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Cortical gamma-synchrony measured with magnetoencephalography is a marker of clinical status and predicts clinical outcome in stroke survivors

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ABSTRACT

Background: The outcome of stroke survivors is difficult to anticipate. While the extent of the anatomical brain lesion is only poorly correlated with the prognosis, functional measures of cortical synchrony, brain networks and cortical plasticity seem to be good predictors of clinical recovery. In this field, gamma (>30 Hz) cortical synchrony is an ideal marker of brain function, as it plays a crucial role for the integration of information, it is an indirect marker of Glutamate/GABA balance and it directly estimates the reserve of parvalbulin-positive neurons, key players in synaptic plasticity. In this study we measured gamma synchronization driven by external auditory stimulation with magnetoencephalography and tested whether it was predictive of the clinical outcome in stroke survivors undergoing intensive rehabilitation in a tertiary rehabilitation center.

Material and methods: Eleven stroke survivors undergoing intensive rehabilitation were prospectively recruited. Gamma synchrony was measured non-invasively within one month from stroke onset with magnetoencephalography, both at rest and during entrainment with external 40 Hz amplitude modulated binaural sounds. Lesion location and volume were quantitatively assessed through a high-resolution anatomical MRI. Barthel index (BI) and Functional Independence Measure (FIM) scales were measured at the beginning and at the end of the admission to the rehabilitation unit.

Results: The spatial distribution of cortical gamma synchrony was altered, and the physiological right hemispheric dominance observed in healthy controls was attenuated or lost. Entrained gamma synchronization (but not resting state gamma synchrony) showed a very high correlation with the clinical status at both admission and discharge (both BI and FIM). Neither clinical status nor gamma synchrony showed a correlation with lesion volume.

Conclusions: Cortical gamma synchrony related to auditory entrainment can be reliably measured in stroke patients. Gamma synchrony is strongly associated with the clinical outcome of stroke survivors undergoing rehabilitation.

1. Introduction

Every year more than 3 million stroke survivors are left chronically disabled (Dobkin, 2005). The long-term outcome of stroke patients is difficult to anticipate (Di Pino et al., 2014; Stinear, 2010). While the size of the anatomical lesion does not seem to be strongly predictive of the recovery (Chen et al., 2000; Pantano et al., 1996), its effects on cortical synchronization (brain ability to generate synchronous oscillations) and connectivity (pattern of relationship across brain signals generated in different brain areas) seem to have a better prognostic value (Quinlan et al., 2015). Indeed, long-term disability exhibits a remarkable relation with the disruption of brain synchronization and networks (Silasi and Murphy, 2014), and functional recovery is related to restoration of quasi-normal connectivity patterns (Pellegrino et al., 2012; Siegel et al., 2018).

In this proof-of-principle study we tested the specific hypothesis that cortical gamma (>30 Hz) synchronization can be predictive of post-rehabilitation outcome in stroke survivors. The formulation of this hypothesis is strongly supported, as: (a) gamma activity is a key player in a wide spectrum of brain functions and is significantly impaired in a number of different neuro-psychiatric conditions, ranging from schizophrenia to stroke to epilepsy (Kwon et al., 1999; Larsen et al., 2017;

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Pellegrino et al., 2012; von Ellenrieder et al., 2016); (b) gamma synchrony is an indirect marker of glutamate/GABA balance, which is relevant to stroke recovery (Bartos et al., 2007; Brenner et al., 2009; Di Pino et al., 2014; Javitt et al., 2008); (c) gamma synchronization is a marker of functional reserve of parvalbulin-positive neurons, key players in synaptic plasticity (Donato et al., 2013; Galarreta and Hestrin, 2002).

Therefore, our primary goal was: (a) to test the relationship between gamma synchronization and clinical status; (b) to test the relationship between gamma synchronization and clinical outcome; (c) to investigate whether the study of gamma synchrony could be potentially translated to a clinical setting, if a relationship were found.

While cortical connectivity can be measured with several different techniques, ranging from anatomical MRI (structural connectivity) to functional MRI (functional connectivity) to PET, neuronal synchrony can only be measured with neurophysiology techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG). EEG and MEG are non-invasive techniques measuring the oscillations of excitatory and inhibitory post-synaptic potentials of large and synchronized parcels of cortical surface, with a very high temporal resolution and an acceptable spatial resolution (Pellegrino et al., 2018a, 2016). In this study we opted for applying magnetoencephalography, which owns better spatial resolution than EEG and ensures more comfort for the patient, as it does not require the montage of electrodes on the scalp. We studied both the level of gamma synchrony at rest and the ability of cerebral cortex to become synchronized in gamma band when pushed to the maximum with an external cortical entrainment (Brenner et al., 2009; Thut et al., 2011). The latter provided an estimation of the synchronization 'reserve', was obtained via non-invasive auditory stimulation at regular gamma frequency of 40Hz, and might be more sensitive to cortical dysfunction than resting state gamma synchrony (Pellegrino et al., 2019a). When listening to gamma sounds, the phase of cortical oscillations in gamma band become progressively aligned with the sound (auditory entrainment or Auditory Steady State Responses – ASSR). Gamma entrainment is right hemisphere dominant and covers a very large cortical region including bilateral auditory cortices, insulae, sensory-motor regions. Virtually, when pushing gamma synchronization with auditory stimulation the entire cortical surface exhibits some degree of gamma synchrony increase (Pellegrino et al. 2019a,b).

2. Materials and methods

2.1. Participants and experimental design

This is a prospective study performed at IRCCS San Camillo Hospital in Venice, Italy. The IRCCS San Camillo is a tertiary rehabilitation center, largely devoted to advanced treatment of stroke survivors. The study was proposed to all stroke survivors admitted at the IRCCS San Camillo hospital between January 2017 and February 2018 who fulfilled the following inclusion/exclusion criteria. Inclusion: (1) age between 18 and 80 years; (2) ischaemic or haemorrhagic stroke in subacute phase, within one month from stroke onset (Adeyemo et al., 2012; Bahn et al., 1996; Di Pino et al., 2014); (3) residual ability to express an informed consent. Exclusion: (1) other neurological comorbidity; (2) hearing defects; (3) CNS acting medications; (4) previous stroke or previous severe brain lesion. The study was performed in agreement with the Helsinki declaration and approved by the Ethic Committee of Venice. All patients gave a written informed consent prior to participation. Eleven patients were recruited (Table 1) and underwent a MEG scan and a high resolution 3T anatomical MRI in the subacute phase and within about one month from stroke onset. Clinical status was evaluated at the beginning and at the end of the rehabilitation. All patients underwent a standard intensive neurorehabilitation protocol, as per clinical need. No changes in the rehabilitation procedure were made because of this study. To assess the patients' degree of disability

Table. 1
Demographic and clinical features. AH = Affected Hemisphere; Days from onset = time between stroke and neuroimaging study in days; BI = Barthel Index; FIM = Functional Independence Measure.

