Impaired Spike Timing Dependent Cortico-Cortical Plasticity in Alzheimer's disease Patients

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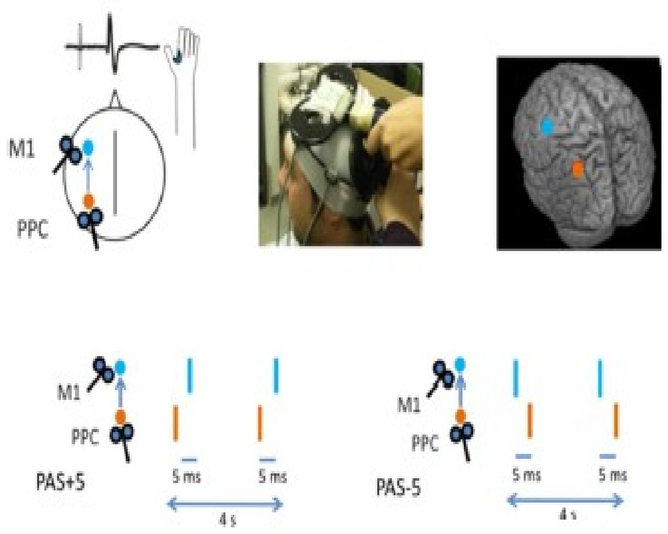
INTRODUCTION

Mechanisms of cortical plasticity have been widely investigated in Alzheimer's disease (AD) patients with transcranial magnetic stimulation (TMS) protocols as Theta Burst Stimulation (TBS), showing a clear impairment of Long-Term Potentiation (LTP) cortical-like plasticity and a relative sparing of Long Term Depression (LTD) mechanisms. Recently a new TMS protocol, investigating the connections between posterior parietal cortex (PPC) and primary motor cortex (M1), elicited in a bidirectional way LTP and LTD effects. The aim of our study is to investigate mechanisms of spike-timing dependent plasticity (STDP) in Alzheimer's disease patients and furthermore to investigate the effects of the modulation of PPC-M1 pathway on cholinergic transmission, greatly impaired in AD patients.

