Peripheral and Central Stimulation

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Investigating Hebbian principles of neural plasticity in humans
"Cells that fire together, wire together"

How can we induce plastic changes at the brain level?

*Paired Associative Stimulation (PAS)*
*Or when the peripheral stimulation meets the MEP*

How can we induce plastic changes at the spinal level?

*Spinal Associative Stimulation (SAS)*
*Or when the central stimulation meets the H-reflex*
How do we measure cortical excitability? The MEP
Induction of plasticity in the human motor cortex by paired associative stimulation

Katja Stefan, Erwin Kunesch, Leonardo G. Cohen, Reiner Benecke and Joseph Classen

Test
pre

Interventional paired stimulation

Test
post

Electrical stimulation of right median nerve

TMS of left M1 hand representation

90 pairs
ISI 25 ms
Induction of time-dependent plasticity in the motor cortex

(A) ISI 25 ms, ISI 100 ms, ISI 525 ms, ISI 5000 ms

(B) Amplitude (mV) vs ISI (ms)

(C) Amplitude change (percent of baseline) vs Interstimulus interval (ms)

(D) Silent period duration (ms) vs ISI (ms)

Stefan et al, Brain, 2000
PAS summary:

- The increase of cortical excitability (MEP amplitude) was dependent on the synchronous **timing** between the afferent and the magnetic stimulation.

- Plasticity induced by PAS:
  - 1. evolved rapidly (within 30 min),
  - 2. was persistent (minimum duration 30-60 min) yet reversible, and
  - 3. was topographically specific properties signature of associative **long-term potentiation (LTP)**.
How do we measure spinal excitability? The H-REFLEX
Effect of Stimulus Intensity - M Response & H Reflex

Low Intensity PNS

M-Response

H-Reflex

Increased Intensity PNS

Smaller H-Reflex

Larger M Response
SAS protocol

Spinal associative stimulation: A non-invasive stimulation paradigm to modulate spinal excitability

Mar Cortes, Gary W. Thickbroom, Josep Valls-Sole, Alvaro Pascual-Leone, Dylan J. Edwards

PRE
H-Reflex RC

INTERVENTION
(15 min)

POST
H-Reflex RC

0.1 Hz

20ms

90 paired stimuli

sec
Peripheral stimulation of somatosensory afferents conditioned by low frequency TMS, increases spinal excitability.
Repetitive paired stimulation can induce changes in spinal excitability

Cortes et al, Clin Neurophysiology, 2011
Left shift of the RC post-intervention

Amplitude

PRE H-Reflex Recruitment Curve

Individual POST Recruitment Curves

Standard Deviation

Cortes et al, Clin Neurophysiology, 2011
SAS experimental set up

Figure-8 TMS Coil (vertex)

Posterior Tibial nerve Stimulation

Soleus EMG
## Pharmacology of PAS

<table>
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<tr>
<th>Drugs</th>
<th>Study</th>
<th>Main findings</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td><strong>NMDA receptor</strong></td>
<td>Stefan et al. (2002)</td>
<td>NMDA receptor antagonist Dextromethorphan blocks both LTP-like and LTD-like PAS-induced plasticity</td>
<td>NMDA receptors play a central role in LTP-like and LTD-like PAS-induced plasticity. L-type VGCCs might gate PAS-induced plasticity while LTP-like plasticity requires higher postsynaptic Ca²⁺ concentrations. STDP temporal rules may be overridden by other factors influencing Ca²⁺ dynamics.</td>
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<td></td>
<td>Wolters et al. (2003)</td>
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<td>Weise et al. (2016)</td>
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<tr>
<td><strong>Ca²⁺-channels</strong></td>
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<td>L-type voltage-gated Ca²⁺ channel antagonist Nimodipine blocks LTP-like PAS-induced plasticity. T-type voltage-gated Ca²⁺ channel antagonist Ethosuximide shifts LTP-like plasticity to LTD-like plasticity.</td>
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### Dopaminergic neuromodulators

