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# INCREASED CORTICAL PLASTICITY IN THE ELDERLY: CHANGES IN THE SOMATOSENSORY CORTEX AFTER PAIRED ASSOCIATIVE STIMULATION

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**Abstract—A fundamental feature of the human cortex is the capability to express plastic changes that seem to be present even during physiological aging. The paired associative stimulation (PAS) protocol is a paradigm capable of inducing neuroplastic changes, possibly by mechanisms related to spike timing-dependent associative neuronal activity, and represents a suitable tool for investigating age-dependent neuroplastic modulations of the primary somatosensory cortex (S1). To examine age dependency of S1 plasticity, the amplitude changes of median nerve somatosensory evoked potential (SEP) before and after PAS intervention were investigated in young and elderly subjects. The main finding of our study is that low-frequency medial nerve stimulation paired with transcranial magnetic stimulation over the contralateral cortex enhances S1 excitability. Moreover, the S1 long term potentiation–like plasticity changes as a function of aging, with a significant increase of N20–P25 complex in the elderly compared to young subjects. These results are congruent with the hypothesis that some elderly subjects retain a high level of plasticity in specific neuronal circuits. Such plasticity could represent a compensatory mechanism, in terms of functional reserve of somatosensory cortex, used by the aging brain to counterbalance the cortical degeneration associated with aging. © 2009 Published by Elsevier Ltd on behalf of IBRO.**

**Key words: age, somatosensory cortical plasticity, paired associative stimulation, TMS.**

Several studies have suggested that the cerebral cortex is not a static structure but has dynamic organization associated with mechanisms of plasticity (Recanzone et al., 1992; Rossini et al., 1994a; Castro-Alamancos et al., 1995; Sanes and Donoghue, 2000; Stavrinou et al., 2007; Mercado, 2008). One mechanism that could be responsible for cortical plasticity is the modulation of the synaptic strength of cortical horizontal connections by long-term potentiation (LTP) and long-term depression (LTD) (Castro-Alamancos et al., 1995; Rioult-Pedotti et al., 1998; Sanes and Donoghue, 2000).

Cortical plasticity appears to be reduced during physiological aging in association with extensive neurochemical and neurophysiologic changes (Burke and Barnes, 2006; Rossini et al., 2007). Normal aging is associated with a loss of synaptic contacts and a relative decrease in the excitability of intracortical inhibitory circuits (Peinemann et al., 2001; Hortobagyi et al., 2006; Oliviero et al., 2006), which then cause a decline in sensory processing, motor performance and cognitive function. Moreover, age-dependent synaptic plasticity is highlighted by behavioral impairments correlated with region-specific changes in dendritic morphology, cellular connectivity, and gene expression (Godde et al., 2002; Sawaki et al., 2003; Burke and Barnes, 2006; Mora et al., 2007; Ward et al., 2007).

Plastic cortical changes can be investigated with paired associative stimulation (PAS), which is shaped like associative LTP in animal studies (Markram et al., 1997; Stefan et al., 2002; Classen et al., 2004). This protocol couples a single electric stimulus delivered at specific time intervals to a peripheral nerve with a single transcranial magnetic stimulation (TMS) pulse over primary motor cortex (M1) or primary somatosensory cortex (S1), causing changes in their excitability (Mariorenzi et al., 1991; Stefan et al., 2002; Wolters et al., 2003). Therefore it is believed that this repetitive associated stimulation can induce LTP-like phenomena.

Specifically, LTP occurs if the action potential follows an excitatory post-synaptic potential elicited by sub-threshold afferent stimulation within a few milliseconds (Markram et al., 1997; Bi and Poo, 1998; Feldman, 2000). PAS-induced plasticity evolves rapidly and is persistent, topographically specific, and reversible (Stefan et al., 2002). An involvement of LTP-like processes is supported by all these properties and by its blockade by NMDA receptor antagonists (Malenka and Nicoll, 1993). These LTP-like changes can be quantified by recording motor evoked potential (MEP) (Stefan et al., 2002; Wolters et al., 2003; Ziemann, 2004; Fratello et al., 2006) or somatosensory evoked potential (SEP) (Wolters et al., 2005; Litvak et al., 2007) amplitude. The site of PAS-action has been local-

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*Abbreviations:* ANCOVA, analysis of covariance; ANOVA, analysis of variance; APB, abductor pollicis brevis; EEG, electroencephalogram or -graphy or -graphic; EMG, electromyogram or -graphy or -graphic; EOG, electrooculogram or -graphy or -graphic; LTP, long-term potentiation; MEP, motor evoked potential; MN, median nerve; M1, primary motor cortex; PAS, paired associative stimulation; RMT, resting motor threshold; SEP, somatosensory evoked potential; S1, primary somatosensory cortex; TMS, transcranial magnetic stimulation.

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ized to the cortex (Stefan et al., 2002; Wolters et al., 2003) but mechanisms at the level of the spinal cord may contribute to PAS-induced changes in corticomotor excitability (Meunier et al., 2007).

The PAS protocol has been used to investigate the effects of physiological aging on motor cortex plasticity (Muller-Dahlhaus et al., 2008; Tecchio et al., 2008). However, age-dependent changes in cortical plasticity have never been investigated in S1.

