jackson 2006) it was shown that artificially pairing two sites in the motor cortex of non-human primates generated a stable reorganization of the motor output. Pairing was obtained using an implanted "neurochip"' which, repeatedly over days, upon detecting spikes from the first site, triggered (with appropriate delay) an electrical stimulation to the second site; in time, the pairing made the output generated by the activity of the two sites more and more similar, consistently with the Hebbian plasticity paradigm. This work provided an inspiring example of in-vivo functional reorganization at the cortical level, obtained from brain stimulations determined in turn from the brain activity.

The above examples may provide both conceptual foundations, and technological options,

towards adaptive closed-loop PAS systems; for instance, along the line proposed by Royter et al. (2016), in which PAS was modulated by brain state related to mental imagery, one could imagine a neuromorphic device implementing specific functions of the observed brain state, to be learnt (thanks to adaptive/plastic capability) according to some behavioral optimality criteria.

CONCLUSIONS

The introduction of the PAS protocol was a major step forward for the field of non-invasive brain stimulation. It showed that TMS could be used to probe basic mechanisms of synaptic plasticity at a "system" level in intact human cortex that until then had been accessible only in reduced animal preparations. Data from pharmacological and behavioral experiments shows that PAS is highly likely to involve activity at NMDA receptors and participation of dendritic calcium channels. In addition, the resulting plasticity is modulated in dose-dependent ways by activity at D1 and D2 dopamine receptors (Kuo et al., 2008), and by levels of GABA. The level of PAS is changed by pathologies such as Parkinson's disease and dystonia and, importantly, appears to be behaviorally relevant since it can influence the rate at which healthy participants can learn a new motor skill. Furthermore, is seems as if PAS is not limited to pairing mixed nerve input with TMS to motor cortex, but can also involve natural inputs caused by movement or imagination, or even pain. Indeed, the inputs paired with TMS need not involve sensory inputs but can utilize inputs from other brain areas such as contralateral cortex or parietal and premotor cortex.

However, as time has passed, problems have accumulated around this positive view, and have raised questions that should be tackled before the field moves further forward. As noted in many sections above, a principle problem is lack of reliability of the method itself. Some reports put the chance of an individual "responding" to PAS as no greater than 50% (Lopez-Alonso et al., 2014); and although some reports suggest that reliability is better within a given individual from

day to day, others find it no better than random (e.g. Fratello et al., 2006). At its worst case then, are all these positive reports of the usefulness of PAS simply random events that have been chosen for publication because they happen to confirm pre-existing expectations based on previous data from reduced animal preparations?

It seems unwise to dismiss the whole literature on PAS without some serious consideration. However, the reality is that the majority of studies has never been repeated, and have in many cases been conducted on only a small number of individuals. In some cases, repeated observations have failed to give the same answers: for example, not all studies show that PAS is deficient in patients with Parkinson's disease or enhanced in dystonia. Similarly, although many reports emphasize the spatial specificity of PAS (i.e. median nerve PAS increases MEPs in median nerve innervated muscles but not in those innervated by ulnar or other nerves), others have failed to do so (e.g. Pötter-Nerger et al., 2009).

It is tempting to dismiss such apparent contradictions as being due to small differences in methodology, time of day, age of participants etc. However, it may be more fruitful to re-examine the assumptions on which the PAS experiments are based. When PAS was introduced in 2000, the prominent model of STDP was the one that is found in textbooks today. It uses a model in which synaptic input to a dendrite is active just before a somatic action potential. The latter produces a back-propagating dendritic spike that depolarizes the postsynaptic membrane. Presynaptic activity provides glutamate and postsynaptic depolarization removes the Mg2+ block of NMDA receptors to allow entry of Ca2+ into the neuron. This then, via a cascade of reactions, strengthens the synapse. This model is now regarded as highly simplified (e.g. Lisman and Spruston, 2010). In fact, a number of other factors can contribute to depolarization of the dendrite in addition to the back-propagating action potential such as local calcium spikes, and activity at other AMPA and NMDA receptors. In some conditions these may be more important than the action potential itself, particularly during periods of activity such as are likely to exist in the conscious human brain. It is also important to recognize that the classic rule that pre- before post- pairing will always generate

LTP can be inverted ("anti-Hebbian") even at synapses made by the same axon if these are onto different classes of neurons.