ID	Sex	Age	AH	Vascular district	Cortical/Subcortical	Ischaemic/Hemorrhagic	Days from onset	BI admission	BI discharge	FIM Mot Admission	FIM Mot Discharge	FIM Tot Admission	FIM Tot Discharge
PA01	F	57	R	MCA	Subcortical	Ischaemic	9	60	100	51	85	86	120
PA02	M	74	R	MCA	Subcortical	Ischaemic	12	15	70	23	77	42	107
PA03	M	35	L	MCA	Subcortical	Ischaemic	7	10	85	17	68	39	95
PA04	M	65	R	MCA	Cortical/Subcortical	Ischaemic	18	10	60	16	57	29	82
PA05	F	74	L	MCA	Subcortical	Ischaemic	12	20	65	28	54	57	82
PA06	M	66	L	MCA	Subcortical	Haemorrhagic	32	10	90	18	69	33	94
PA07	M	64	L	ACA	Cortical/Subcortical	Ischaemic	13	25	80	25	75	51	103
PA08	M	71	R	MCA	Subcortical	Haemorrhagic	27	5	75	17	60	39	91
PA09	M	61	R	MCA	Cortical/Subcortical	Ischaemic	21	5	50	17	30	41	77
PA10	M	74	R	PCA	Cortical/Subcortical	Ischaemic	12	45	95	45	84	76	117
PA11	M	72	L	MCA	Subcortical	Ischaemic	10	30	80	32	63	63	94

we used two measures: the Barthel Index (BI) and the Functional Independence Measure (FIM). The BI was developed in 1955 as a simple index of independence useful in scoring disability. It is a 10-item instrument measuring disability in terms of a person's level of functional independence in personal activities of daily living (van der Putten et al., 1999). The BI is considered a reliable disability scale for stroke patients. The items can be divided into a group that is related to self-care (feeding, grooming, bathing, dressing, bowel and bladder care, and toilet use) and a group related to mobility (ambulation, transfers, and stair climbing). The maximal score is 100, if 5-point increments are used, indicating that the patient is fully independent in physical functioning. The lowest score is 0, representing a totally dependent bedridden state. The FIM is an 18-item instrument measuring a person's level of disability in terms of burden of care. It was developed specifically to measure functional outcomes of rehabilitation. Each item is rated from 1 (requiring total assistance) to 7 (completely independent). Three independent FIM scores can be generated by summing item scores: a total score (FIM Total: 18 items), a motor score (FIM Mot: 13 items), and a cognitive score (FIM cognitive: 5 items) (van der Putten et al., 1999). A summary of the experimental design is described in the cartoon of Fig. 1.

2.2. Anatomical MRI: acquisition and analysis

Each patient underwent a high-resolution anatomical MRI scan. The MRI scan was performed with a Philips 3T Ingenia CX (Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil. The following sequences were acquired: (a) 3-dimensional sagittal T1-weighted-3D-TFE scan (TR = 10 ms; TE = 4.9 ms; FOV = 250 × 250 × 240 mm; acquisition matrix 312 × 312; acquisition voxel = 0.8 mm, isotropic; flip angle = 8°); (b) 3-dimensional sagittal T2-weighted-3D-FLAIR scan (TR = 4800ms; TE = 278 ms; IR delay = 1650 ms FOV = 250 × 250 × 183 mm; acquisition matrix 312 × 312; acquisition voxel = 1,2 mm, isotropic; flip angle = 40°); (c) 3-dimensional sagittal T2-weighted-3D-TSE scan (TR = 3500 ms; TE = 240 ms; IR delay = 1650 ms FOV = 250 × 262 × 174 mm; acquisition matrix 252 × 263; acquisition voxel = 1 mm, isotropic; flip angle = 90°). Brain segmentation and cortical reconstruction for MEG head model were performed with FreeSurfer (version 6.00), which is freely available at http://surfer.nmr.mgh.harvard.edu/ (Dale et al., 1999; Fischl et al., 1999). Mapping between participant and the Talairach standard atlas was performed using a non-rigid registration on the inflated surface. The end-result is the parcellation of the human