The main aim of present study was to investigate the functional modulation of S1 cortical plasticity during physiological aging. Hence, we investigated differences between young and elderly healthy subjects by evaluating LTP-like changes related to spike-timing dependent plasticity of neuronal synapses and induced by the PAS protocol on SEP component amplitude.

The influence of gender was also taken into account, since (Tecchio et al. 2008) showed that PAS-induced motor cortex plasticity is gender-dependent.

## EXPERIMENTAL PROCEDURES

### Subjects

Thirty-two healthy volunteers subjects took part in the experiment. They were divided into two groups: 16 elderly subjects [eight males and eight females; mean age and standard error (±SE) 62.1±1.5 years] and 16 young subjects (eight males and eight females; mean age 26.2±0.8 years). Elderly subjects were selected from an institute's normative archive, whereas young subjects were selected from a university student population. All subjects reported themselves as right-handed and had no history of peripheral or neurological impairment. In particular, exclusion criteria were: cognitive decline or memory disturbance ever experienced, previous transient ischemic attack or stroke, brain injury, alcohol abuse or drug addiction and contraindications to TMS (Wassermann, 1998). All subjects were informed about the experimental procedures and provided written informed consent. The experimental protocol was approved by the Ethics Committee of IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy.

### Study design

The principal aim of the experiment was to determine the effect induced by PAS protocol on SEPs recorded from the scalp positions overlying S1 in elderly and young subjects. Participants were seated in a comfortable chair in a Faraday cage soundproof room. They were required to keep their right arm completely relaxed and to pay attention to the stimulated hand during the entire experimental session (Stefan et al., 2004). All subjects were tested within the same time period of the day (10:30 AM to 1:30 PM), with the aim to control for potential circadian effects (Sale et al., 2007).

### TMS

TMS was applied using a figure-of-eight double 70 mm coil connected to a Magstim SuperRapid magnetic stimulator (Magstim, Whitland, UK). The coil was placed tangentially to the scalp with the handle pointing backwards and laterally at about a 45° angle away from the midsagittal axis of the subject's head. The optimal site of stimulation for eliciting MEPs in the right abductor pollicis brevis (APB), termed the "motor hotspot," was chosen by positioning the coil approximately over the central sulcus and moving it on the scalp in 0.5 cm steps over M1 of the left cortex, assessed at a moderately suprathreshold stimulation intensity and marked directly on the scalp with a soft-tip pen. On this site, the resting motor threshold (RMT) was determined as the stimulator intensity needed to produce a response of at least 50 $\mu$V in amplitude in the relaxed APB in at least five of 10 consecutive stimulations at a resolution of 1% of the maximal stimulator output (Rossini et al., 1994b). Complete muscle relaxation was monitored throughout the experiment and regulated by audiovisual feedback.

### Electrical somatosensory stimulation

Electrical nerve stimulation used to induce SEPs was performed with a constant current electrical stimulator (STM140 rev 1.0, HTL, Udine, Italy) with standard parameters (cathode proximal). The stimulating electrode was placed on the right median nerve (MN) at the level of the wrist. MN stimulation was performed using a pulse with a 200 $\mu$s width at a frequency of 3 Hz and a stimulation intensity of ~300% of the individual perceptual threshold (Wolters et al., 2005). The hand representation at S1 ("somatosensory hot-spot") was marked 2 cm posterior to C3 position, corresponding to CP3 (Nuwer et al., 1994; Wolters et al., 2005; Litvak et al., 2007). Before and after PAS intervention, 500 electric stimuli were recorded (500 pre-PAS+500 post-PAS). During PAS intervention, the same parameters of nerve stimulation were utilized.

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### PAS

The PAS protocol reproduces the experimental procedure of Wolters et al. (2005), which represented a modification of PAS protocol generally used for the M1 area (Stefan et al., 2002). The protocol consisted of single electrical stimuli delivered to the right MN at the level of the wrist at 300% of the perceptual threshold and followed by TMS delivered over the hand representation of S1. Namely, the left S1 was stimulated by placing the central area of the junction of the two coil wings at a scalp site on CP3 along a line parallel to the midline with induced current directed in a posterior–anterior axis. TMS was applied at an intensity of 1.3 times the RMT. The interval between MN stimulation and the subsequent TMS pulse was 20 ms. This interval is the modal time for an afferent signal arising from MN at the level of the wrist to travel to S1 (i.e. N20 latency) (Wolters et al., 2005). One hundred forty pairs of stimuli were delivered at 0.1 Hz over 25 min. During PAS, subjects were asked to watch their own right hand, since this condition has been demonstrated to give the maximal PAS-induced plasticity (Classen et al., 2004). The entire experimental time session lasted 30 min.

### Recording

Electroencephalographic (EEG) signals were recorded from 12 sites using TMS-compatible Ag/AgCl-coated electrodes mounted on an elastic cap (EasyCap GmbH, Herrsching, Germany). TMS-compatible EEG equipment (BrainAmp DC/MRplus, Brain Products GmbH, Munich, Germany) was used to record continuous EEG activity during PAS. The montage included four midline sites (Fz, Cz, Pz, Oz) and eight sites over each hemisphere (C4, C3, CP1, CP2, CP3, CP4, CP5, CP6) and left and right mastoid (M1, M2) positioned according to the International 10–20 system. Additional electrodes were used as the ground and reference. The ground electrode was placed in the midfrontal (Fpz) position. The reference electrode was placed at the tip of the nose during EEG recording. Recordings obtained from an M1 and M2 electrode were used off-line to re-reference the scalp recordings to the conventional linked mastoids (i.e. average of M1 and M2).