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<tr>
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<th>Main findings</th>
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<tbody>
<tr>
<td>Kuo et al. (2008)</td>
<td>A single oral dose of 100 mg of the dopamine precursor L-Dopa prolongs PAS₂₅ after-effects by a factor of about 20 Low-dose L-DOPA (25 mg) abolished the after-effects of PAS₂₅, medium-dose L-DOPA (100 mg) prolonged LTD-like plasticity, and high-dose L-DOPA (200 mg) flipped LTP-like to LTD-like plasticity</td>
<td>Dopaminergic neuromodulators have strong effects on the ability of PAS to change corticomotor excitability. Some deviations between different agonists may be caused by different receptor affinity to the five dopamine receptors. Modulation of D₁-like and D₂-like receptor activity exerts a nonlinear dose-dependent effect on neuroplasticity in the human M1.</td>
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<tr>
<td>Thirugnanasambandam et al. (2011b)</td>
<td>Different doses of the D₂/D₃ agonist ropinirole (0.125, 0.25, 0.5, 1.0 mg) produced an “inverted U-shaped” dose-response curve on plasticity both for PAS₂₅ and PAS₁₀. The medium dose of 0.5 mg ropinirole was the optimal dose for facilitating PAS₂₅-induced LTD-like plasticity but the most inefficient dose to boost PAS₁₀-induced LTD-like plasticity. Different doses of the D₂ agonist bromocriptine produced an “inverted U-shaped” dose-response curve on plasticity for PAS₁₀ and, to a lesser extent, for PAS₂₅.</td>
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<td>Monte-Silva et al. (2009)</td>
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<td>Fresnoza et al. (2014b)</td>
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<tr>
<td>Nitsche et al. (2009)</td>
<td>A single oral dose (400 mg) of selective D₂-agonist ropinirole abolished PAS₂₅-induced LTD-like plasticity, but did not affect PAS₁₀-induced LTP-like plasticity. Selective D₁-like receptor activation produced an inverted U-shaped dose-response curve on plasticity induced by PAS. For PAS₁₀, LTD-like after-effects were abolished or converted into LTD-like plasticity.</td>
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<td>Fresnoza et al. (2014a)</td>
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### Non-dopaminergic neuromodulators

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<th>Study</th>
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<tr>
<td>Korchounov and Ziemann (2011)</td>
<td>Haloperidol (dopamine antagonist), prazosine (norepinephrine antagonist), and biperiden (acetylcholine antagonist) depressed significantly the PAS₂₅-induced LTP-like plasticity observed under placebo, whereas cabergoline (dopamine agonist), methylphenidate (indirect norepinephrine agonist) and tacrine (acetylcholine agonist) had no effect. The acetylcholinergic drug rivastigmine (3 mg) prolonged PAS₁₀ after-effects. PAS₁₀ after-effect was prolonged by a factor 4 from 30 to 120 min.</td>
<td>Haloperidol, prazosine, biperiden and rivastigmine have powerful effects on PAS-induced excitability changes in M1, whereas cabergoline, methylphenidate and tacrine do not.</td>
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<tr>
<td>Kuo et al. (2007)</td>
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<td>Batsikadze et al. (2013)</td>
<td>After the administration of the serotonin reuptake inhibitor citalopram, PAS₂₅-induced after-effects were abolished and PAS₁₀-induced after-effects were enhanced trend-wise. Nicotine abolished or reduced both effects of PAS₂₅- and TDCS-induced inhibitory neuroplasticity. Non-focal facilitatory plasticity was also abolished, whereas focal facilitatory plasticity was slightly prolonged. Low-dose of α₂β₂-nicotinic receptor partial agonist Varenicline (0.1 mg) had no impact on stimulation-induced neuroplasticity; medium-dose (0.3 mg) kept PAS₂₅ plasticity and abolished TDCS-induced facilitatory after-effects, favoring focal excitatory plasticity; high-dose (1 mg) application preserved cathodal TDCS-induced excitability diminution and focal excitatory PAS₂₅-induced facilitatory plasticity.</td>
<td>Serotonin modulates PAS-induced neuroplasticity by shifting it in the direction of facilitation. Nicotine modulates significantly responses to PAS₂₅ and PAS₁₀. Modulation of α₂β₂-nicotinic receptor activity exerts a dose-dependent effect on PAS-induced plasticity in the human M1. The effects of nicotine spray on PAS-induced plasticity in non-smokers differ clearly from those of prolonged nicotine application.</td>
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<tr>
<td>Thirugnanasambandam et al. (2011a)</td>
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<td>Batsikadze et al. (2015)</td>
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## Pharmacology of PAS

