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ORIGINAL PAPER

Physiological Aging Impacts the Hemispheric Balances of Resting State Primary Somatosensory Activities

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Abstract To hone knowledge of sensorimotor cerebral organization changes with physiological aging, we focused on the primary somatosensory cortical area (S1). S1 neuronal pools (FS_S1) were identified by the functional source separation (FSS) algorithm applied to magnetoencephalographic recordings during median nerve stimulation. Age-dependence of FS_S1 was then studied at rest separately in the left and right hemispheres of 26 healthy, right-handed subjects between the ages of 24 and 95 years. The resting state FS_S1 spectral features changed with increasing age: (1) alpha activity slowed down; (2) total power increased only in the right hemisphere; (3) right>left interhemispheric asymmetry increased in the whole spectrum; (4) spectral entropy increased with age selectively in the left hemisphere. The present FSS-enriched electrophysiological procedure provided measures of resting state hand representation area sensitive to changes with age. Alterations were stronger in the right hemisphere. Relationships between resting state S1 activity and its responsiveness to external stimuli, revealed that the interhemispheric unbalances which emerged with age were conceivably due to an increased excitability within the right thalamocortical circuit impacting left versus right unbalances of spontaneous firing rates and of local inhibitory-excitatory networks.

Keywords Magnetoencephalography (MEG) · Interhemispheric asymmetries · Median nerve stimulation · Functional source separation (FSS)

Introduction

To contribute to the wide-ranging investigations of mechanisms physiologically coupled with aging, our pilot study focuses on age-related cortical electrophysiological features. We aimed to explore whether resting state hemispheric primary networks devoted to hand perception are sensitive to changes with age.

Previous neurophysiologic assessments described changes with age of the resting state activity of the whole cortical mantle (Babiloni et al. 2006; Chiang et al. 2011) or focused on sensorimotor cortical areas only in animal models (David-Jurgens et al. 2008; Dinse 2006). Here, we are well equipped for non-invasively assessing resting state properties of specific somatosensory neuronal pools (S1) within each hemisphere along the lifespan.

Carlo Cottone and Leo Tomasevic have equally contributed to the study.

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Based on previous evidence, we had four working hypotheses (wp):
wp1. S1 power will increase in elderly people, reflecting both deafferentation-like and structuring-reduction phenomena. We derive this hypothesis from the observations of power increases in disconnected cortical regions (Patino et al. 2006; Topolnik et al. 2003). Furthermore, finer cortical organization of areas controlling finer functional abilities implies lower local neuronal power, as shown by dominant hemisphere rolandic regions displaying lower power than non-dominant ones (Tecchio et al. 2005);
wp2. S1 activity in high frequency bands (above beta) will increase with age (Duffy et al. 1993; Marciani et al. 1994);
wp3. This power increase will be more evident in the right than in the left hemisphere (Duffy et al. 1984);
wp4. Alpha activity will slow down with age (Wang and Busse 1969; Zappasodi et al. 2006).

The primary sensorimotor area is the last station dispatching signals to body districts controlling the interaction with other people and the environment. In particular, its somatosensory portion (S1) plays a crucial role in movement control, as clearly evident in physiological and pathological conditions. In healthy people, the interplay between S1 and the primary motor area (M1) modulates the performance of elementary (Tecchio et al. 2008) and more complex (Catalan et al. 1998; Szurhaj and Derambure 2006) movements and modifies the ability of empathic sharing (Betti et al. 2009). From clinical experience, the ability to recover sensorimotor function from stroke depends on parietal sensory region impairments (Assenza et al. 2009; Binkofski et al. 1996; Forss et al. 2011; Rose et al. 1994), somatosensory stimulation (Conforto et al. 2010; Laufer and Elboim-Gabyzon 2011), and within somatosensory area plasticity (Tecchio et al. 2006a, b, 2007a, b, c, d). Patients suffer major motor control impairments when affected by diseases that selectively involve somatosensory pathways (Botez and Herrmann 2010). Such functional relevance is revealed by the hierarchical anatomical organization, with the main direct projection to M1 originating from S1 (Jones et al. 1978; Hikosaka et al. 1985; Rizzolatti and Luppino 2001). It is noteworthy that M1 and S1 are the cortical areas earliest to develop in embryonic growth (Juenger et al. 2011; Chittajallu and Isaac 2010).

We attempted to estimate the age dependency of specific features of cortical organization by means of a simple and easy accessible procedure. Neuronal networks constituted by few nodes present low complexity; therefore, repeatable behaviours that can be parameterized by indexes with low variability can conceivably lead to more reliable normative datasets. Accordingly, we focused on a cortical relay part of a simple circuit, which presents highly repeatable activation not affected by the subject's attention (Allison et al. 1980; Garcia-Larrea et al. 1991; Rossini et al. 1989). This makes our investigation suitable for future studies in aging and clinical contexts, where subject compliance could be limited. The hand region within S1 is also particularly suitable for non-invasive electrophysiological investigation due to its placement in proximity to the scalp. In particular, area 3b of S1 is well sensed by magnetoencephalography (MEG, Del Gratta et al. 2001), since its pyramidal cell columns are tangential to the scalp (Geyer et al. 1999; Wall et al. 1986). The experimental procedure to identify S1 cortical patches involves simple median nerve stimulation, a passive condition that requires subjects' minimal cooperation.

Recent evidence indicates that networks devoted to specific functional domains maintain typical functional properties in the resting state (Deco and Corbetta 2011), and these features have been suggested as useful for assessing the health of brain networks (Carter et al. 2010). Moreover, the advantage of investigating brain organization while the subjects are at rest emerges in studies involving patients, especially for the sensorimotor function. Prototypical examples are stroke patients: the resting state allows for the elimination of different task-related neural engagements (i.e., attention and monitoring in task planning and execution) that are hardly comparable between patients and controls or between paretic and non-paretic hands. Furthermore, activity evoked by nerve stimulations relates mainly to conduction velocity and node-to-node excitability in a single experimental condition, whereas resting state spectral features express an overall state of neuronal patches associated with their global ability to be engaged in any process they contribute to. In our experience, even when a condition such as stroke strongly impacts brain organization, in both acute and chronic phases, the resting state features are more sensitive to alteration and recovery than are evoked ones (Assenza et al. 2009; Tecchio et al. 2005, a; Oliviero et al. 2004; Rossini et al. 2001). In particular, spectral properties at rest provided new prognostic information absent in the subjects' responsiveness to external galvanic stimulation (Tecchio et al. 2007a, b, c, d).