Horizontal and vertical eye movements were detected by recording electrooculograms (EOGs) in order to monitor subject behavior on-line and reject, off-line, trials with ocular artefacts. Surface electromyography (EMG) activity was recorded from the right APB muscle with the active electrode mounted on the belly muscle and the reference electrode placed over the base of the metacarpophalangeal joint of the thumb. EEG, EOG and EMG



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signals were acquired with a band-pass filter at 0.02–1000 Hz, and then filtered off-line at 0.2–1000 Hz for EEG, EMG and 0.02–15 Hz for EOG. All signals were digitized at a sampling rate of 5 kHz using a 16 b A/D-converter. The skin-electrode impedance was kept below 5 kΩ.

### Data and statistical analysis

The optimal site for SEP analysis was the CP3 electrode, which was the electrode with the largest amplitude response, likely dominated by S1 activity. The epoching of the MN SEPs was performed off-line. All data collected were epoched between −50 and +100 ms relative to the MN stimulation. Epochs where voltage exceeded ±100 μV at the VEOG and HEOG electrodes or those containing artefacts were rejected. All amplitude values were calculated with reference to the 50 ms pre-stimulus baseline. Measurement windows were determined from an inspection of the group grand-average waveform. The P14 amplitude was measured as the difference between the baseline and the first positive peak occurring at a latency of around 13–18 ms after the time of MN stimulation. The amplitude of N20 was measured as the first negative peak between 18 and 23 ms. The N20–P25 complex was determined as the difference between the N20 peak and the subsequent positivity peak (P25), occurring at a latency of around 23–29 ms. P25 amplitude was subsequently calculated as the difference between the amplitude of the N20–P25 complex and the N20 amplitude. Finally, the N30 and P40 peak amplitudes were measured between 29 and 38 ms and between 38 and 45 ms, respectively.

According to previous studies (Wolters et al., 2005; Murakami et al., 2008; Litvak et al., 2007; Tamura et al., 2009), the statistical analyses compared absolute amplitude values recorded before-PAS to those after-PAS intervention. The main dependent variable was the amplitude of the N20–P25 complex. A three-way mixed design analysis of variance (ANOVA), age group (young vs. elderly)×gender (male vs. female)×condition (pre- vs. post-PAS) was carried out.

The same ANOVA was also performed on the amplitude of the P14, N30, and P40 components. To assess significant interactions, selected two-sample comparisons were performed by means of one-tailed *t*-tests. The one-tailed probability has been used since an a priori directional hypothesis does exist with respect to the increase of MEP amplitude. The appropriate *t*-tests have been used according to the repeated/non-repeated factors. The Bonferroni correction was applied to correct for multiple comparisons. Considering the mean correlation between the dependent variables ($r$=0.70), the alpha level was then adjusted to ≤0.03 (Sankoh et al., 1997).

## RESULTS

The PAS intervention affected SEPs in the time-window between 20 and 25 ms in both groups, inducing an average increase of the N20–P25 complex by 5.4% in young and by 9.4% in elderly subjects (Fig. 1). F1

The main effects and interactions of the ANOVAs on the main dependent variables are reported in Table 1. The T1 N20–P25 complex was significantly affected by aging, with the elderly population having a larger amplitude (5.87 SE=±0.74 μV) than the young (4.20 SE=±0.33 μV) subjects. A robust effect of increased amplitude was found after the PAS intervention (pre-PAS=4.86 SE=±0.41 μV; post-PAS=5.20 SE=±0.44 μV). As shown in Fig. 2, both F2 aging and gender influence this increase. Indeed, the significant Age group×Condition interaction showed that the post-PAS increase of the N20–P25 amplitude was larger in the elderly (one-tailed paired *t*-test: $t_{15}$=5.23; $P$<0.0001)