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<tr>
<td>GABA-ergic</td>
<td>Grundey et al. (2012a)</td>
<td>In smokers during nicotine withdrawal, facilitatory plasticity induced by TDCS and PAS was abolished, but could be restored by nicotine. In contrast, excitability diminishing plasticity was not affected by nicotine withdrawal. Under nicotine, the inhibitory after-effects of PAS were delayed and prolonged, while the TDCS-generated excitability reduction was abolished.</td>
<td>The putative high affinity of alcohol but not alprazolam/zolpidem to extrasynaptic tonic inhibitory GABA-A-receptors and to NMDA-receptors might explain the reduction of LTP-like plasticity. GABA-B receptor negatively affects PAS-induced LTP-like plasticity in human M1 AEDs with different modes of action, show different effects on PAS-induced plasticity.</td>
</tr>
<tr>
<td>GABA-ergic</td>
<td>Grundey et al. (2012b)</td>
<td>In non-smokers, nicotine spray abolished facilitatory plasticity irrespective of selectivity and PAS induced excitability diminution, while cathodal TDCS-derived excitability reduction was delayed and weakened.</td>
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<tr>
<td>GABA-ergic</td>
<td>Lücke et al. (2014)</td>
<td>Low levels of alcohol suppressed LTP-like plasticity but did not affect saccadic peak velocity. Alprazolam (1 mg) or Zolpidem (10 mg) decreased saccadic peak velocity but did not significantly affect LTP-like plasticity as measured by PAS.</td>
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<td>Antiepileptic</td>
<td>Delvendahl et al. (2013)</td>
<td>A single oral dose (300 mg) of the antiepileptic drug lamotrigine impaired PAS in LTP-responders and led to a reduction of the LTD-like MEP decrease in the LTD-responders, with the majority of LTD-responders even showing a MEP increase.</td>
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<tr>
<td>Antiepileptic</td>
<td>Heidegger et al. (2010)</td>
<td>Lovastatin significantly reduced LTP-like plasticity whereas tiagabine, diazepam, lamotrigine and picrotiam resulted in nonsignificant trends towards reduction of LTP-like plasticity while gabapentin and topiramate had no effect.</td>
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<td>Lithium</td>
<td>Voytovych et al. (2012)</td>
<td>After stratification of subjects into PAS LTP responders, PAS LTP LTD responders, a single oral dose of 900 mg of lithium did not affect the PAS LTP-induced LTP-like plasticity in LTD responders, but switched the PAS LTP-induced LTD plasticity in the LTD responders to LTP-like plasticity.</td>
<td>Lithium which inhibits glycogen synthase kinase-3beta leads to up-regulation of LTP and down-regulation of LTD.</td>
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<tr>
<td>Cortisol</td>
<td>Sale et al. (2013)</td>
<td>Oral hydrocortisone prevented facilitation of the abductor pollicis brevis (APB) MEP after PAS, whereas mean salivary cortisol levels were negatively associated with PAS effectiveness. The GABA-B-mediated cortical silent period for APB was longer in the morning than in the evening, and was lengthened by PAS and oral hydrocortisone.</td>
<td>GABA-B-dependent intracortical plasticity is influenced by time of day and by circulating levels of cortisol. This might explain the higher PAS effects in the evening than those in the morning.</td>
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<tr>
<td>Lovastatin</td>
<td>Maintzeger et al. (2013a)</td>
<td>Administration of 200 mg of lovastatin 4 days before PAS led to restored responses to PAS in patients with Neurofibromatosis type 1 (NF1).</td>
<td>Lovastatin seems to be able to restore PAS plasticity in a disease claimed to go ahead with increased GABA-mediated inhibition (NF1).</td>
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## PAS clinical applications