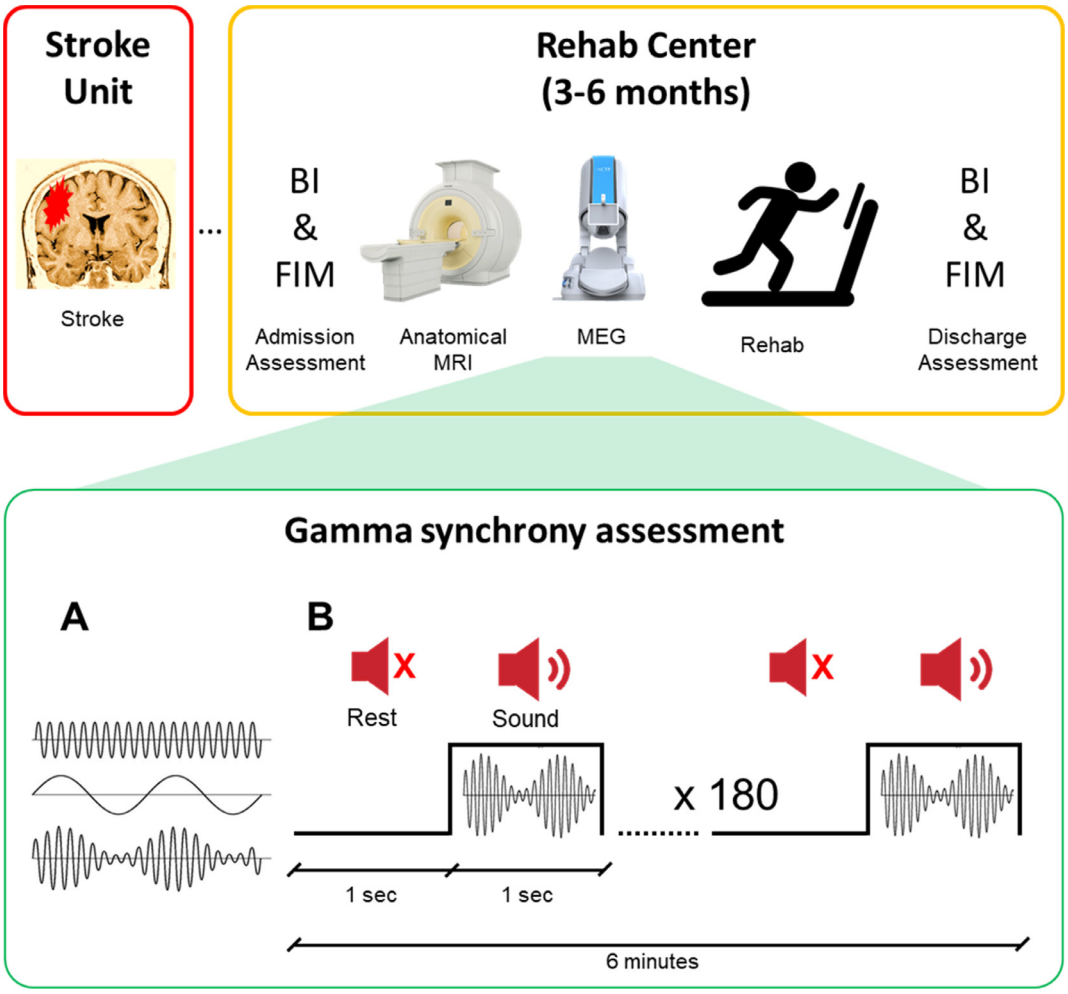

Fig. 1. Experimental design. Upper panel. After first line treatment in stroke unit (red box), patients were transferred to the tertiary rehabilitation center (orange box). Here, length of inpatient stay for neuroriabilitation varied between 3 to 6 months. Clinical outcome scales (BI and FIM) were administered at admission and at discharge. MRI and MEG were performed within 1 month from stoke onset. The MEG recording was aimed at investigating resting state and auditory entrained gamma synchrony (green box). Green box, Panel A. Gamma entrainment was obtained delivering binaurally a 40 Hz amplitude modulated tone (lower line), generated with the following parameters: Carrier Frequency = 1000 Hz (upper line), Amplitude Modulating Frequency = 40Hz (middle line). Green box, Panel B. This sound was delivered binaurally with an intensity of 85 dB. The duration of each sound was 1 s and it was interleaved with 1 s rest (silence) for the investigation of resting state gamma synchrony. The sequence 1 s 40 Hz auditory sound – 1 s rest was repeated 180 times, for an overall 6-min duration of the MEG task. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cortex into 34 cortical regions of interest in each hemisphere (Desikan et al., 2006).

2.3. Lesion mapping and volume assessment

A semi-automatic FSL-based pipeline starting from 3D FLAIR and T1w3D images was used for lesion delineation (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) (Smith et al., 2004). This process included: (a) brain tissue extraction using BET2 FSL tool on 3D FLAIR; (b) intra-subjects FLAIR-T3w3d linear registering using FLIRT FSL tools; (c) FLAIR/3D T1 to MNI registration and normalization using two step FLIRT/FNIRT FSL-tools; (d) T1w3D and FLAIR intensity normalization using fslmaths; (e) k-kluster-based multichannel segmentation on 3D-FLAIR and T1w3D segmenting 5 classes (CSF, GM, WM, WMH, lesion); (f) hemisphere constrained lesion map in the MNI space using fslmaths-FSL tool. After this process, the lesion mask was visually inspected by an expert (LW) in axial orientation overlaid on both T1w3d and FLAIR images. After lesion margins refinement, volumes were calculated using MRIcron software (http://www.mricro.com/mricron/).

2.4. MEG data acquisition and auditory stimulation paradigm

MEG data were acquired in a quiet shielded room at the MEGLab of the IRCCS San Camillo Hospital in Venice (https://sites.google.com/site/meglabsc/). MEG scans were performed with a CTF-MEG (MISL, Vancouver, Canada) equipped with 275 gradiometers. Eye movements and EKG were recorded with dedicated electrodes. Data were sampled at 1200Hz. The position of patient's head with respect to the scanner was continuously monitored thanks to localization coils placed on three anatomical landmarks (nasion, left and right preauricular points) and tracked by the CTF Continuous Head Localization System. All scans were performed with patients lying down, with eyes closed. Patients were instructed to relax and not to pay attention to the auditory stimuli.

Auditory stimulation for gamma entrainment was delivered binaurally through earplugs connected to the CTF system via plastic tubes. The sound pressure level was set to 85 dB and measured at the earplugs prior to every MEG scan. All patients could properly hear the sound.

The MEG scan lasted 6 min during which 180 trains of gamma auditory stimulation lasting 1 s were interleaved with 180 segments of resting activity. Gamma auditory stimulation was performed with 40Hz amplitude-modulated tones. The tones were designed as follows: carrier frequency = 1000 Hz; amplitude modulation = 100%; fade-in and fade-out = 6 ms; normalization to prevent clipping. The above-mentioned parameters have been already successfully tested (Pellegrino et al., 2019b). Sounds were generated in MATLAB (The Mathworks) with the following equation:

$$A = \sin(2\pi f_c t)*(1 + m* \cos(2\pi f_m t))$$

where A is the amplitude, f_c is the carrier frequency, m is the modulation depth, f_m is the frequency of modulation, set to 40 Hz and t is the vector of time points for 1 s of stimulus, at a sampling rate of 44.100 Hz. The instructions and MATLAB code to generate the sounds can be found online (https://sites.google.com/site/meglabsc/utilities). The auditory stimuli were presented with PsychoPy, a freely available toolbox (http://www.psychopy.org/) (Peirce, 2008, 2007). The exact onset of each sound was detected through an analogic channel registering the actual sound delivered in the MEG environment.

2.5. MEG data preprocessing

All analyses were performed in MATLAB version 2017b, with dedicated code and the freely available Brainstorm toolbox (Tadel et al., 2011). Data cleaning included: third-order spatial gradient noise cancellation, Signal Space-Separation (SSP) to remove EKG and eye movement artifacts (Taulu and Simola, 2006; Tesche et al., 1995), high-pass filter = 1 Hz, low-pass filter = 70 Hz, notch filter = 50 Hz. Furthermore, continuous data was segmented into three-second-long epochs, ranging from −1.5 s to +1.5 s, being 0 s the onset of each sound. All epochs were visually inspected and those affected by artifacts were rejected.