While the present investigation was focused on resting state features of S1 neuronal activity, we obtained its anatomical position, as well as the latency and strength in response to contralateral median nerve stimulation. A wide literature describes the changes with age of somatosensory evoked activity investigated by EEG and MEG and reports that nerve conduction velocity decreases and strength increases with age (Hume et al. 1982; Shaw 1992; Huttunen et al. 1999; Tanosaki et al. 1999; Zappasodi et al.

2006). The reliability of the identification procedure will additionally be strengthened by the consistency of the evidence presented in this study.

The functional source separation method (FSS) (Tecchio et al. 2007a, b, c, d), which is analogous to the independent component analysis (ICA), models the set of MEG signals as a linear combination of several sources. FSS differs from ICA in that FSS identifies a single source at a time, building a contrast function for that source that exploits some 'fingerprint' information typical of the neuronal pool to be identified. FSS was used to identify hemispheric cortical sources devoted to hand representation within S1 (FS_S1, (Barbati et al. 2006; Porcaro et al. 2008, 2009), using as fingerprint information the earliest response to the median nerve stimulation that is known to be generated within S1 area 3b. Once the sources are identified, FSS allows us to investigate them in other experimental conditions. Here, S1 cortical patches were tracked while the subject was at rest.

Methods

Subjects

Twenty-six healthy, right-handed volunteers participated in the study (15 males, mean age 51.2 ± 23.5 years, range 24–95; 11 females, mean age 43.2 ± 26.4 years, range 24–91). Handedness was evaluated by means of the Edinburgh Handedness test; the average score across subjects was 83.7 ± 18.2. All subjects had normal neurological exams and did not receive any pharmacological treatment at the time of recording. All subjects above 55 years of age underwent brain magnetic resonance examinations to exclude major atrophies or vascular damage. The approval of the 'S. Giovanni Calibita' Hospital's Ethical Committee was obtained, and subjects signed informed consent forms.

MEG Recordings

A 28-channel system (16 internal axial gradiometers and 11 peripheral magnetometers, 1 magnetometer devoted to noise-reduction) covering a total scalp area of about 180 cm^2 inside a magnetically shielded room (Vacuumschmelze GMBH) was used to record brain magnetic activity in the rolandic region of each hemisphere by the sensors centered on C3 and C4 of the international 10–20 electroencephalographic system. Subjects were comfortably lying in a bed, with eyes open to reduce the effects of occipital rest activity in the studied rolandic region. Rest activity was recorded for 3 min in each hemisphere. MEG activity was also collected during the electrical stimulation of the contralateral median nerve at the wrist (Fig. 1) via surface disks (cathode proximal). The stimulation involved .2 ms duration electric pulses and 631 ms of inter-stimulus interval, with the stimulus intensity set just above threshold, inducing a painless thumb twitch, which was visually

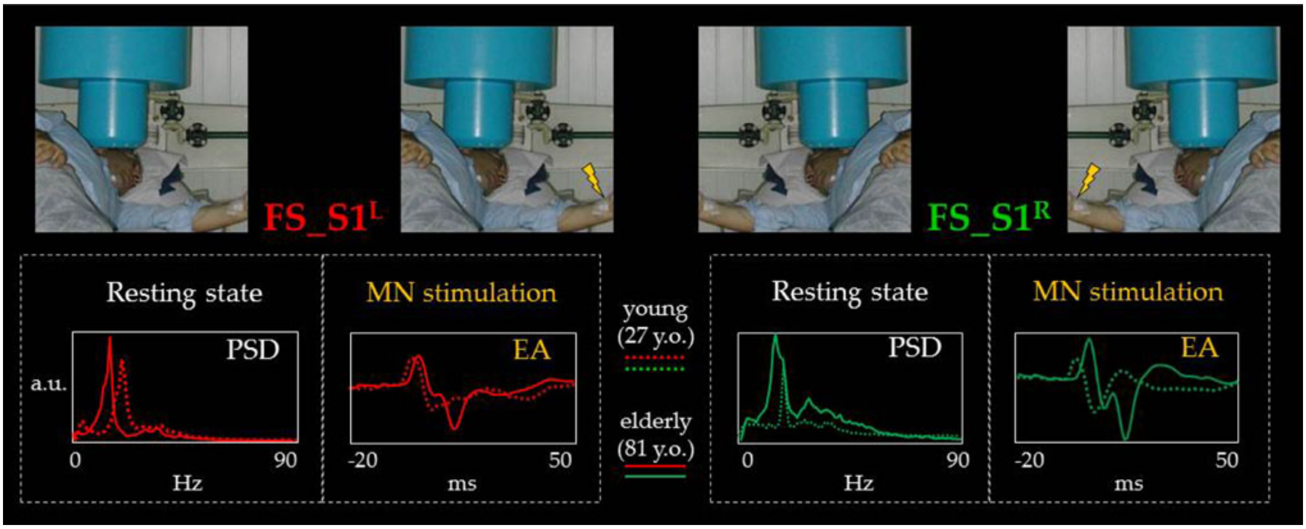

Fig. 1 Experimental setup and FS_S1 variables. Experimental setting and the primary somatosensory functional source (FS_S1) variables in cases representative of age-dependence. *Top* subject position during MEG recordings at rest and during median nerve electrical stimulation at wrist (*yellow arrow*). *Bottom* superimposed traces of one young (*dashed line*) and one elderly (*continuous line*) subjects of left (FS_S1^L, red) and right (FS_S1^R, *green*) sources: power spectral density (PSD) function of resting state activity in the [1,90] Hz frequency range (*left plot*) and averaged activity on the nerve stimulation (EA) in the time window [−20, 50] ms. The scales (arbitrary units, a.u.) are fixed at [0, 15] for resting state PSD and at [−20, 20] for EA. The following changes in the elderly with respect to the young subjects are evident: slower alpha activity (bilaterally), higher total power in the right hemisphere, right power becoming higher than left and higher evoked activity in both hemispheres (Color figure online)

monitored and stimulus position adjusted if required by the experimenter throughout the stimulation. Left and right median nerves were separately stimulated, totaling about 200 artifact-free trials.

MEG signals were sampled at 1 kHz after proper analogue conditioning (band-pass filtering between .48 and 250 Hz) and processed off-line. The entire recording procedure lasted about half an hour, including the investigation of left and right rolandic regions.