Given these considerations it is probably a little naïve to think that with non-invasive methods we can guarantee that we will be able to control both the time of synaptic input and the time of the back-propagating action potential to the same degree as is possible in quiescent pairs of neurons in a brain slice. If we couple this with the fact that TMS activates a number of different synapses in the cortex, and that each of these may be depolarized to different degrees and even have different plasticity rules we probably begin to approach something of the underlying complexity of the PAS protocol. In the future, it may be possible to increase control over these many factors by using EEG monitoring to provide a moment-to-moment read-out of overall levels of ongoing activity (e.g. Bergmann et al., 2012; Zrenner et al., 2016) and by employing new TMS devices to give more selective stimulation of particular neural circuits (d'Ostillio et al., 2016). Finally, PAS protocols may be helpful in designing new BCI approaches to harness plasticity processes in the human motor cortex. The future may be an exciting time for PAS.

TABLES

Table 1: *Pharmacology of PAS*

Table 2: *PAS studies in neurological and psychiatric disorders*

FIGURE LEGENDS

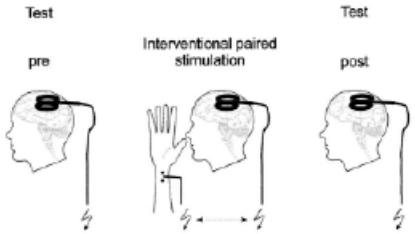
Figure 1: Paired associative stimulation induces LTP- and LTD-like plasticity in the human primary motor cortex.

A: Experimental design. In the original set-up paired associative stimulation (PAS) consists of electrical median nerve stimulation (MNS) and transcranial magnetic stimulation (TMS) of the contralateral primary motor cortex (M1) over the optimal site for eliciting motor evoked potentials (MEPs) in Abductor pollicis brevis muscle (APB). Pairs of stimuli (typically 90-180) are applied with a constant interstimulus interval at a frequency of 0.05-0.1 Hz. Corticospinal excitability is probed pre and post PAS by monitoring MEP amplitude in the right APB elicited by single-pulse TMS (from Stefan et al. 2000).

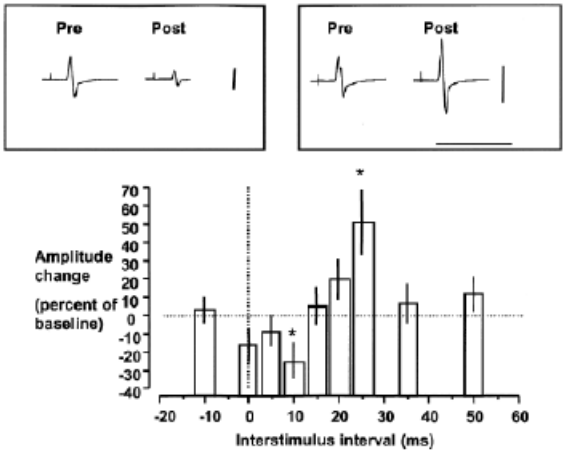
B: Bidirectional changes of MEP-amplitude induced by varying the timing of PAS. (a) Examples of averaged (20 trials each) MEP responses in APB muscle recorded before ("Pre") and after ("Post") PAS at ISI=10 ms (left box) or ISI=25 ms (right box). Vertical calibration bar 1 mV, horizontal calibration bar 100 ms. (b) Group data (means+s.e.m.) Asterisks indicate significant change of MEP amplitudes ($p<0.05$) (from Classen et al., 2004).

C: Grossly simplified schematic illustration of modulation of PAS_{25}-induced plasticity by different species of voltage-gated Ca^{2+}-channels. PAS_{25}-induced facilitation requires backpropagating action potentials, which under the influence of blockade of L-type VGCC are so strongly attenuated that sufficient increase of dendritic $[Ca^{2+}]$ is prevented and no postsynaptic signal is generated. Conversely, T-type voltage gated Ca^{2+}-channels may control Ca^{2+} -influx more proximal to the altered synapse (adapted from Weise et al., 2016).