2.6. MEG forward model and inverse solution

The cortical surface ("mid" cortical layer, equidistant from white/grey matter and pia) was imported into the brainstorm toolbox and downsampled to 8000 vertices. Skull surface was reconstructed from the original MRI file in brainstorm. The co-registration between anatomical (MRI) and functional (MEG) data was made possible by the continuous localization of the head position in the dewar. Only head movement smaller than 0.5 cm were tolerated (Pellegrino et al., 2016). A personalized Boundary Element Method (BEM) model was estimated with the implementation offered by the freely available OpenMEEG toolbox (Gramfort et al., 2010). The inverse problem was solved with the whitened and depth-weighted linear L2-minimum norm estimate approach, with the dipole orientation constrained to be normal to the cortical surface (Hämäläinen and Ilmoniemi, 1994). Noise covariance was computed from about 6 s of resting state recording acquired at the beginning of every MEG scan.

2.7. Gamma synchronization

In order to estimate gamma synchronization, we ran a time-frequency decomposition of the data reconstructed at cortical level. We applied a Morlet wavelet transformation centered around the frequency of interest (40 Hz), considering a range of frequency between 39 Hz and 41 Hz. TF decomposition was applied for each epoch and its entire duration, for each vertex of the cortical surface. Gamma synchronization was estimated as Inter-Trial Phase Consistency (ITPC) at 40 Hz and computed as follows:

$$ITPC = \left| n^{-1} \sum_{r=1}^{n} e^{ik_{tr}} \right|$$

where n is the number of trials, e^{ik} is the complex polar representation of phase angle k on trial r, at the timepoint t. It is a measure of phase consistency estimated across epochs. The phase of the signal was extracted from the wavelet coefficients. ITPC can take values between 0 and 1, with higher values meaning high synchronization (Makeig et al., 2002). ITPC was estimated for the entire epoch, so to capture both resting state gamma synchronization (−1 s to 0) and auditory entrained gamma synchronization (0–1 s). The main focus was on the auditory driven synchronization, which is a more reliable marker of the ability of cortical surface to synchronize in gamma band (Pellegrino et al., 2019b). For the study of resting state synchronization, ITPC was averaged over the −1 to 0 s time window. For the study of auditory driven synchronization, ITPC was z-normalized considering the −0.5 and −0.2 s time window as baseline (Pfurtscheller and Lopes da Silva, 1999). Then, data was averaged over the 0.4 s–0.7 s time window. This measure of synchronization indeed provides an estimate of the synchronizing effect of an external stimulus in comparison to the baseline synchronization pattern (Pellegrino et al., 2019b). The measure of synchronization was then extracted from the primary auditory cortex (A1) corresponding to the banks of superior temporal sulcus where the auditory gamma stimulation is known to produce the maximum effect. This region was identified based on the individual Desikan–Killiany atlas reconstructed by Freesurfer (Desikan et al., 2006).

2.8. Strategies for translation to clinical setting

The procedures described so far require the application of advanced technology and are not necessarily suitable in an average clinical setting. Once characterized the relationship between the A1 auditory

driven gamma synchronization and clinical scores, we explored whether a simplified approach would still be unveiling the same pattern of correlation. We acted on two different aspects of data analysis: (a) we considered the entire affected and unaffected hemispheres (AH and UH, respectively), and (b) we computed data power at 40 Hz instead than ITPC. The first point would avoid the need of solving complex forward and inverse problems which are necessary for the proper identification of A1. The second point would allow an easier estimation of gamma synchronization, as power spectral analysis is currently available in any EEG/MEG commercial software. 40 Hz power was estimated from the Morlet transformation, as time-frequency magnitude at 40 Hz, averaged across epochs, so to keep both evoked and induced responses. As previously described for ITPC, this measure was z-normalized over the baseline (-0.5 and -0.2 s), before being averaged in the 0.4–0.7 s time window. 40 Hz power is indeed an indirect measure of cortical synchronization, although less sensitive than ITPC (Larsen et al. 2017; Pellegrino et al. 2019b).

2.9. Statistical analysis

Data distribution was checked by means of the Kolmogorov–Smirnov test. Differences of synchronization between cortical regions and conditions were tested by means of two-tailed paired sample t-tests. The relationship between the level of synchronization and disability (BI and FIM) at the beginning and at the end of the rehabilitation program was estimated by means of Pearson's correlations. Alpha inflation due to multiple comparisons was controlled according to Bonferroni's procedure. Statistical analysis was performed in MATLAB (Mathworks) environment and with the software IBM SPSS Statistics (Ver. 24).

3. Results

No patients reported side effects related to the procedures. All patients reported a significant and remarkable clinical improvement post-rehabilitation, as appreciated by both BI and FIM.

3.1. Gamma synchronization

Synchronization data could be reliably extracted at subject level (Fig. 2 for an example). The study of auditory driven gamma synchronization of the primary auditory cortex (banks of superior temporal sulcus) did not show a physiologic right hemisphere dominance ($t = 1.121$, $df = 10$, $p = 0.288$). It conversely showed a significantly lower synchronization for the affected hemisphere (either right or left, depending on the patient) as compared to the unaffected hemisphere ($t = -3.280$, $df = 10$, $p = 0.016$). No significant gamma differences were found between the left and right hemispheres and the affected and unaffected hemispheres at rest ($p > 0.500$ consistently) (Fig. 2).

3.2. Relationship between lesion volume, gamma synchronization and clinical scales

There was no significant correlation between the lesion volume and the clinical status at both admission and discharge ($p > 0.200$ consistently). Auditory induced gamma synchrony of the primary auditory cortex of the affected hemisphere showed a strong and significant correlation with both the clinical scores at admission and at discharge (BI admission: $R(11) = 0.924$, $p < 0.001$; BI discharge $R = 0.711$, $p = 0.028$; FIM Motor Admission $R = 0.910$, $p < 0.001$; FIM Motor Discharge $R = 0.699$, $p = 0.034$; FIM Tot Admission $R = 0.888$, $p < 0.001$; FIM Tot Discharge $R = 0.836$, $p = 0.002$ – Fig. 4). This correlation pattern resisted when partialling out the effect of the lesion volume. The relationship between auditory induced gamma synchrony of the primary cortex of the unaffected hemisphere and clinical scores showed a similar pattern as for the affected hemisphere, but the statistical significance did not survive after correction for multiple comparisons ($p > 0.1$ consistently). No significant correlation was found between resting gamma synchrony and clinical scores on admission and/or discharge ($p > 0.05$ consistently).