Data Analysis

Functional Source Separation (FSS)

After visual data inspection to exclude trials with saturated signal, the FSS procedure was applied. Detailed in previous articles (Barbati et al. 2006; Tecchio et al. 2007a, b, c, d), FSS can be briefly explained as assuming the recorded data **x** as a linear mix of a set of sources **s** via a mixing matrix **A** (Cichocki 2002). The contrast function (F) of FSS includes a functional requirement (R) chosen on the basis of the particular neuronal pool under study (Barbati et al. 2006; Tecchio et al. 2007a, b, c, d) summed with proper weight (λ) to the statistical constraint typical of ICA (J), resulting in: $F = J + \lambda R$ (Porcaro et al. 2008).

Since we are interested in the primary somatosensory area devoted to hand control (FS_S1), FSS maximized the responsiveness to the median nerve at the latency known to correspond to the stimulus' arrival in S1 (Allison et al. 1980; Hari and Kaukoranta 1985). Formally, the $R(FS\_S1)$ term of the contrast function is:

$$R(FS\_S1) = \sum_{t_{20}-\Delta_1 t_{20}}^{t_{20}+\Delta_2 t_{20}} |EA(FS\_S1, t)| - \sum_{10}^{15} |EA(FS\_S1, t)|$$

with the evoked activity (EA) computed by averaging the source (FS_S1) signal epochs triggered on the median nerve stimulus at the wrist ($t = 0$); t_{20} is the time point with the maximum magnetic field value on the maximal original MEG channel around 20 ms after the stimulus' arrival (found in the [16–24] ms window); $\Delta_1 t_{20}$ ($\Delta_2 t_{20}$) time point corresponds to a field amplitude of 50 % of the maximal value, by definition in t_{20}, before (after) t_{20}; the baseline was computed in the no-response time interval from 10 to 15 ms. Once the source that optimizes the contrast function F has been obtained, the estimated solution is multiplied by the Euclidean norm of its weight vector, allowing for amplitude comparisons among sources under the hypothesis of fixed depth.

The FSS algorithm was applied to MEG recordings in the left and right hemispheres during contra-lateral median nerve stimulation to identify time signal and field distribution of FS_S1^{L} and FS_S1^{R} neuronal pools. MEG channel weights, in turn, allowed position identification of the two sources by applying proper inverse problem algorithms.

FS_S1 Rest Activity

A semi-automatic artifact rejection procedure (Barbati et al. 2004) was applied to MEG data recorded in a resting state to minimize the contribution of non-cerebral sources (such as the heart, eyes, muscles) which can critically exceed the brain signal in absence of stimulus-synchronized average noise-reduction. Thereafter, artifact-free rest MEG data were multiplied by the inverse of the demixing matrix of FS_S1 ($W_{FS\_S1} = 1/A_{FS\_S1}$) to obtain activity in the resting state.

The power spectral density (PSD) was then estimated for FS_S1 at rest using the Welch procedure (2,048 ms duration, Hanning window, 60 % overlap). The total power was obtained by integrating the PSD in the 1–90 Hz frequency range. Spectral properties were investigated in the classical frequency bands (IFSECN 1974) defined on the basis of individual alpha frequency (IAF: the frequency with maximal PSD in the [6, 13.5] Hz, (Klimesch 1999)). In detail: *delta* [1, 3.5] Hz; *theta* [4, IAF−2.5] Hz; *alpha* [IAF−2, IAF+2] Hz; *low beta* [IAF+2.5, 23] Hz; *high beta* [23.5, 33] Hz; *low gamma* [33.5, 48] Hz; *high gamma* [52, 90] Hz. Personalized frequency bands were preferred in the present approach because IAF is affected by age (Wang and Busse 1969; Zappasodi et al. 2006). Moreover, our pilot study aims at grounding future data collections in diseases also impacting IAF (Tecchio et al. 2006a, b; Tecchio et al. 2005; for a review see Klimesch 1999).

In addition to left (L) and right (R) hemispheric values of FS_S1 spectral powers and responsiveness to nerve stimulation, we considered their interhemispheric symmetry (symmetry index, SI, (van Putten 2007)) by calculating:

$$SI_y = 1 - \frac{x^R - x^L}{x^R + x^L}$$

where y refers to resting state activity (RSA) or responsiveness to median nerve stimulation (mnR see below), and $\chi^{R(L)}$ indicates the right (left) FS_S1 band power for SI_{RSA} and the ECD strength at about 20 ms for SI_{mnR}. For the SI_{RSA} in the whole spectrum, the mean SI_{RSA} for the seven bands was calculated. With respect to van Putten definition, we maintained the information about the direction of the interhemispheric asymmetry (R>L or L>R).

FS_S1 Spectral Entropy

The spectral entropy was calculated according to Inouye and colleagues (Inouye et al. 1991):FS_S1spectralentropy

$$= -\sum_{f=2}^{45} r\mathrm{PSD}(f)\log_2 r\mathrm{PSD}(f)$$

The FS_S1 spectral entropy gives a quantitative measurement of the frequency content spread of somatosensory area neuronal activity. It is sensitive to the level of 'wideness' or 'compactness' of the signal spectrum: a sinusoid characterized by a single spectral component has minimal entropy; at the opposite side, white noise with constant PSD in the whole band has maximal entropy. Therefore, the more concentrated the FS_S1 oscillatory activity is around a specific frequency, the lower the entropy is. In our case, since the frequency resolution was .49 Hz, the entropy values ranged between 4.882 (one peak 99 % above the basal level) and 6.182 (flat spectrum).

FS_S1 Responsiveness to Sensory Stimulation

The average of the FS_S1 signal synchronized with the median nerve stimuli at the wrist was calculated after digital band-pass filtering in the [1, 150] Hz range.

The proper inverse problem-solving algorithm was applied to the FS_S1 magnetic field distribution obtained by retro-projecting the source over the channels. The equivalent current dipole (ECD) inside an homogeneously conducting sphere was chosen as the widely accepted model for the source of interest. The localization results were accepted if and only if their explained variance was above 90 %. Source position was expressed in the coordinate system defined as follows: the y axis runs through the midpoint between the subject's pre-auricular points and his/her nasion; the z axis is the line perpendicular to the y axis that passes through the vertex; the x axis is defined consequently in a Cartesian space (i.e., it is the line perpendicular to both y and z axes that runs through their intersection). x is positive on the head's right side, y toward nasion, and z toward the vertex. To have an estimate of consistency of the FS_S1 position, we also calculated the ECD position from original averaged channels with maximal explained variance around t_{20}(M20). The latency and ECD strength of the earliest evoked component were measured. In addition to hemispheric values, the interhemispheric strength imbalance of the responsiveness to peripheral stimulation was evaluated by the above defined SI $\mathrm{SI}_{\mathrm{mnR}}$.