### Disease

<table>
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<tr>
<th>Study</th>
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<tr>
<td><strong>Stroke</strong></td>
<td>In post-stroke patients with subcortical strokes, responses to PAS may change in parallel to motor recovery. PAS increases MEPs in the paretic side 5 months and, in lesser extent, 12 months after stroke.</td>
<td>PAS might help promote motor recovery after stroke. Response to PAS is higher in an earlier than later period after stroke.</td>
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<tr>
<td>Castel-Lacanal et al. (2007)</td>
<td>Inhibitory PAS applied to the contralateral lower limb motor system of stroke survivors increases paretic lower limb and decreases non-paretic lower limb motor excitability assessed during walking.</td>
<td>Reducing the poststroke asymmetry of between-hemisphere motor excitability by down-regulating motor excitability of the contralateral M1 may be a candidate adjuvant therapy for patients with neurological walking impairments. The extent of induced modulation might be unpredictable.</td>
</tr>
<tr>
<td>Jayaram and Stinear (2008)</td>
<td>Inhibitory PAS applied to the contralateral proximal lower limb motor system reduces MEP amplitudes in the non-paretic limb while post-PAS paretic limb MEP amplitudes increase for some patients and decrease for others.</td>
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<tr>
<td>Jayaram and Stinear (2009)</td>
<td>PAS applied to the unlesioned pharyngeal cortex reversed the suppression induced by virtual lesion in healthy subject. In patients with chronic post-stroke dysphagia, PAS applied to the unaffected pharyngeal cortex resulted in increased excitability associated with reduced penetration-aspiration scores and changes in swallowing biomechanics.</td>
<td>PAS, by promoting or enhancing cortical inter-hemispheric connectivity, provides a promising rehabilitative approach for patients with dysphagia from stroke, when applied to unlesioned brain, and increases swallowing safety.</td>
</tr>
<tr>
<td>Rogers et al. (2011)</td>
<td>Corticobulbar excitability of pharyngeal motor cortex is increased by PAS with functionally relevant changes in the unaffected hemisphere and an associated reduction in aspiration compared to sham.</td>
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<tr>
<td>Michou et al. (2012)</td>
<td>Enhanced rapid-onset responses to PAS in patients with CADASIL and extensive subcortical brain damage.</td>
<td>Increased responses to rapid-onset cortical plasticity may play a role as a compensatory mechanism in cognitive and motor function preservation despite extensive ischemic SVD. The impairment in acetylcholine and glutamate circuits could be involved in the dementia process and in the abnormal sensorimotor plasticity observed in CADASIL.</td>
</tr>
<tr>
<td>Michou et al. (2014)</td>
<td>In CADASIL patients, a lack of sensorimotor plasticity after PAS is observed and is correlated with neuropsychological alterations.</td>
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<tr>
<td><strong>CADASIL/SVD</strong></td>
<td>Cortical plasticity, induced with a PAS protocol, as well as memory functions are preserved in patients with severe SVD. Larger cortical plasticity is positively correlated with the degree of white matter lesions in parahippocampal regions and posterior parts of the corpus callosum.</td>
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<tr>
<td>List et al. (2011)</td>
<td>PAS applied for 20-24 weeks partially restored motor ability of the upper and lower limbs in two patients with chronic spinal cord injuries.</td>
<td>Repeated sessions of PAS improved voluntary movement in previously paralyzed muscles by strengthening neural connections. The hypothesis of a progressive loss of M1 plasticity in parallel to AD-related neurodegenerative processes seem to be unlikely.</td>
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<tr>
<td><strong>Spinal cord injury</strong></td>
<td>Patients with Alzheimer’s dementia (AD) show reduced PAS-induced-LTP-like plasticity</td>
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<tr>
<td>Battaglia et al. (2007)</td>
<td>There is no clear difference in PAS between patients with Mild Cognitive Impairment (MCI) and healthy controls.</td>
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<td>Terranova et al. (2013)</td>
<td>Normal responses to PAS-LTP discriminate patients with good recovery after relapse from those with incomplete recovery.</td>
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<tr>
<td>Lahr et al. (2016)</td>
<td>Reduced LTP-like plasticity is found when PAS is applied in patients with juvenile myoclonic epilepsy.</td>
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<td><strong>Multiple Sclerosis (MS)</strong></td>
<td>In AD, responses to PAS are within normal range.</td>
<td>In patients with MS, the capacity of the central nervous system for plasticity is preserved, probably in order to compensate for lesions.</td>
</tr>
<tr>
<td>Zeller et al. (2010)</td>