3.3. Translation to clinical setting

Once characterized the strong and significant relationship between auditory driven gamma synchronization of the A1 of the affected hemisphere and clinical scores, we evaluated whether such correlation pattern would still be present when considering the synchronization over the entire affected and unaffected hemispheres (average of synchronization for all cortical parcels of the Desikan–Killiany atlas) and when considering 40 Hz power as indirect measure of cortical synchronization. This analysis showed that a simpler approach may still be able to appreciate a definite and significant relationship between auditory driven gamma synchronization and clinical scores. The results of this analysis are reported in Table 2. Note that significance levels are provided without Bonferroni correction for multiple comparisons, as this was an explorative analysis.

4. Discussion

The main finding of this study is that gamma synchrony measured in stroke survivors with magnetoencephalography is highly correlated with the clinical status at rehab admission and discharge. In the past decades several techniques (MRI-based, EEG-based and brain-stimulation based) have been tested as tool to predict the clinical outcome of stroke survivors, none of which have reached clinical application (Di Pino et al., 2014). The reasons for such disappointing results are diverse, but mostly depend on two factors: (a) some measures do work for specific groups of patients, but not for all, and (b) many measures are too difficult to be obtained (because of the experimental setting required or because of the data processing), and do not provide sufficiently accurate information for a clinical setting (Cramer, 2004; Di Pino et al., 2014; Gramigna et al., 2017; Rossini et al., 2007; Pellegrino et al., 2012; Tombini et al., 2012). This study does not solve the previously mentioned issues but has made a significant and successful attempt to tackle the problem with an innovative approach.

First of all, we investigated gamma synchronization, which correspond to the ability of the cerebral cortex to locally generate gamma activity in phase, a simple but fundamental mechanism by which cerebral cortex integrates information (Fries, 2009; Herrmann et al., 2010; Herrmann and Demiralp, 2005; Kwon et al., 1999; Tombini et al., 2009). The study of these cortical properties is relatively new in the field of stroke and rehabilitation, but has been extremely fertile in understanding other neuropsychiatric conditions such as – for instance – depression, Alzheimer's disease, schizoaffective bipolar disorder, and epilepsy (Başar et al., 2017; Fitzgerald and Watson, 2018; von Ellenrieder et al., 2016). The very few previous studies of gamma activity in the field of stroke recovery largely focused on connectivity across distant cortical regions (Pellegrino et al., 2012; Wu et al., 2011). Here, we purposely focused on synchrony and we did not limit the investigation to resting state data. We rather concentrated on the ability of the cerebral cortex to generate synchronous gamma activity on demand, when challenging the underlying mechanisms of generation with a 40 Hz external auditory pacemaker. In other words, we attempted to estimate the cortical reserve of gamma synchronization. This is very important, as driven (entrained) and resting state gamma synchrony depend on different neural mechanisms (Gandal et al., 2012) and are differently affected in neuropsychiatric conditions (Gandal et al., 2012; Hong et al., 2004; Winterer et al., 2004). Auditory driven gamma synchronization ultimately depends on several factors and especially on the functional reserve of inhibitory parvalbumin-positive GABA interneurons. The latter are located in the cortical layers 2 and 3 and are activated by glutamate transmission, so that NMDA blockage depresses