Statistical Analysis

Logarithmic transformations were applied when appropriate (according to the Shapiro–Wilk statistic) to better fit the Gaussian distribution.

A bivariate analysis was conducted to estimate the dependency of FS_S1 resting state features on age by calculating parametric Pearson's coefficients and relative significances.

While our study focuses on S1 resting state features, we also examined the FS_S1 source position and its latency and strength in response to median nerve stimulation.

Finally, we took into account that resting state powers depend on the synchronization levels of the generating neuronal pools, which in turn depend on the responsiveness to intra-cortical horizontal structures and to the projections from other connected neuronal areas. We considered the strength of earliest recruitment of S1 neuronal pool in response to the median nerve stimulation (FS_S1 ECD strength at around 20 ms) as an indicator of the S1 responsiveness to connected network nodes. Thus, to evaluate the prevalence of the local horizontal networks or other neuronal area projections at the origin of synchronization modulation contributing to power modulation with age, we studied the relationship between spectral features and ECD strength at 20 ms. Partial correlations controlling for age were calculated to eliminate possible associations between resting state power and responsiveness to median nerve stimulation generated by the dependence on age of one or both variables.

Results

FS_S1 functional sources were obtained in all 26 subjects bilaterally.

FS_S1 Activity in Resting State in Dependence on Age

At least 180 s artifact-free epochs at rest were obtained, so that spectral estimates (IAF, PSD, spectral entropy) were calculated on a number of epochs set to 180 across subjects.

IAF inversely correlated with age (Pearson's $r = -.615$, $p = .001$ in the left and $r = -.554$, $p = .003$ in the right hemisphere).

Right hemispheric FS_S1 spectral power increased with age in delta, beta, and gamma bands, but only in low beta and high gamma band in the left hemisphere (Table 1; Fig. 2). The FS_S1 total power increased with age in the right hemisphere, while it did not change at all in the left (Table 1; Fig. 2).

Interhemispheric SI $\mathrm{SI}_{\mathrm{RSA}}$ decreased with age in delta, theta, alpha, and low beta bands (Table 1). Interestingly, alpha band $\mathrm{SI}_{\mathrm{RSA}}$ reduced with age, in the absence of either right or left FS_S1 alpha power dependence on age.

Left hemispheric FS_S1 spectral entropy increased with age (Pearson's $r = .435$, $p = .026$; range [4.883, 6.192], 5.817 ± .343), whereas the right values did not display any age-dependence (Pearson's $r = .238$, $p = .242$; range

Table 1 Correlation between age and FS_S1 spectral powers at rest

	Delta	Theta	Alpha	Low beta	High beta	Low gamma	High gamma	Total power
Left hemisphere	−.261	−.183	−.140	.398*	.312	.356	.461*	.090
	(.197)	(.371)	(.496)	(.049)	(.120)	(.074)	(.018)	(.661)
Right hemisphere	.418*	.183	.148	.607**	.618**	.431*	.476*	.433*
	(.034)	(.370)	(.471)	(.001)	(.001)	(.028)	(.014)	(.027)
$\mathrm{SI}_{\mathrm{RSA}}$	−.531**	−.397*	−.429*	−.421*	−.232	−.133	−.118	−.489*
	(.005)	(.045)	(.029)	(.036)	(.265)	(.517)	(.567)	(.015)

Pearson's correlations (uncorrected two-tailed significance) between Age and FS_S1 spectral powers in each frequency band and in the whole spectrum in left and right hemisphere and the interhemispheric asymmetry. Significance level at .01 and .05 are indicated respectively by two and one asterisks