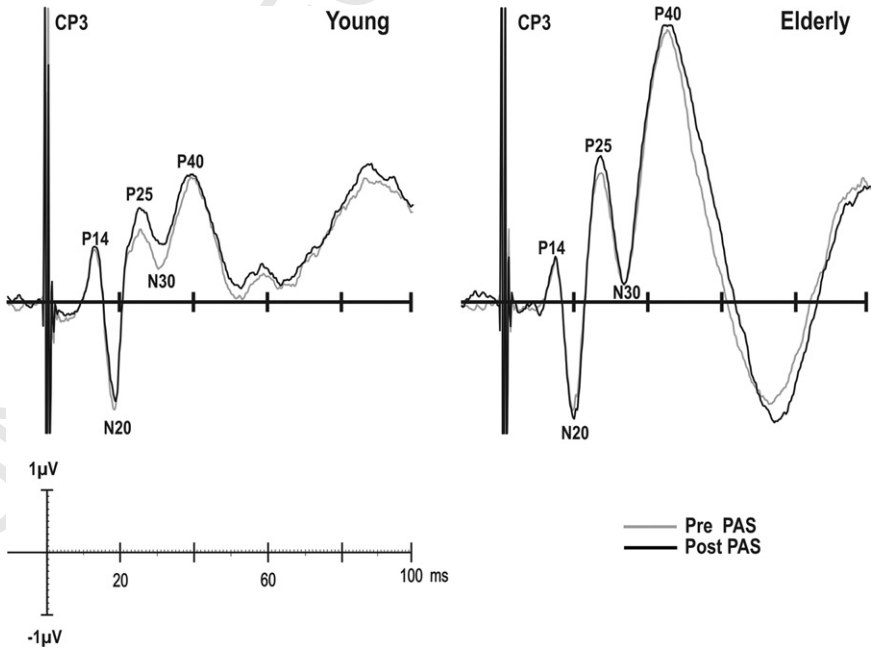


**Fig. 1.** Grand average waveforms of SEPs following right MN stimulation before and after intervention with PAS of 16 young (left) and 16 elderly (right) subjects. Two traces are superimposed: the thin line represents the response before PAS, the thick line shows the response after PAS. Amplitude of N20/P25 component increases after PAS, whereas others components were unaffected by intervention. Notably, the amplitude of all components of SEP is greater in the elderly than in young subjects. It should be noted that there is a discrepancy between the samples of grand average ERP waveforms figure and real data. This is due to the fact that for data analysis amplitude of components is measured at single subject peak latency (see Experimental Procedures), while for the figure this factor cannot be considered and therefore the time jitter of those peaks results in a smoothed figure.

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**Table 1.** Results of the Age group×Gender×Condition ANOVAs on amplitudes of N20–P25 complex, and of N20 and P25 components

| | $F_{1,28}$ | | | $P$ | | |
|---|---|---|---|---|---|---|
| | N20–P25 | N20 | P25 | N20–P25 | N20 | P25 |
| Age group (A) | 4.58 | 0.50 | 5.49 | 0.04 | 0.49 | 0.03 |
| Gender (G) | 3.91 | 2.42 | 2.64 | 0.06 | 0.13 | 0.11 |
| Condition (C) | 38.66 | 1.83 | 8.86 | <0.001 | 0.19 | 0.006 |
| A×G | 0.39 | 2.23 | 0.008 | 0.54 | 0.15 | 0.93 |
| A×C | 6.77 | 5.46 | 0.33 | 0.01 | 0.03 | 0.57 |
| G×C | 5.59 | 1.28 | 0.25 | 0.02 | 0.27 | 0.62 |
| A×G×C | 3.57 | 0.37 | 0.49 | 0.07 | 0.55 | 0.49 |

than in young subjects ($t_{15}$=2.49; $P$=0.01). The significant Gender×Condition interaction indicated that PAS induced an increase of the N20–P25 complex in females, with a larger effect size ($t_{15}$=4.83; $P$<0.0001, Cohen's d=1.24) than in male subjects ($t_{15}$=2.76; $P$=0.007, Cohen's d=0.79). Notably, the triple interaction, although not significant ($P$<0.10), suggested that the increase of the N20–P25 amplitude was significant in young females ($t_7$=1.85; $P$=0.05) and in both elderly groups (males and females $t_7$=2.24; $P$=0.03 and $t_7$=7.73; $P$<0.0001, respectively), but not in young males ($t_7$=1.56; $P$=0.08).

The extent of the individual PAS-induced effects on N20–P25 amplitude, expressed as a percentage of pre-PAS condition (post-PAS/pre-PAS), is detailed in Fig. 3. F3 The scattergram shows the between-group differences and confirms the large inter-subject variability. Furthermore, it suggests the existence of a linear relationship between aging and PAS changes, a property limited to

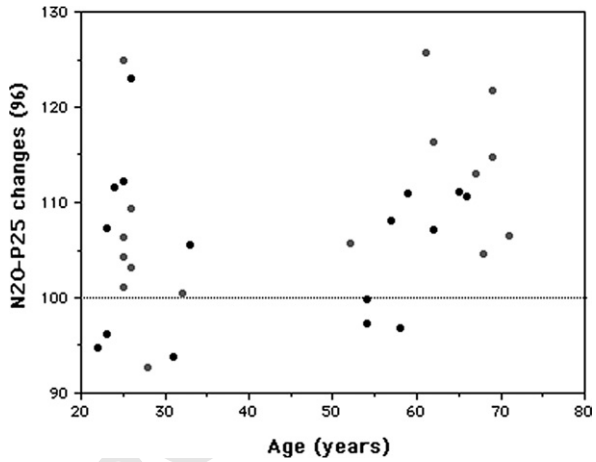


**Fig. 3.** Scattergram of individual PAS-induced effects on N20–P25 amplitudes expressed as a percentage of pre-PAS condition (post-PAS/pre-PAS) as a function of age. Zero corresponds to the pre-PAS N20–P25 amplitude. Grey circles indicate female subjects and black circles represent the male subjects.