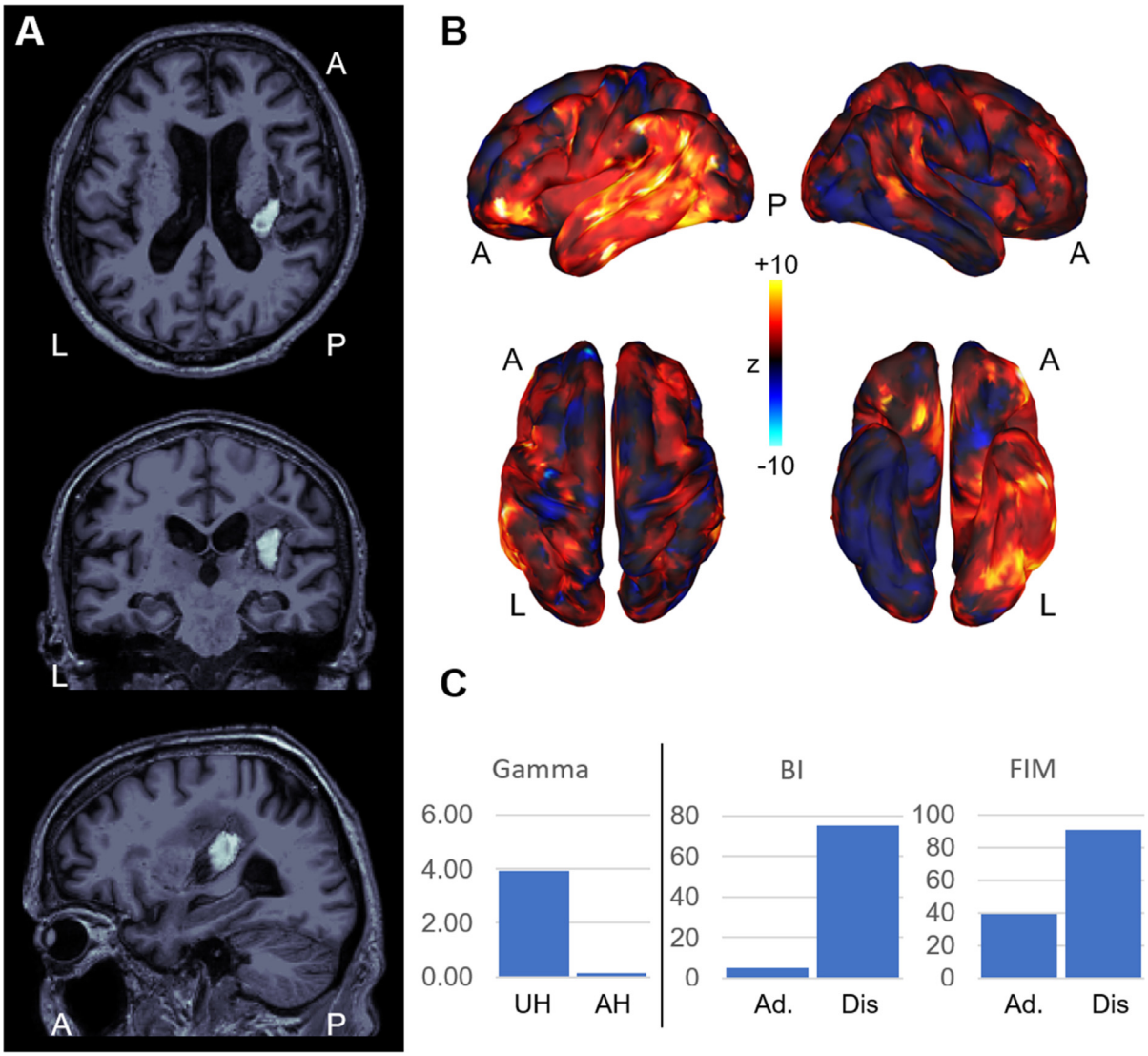

Fig. 2. Illustrative case – PA08. Panel A. T1 MRI showing the haemorrhagic stroke located in the right hemisphere. From top to bottom: axial, frontal and sagittal cut. A = Anterior; P = Posterior; L = Left. Panel B. Individual map [0.4 to 0.7 s] of auditory driven gamma synchronization expressed as ITPC z-values. From left top and clockwise: left, right, bottom and top views. Cortical surface has been inflated (50%) to improve visibility. Gamma synchronization did not show the physiologic right hemisphere dominance. It conversely showed a significantly lower synchronization for the right/affected hemisphere as compared to the left/unaffected hemisphere. A large portion of cortical surface still showed positive z-values denoting an increase in gamma synchronization related to auditory stimulation as compared to rest but notably less than in healthy subject for whom the entire cortical surface becomes synchronized (Pellegrino et al., 2019b)). Panel C. From left to right: A1 synchronization of the unaffected and affected hemisphere (UH and AH, respectively); BI and FIM on admission and discharge (Ad. and Dis).

their function and -in turn- the generation of synchronous gamma (Bartos et al., 2007; Brenner et al., 2009; Javitt and Sweet, 2015; Plourde et al., 1997; Traub et al., 2003, Traub et al., 1996; Whittington et al., 1995).

In line with our hypothesis, our results suggest that stroke survivors do not present a generic impairment of gamma synchronization, but a selective deficit of the reserve of gamma synchrony. In more details, the physiologic right hemispheric dominance is attenuated or lost and the degree of auditory driven gamma synchrony has a linear relationship with the clinical presentation and with the clinical outcome: the higher is the reserve of the affected hemisphere in generating gamma synchrony, the better is the clinical status and the clinical outcome achieved after intensive rehabilitation. The similar relationship between externally driven gamma synchrony and clinical status at both admission and discharge underlines that gamma synchrony accompanies the clinical status all along the rehabilitation process and might be one of the determinants of the therapeutic efficacy. It also underlines that the most important predictor of outcome remains the clinical presentation at stroke onset and at admission to the rehabilitation unit.

Although the focus of this study was on cortical gamma synchronization of spontaneous brain rhythms and induced by exposure to rhythmic sounds, it should be acknowledged that there is a significant body of literature addressing the relationship between stroke recovery and oscillations of brain networks and in other frequency bands than gamma, especially delta activity (Assenza et al., 2017, 2013; Assenza and Di Lazzaro, 2015; Zappasodi et al., 2017, 2014). For a complete and extensive review of this literature, the reader is referred to (Assenza et al., 2017).

To be noted, we did not find a correlation between lesion volume and clinical presentation. The possibility to predict clinical outcome by measuring lesion volume has been disputed since about two decades ago, when newer neuroimaging methods became widely available (Barber et al., 1998; Beaulieu et al., 1999; Löuvbld et al., 1997; Gerhard et al., 2012). Some studies suggest that acute lesion volume is an independent predictor of outcome at 3 months (Gerhard et al., 2012), whereas other studies do not support such link (Dromerick and