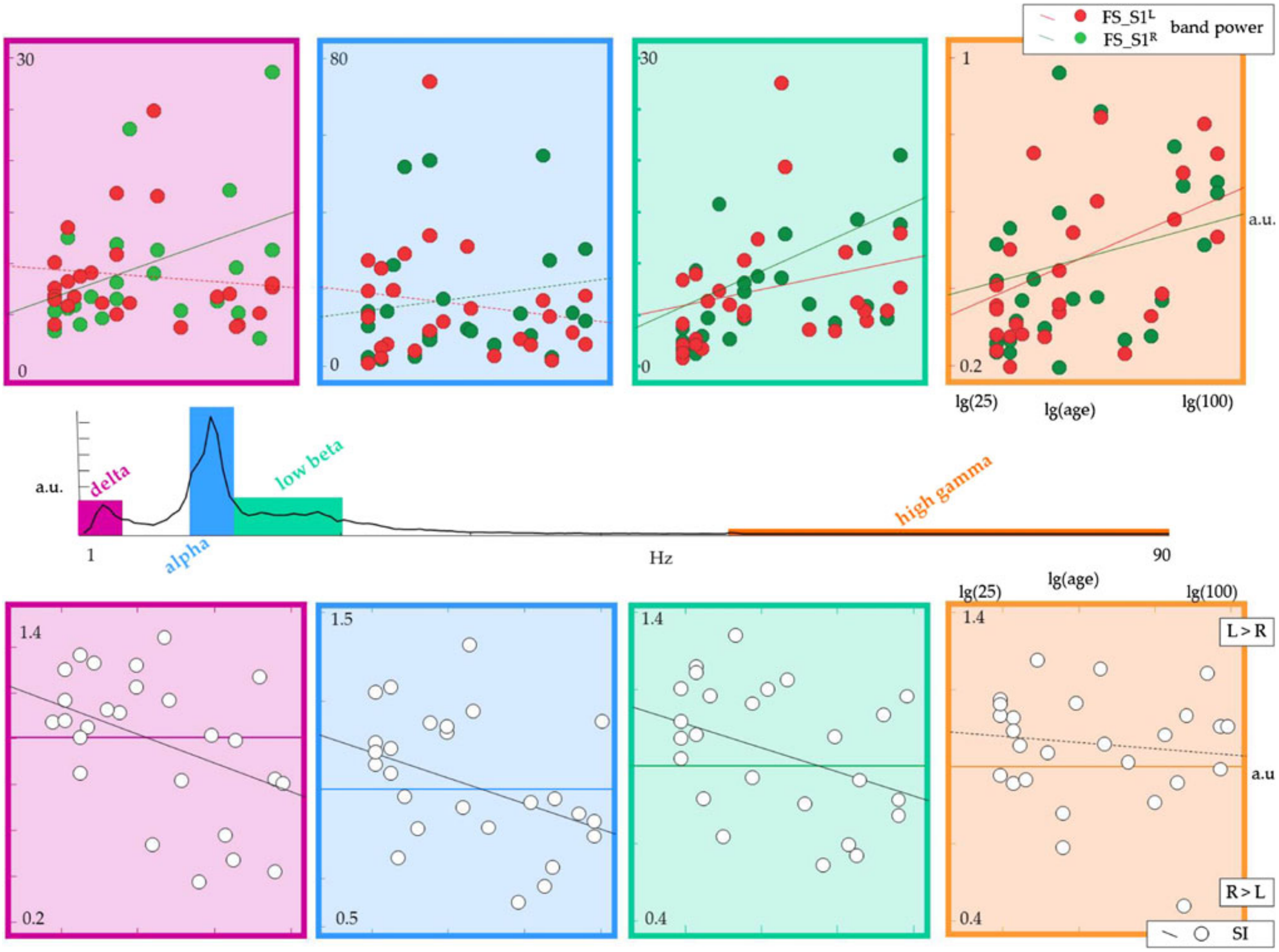

Fig. 2 Resting state FS_S1 spectral changes with age. Top delta (*pink*), alpha (*blue*), low beta (*green*) and high gamma (*orange*) band powers in the left (*green closed circles*) and right (*red closed circles*) hemisphere are presented in *scatter plot* with age, as representative of spectral power changes along the lifespan. Full (*dashed*) *lines* indicate significant (non-significant) correlations. Theta, high beta and low gamma bands are omitted since they display similar behaviors to respectively alpha, low beta and high gamma in both hemispheres and interhemispheric symmetry. *Bottom* the symmetry index (SI, *white closed circles*) is presented in *scatter plot* with age in the same band powers (*same color codes*). SI = 1 corresponds to symmetric values (*horizontal colored lines*), values above (*below*) 1 corresponding to left (L) higher (*lower*) than right (R) hemispheric band powers (Color figure online)

[5.269, 6.182], 5.840 ± .256). The different age-dependence of the two hemispheric S1 entropies was confirmed by the increase in the entropy SI with age (Pearson's $r = .405$, $p = .040$). It is noteworthy that the entropy SI did not display any association with hemispheric S1 powers (consistently $p > .200$), selectively increasing the S1

Table 2 FS_S1 position and responsiveness to median nerve stimulation

	Left hemisphere				Right hemisphere			
	x	**y**	**z**	**s**	**x**	**y**	**z**	**S**
FS_S1 ECD	−43.6 ± 13.8	8.5* ± 11.0	96.2 ± 7.2	21.4 ± 11.5	44.3 ± 10.2	14.6* ± 11.5	98.0 ± 9.0	18.8 ± 11.8
M20 ECD	−43.5 ± 14.7	8.7* ± 10.7	96.3 ± 6.9	21.9 ± 12.0	43.6 ± 10.7	13.9* ± 11.1	97.5 ± 9.5	19.6 ± 11.7

Mean ± SD of FS_S1 ECD positions (see text for coordinate system)

* Statistically significant interhemispheric differences

power's SI in the alpha band (partial correlation corrected for age, $r = .610$, $p = .002$).

FS_S1 Position and Responsiveness to Median Nerve Stimulation in Dependence on Age

The 3D coordinates of FS_S1 and M20 ECD positions depended on hemisphere [$F(1, 23) = 9.687$, $p = .005$], with more posterior position in the left than the right hemisphere (Table 2). Comparison between functional source and M20 ECD positions (by ANOVA with source (FS_S1 ECD, M20 ECD)) indicated no differences between them (source and interaction effects >.200). No dependence of FS_S1 position on age was found.

The earliest cortical response was bilaterally delayed with age increasing (Pearson's $r = .553$ and .559 $p = .003$ for left and right hemispheres, range [18, 24] ms and [17, 28] ms respectively).

FS_S1 ECD strength at earliest (around 20 ms) response to median nerve stimulation increased with age (Pearson's $r = .522$, $p = .006$ and .531 $p = .005$ for left and right hemispheres, total range [4.6–42.1] and [4.8–49.0] nA m). These increases were similar in the two hemispheres, as documented by SI_{mnR} not showing any dependence on age (Pearson's $r = .019$, $p = .927$; range [−.52, .39], mean −.069 ± .266).

Relationship Between FS_S1 Resting State Spectrum and Responsiveness to Median Nerve Stimulation

Resting state FS_S1 band powers did not display correlations with responsiveness to median nerve stimulation (FS_S1 strength at around 20 ms) in either the left or right hemisphere (Table 3 first and third rows; Fig. 3).

On the contrary, FS_S1 band power asymmetries (SI_{RSA}) displayed a definite correlation with interhemispheric imbalances of its responsiveness to median nerve stimulation (SI_{mnR}, Table 3 last row; Fig. 3). The effect was definitely due to the responsiveness increases in the right non-dominant hemisphere, as documented by complete absence of any correlation between left hemispheric responsiveness and resting state power asymmetries (FS_S1^L $strength_{20}$, Table 3 second row), while the right hemispheric responsiveness correlated with resting state power asymmetries in theta, alpha, and beta bands as well as in the whole spectrum (FS_S1^L $strength_{20}$, Table 3 fourth row; Fig. 3).

Discussion

We revealed age effects in the resting state primary somatosensory area devoted to hand control in healthy, right-handed people. Power increases with age were more evident in the right non-dominant hemisphere than in the left dominant one, but that was not the origin of interhemispheric imbalances emerging with age.

S1 Resting State Power Increased with Age (in Agreement with wp1)

The total power generated by a cortical area, revealed by extra-cerebral electrophysiological recordings, reflects the amount of synchronously firing neurons. Thus, higher total powers will be the consequence of the increase of three non-mutually exclusive factors: (1) the amount of active neurons; (2) their firing rate; (3) their synchronization level. Since it is known that approximately 10 % of all neocortical neurons are lost over the life span (Pakkenberg and Gundersen 1997) and no exceptions are reported for the S1 area in the literature, growth in the number of neurons can be excluded for the presently documented power increase with age. Thus, an activity enhancement of single neurons (firing rate), or wider regions of synchronous neurons, or higher inter-neuronal synchronization (both enhancing the overall synchronization level) can explain the power increase with age. According to the first hypothesis, our findings could reveal resting state 'deafferentation-like' phenomena secondary to age-related decrements of peripheral proprioceptive and tactile receptors, in large part accounting for a reduction of the sense of position of the distal body segments (Ferrell et al. 1992) and lower accuracy in a standard task scoring for the dexterity of the sense of touch (recognizing raised letters on the fingertip (Manning and Tremblay 2006)). Neuronal networks strongly depend on incoming signals, whose reduction generates a