<td>Normal responses to PAS-LTP discriminate patients with good recovery after relapse from those with incomplete recovery.</td>
<td>Reduced plasticity may act as a compensatory mechanism to protect from developing seizures.</td>
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<tr>
<td>Mori et al. (2014)</td>
<td></td>
<td>Structural and physiological abnormalities of M1 and abnormal motor cortical functions and sensorimotor integration may play a role as possible pathological contributors to the motor symptoms in Unverricht-Lundborg disease.</td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td>The patients with Unverricht–Lundborg disease (progressive myoclonus epilepsy type 1) show a reduction in MEP amplitudes after PAS.</td>
<td>Evaluation of PAS-induced plasticity may help to determine disease severity in NMDAR encephalitis.</td>
</tr>
<tr>
<td>Strigaro et al. (2015)</td>
<td>In patients with NMDAR encephalitis, PAS decreases MEP amplitudes. Reduced plasticity is correlated with lower functional connectivity within the motor network.</td>
<td>Associative sensorimotor plasticity impairment in MHE might represent a functional correlate of clinical manifestations of the disease.</td>
</tr>
<tr>
<td>Danner et al. (2011)</td>
<td>In patients with NMDAR encephalitis, PAS decreases MEP amplitudes. Reduced plasticity is correlated with lower functional connectivity within the motor network.</td>
<td>The malfunctioning in PAS-induced plasticity in MHE might reflect low cortical plasticity preventing changes in cortical synaptic effectiveness.</td>
</tr>
<tr>
<td><strong>NMDAR encephalitis</strong></td>
<td>In patients with NMDAR encephalitis, PAS decreases MEP amplitudes. Reduced plasticity is correlated with lower functional connectivity within the motor network.</td>
<td>A state-dependent partial occlusion of cortical LTP-like plasticity is present in MDD.</td>
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<tr>
<td>Voll et al. (2016)</td>
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<tr>
<td><strong>Minimal hepatic Encephalopathy (MHE)</strong></td>
<td>In patients with MHE the MEP amplitude was slightly reduced after PAS.</td>
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<tr>
<td>Olszewski et al. (2016)</td>
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<td><strong>Migraine</strong></td>
<td>In migraine without aura patients between attacks, PAS increases MEP amplitudes and PAS does not significantly enhance baseline MEP amplitudes.</td>
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<td>Perelli et al. (2013)</td>
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<td><strong>Major Depressive disorder (MDD)</strong></td>
<td>After PAS, MEP amplitudes significantly increase in healthy controls compared with depressed subjects.</td>
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<td>Disease</td>
<td>Study</td>
<td>Main findings</td>
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<tr>
<td>High functioning autism and Asperger syndrome (HFA/AS)</td>
<td>Kuhn et al. (2016)</td>
<td>PAS-induced LTP-like plasticity is significantly reduced in patients with an acute episode of MDD. Synaptic plasticity is restored in patients with remission while the deficits persist in patients without remission.</td>
</tr>
<tr>
<td>Down's syndrome (DS)</td>
<td>Battaglia et al. (2008)</td>
<td>PAS induces significantly lower increase of MEP amplitude in young patients with DS than in healthy controls.</td>
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<tr>
<td>Noonan syndrome (NS)</td>
<td>Mainberger et al. (2013b)</td>
<td>PAS does not significantly increases MEP amplitudes in patients with Noonan-Syndrome (NS) when using an unspecified attention control while, under specific electrical attention control, MEP amplitudes decreases significantly.</td>
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<tr>
<td>Schizophrenia (SCZ)</td>
<td>Frantseva et al. (2008)</td>
<td>Patients with schizophrenia show significant MEP facilitation deficits following PAS and impaired rotary-pursuit motor learning.</td>
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<td>Costello Syndrome (CS)</td>
<td>Dileone et al. (2010)</td>
<td>PAS-induced LTP-like plasticity is significantly increased in CS patients.</td>
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<td>Cerebellar degeneration</td>
<td>Dubbioso et al. (2015)</td>
<td>No increase in MEP amplitudes after PAS is observed in patients with schizophrenia.</td>
</tr>
<tr>
<td>Restless legs syndrome (RLS)</td>
<td>Rizzo et al. (2009a)</td>
<td>In RLS patients, PAS elicits reduced MEP changes. Dopaminergic treatment restores PAS-induced plasticity.</td>
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<tr>
<td>Complex regional pain syndrome type I</td>
<td>Morgante et al. (2017)</td>
<td>PAS responses are normal in patients with CRPS type I.</td>
</tr>
<tr>
<td>Unresponsive wakefulness syndrome (UWS)</td>
<td>Naro et al. (2015b)</td>
<td>L-PAS-induced responses help as diagnostic and prognostic marker in NPC.</td>
</tr>
<tr>