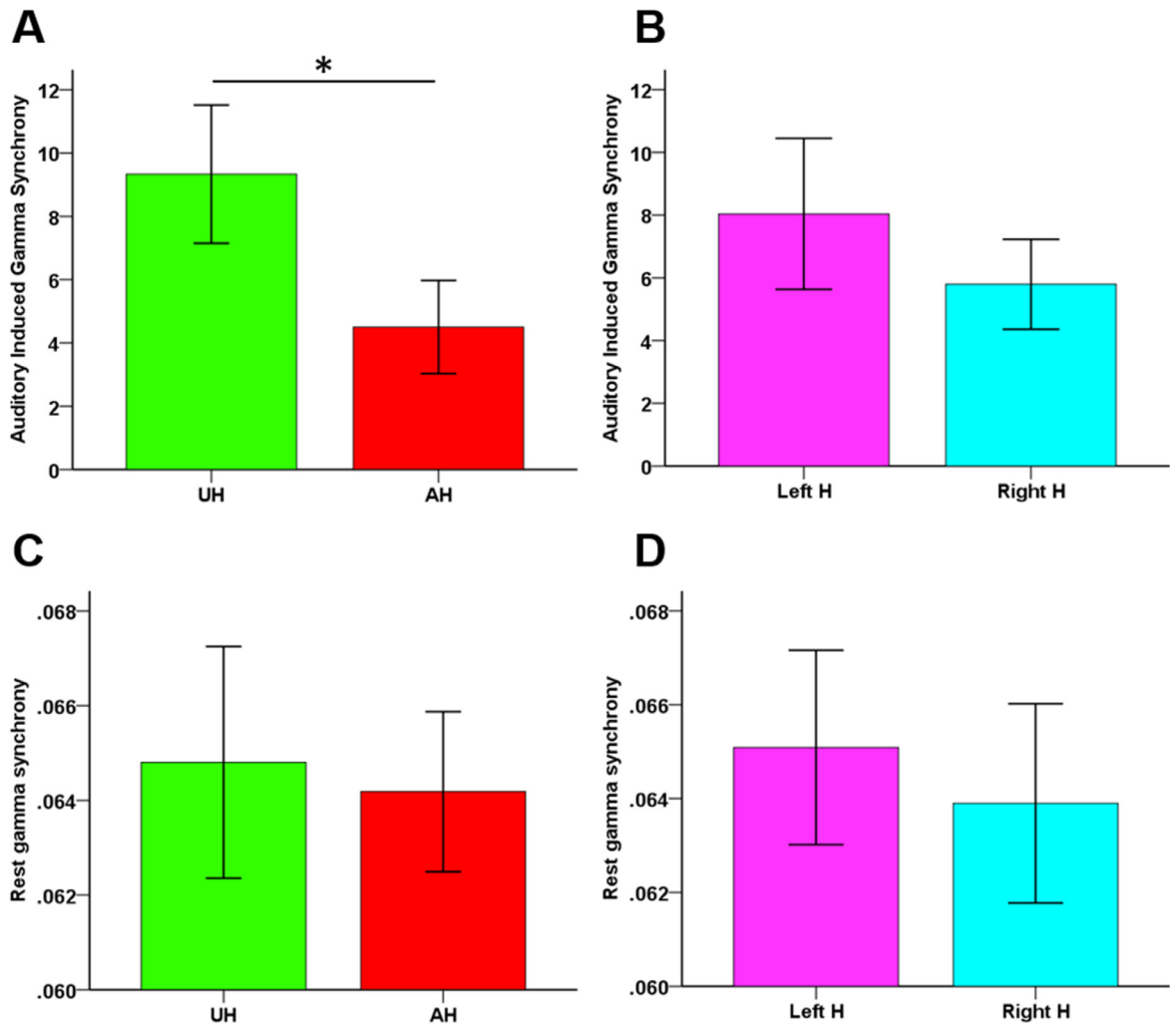

Fig. 3. Gamma synchronization in the primary auditory cortex (A1). Panel A. Auditory driven gamma synchronization in the primary auditory cortex was significantly higher for the unaffected hemisphere (UH) as compared to the affected hemisphere (AH). Gamma synchronization is expressed as z-score vs the resting state synchronization level (y axis). The physiologic right hemispheric (Right H) dominance was lost, with no significant difference between the auditory driven synchronization level of the left and right A1 (Panel B). No significant gamma synchronization differences between the affected and unaffected hemispheres and left and right hemisphere were found at rest (Panel C and D). To be noted, for Panel C and D the synchronization level is expressed as ITPC and was not normalized. * denotes $p < 0.05$.

Reding, 1995; Miyai et al., 1997; Pantano et al., 1996). More recently the interplay between lesion burden and outcome has been reconciled within the framework of the bimodal balance–recovery model, which links the structural reserve spared by the lesion to interhemispheric balancing and functional recovery (Di Pino et al., 2014). Within this framework, it is not surprising that functional measures (how the brain works) are rather more informative than anatomical ones (how the brain is). In our study we did not find a relationship between lesion volume and outcome, but only a strong link between clinical outcome and level of gamma entrainment. Our results are in fully agreement with a previous study of Di Lazzaro and colleagues which did not detect any relationship between lesion size and outcome, but demonstrated a link between alteration of GABA transmission -as measured by transcranial magnetic stimulation (TMS) short afferent inhibition (SAI)- and later recovery (Di Lazzaro et al., 2012). Although SAI and gamma synchrony might depend upon different cortical circuitry, both are influenced by the level of GABA transmission (Di Lazzaro et al., 2007; Di Lazzaro, Oliviero et al., 2005; Di Lazzaro, Pilato et al., 2005).

The results discussed so far were obtained focusing on the primary auditory cortex. The study of this restricted cortical region was made possible by the application of magnetoencephalography, a technique with excellent temporal resolution (for the study of gamma synchrony) and good spatial resolution (Chowdhury et al., 2018; Hedrich et al., 2017; Pellegrino et al., 2018a, 2016). The primary auditory cortex was the region of choice as cortical synchrony was driven by auditory stimulation. If the effects were to be restricted to this cortical parcel, the clinical translational potential of this study would be severely diminished. We attempted to test procedures for an easier application in the clinical setting. We especially verified that a similar –although weaker– correlation pattern was present when considering the synchronization over the entire affected hemisphere and applying a less robust measure of gamma synchronization. The study of the entire affected hemisphere would facilitate clinical application, as it would remarkably reduce the need of accurate forward and inverse model for source imaging. Such approach would be reasonable as the effect of 40Hz auditory stimulation in increasing cortical gamma synchrony is not restricted to the primary auditory cortex but virtually involves the entire cortical surface. We speculate that, now that the most sensitive mechanisms at play in stroke recovery have been identified, a more clinically friendly EEG recording with a far lower number of sensors might be applied (Pellegrino et al., 2018b, 2018c, Pellegrino et al.,2017). The study of gamma band in EEG may certainly be more challenging with respect to the management of data artifacts (Castellanos and Makarov, 2006; Makeig et al., 2004; Yuval-Greenberg et al., 2008), nonetheless