Table 3 Correlation between FS_S1 resting state activity and responsiveness

		Resting state spectrum							
		Delta	Theta	Alpha	Low beta	High beta	Low gamma	High gamma	Total power
Responsiveness to median nerve stimulation	FS_S1^{L} strength$_{20}$	Power FS_S1^{L}							
		.374	.191	.143	.030	.239	.133	.122	.275
		(.065)	(.372)	(.505)	(.890)	(.261)	(.537)	(.561)	(.184)
		SI$_{RSA}$							
		.321	−.096	.042	−.008	−.101	−.097	−.008	−.062
		(.118)	(.662)	(.841)	(.973)	(.646)	(.660)	(.968)	(.779)
	FS_S1^{R} strength$_{20}$	Power FS_S1^{R}							
		.376	.283	.296	.171	.417*	.257	.126	.346
		(.064)	(.180)	(.160)	(.425)	(.043)	(.225)	(.550)	(.090)
		SI$_{RSA}$							
		−.394	−.558**	−.597**	−.604**	−.512*	−.411	−.206	−.634**
		(.051)	(.006)	(.002)	(.002)	(.012)	(.051)	(.322)	(.001)
	SI$_{mnR}$	Power FS_S1^{L}							
		.363	.412	.146	.295	.223	.128	.049	.323
		(.082)	(.045)	(.495)	(.161)	(.296)	(.551)	(.821)	(.124)
		Power FS_S1^{R}							
		−.314	−.081	−.098	−.054	−.084	−.097	.002	−.116
		(.135)	(.706)	(.649)	(.803)	(.697)	(.653)	(.994)	(.591)
		SI$_{RSA}$							
		.580**	.544**	.423*	.607**	.380	.292	.031	.551**
		(.004)	(.007)	(.044)	(.002)	(.074)	(.176)	(.889)	(.006)

Pearson's partial correlations (uncorrected two-tailed significance) corrected for Age between FS_S1 spectral powers (power) and symmetry index (SI) in each frequency band and in the whole spectrum in left and right hemisphere and the strength of the ECD at earliest component in response to the contralateral median nerve stimulation in the left (ECD$_{20}$ FS_S1^{L}) and right (ECD$_{20}$ FS_S1^{R}) hemisphere. Significance level at .01 and .05 are indicated respectively by two and one asterisks

chain of effects, typically associated with higher spontaneous firing of intact nodes after deafferentation (Nita et al. 2006). The third non-mutually exclusive cause can be a neuronal synchrony increase as a consequence of an altered activity of intra-cortical inhibitory and excitatory structures or responsiveness to other neuronal areas. In fact, extra-cerebral electrophysiological recordings are mainly sensitive to cortical pyramidal neurons' synchronized activity, which is the result of intrinsic properties and the responsiveness to incoming signals from all projecting neuronal networks. Balanced excitation and inhibition provokes sustained periodic alternations between distinct oscillatory states of a network of pyramidal cells and inhibitory interneurons (Frohlich et al. 2006). The S1 responsiveness to glutamate transmitted thalamic input was enhanced with increasing age, as shown by the FS_S1 ECD strength increase with age (Tecchio et al. 2011), but this excitability augmentation was not associated with power increase, suggesting that the activity of local inter-neuronal more than recurrent thalamocortical networks impacts the resting state S1 power increase. Other authors observed that age-related over-activations in primary sensorimotor cortical areas were not related to functional demands (Riecker et al. 2006), thus suggesting an intrinsic change in neuronal activity properties rather than compensating mechanisms in sustaining proper recruitments against neurobiological changes with age. Biological aging and chronological age are characterized by evident alteration of GABAergic transmission, which is less efficacious in the elderly compared to young humans and animals (Clark et al. 2011; Stanley et al. 2011; Pinto et al. 2010). Among the effects of local horizontal networks on power increase with age, a further role of excitatory inter-neurons can be hypothesized as gamma band activity, which we documented to be associated with local excitatory inter-neuronal activity (Tecchio et al. 2007a, b, c, d), incremented bilaterally with age (in agreement with wp2). In favor of local excitatory network imbalances with advancing age, in primary somatosensory areas of animal models the receptive fields showed severe expansion selectively for hindpaw representation with minor changes for forepaw (David-Jurgens et al. 2008). These age-related alterations were suggested to be composed of plastic-adaptive alterations in response to modified use and degenerative changes developing with age (David-Jurgens et al. 2008).