<td>Niemann-Pick Disease Type C (NPC)</td>
<td>Benussi et al. (2017)</td>
<td>Responses to PAS are reduced in patients with NPC and symptomatic heterozygous NPC1 gene mutation carriers.</td>
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<td>Modified PAS protocol</td>
<td>Study</td>
<td>Afferent input</td>
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<td>PAS targeting the primary motor leg area</td>
<td>Stinear and Hornby (2005)</td>
<td>Peroneal nerve stimulation</td>
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<td>Prior and Stinear (2006)</td>
<td>Peroneal nerve stimulation</td>
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<td>Mrachacz-Kersting et al. (2007)</td>
<td>Peroneal nerve stimulation</td>
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<td>Roy et al. (2007)</td>
<td>Peroneal nerve stimulation</td>
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<td>Mrachacz-Kersting and Stevenson (2017)</td>
<td>Peroneal nerve stimulation</td>
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<td>Rapid-rate PAS of the primary motor hand area</td>
<td>Quartarone et al. (2006)</td>
<td>Median nerve stimulation</td>
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<td>Srivanitchapoom et al. (2016)</td>
<td>Median nerve stimulation</td>
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<td>Wolters et al. (2005)</td>
<td>Median nerve stimulation</td>
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<td></td>
<td>Tsang et al. (2015)</td>
<td>Median nerve stimulation</td>
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<tr>
<td>PAS targeting the primary somatosensory cortex (S1)</td>
<td>Taylor and Martin (2009)</td>
<td>Brachial plexus stimulation + Cervico-medullar TMS</td>
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<td></td>
<td>Cortes et al. (2011)</td>
<td>Tibial nerve stimulation + TMS on M1</td>
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<td>Bunday and Perez (2012)</td>
<td>Tibial nerve stimulation + TMS on M1</td>
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<td>Leukel et al. (2012)</td>
<td>Tibial nerve stimulation + TMS on M1</td>
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<td>Suppa et al. (2013, 2016)</td>
<td>Laser stimulation of the hand + TMS on M1</td>
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<td>Naro et al. (2015a)</td>
<td>Laser stimulation of the hand + TMS on M1</td>
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<td></td>
<td>Edwards et al. (2014)</td>
<td>Passive wrist flexion and extension + TMS on M1</td>
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<td>Suppa et al. (2015a, b)</td>
<td>Pattern-reversal visual stimulation + TMS on M1</td>
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<td>Schecklmann et al. (2011)</td>
<td>Monoaural auditory stimulation + TMS on M1</td>
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<td>Sowman et al. (2016)</td>
<td>Auditory cues consisting of brief vocalizations + TMS on M1</td>
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<td>PAS with other afferent sensory inputs to M1</td>
<td>Naro et al. (2015b)</td>
<td>Auditory nerve stimulation + TMS on M1</td>
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<td>Rizzolatti et al. (2009, 2011)</td>
<td>TMS on M1 + TMS on Contralateral M1</td>
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<td></td>
<td>Koganeizumi et al. (2009)</td>
<td>TMS on M1 + TMS on Contralateral M1</td>
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<td></td>
<td>Buech et al. (2011)</td>
<td>TMS on M1 + TMS on PMv</td>
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<td>Ara et al. (2011)</td>
<td>TMS on M1 + TMS on SMA</td>
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<td>Koch et al. (2013)</td>
<td>TMS on M1 + TMS on PPC</td>
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<td>Venero et al. (2013)</td>
<td>TMS on M1 + TMS on PPC</td>
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<td>Choi et al. (2015)</td>
<td>TMS on M1 + TMS on PPC</td>
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<td>PAS with afferent volleys to M1 driven by other cortical areas</td>
<td>Lu et al. (2012)</td>
<td>TMS on Cerebellum + TMS on Contralateral M1</td>
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<td></td>
<td>Udupa et al. (2016)</td>
<td>DBS stimulation of STN + TMS on M1</td>
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<td>Thabit et al. (2010)</td>
<td>Endogenous activation of M1 + TMS on M1</td>
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<td>Mrachacz-Kersting et al. (2012)</td>
<td>Electric peroneal nerve stimulation + contingent negative variation</td>
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<td>Jochumsen et al. (2015)</td>
<td>Electric tibial nerve stimulation + contingent negative variation</td>
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<td>Olsen et al. (2017)</td>
<td>Electric tibial nerve stimulation + contingent negative variation</td>
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Recommendation for best technical results in PAS studies.