A


Test
pre
Interventional paired stimulation
Test
post

B


Pre
Post
Pre
Post
Amplitude change (percent of baseline)
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-20
-10
0
10
20
30
40
50
60
Interstimulus interval (ms)

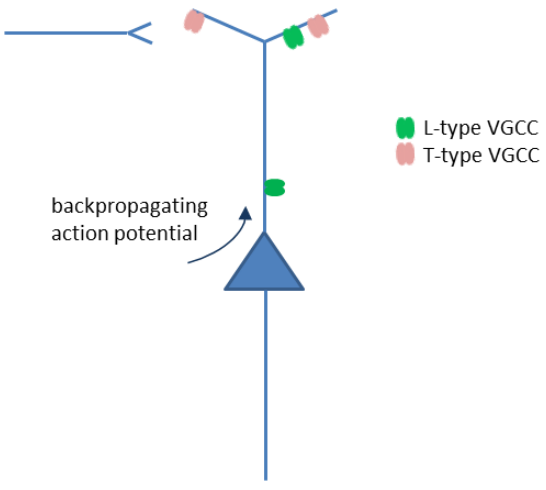

L-type VGCC
T-type VGCC
backpropagating action potential

Figure 2:

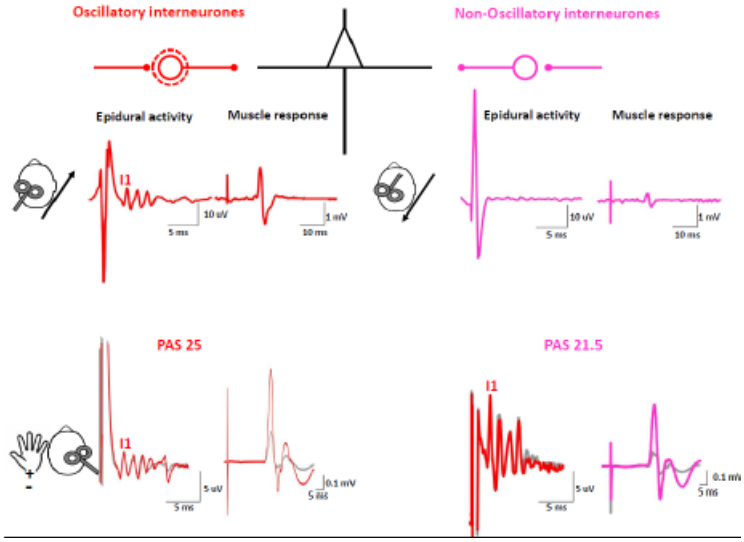
Upper and middle part: schematic representation of motor cortex circuits activated by transcranial magnetic stimulation and projecting upon the corticospinal cells (black triangle). It is proposed that there two main interneuronal circuit: the first (left upper part) is composed of bursting interneurons (red circle inside a dotted circle) projecting upon the corticospinal cells, this circuits is preferentially activated by PA magnetic stimulation and produces the I waves (the first I1 wave is indicated) and a muscle response (left middle); the second (right upper part) is composed of non-oscillatory interneurons (magenta circle) projecting upon the corticospinal cells, this circuits is preferentially activated by low intensity AP magnetic stimulation and produces a clear muscle response but no clear descending activity.

Lower part: effects of PAS on epidural activity and muscle responses.

Left: Epidural volleys and muscles responses recorded in baseline conditions (gray trace) and after PAS25 (red trace). Each trace is the average of the responses to 10-25 cortical magnetic stimuli. After PAS, there is a remarkable increase in the amplitude of muscle responses that is paralleled by an increase in the number and amplitude of the I waves;

Right: epidural volleys and muscles responses recorded in baseline conditions (gray trace) and after PAS_{25} (red trace for volleys and magenta trace for muscle response). Each trace is the average of the responses to 10-25 cortical magnetic stimuli. After $PAS_{21.5}$ there is a pronounced increase in the amplitude of the muscle response but the epidural activity is unchanged.

It is proposed that the facilitation of the muscle response after PAS_{25} is due to the enhancement in the excitability of the oscillatory circuit producing the I-waves whereas the facilitation observed after $PAS_{21.5}$ is due to the facilitation of the non-oscillatory circuit.


Oscillatory interneurones
Non-Oscillatory interneurones
Epidural activity
Muscle response
Epidural activity
Muscle response
I1
10 uV
5 ms
1 mV
10 ms
10 uV
5 ms
1 mV
10 ms
PAS 25
PAS 21.5
I1
5 uV
5 ms
0.1 mV
5 ms
I1
5 uV
5 ms
0.1 mV
5 ms

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