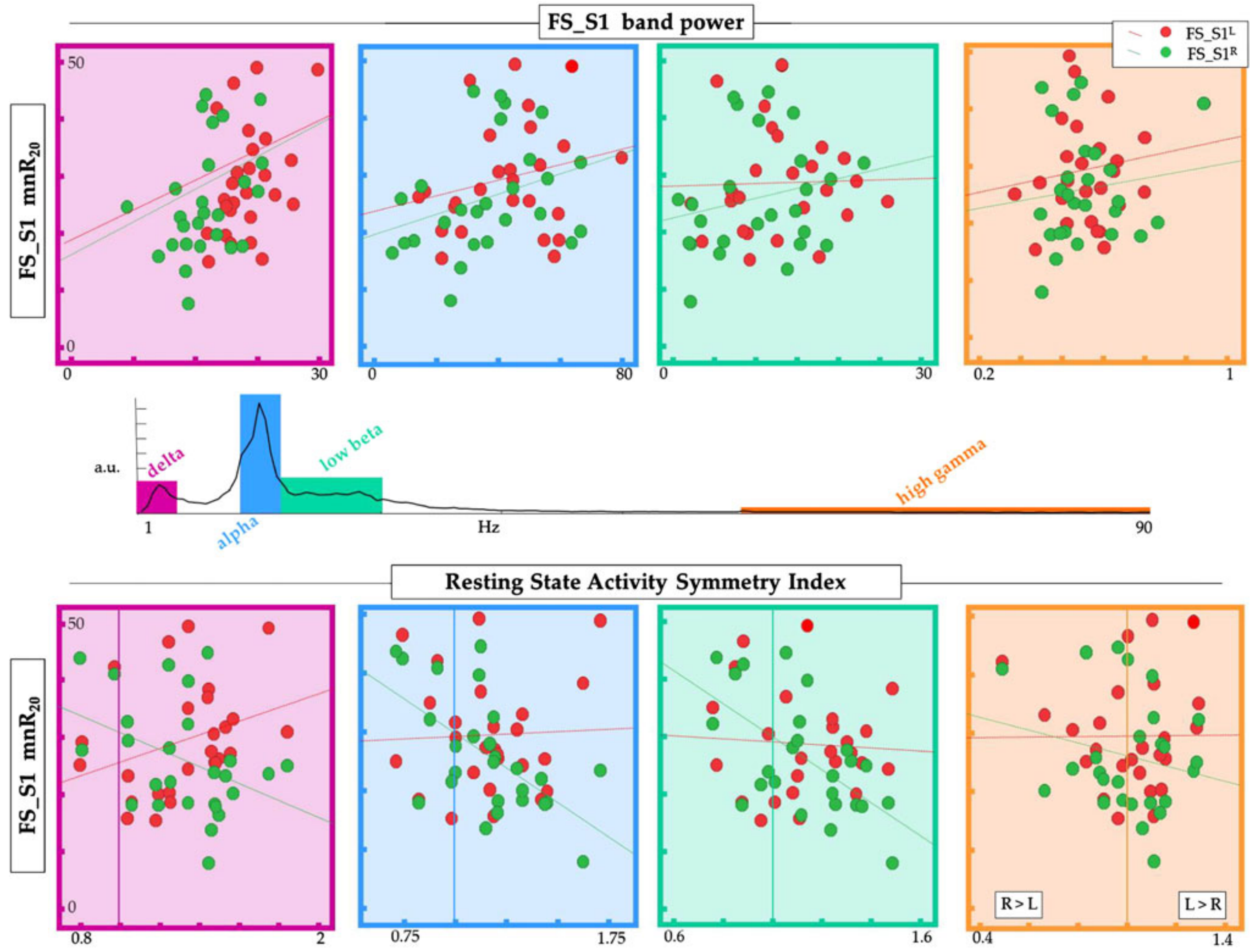

Fig. 3 FS_S1 resting state activity and responsiveness. By a similar schema as in Fig. 2, FS_S1 hemispheric band powers and Symmetry indices are presented in *scatter plot* with the strength of the FS_S1 ECD of the earliest response component (around 20 ms) to median nerve stimulation (FS_S1 ECD strength$_{20}$). All values are corrected for the dependence on age. Full (*dashed*) lines indicate significant (non-significant) partial correlations. Theta band is omitted since it does not display any dependence on age; high beta and low gamma are omitted since display the same behavior as low beta and high gamma respectively in both hemispheres. *Bottom* the symmetry index (SI, *white closed circles*) in *scatter plot* representation with age in the same band powers (*same color codes*). SI = 1 corresponds to symmetric values (*horizontal colored lines*), values above (*below*) 1 corresponding to left (L) higher (*lower*) than right (R) hemispheric band powers

No variation with age of resting state beta (and gamma) band activity was evidenced by Babiloni et al. (2006), probably because the MEG technique is more sensitive to high frequency activities than is the EEG. A second cause of the present study sensitivity to resting state beta and gamma bands' power increases with age can be that those authors studied EEG activity across large cortical areas while we are here focusing on specific neuronal pools devoted to hand control. In fact, it is well known that oscillatory activities are synchronized on smaller regions at higher rather than lower frequencies (Crone et al. 1998a vs. b; Demandt et al. 2012). Similarly, the observed reduction of parieto–occipital alpha activity with age (Babiloni et al. 2006) is hardly in contrast with our documented absence of alpha band activity change with age in either left or right S1. It is in fact conceivable that a single estimate of overall left and right post-central areas heavily sensitive to occipital activity is substantially incomparable to a selective measure of specific neuronal pools within S1.

Changes with age of beta band activity was previously evidenced both during development (Gaetz et al. 2010; Wilson et al. 2010) and senescence (Sailer et al. 2000) as modulated by sensorimotor tasks. Furthermore, rolandic sensorimotor oscillatory activity in resting state was bilaterally reduced selectively in beta band in the acute phase after a middle cerebral artery territory monohemispheric ischemic stroke (Tecchio et al. 2005). Here, for the first time, the oscillatory activity of primary cortical patches devoted to hand perception displayed bilaterally a power increase with age in low beta band (IAF+2.5, 23) in resting state in healthy people. Furthermore, in this frequency range, the interhemispheric asymmetries (SI) of the S1 responsiveness and its resting state power were most strongly associated. This seems to underline a special role of low beta band activity in the impairment of transcallosal projections efficacy (see the last part of the next section).

S1 Resting State Interhemispheric Unbalances Emerging with Age

We found that interhemispheric asymmetries of resting state powers of primary somatosensory hand areas emerged with age originating from different mechanism rather than emerging because of odd variations of S1 power in one hemisphere with respect to the other. Specifically, the SI decreased with age in alpha and theta bands while hemispheric band powers did not depend on age in these bands ($p > .200$ consistently). This finding leads us to hypothesize that healthy aging introduces novel mechanisms unbalancing the homologous S1 areas' interplay typical of younger ages, independent of the phenomena discussed above that impact local neuronal pool synchronization levels more in the right than in the left hemisphere. The disjunction of these two phenomena (asymmetry of hemispheric S1 power increases and interhemispheric asymmetry increase) is definitely supported by the 'dissociation' between hemispheric values and symmetry indices when studied with respect to dependence on S1 responsiveness to peripheral stimulation. While no association at all appeared with either left or right S1 hemispheric power, a selective increase in the right S1 response to thalamus projection corresponded to a reduction in interhemispheric S1 power symmetry. This finding was not related to any wp, underlining that this was a new unexpected age-related phenomenon.

Analogously to the spectral power, interhemispheric asymmetry can originate from three non-mutually exclusive factors, or imbalances in S1 hemispheric neurons in terms of: (1) number, (2) firing rate, and (3) synchronization levels. In addition to local power, a direct effect of asymmetries of transcallosal projections' efficacy (dominant S1 to non-dominant S1 projection and vice versa) can also provoke interhemispheric asymmetry.

We can exclude as a main role the first factor. No interhemispheric asymmetry occurred with age in the S1 pyramidal neurons' excitability to peripheral stimulation (scored by FS_S1 ECD strength at 20 ms). In fact, both left and right S1 showed a responsiveness increase with age, but no signs of imbalances emerged with age ($\mathrm{SI}_{\mathrm{mnR}}$ completely independent of age), thus making implausible an asymmetric reduction in the number of neurons.

The idea that S1 spontaneous firing rates vary with age in a different way in the two hemispheres is suggested by the spectral entropy asymmetry increase with age and the different age-dependence of specific bands in the two hemispheres: while beta and gamma bands increase bilaterally, S1 oscillatory activity increased in delta to alpha bands in the right hemisphere with no variation (with reductions not reaching statistical significance) in the left.