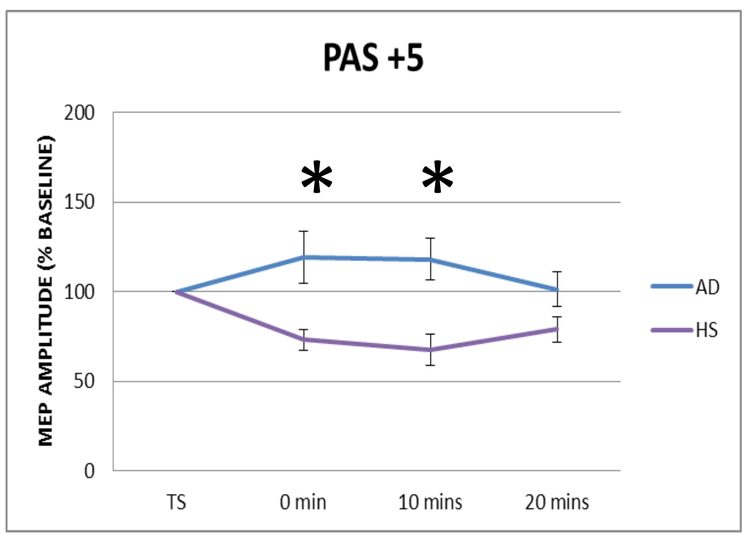
METHODS

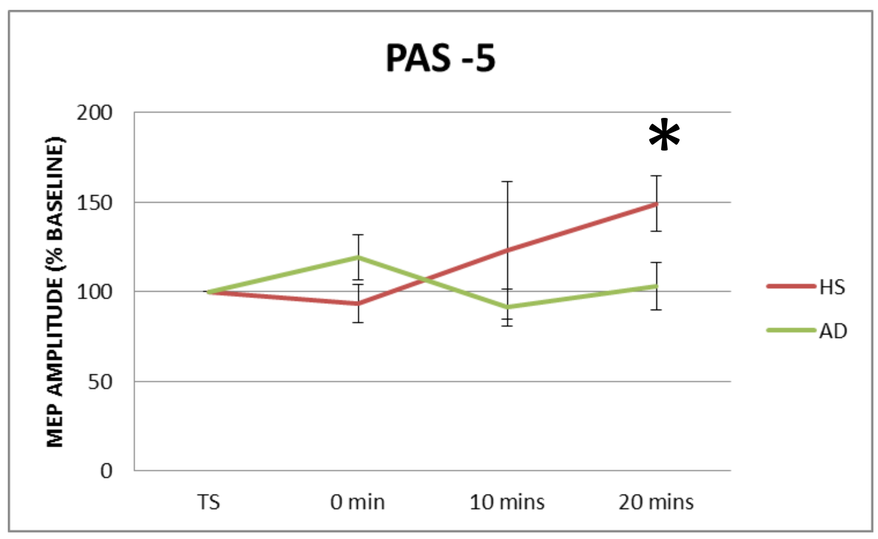


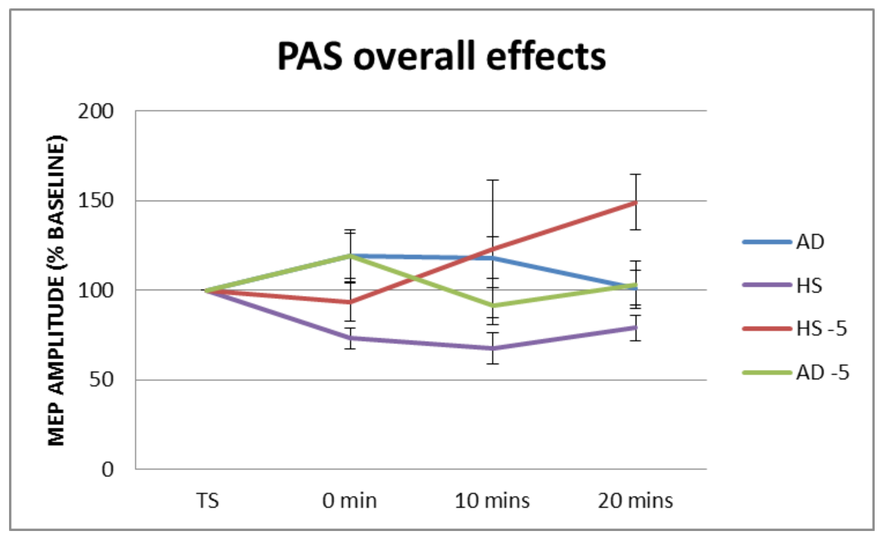
The temporal proximity of novel encoding stimuli is a key element in determining the formation of a new memory. These ideas have been formalized by the Hebbian rule, proposing that neurons near-simultaneously activated increase their efficacy if the synapse consistently assists the postsynaptic target neuron to generate action potentials. Typically, LTP is induced when presynaptic activity occurs just before postsynaptic spiking in the target cell (pre-pairing □post-pairing). Conversely, long-term depression (LTD) is usually induced when the postsynaptic cell fires before the presynaptic input (post-pairing □ pre-pairing). This type of plasticity is referred to as spike timing- dependent plasticity (STDP). Recent studies have also formalized a location-dependency rule pointing to opposite timing requirements of distal inputs, named anti-hebbian STDP. As dendritic distance increase, a gradual shift of the timing requirements occurs, so that at apical dendrite the conventional rules are completely reversed. In line with these anti-hebbian rules, LTD is generated when presynaptic activation precedes the postsynaptic one and LTP during postsynaptic/presynaptic pairing. Recently, by targeting the PPC and M1, it has been provided evidence suggesting the existence of both hebbian and anti-hebbian phenomena in humans. As indexed by Motor Evoked Potentials (MEPs) amplitude, the effects of repetitive PPC-M1 activation depended on the timing between the stimuli and, crucially, on the stimulation of specific neuronal populations. When PPC preceded M1, the paired associative stimulation protocol (PAS) led to a long-lasting decrease of M1 excitability (up to 20 min) pointing to an LTD-like effect. When PPC followed M1stimulation, the same protocol induced a long-lasting increase of M1 excitability (up to 20 min) indicating an LTP-like effect, satisfying the anti-hebbian STDP.

We used bifocal TMS to repeatedly activate the connections between the PPC and M1 of the left-dominant hemisphere. Left PPC TMS preceded or followed the M1 stimulation by 5 ms, respectively PAS +5 and PAS -5. To best activate the ipsilateral PPC–M1 connection, the conditioning stimulus was applied over the left PPC at an intensity of 90% of the ipsilateral resting motor threshold. For the PAS protocol, 100 pairs of stimuli were continuously delivered at a rate of 0.2 Hz for ~8.3 min. Motor evoked potentials and central cholinergic way, evaluated with Short-latency afferent inhibition (SAI) protocol, were evaluated before and after PAS (+5 or-5) protocol. Twelve AD patients and ten age-matched healthy subjects (HS) were evaluated.