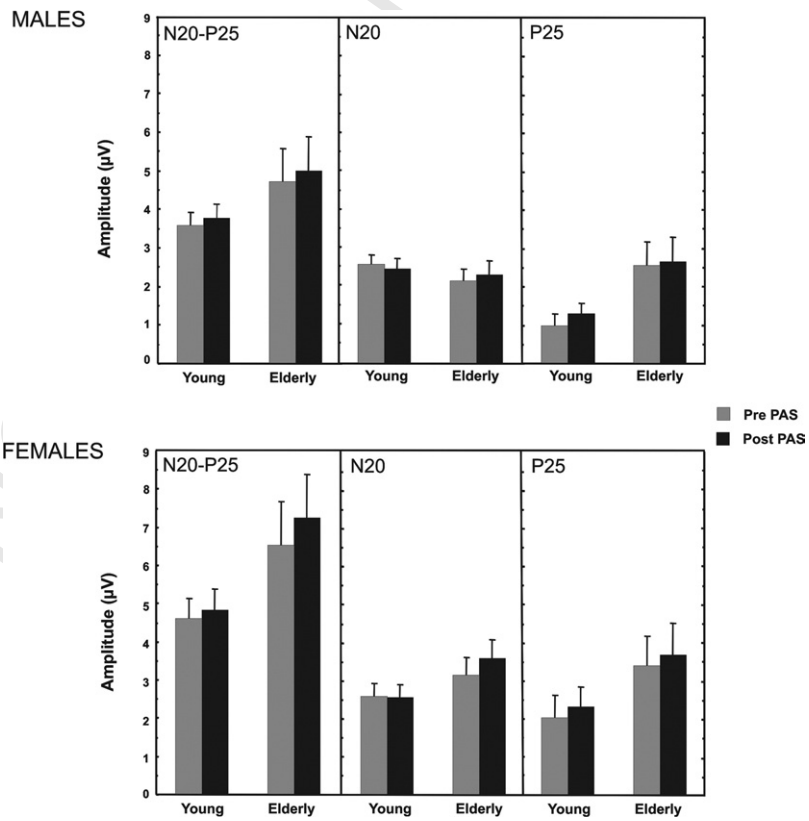


**Fig. 2.** Effect of PAS on amplitude (expressed in μV) of the N20-P25 complex, N20, and P25 component of SEP, in 16 male and 16 female subjects (eight young and eight elderly in each group). The bars illustrate the mean amplitude in pre-PAS (grey bars) and post-PAS (black bars); error bars represent the standard errors.

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elderly subjects. The product-moment correlation between age and N20–P25 changes was $r=0.48$ ($P=0.06$) in elderly subjects and $r=0.18$ ($P=0.51$) in young subjects.

Since the average resting motor (young=52.5%±1.8% and elderly=58.3%±2.2%; $F_{1,30}=4.12$; $P=0.05$) and perceptual thresholds (young=2.5±0.2 mA and elderly=3.1±0.1 mA; $F_{1,30}=6.94$; $P=0.01$) recorded with magnetic and electrical stimulations were higher in the elderly than in young subjects, these differences may have influenced the magnitude of PAS-induced changes. Hence, we have verified the possible effects of both thresholds values on N20–P25 changes after PAS, and no correlation was significant (motor threshold: $r=0.13$, $P=0.48$; perceptual threshold: $r=0.21$, $P=0.24$). Moreover, we have performed an analysis of covariance (ANCOVA) on the N20–P25 amplitude taking the motor and perceptual thresholds as covariates. The ANCOVA confirmed the effects for the Age group ($F_{1,26}=9.57$, $P=0.005$) and Condition factors ($F_{1,26}=35.90$, $P<0.001$), the Age group×Condition ($F_{1,26}=6.29$, $P=0.02$), and Gender×Condition ($F_{1,26}=5.20$, $P=0.03$) interactions, pointing to a lack of thresholds influence on PAS effects.

Since baseline SSEPs were higher in elderly than in young subjects ($F_{1,28}=3.92$; $P=0.05$), these differences may have influenced the magnitude of PAS-induced changes. Nevertheless, the relative increase in the N20–P25 amplitude after PAS does not correlate with the N20–P25 amplitude at pre-interventional baseline ($r=-0.10$; $P=0.60$). As a further control for specificity of PAS effects, we have performed an ANCOVA on percentages of the N20–P25 amplitude changes, considering the pre-PAS N20–P25 amplitude as a covariate. The ANCOVA substantially confirmed the effects for the Age group ($F_{1,27}=3.78$, $P=0.06$) and Gender factors ($F_{1,27}=4.69$, $P=0.04$). The effect of the covariate also was close to the significance ($\beta=-0.34$; $t=0.07$).

As a final control for the specificity of PAS effects, we verified the influence of possible differences in conduction slowing in afferent pathways in elderly subjects since the timing between the peripheral and central stimuli in the PAS paradigm critically influences the direction and magnitude of induced changes (Hebb, 1949; Cooke and Bliss, 2006).

These differences do appear to be affected by aging and gender. The two-way ANOVA of Age group (young vs. elderly)×Gender (male vs. female) on the N20 latency before the PAS protocol pointed to a significant effect for the Age group (young=19.05±0.24 ms, elderly=20.24±0.29 ms; $F_{1,28}=17.87$, $P=0.0002$) and for Gender (males=20.32±0.23 ms, females=18.96±0.27 ms; $F_{1,28}=23.53$, $P<0.001$).

As a consequence of these differences, we have carried out an ANCOVA on the N20–P25 amplitude, considering the N20 latency as a covariate. The ANCOVA confirmed the effects of the Age group ($F_{1,27}=7.18$, $P=0.01$) and Condition factors ($F_{1,27}=37.28$, $P<0.001$), for the Age group×Condition ($F_{1,27}=6.53$, $P=0.02$), and Gender×Condition ($F_{1,27}=5.40$, $P=0.03$) interactions. Therefore, the magnitude of the PAS effects as a function of aging and gender does not seem to be influenced by the between-group differences in the N20 latencies.