A key to understand the novel phenomenon at the origin of interhemispheric asymmetry of S1 oscillatory activities emerging with age can be the right responsiveness increases associated with resting state activity asymmetry increases once age-dependences are eliminated. In fact, the enhanced responsiveness of the right S1 to the projection from other connected network nodes paired with the interhemispheric resting state power imbalances suggests that stronger thalamocortical circuit responsiveness in the right non-dominant hemisphere produces a kind of functional disconnection with the left dominant one.

Inter-hemispheric balance between homologous cortical control areas plays a crucial functional role. In particular, transcranial magnetic stimulation (TMS, Sale and Semmler 2005; Salerno and Georgesco 1996) can precisely assess interdependences between homologous primary motor areas, indirectly measured by an ipsilateral silent period or more directly by interhemispheric paired-pulse motor evoked potential modulations, and it revealed that older adults have signs of less efficacious contralateral inhibition compared to younger adults (McGregor et al. 2011; Talelli et al. 2008). Interhemispheric inhibition phenomena were asymmetric, with the dominant left hemisphere inhibiting the non-dominant right more than the other way around (Netz et al. 1995; van den Berg et al. 2011). In a resting state, the age-dependent efficacy of local inhibitory structures, which are the target of dominance-dependent transcallosal fiber projections, can be a further substrate of the interhemispheric imbalances we documented in old subjects. Furthermore, local inhibitory networks can suffer from impairment of the physiological input from primary somatosensory regions of the contralateral hemisphere. This phenomenon of altered transcallosal projections efficacy is supported by the imbalance between the two hemispheres, revealed in our data by the interhemispheric asymmetry that appeared in the elderly people in contrast with the symmetric condition in younger ages.

Right Hemisphere 'Getting Old' More than the Left (in Agreement with wp3)

Age effects were definitely more evident in the non-dominant right hemisphere than in the left dominant hemisphere. More severe right hemispheric alterations with age were also found by a functional magnetic resonance (fMRI) study of movement-related cerebral activation (Ward et al. 2008). This can be an effect of the general rule that the more often a neuronal network is used, the more resilient to damaging phenomena it is. Cognitive reserve is a crucial protective factor in brain aging as well as in neurodegenerative diseases and dementia (for review see Nithianantharajah and Hannan 2009). Specifically, lifestyle habits, especially physical activity, influence both the risk of developing Alzheimer's disease and the path of cognitive decline (Arab and Sabbagh 2010; Radak et al. 2010; Buckner 2004). In fact, regular physical activity increases the endurance of cells and tissues to oxidative stress, vascularization, energy metabolism, and neurotrophin synthesis, all important in neurogenesis, memory improvement, and brain plasticity (Nithianantharajah and Hannan 2006). Furthermore, exercise has been suggested to ameliorate aging-related decline in humans (McGregor et al. 2011). In our case, dominant hemisphere sensorimotor networks, accounting for more frequent and finer tasks, might be more resistant to 'aging attacks'. In particular, recent evidence has showed that increased physical activity may play a role in the decrease of aging-related losses of physiological inhibition exerted on the primary motor cortex from the homologous area (McGregor et al. 2011).

Individual Alpha Activity Slowing with Age (in Agreement with wp4)

In agreement with previous findings (Wang and Busse 1969; Babiloni et al. 2006; Zappasodi et al. 2006), S1 area's alpha rhythm slowed down with age.

S1 Position More Posterior in the Left than in the Right Hemisphere

Despite the great variability in the configuration of the central sulcus, not only among different subjects but also between the two hemispheres of individuals (White et al. 1997), recent non-invasive investigations carried out with advanced technologies and analysis algorithms revealed a slightly but consistently more medial, posterior, and inferior localization of the hand area in the left dominant primary sensory area than in the right non-dominant one (Boakye et al. 2000; Jung et al. 2008; Zappasodi et al. 2006; present data). There are two hypotheses for this finding. First, the whole central sulcus lies posteriorly in the left dominant hemisphere, but no indications are present in this direction from literature investigating structural brain properties in relation to the central sulcus position (Del Gratta et al. 2002; Korvenoja et al. 2006; Stoeckel et al. 2007) or in relation to individual handedness and hand dexterity (White et al. 1997). The second hypothesis concerns the interhemispheric asymmetries of the topographical distribution of the hand representation along the Ω-region (Pizzella et al. 1999). In particular, wider sections of the Ω-region in the left compared to the right hemisphere can explain this posterior shift of the barycenter position (Rossini and Tecchio 2008).

These spatial FS_S1 features, in addition to latency and strength properties of the responsiveness to somatosensory stimulation, have strengthened the reliability of the previously demonstrated ability of FSS to identify hand S1 sources (Barbati et al. 2006; Porcaro et al. 2008).

Potential of the Present Procedure for Clinical Studies

The protocols used in this study can be easily implemented in a clinical setting, providing background for future age-related studies. FSS analysis can assess resting state power properties, eliminating possible generator position changes, thus eliminating atrophy-related deepening of cerebral sources in an age-related context.

Our procedure, including the experimental protocol with recordings at rest and during passive median nerve stimulation and the analysis tool, is typically feasible in most patients and can be especially useful in subjects with pathologies involving the sensorimotor system. In particular, since the functional sources are identified by exploiting their specific response to the hand stimulation (Tecchio et al. 2007a, b, c, d), they can be suitably investigated even when sensorimotor area displacements occur due to plastic reorganization phenomena, as can happen in middle cerebral artery stroke (Tecchio et al. 2006a, b, 2007a, b, c, d). Complementary to the description of cortical arrangement, behavioral scores are relevant for understanding the functional significance of brain organization changes with age.

Of note regarding the inverse problem-solving, changes with increasing age in the conductivity properties of meninges, cerebrospinal fluid, skull, and scalp minimally affect the MEG magnetic field, which can be considered transparent to the discontinuities between these tissues, since their magnetic permeability is almost constant and equal to the magnetic permeability of a vacuum (Del Gratta et al. 2001).

Conclusion

The present non-invasive electrophysiological procedure, requiring a passive experimental setup equipped with FSS algorithm, provides a sensitive measure of resting state activity of primary somatosensory areas, even in elderly people and in patients with minimal compliance. This study showed that the primary cortical representation of the hand displays more severe signs of aging in the right hemisphere than in the left. An interhemispheric asymmetry emerged in elderly subjects, specifically in the alpha band, conceivably caused by the imbalances in bilateral spontaneous firing rates and in local inhibitory-excitatory networks and by an increase in the right thalamocortical circuit excitability.

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