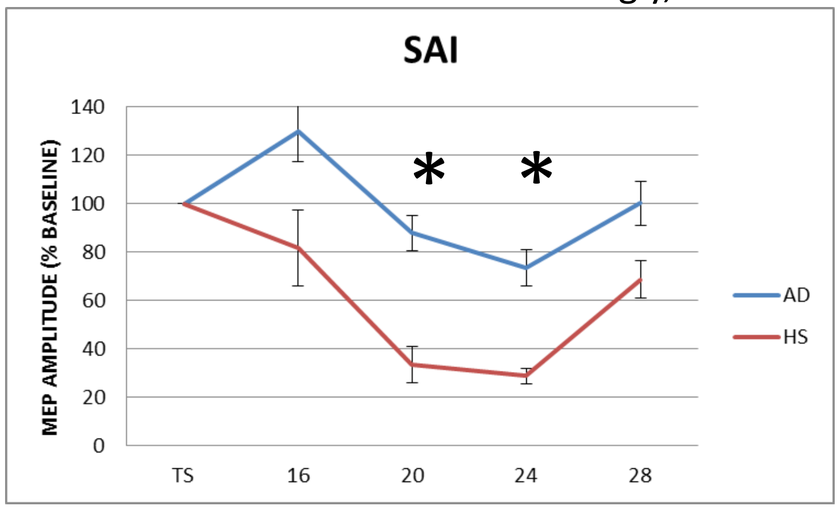
RESULTS

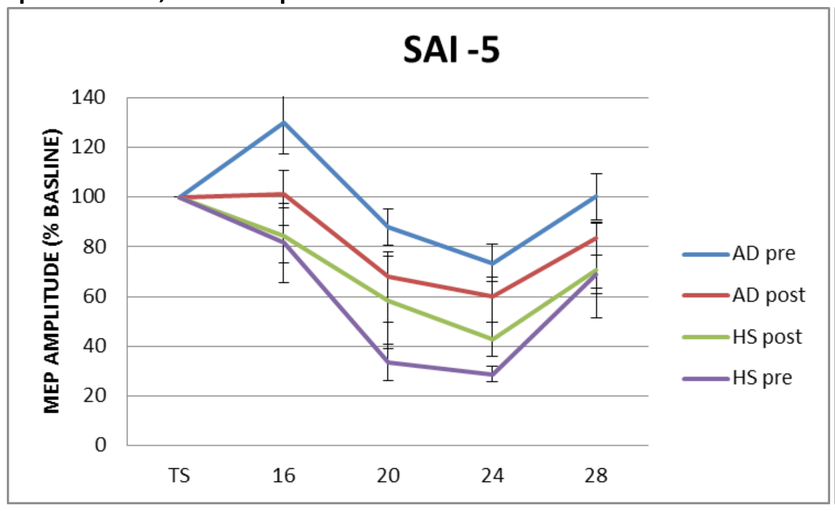


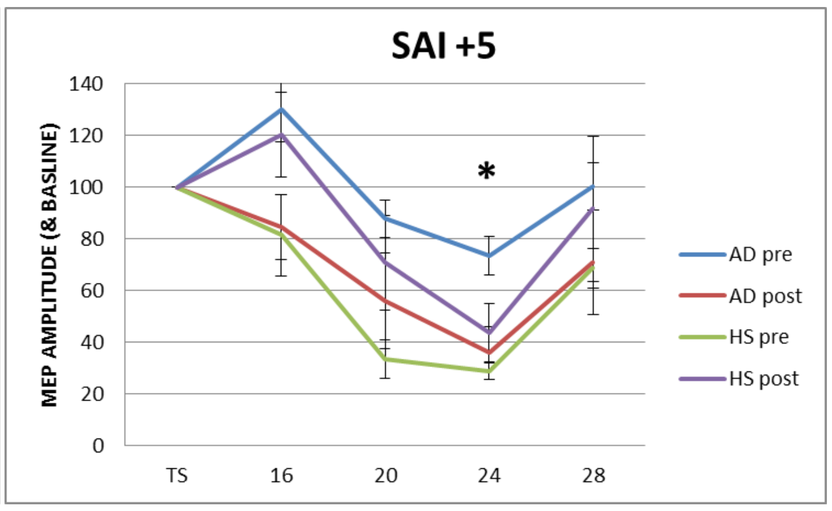




HS showed an LTP-like cortical plasticity following PAS -5 protocol and an LTD-like cortical plasticity after PAS+5 protocol, while AD patients didn't show any significant modification of the amplitude of MEP after repeated activation of PPC-M1 connections. As compared to HS, AD patients showed worst SAI values. Interestingly, after PAS+ 5 protocol, in AD patients SAI levels were restored.







CONCLUSIONS

The data here presented confirm that in AD patients there is an altered cortical plasticity, elicited with a new TMS protocol able to investigate the connections between PPC-M1, showing an altered form of anti-hebbian STDP, compared to HS that on the other hand satisfy the physiological rules of STDP. The central cholinergic way, known to be deeply impaired in AD pathology, is altered in our sample of AD patients, but, interestingly, after the application of PAS + 5 protocol his levels are restored, suggesting a possible role of PPC-M1 pathway on the modulation of this inhibitory intracortical circuit, and fascinatingly, opening new possible therapeutic scenarios in the field of neuromodulation.

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