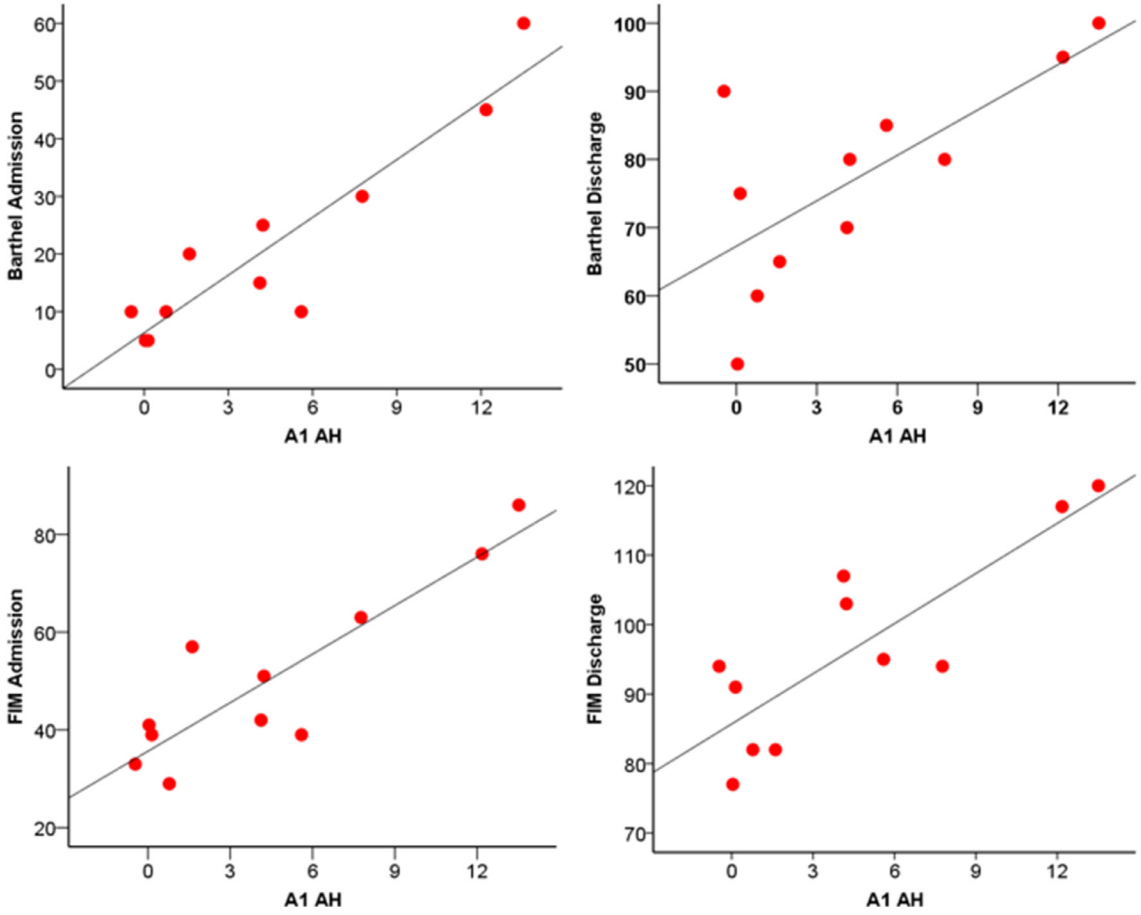

Fig. 4. Relationship between gamma synchrony and clinical scales. Auditory induced gamma synchronization of the primary auditory cortex (A1) of the affected hemisphere (AH) exhibited a strong and significant linear relationship with the clinical scores, both at admission and at discharge.

Table. 2. Explorative analysis of the relationship between the auditory induced gamma synchronization computed as 40 Hz z-normalized power over the affected hemisphere, unaffected hemisphere and entire cortex and clinical scores. Although both the correlation coefficients and the significant value are weaker when compared with the previously reported A1 analysis, a similar pattern of correlation is present, suggesting that an attempt could be made to simplify the analysis pipeline and tailor it to an average clinical setting. R values corresponding to $p < 0.05$ are highlighted with a *.

		BI Admission	BI Discharge	FIM Motor Admission	FIM Motor Discharge	FIM Tot Admission	FIM Tot Discharge
AH	R	.663*	.559	.715*	.559	.668*	.657*
	p	.026	.074	.013	.074	.025	.028
UH	R	.531	.450	.591	.462	.541	.563
	p	.093	.165	.056	.153	.085	.072
Whole	R	.582	.492	.639*	.500	.590	.600
Cortex	p	.060	.124	.034	.118	.056	.051

previous studies demonstrate that proper, yet simple, processing can achieve clean and informative data (Assenza et al., 2017, Assenza et al., 2013; Pellegrino et al., 2018c; Zappasodi et al., 2014). Furthermore, exposure to auditory gamma sounds increases the signal to noise ratio as compared to resting state, and allows proper EEG estimation, even with only 1 electrode (Larsen et al., 2017).

In the same line goes the study of power as surrogate of gamma synchronization. Previous studies certainly demonstrate that this measure is less sensitive and less specific as compared to ITPC, but would undoubtedly be of easier application in a peripheric clinical center (Larsen et al. 2017; Pellegrino et al. 2019b).

There are several limitations of this study that we need to acknowledge. Firstly, the limited sample size does not allow to draw definitive conclusions, and further studies are needed. The study was proposed to a much larger number of patients, who however denied participating in the study. Multiple reasons account for this, but especially many patients reported concerns about magnetoencephalography and the need to stay completely still in the scanner for a prolonged time. This limitation could be attenuated in the future by performing simpler EEG studies with the same paradigm. Secondly, the small sample size did not allow any stratification of the patients: it is in principle possible that – for instance- cortical vs subcortical, ischemic vs hemorrhagic patients have different synchronization patterns. Thirdly, data analysis with combined individual MRI and MEG, albeit relatively standardized and easy in a research center, remains largely operator dependent, time consuming and potentially challenging, especially with respect to MRI segmentation and mesh reconstruction. This limitation could be easily overcome in the future once confirmed that what ultimately matters is global cortical synchronization. In such scenario, an individual MRI would not be required (Giambattistelli et al., 2014). Fourthly, the function and marker tested in this study are rather specific for a cortical function. It should be however acknowledged that several factors are at play in stroke recovery (Cramer, 2008), including -for instance- genetic patterns and medications (Di Pino et al., 2016), and

they can affect neurophysiological and neuroimaging measures (Di Lazzaro et al., 2016; Landi et al., 2015). All patients were recruited and studied in subacute phase (9-32 days, Table1). According to a recent consensus, the time-period between 7 days and 3 months from stroke onset is rather homogeneous with respect to the mechanisms sustaining recovery and can be typically classified as Early Subacute phase (Bernhardt et al., 2017). It is also during this time window that patients typically experience the largest improvement (Di Pino et al., 2014). Therefore, we focused our attention on a rather short subacute time window, ranging between 1 week and 1 month. Further and larger studies are needed to account for the time of investigation variability and to better characterize the temporal dynamic of gamma synchrony and its association with clinical recovery

Conclusions

In conclusion, we demonstrated that in stroke survivors the study of gamma synchronization with magnetoencephalography is feasible, auditory driven gamma synchronization is impaired and measures of auditory induced gamma synchronization of the affected hemisphere significantly and strongly correlate with the clinical presentation and clinical outcome.

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CRediT authorship contribution statement

Giovanni Pellegrino: Conceptualization, Methodology, Formal analysis, Writing - original draft. **Giorgio Arcara:** Conceptualization, Methodology, Software, Writing - review & editing. **Anna Maria Cortese:** Resources, Data curation, Writing - review & editing, Project administration. **Luca Weis:** Methodology, Formal analysis, Writing - review & editing, Software. **Silvia Di Tomasso:** Data curation, Writing - review & editing, Project administration. **Gino Marioni:** Methodology, Writing - review & editing, Supervision. **Stefano Masiero:** Writing - review & editing, Supervision. **Francesco Piccione:** Conceptualization, Methodology, Writing - review & editing, Resources, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

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