As suggested by the data presented in Fig. 1, there was a differential PAS effect on the N20 and P25 components. Aging and PAS affected the amplitude of the P25 component but are not associated with significant changes in the N20 amplitude (Table 1). In fact, the N20 component only showed a significant Age group×Condition interaction, pointing to an increased amplitude only in the elderly ($P=0.01$) without significant changes in young subjects ($P=0.49$). On the other hand, the P25 component was significantly affected by aging, with a higher amplitude in elderly (3.06±0.51 $\mu$V) than young (1.65±0.33 $\mu$V) subjects and was also affected by PAS, with an increased amplitude post-PAS (pre-PAS=2.24±0.32 $\mu$V; post-PAS=2.47±0.33 $\mu$V). Gender differences did not affect the N20 and P25 components.

Finally, the PAS-induced changes were limited to the N20–P25 complex, since the ANOVAs of the amplitude of the P14, N30, and P40 components did not show any significant effects or interactions. Only aging affected the amplitude of the P14 (young=0.93±0.12 $\mu$V, elderly=1.27±0.11 $\mu$V; $F_{1,30}=4.09$, $P=0.05$) and P40 components (young=2.23±0.34 $\mu$V, elderly=5.34±0.50 $\mu$V; $F_{1,30}=30.88$, $P<0.001$). The P40 components also showed a main effect for Gender, with a higher amplitude in females (4.43±0.62 $\mu$V) than males (3.14±0.50 $\mu$V).

## DISCUSSION

The present results confirm that low-frequency MN stimulation paired with TMS over the contralateral cortex enhances S1 excitability, as indicated by SEP analysis. The main finding of our study is that the S1 LTP-like plasticity after PAS intervention changes as a function of age, with a significant increase of the N20–P25 complex in elderly (9.4%) compared to young subjects (5.4%). Notably, the increase found by Wolters et al. (2005) in young subjects was very similar (6.2%). Therefore, our results confirm previous studies (Wolters et al., 2005; Litvak et al., 2007) supporting the efficacy of this protocol in healthy young subjects to induce a significant, although of small extent, LTP-like plasticity in S1 cortex, and the need to follow the original experimental protocol, because even slight differences between the experimental protocols accounted for the lack of overt change in somatosensory cortical excitability after PAS, as highlighted in a previous study (Bliem et al., 2008).

Moreover, our PAS intervention induces an amplitude increase of N20 in elderly but not in young subjects and an increase in the amplitude of P25 in both age groups. At a statistical level, this increase persists despite the significant difference between age groups on N20 latency, an effect which is likely associated with a slowing of conduction afferent pathways in the elderly.

PAS does not induce modulation of P14, N30, and P40 components, although we confirm that these components were affected by aging (Kakigi and Shibasaki, 1991). This lack of significant changes after PAS intervention on the



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subcortically generated P14 (Desmedt and Cheron, 1980b; Lee and Seyal, 1998) supports an interpretation that excludes a contribution of subcortical mechanisms to somatosensory excitability, supporting the idea that the main site of action for PAS-induced synaptic plasticity is the cortical level (Stefan et al., 2002; Wolters et al., 2003) and that cortical excitability changes are due to modulation of excitatory neuronal activity in upper cortical layers of S1 (Wolters et al., 2005). However, further studies will be necessary to directly investigate a possible contribution of spinal mechanisms in excitability of the somatosensory system, as was recently shown in the motor system (Meunier et al., 2007).

Finally, this specificity also allows us to exclude that the increased PAS-induced plasticity effect could simply reflect between-group differences in baseline excitability (Rosenkranz et al., 2007), since differences in baseline excitability should likely affect all SEP components after PAS.

### Cortical plasticity and compensatory changes with aging on somatosensory cortex

SEP components that are more affected by PAS protocol are also those more affected by age-dependent changes. It is now widely accepted that both early SEP components, N20 and P25, are generated in the posterior bank of the central sulcus and primarily reflect activity of S1 (Broughton et al., 1981; Hume and Cant, 1981; Allison et al., 1989, 1991; Urbano et al., 1997). Intracranial recordings in humans (Allison, 1982) indicate that N20 and P25 reflect the initial excitation of neurons in cortical areas 3b and 1, respectively, areas that also show a significant effect of aging (Allison et al., 1984). Therefore, we confirm an increased amplitude of the N20–P25 complex and P25 component in elderly compared to young subjects, independent of PAS intervention, since a general and gradual increase of SEP amplitude as well as of somatosensory evoked field has been repeatedly found in normal elderly subjects (Luders, 1970; Kazis et al., 1983; Kakigi and Shibasaki, 1991; Huttunen et al., 1999; Nakano and Hashimoto, 1999; Stephen et al., 2006). An ultimate explanation of this phenomenon is still lacking, but the foremost hypothesis is that this greater activation may be due (a) to the development of dendritic arborizations in the cortical neurons, which compensate for the degeneration of the synaptic spines (Wisniewski and Terry, 1976; Desmedt and Cheron, 1980a; Kazis et al., 1983) and (b) to a cortical decrease in the inhibitory neurotransmitters (GABA), resulting in a prevalence of excitatory intracortical mechanisms (Paty et al., 1980; Kazis et al., 1983). A decreased inhibition in the elderly has been suggested by animal studies (Drechsler, 1978; McDowd and Oseas-Kreger, 1991) showing an age-related decrease in the number of inhibitory synapses rather than a decrease in neuronal number in the aged S1 (Brunso-Bechtold et al., 2000). There is also evidence that normal aging in humans reduces cortical reciprocal inhibition (Hortobagyi et al., 2006) and is associated with a relative decrease in the excitability of intracortical inhibitory circuits (Peinemann et al., 2001). As a matter of fact, different studies from various view angles (biochemical, neurophysiological, and clinical) indicate that aging impairs GABAergic inhibition in afferent relay nuclei and in the hippocampal cortex (Post-Munson et al., 1994; Caspary et al., 1995) and enhances glutamatergic excitation in the neocortex (Wenk et al., 1989; Saransaari and Oja, 1995). Therefore, aging could be associated with a change in the balance between excitation and inhibition, trending towards an increase in cortical excitability (Huttunen et al., 1999).

The amplitude increase of cortical evoked potentials in aged individuals, together with a decrease of conduction velocity in the peripheral somatosensory pathways and normal central conduction velocity, supports the view that aging does not simply cause a progressive degeneration of the nervous system. On the contrary, it can produce compensatory reactions deviating from the linear retrogression, possibly to actively resist the coming degeneration (Kazis et al., 1983).

Current results suggest that a larger SEP increase induced by PAS in elderly than in young subjects represents an additional and plastic increase in the strength of excitatory transmission. On this basis, it could be speculated that PAS intervention determinates a reduction of intracortical, presumably GABAergic, inhibition or an enhancement of intracortical, presumably glutamatergic, excitation or a mixture of both (Segovia et al., 2001; Ragert et al., 2004). Studies in human and non-human cortex confirmed that the induction of LTP effects should require a reduction in local cortical inhibition by modulation of GABA receptor activity (Hess and Donoghue, 1994) or an increase in NMDA receptor activation (Ziemann et al., 1998).

Additionally, another probable cause of the PAS-induced wider increase in both N20 and P25 in elderly could be a progressive decrease of the specific cortical inhibitory processes during aging (Drechsler, 1978). It is widely accepted that the N20 component represents the initial postsynaptic activity in the S1 cortex (Allison et al., 1989), while the P25 component is assumed to represent the arrival of the sensory volley in S1 (Rossini et al., 1987; Tsuji and Rothwell, 2002). The serial activation of areas 3b and 1 (Jones et al., 1978; Kaas and Garraghty, 1991; Urbano et al., 1997) on a background of enhanced cortical excitability in conjunction with cortical inhibitory decrease could explain the greater LTP-like increase initially seen in N20 and later in P25 in elderly compared to young subjects. We hypothesize that the differential PAS-induced cortical excitability changes between young and elderly subjects could be a result of differential excitatory modulation and inhibitory involvement of neuronal activity in S1, which results in more confined and specific plasticity effects in young and more generalized and wider plasticity in the elderly.

One possible scenario is that the more generalized and wider plasticity in the elderly represents a compensatory mechanism, in terms of functional reserve of somatosensory cortex, activated by the aging brain to counterbalance cortical degeneration associated with aging (Craik, 2006; Heuninckx et al., 2008). According to the compensation



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hypothesis that supports the age-related increases in brain activation, as overactivation or greater brain activity, to compensate for various neurodegenerative deficits (Madden et al., 1999; Cabeza et al., 2002; Reuter-Lorenz and Lustig, 2005; Rossi et al., 2004), our results suggest that greater S1 LTP-like plasticity after PAS in elderly subjects is counteracted to age-related structural and neurochemical decline through greater plastic modulation of neurocortical pathways and reorganization of functional networks.

### Gender effects on cortical plasticity

The results of our study highlight that plastic changes on S1 appear to be not only age-dependent but also gender-dependent, confirming the growing evidence that neuroplastic changes are influenced by gender-specific pressure (Cahill, 2006) and presenting for the first time direct evidence of gender differences in human somatosensory cortical plasticity.

In particular, we point out that gender modulates the PAS-induced increase of the N20–P25 amplitude, with a significant and larger increase in the female elderly group. This gender difference seems further accentuated with aging, modulating neuroplasticity mechanisms that affect both neural excitability and cortical plasticity (Teskey et al., 1999; Inghilleri et al., 2004). Reasonably, the small, but not significant, PAS-induced effect on P25 amplitude found in normal adult subjects, serving as a control group in a recent study (Tamura et al., 2009), should also be explained by these gender differences. In fact, eight out of 10 subjects of that study were males.

In animal studies, sex differences in synaptic plasticity and cognitive functions have been widely demonstrated (Juraska, 1998; Jonasson, 2005) and sex hormones were suggested as modulating these effects (Woolley, 2000; McEwen, 2002). In fact, ovarian steroids influence neural excitability (Fink, 1994; Kawata, 1995), with excitability increasing due to estrogen and decreasing due to progesterone (Beyenburg et al., 2001).

Neuronal function and excitability can be affected by steroid hormones directly by modulating the activity of neurotransmitter receptors (GABA and NMDA receptors) or indirectly by modulating ion channels (Kawata, 1995; Rupprecht and Holsboer, 1999). More directly, the presence of estrogens in women could play an important role in synaptic potentiation and cortical excitability induced by PAS on S1 by enhancing glutamate action on NMDA receptors and by acting on voltage-gated sodium channels (Malenka and Nicoll, 1999; Inghilleri et al., 2004). This suggests that sex hormones, which already contribute to plastic changes in young females, could interact with the wider cortical excitability, which contributes to the greatest plasticity of the elderly compared to young. Moreover, we ascribe the plasticity effects on S1 to hormonal factors and not to the gender-specificities of brain structure, considering that gender itself does not affect the amplitude of SEP but only modulates the PAS-induced increase in SEP.

In accordance with these animal and human studies, our results also point to an effect of sexual dimorphism on human cortical somatosensory neuroplasticity, probably mediated by differences in sex hormones.

### Aging-related plastic changes in somatosensory vs. motor cortex

Plastic changes induced by the PAS protocol seem to differentially affect the S1 and M1 parts of cortex with different age- and gender-dependent effects. Our study highlights the capability of S1 to retain plasticity during physiological aging. On the other hand, studies on M1 showed a decline in the capacity of this area to undergo plastic changes induced by PAS in elderly subjects (Muller-Dahlhaus et al., 2008). Moreover, it has been demonstrated (Tecchio et al., 2008) that PAS-induced motor cortex plasticity is also gender-dependent, with a decrease in plastic change in females after menopause. The former study correlated reduced M1 plasticity to several biochemical mechanisms and cortical–spinal functions affected by aging; while the latter hypothesized an imbalance of intracortical excitatory network activity that differentially affects plasticity in elderly females.

The results of these studies on PAS-induced synaptic plasticity on M1, though partially contrasting, both indicate that S1 and M1 have different plastic capability (Castro-Alamancos et al., 1995). Although these different cortical areas have similar types of neurons and basic pattern of neural circuitry, they are different in their peripheral and cortical pathways, in their inputs and outputs, and in their functional and molecular properties (Bower and Haberly, 1986; Huntley et al., 1994; Castro-Alamancos and Connors, 1996; Barth, 2002). Previous studies have reported that S1 and M1 can reorganize in response to central or peripheral manipulations by expressing a variety of types of synaptic plasticity. Nevertheless, these cortices are not identical in their plastic change capabilities and in their ability to generate LTP (Donoghue et al., 1990; Recanzone et al., 1992; Diamond et al., 1993; Castro-Alamancos et al., 1995; Barth, 2002). Moreover, changes in the structural complexity and susceptibility to plasticity in both these areas appear differentially affected by aging (Adams, 1987a,b; Dickstein et al., 2007). In particular, studies on age-related changes in synaptic architecture highlight that aging is associated with a decrease in synapse number and an increase in the length of the postsynaptic contact zone in the M1 but not in S1 (Adams, 1987b).

It is now known that aging represents a physiological process that occurs asynchronously in different areas of the brain and that the rate of this process is related to the neuronal–synaptic–molecular substrates in each area (Mora et al., 2007). The differential age-related changes produced in several regions of the brain in the anatomy of neurons (Burke and Barnes, 2006), volume tissue density (Hedden and Gabrieli, 2004), and dynamics of several neurotransmitters (Segovia et al., 1999, 2001; Del Arco et al., 2003) support the hypothesis of the differential ability to make plastic changes in different cortical areas. Thus, the different structural and functional features of S1 and M1, and their age- and gender-related modification (Pitcher et al., 2003; Sale and Semmler, 2005; Stephen et al., 2006)



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can explain the differential ability of these cortices to make plastic changes and can explain their involvement in the balance of the intracortical network and spinal activity.

Finally, the different effects of aging on S1 and M1 could be due to a different involvement in how PAS protocol recruits these two areas. Indeed, when PAS is applied to S1, it acts on more localized cortical mechanisms. On the contrary, PAS applied to M1 acts on more complex networks in the cortico-cortical pathway between S1 and M1 (Porter, 1997), which could be more affected by physiological and neurochemical mechanisms correlated with aging.

### Limitations of the study

The main limitation of this study is the absence of a control condition for PAS intervention that allows us to attribute the increase of SEPs to the pairing of MN stimulation with TMS and to exclude the effects of elapsed time or prolonged MN stimulation. However, this possibility is unlikely considering that previous studies have already demonstrated the efficacy of the PAS protocol, at specific time intervals between peripheral and cortical stimulation, to induce somatosensory cortical changes (Wolters et al., 2005; Litvak et al., 2007).

Furthermore, it should be mentioned that, even though sensory perceptual and motor thresholds do not covariate for PAS-induced N20–P25 amplitude changes, this does not exclude a possible contribution of different thresholds across groups and the ultimate possibility that somatosensory and motor thresholds are not equally affected by aging.

Finally, relatively to gender-dependent factors, data regarding hormonal levels, menstrual cycle etc. were not collected at the time of experiment, since we were primarily focused on age factor and this should be considered a limitation of the study.

## CONCLUSION

Our results confirm the efficacy of the PAS protocol in inducing plastic changes in S1 cortex and highlight that these effects are age- and gender-dependent. Specifically, our results are in agreement with the hypothesis that the greater plasticity seen in specific neuronal circuits in the elderly could represent a compensatory mechanism of functional reorganization for the aging brain that makes up for the physiologic and neurodegenerative decline correlated with aging. Moreover, the PAS protocol could represent a valuable tool to improve cortical functionality for sensorial ability that deteriorates during aging due to its ability to induce plastic changes on S1 in the elderly.

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