A) Technical factors

1. General
   a. Stimulation at rest
   b. Stimulation intensity (set to produce an MEP in small hand muscle of 1 mV at baseline)

2. Induction protocol
   a. Coil position at hot spot for target muscle
   b. Peripheral stimulation corresponding to location (not innervation) of target muscle
   c. Peripheral stimulation intensity (above perceptual threshold, subthreshold for motor response)
   d. Duration of intervention (≥15 min); inter-pair-interval (≥10 s)

3. Probing protocol
   a. Number of stimuli (≥30 stimuli)
   b. Frequency (≤0.1 Hz)

B) Subject factors that cannot usually be manipulated individually

1. Age
2. Gender
3. Absence of alcohol and drug abuse, including non-smoking status
4. No medication acting on the central nervous system (antidepressants; antipsychotics; anxiolytics, centrally acting ion channel blockers, in particular calcium channel blockers, antihistaminics and many more)
5. Habitual heavy aerobic physical exercise, professional occupancy with movement control (typist, musician, etc.)
6. BDNF val66met haplotype
7. Physiological factors (resting motor threshold)

C) Subject factors that can usually be controlled individually

1. Caffeine intake (coffee, tea, etc.) as usual; absent alcohol intake for at least 12 h
2. Sufficient duration of night sleep before testing
3. Absence of strenuous activity on the day of testing
4. In females: menstrual cycle
5. If somatosensory stimulation is involved, attention should be directed to the body part receiving peripheral stimulation. Attention can be enhanced by interspersing rare near-threshold stimuli in between the peripheral stimulation pairing component. Degree of attention can be monitored by recording the number of misses during the conditioning

* evidence of significant effect on outcome in at least 2 studies; – evidence of significant effect on outcome in less than 2 studies.
REFERENCES:


