Cortical movement-related high-gamma oscillations in healthy participants and stroke survivors

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1. Darstellung der Publikation

Introduction

High-gamma oscillations (60 – 90 Hz) emerge during movement in several brain regions, including the motor cortex and the basal ganglia. These oscillations have been shown to have a prokinetic role in the motor system, but their exact function remains unclear. In invasive cortical recordings, high-gamma oscillations have been related to different movement parameters like limb position, movement velocity and movement speed (Anderson et al., 2012; Hammer et al., 2016; Wang et al., 2017). While invasive recordings offer a high signal-to-noise ratio (SNR), which is important to be able to detect high-gamma oscillations, they are hard to come by and mostly performed in the context of brain surgeries in individuals with a neurological disease. Therefore, the number of participants in those studies is limited and there usually is no healthy control group. Magnetoencephalography (MEG) offers the opportunity to record oscillatory data non-invasively with a higher SNR for most sources compared to electroencephalography (Piastra et al., 2020). It is hence well-suited to investigate high-gamma oscillations in participants with impaired movement as well as in healthy participants.

Several studies have shown that transcranial alternating current stimulation (tACS) with oscillations in the high-gamma frequency range can amplify different aspects of motor performance and motor skill acquisition (Joundi et al., 2012; Nowak et al., 2017; Santarnecchi et al., 2017; Guerra et al., 2018; Sugata et al., 2018; Bologna et al., 2019; Spooner & Wilson, 2023). Further, a recent study by Akkad et al. (2021) showed that high-gamma oscillations coupled to the peak of a theta oscillation (theta-gamma phase-amplitude coupling (PAC)) increased motor skill acquisition, supporting the idea of the involvement of cross-frequency coupling in motor control.

As most studies regarding cortical high-gamma oscillations have been performed in healthy young participants, there is limited knowledge on cortical high-gamma oscillations in older populations in general and especially in populations with impaired movement. Further, the impact of non-invasive brain stimulation such as tACS in these populations is unclear. A common disease that causes lasting movement impairments is an ischemic stroke, which often leaves survivors with a motor deficit of the upper extremity that can lead to impairments in their daily life (Broeks et al., 1999; Ekstrand et al., 2016). Non-invasive brain stimulation in the high-gamma range could be a tool to help stroke survivors with post-stroke motor recovery and improve their ability to perform activities of the daily life. But as of now, we do not fully understand the neurophysiological mechanisms of high-gamma oscillations in the motor cortex and there is no literature on whether and how high-gamma oscillations change after an ischemic stroke.

This work aims to investigate physiological function and pathophysiological changes of high-gamma oscillations as well as theta-gamma PAC in the healthy motor system and after an ischemic stroke. It further aims to explore the capability of tACS with frequencies in the high-gamma range to increase motor performance and enhance motor rehabilitation after stroke. The work is based on two publications. The first and main publication of this dissertation is the MEG-study 'Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors' (Haverland et al., 2025), which I am the first author of. It characterises cortical movement-related high-gamma oscillations in three groups with different levels of motor performance, one of which consists of stroke survivors. The study aimed to broaden the understanding of the physiological role of high-gamma oscillations in the motor system and wanted to investigate changes in high-gamma oscillations after an ischemic stroke. The insights gained in this study laid the groundwork for the second publication, 'Differential effects of theta-gamma tACS on motor skill acquisition in young individuals and stroke survivors: A double-blind, randomized, sham-controlled study' (Grigutsch et al., 2024), in which I participated as a co-author. Here, we investigated the effects of tACS with high-gamma oscillations coupled to the phase of theta oscillations on motor performance and motor skill acquisition in healthy young participants and stroke survivors. Finally, in an additional analysis not included in one of the publications, I investigated theta-gamma PAC and theta power during movement in the data used in Haverland et al.

Methods

Study 1: Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors, Haverland et al.

The publication is based on multimodal data recorded in 30 young participants, 16 stroke survivors, and 18 control participants, age-matched to the stroke survivors. We recorded MEG data during the performance of a thumb movement task. We further recorded MRI images and raised several clinical scores, including the Fugl-Meyer Assessment of the Upper Extremity. After applying the exclusion criteria, 29 young participants, 14 stroke survivors, and 15 control participants were included in the study.

We designed the motor task which the participants performed during the MEG measurement based on a simple thumb abduction task used by Akkad et al. (2021) in their publication. We modified the task in a way that it required the participants to perform four alternating button presses as fast as possible in six blocks with 40 trials each (Figure 1A). We deviated from the thumb abduction task to have a larger time window of interest for the data analysis, which was important to capture more robust oscillatory data and allow for the analysis of theta oscillations

and therefore cross frequency coupling between theta and gamma oscillations. Another goal of the task design was to make the task easy enough to perform so that stroke survivors were able to quickly understand and perform it while still having enough complexity to show finer differences in the young participant group with overall high levels of motor performance.

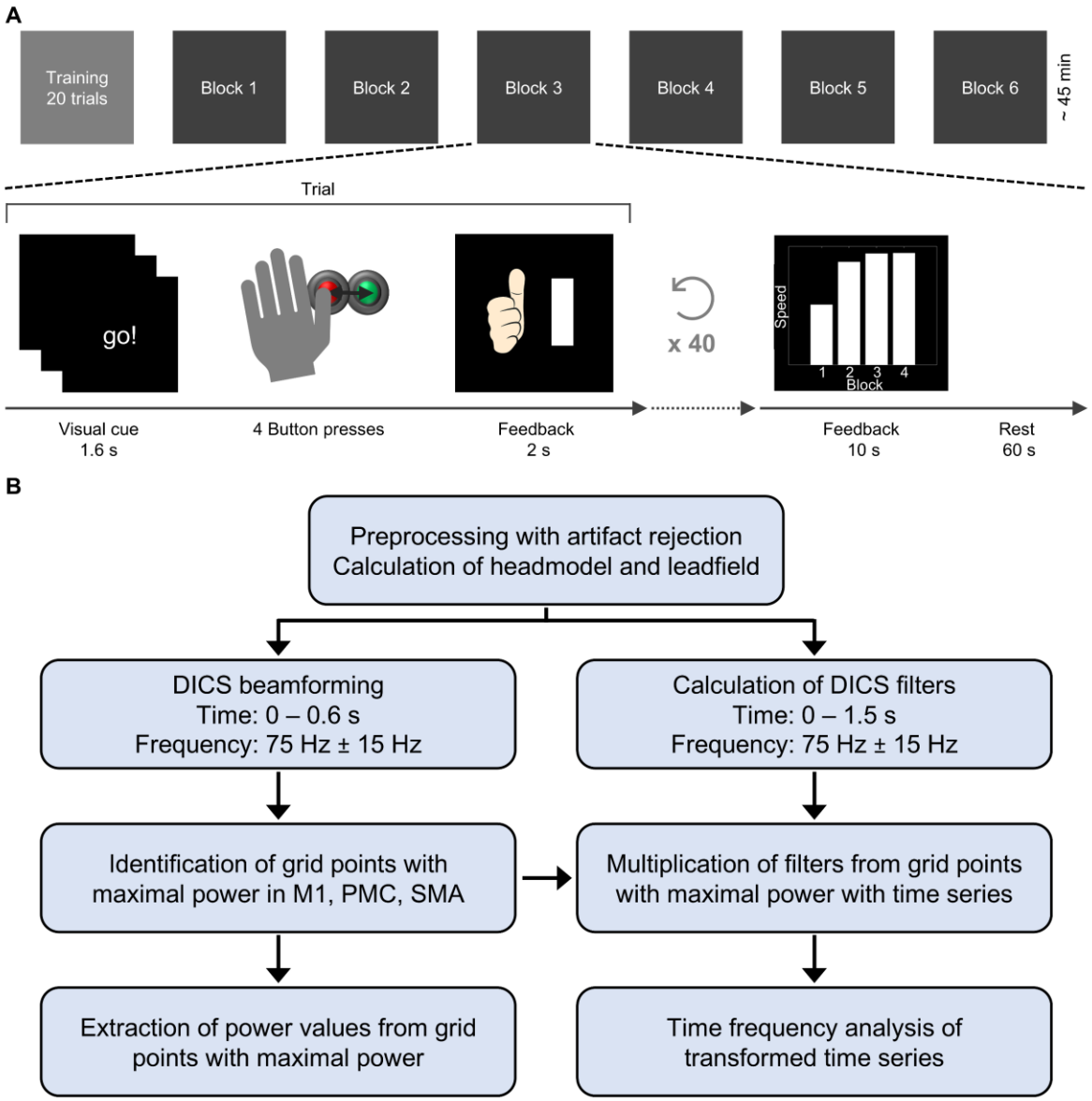

Figure 1 Motor task and analysis pipeline of MEG data. (**A**) The motor task contained one training block with 20 trials and six measurement blocks with 40 trials each. In each trial, participants had to perform four alternating button presses as fast as possible in response to a visual cue. They received feedback on their movement rate in each trial. Additional feedback showing the block mean of movement rate was given after each block. There was a 1-minute rest period between blocks. (**B**) Main analysis pipeline of the MEG data. The results were high-gamma power values of the grid point with maximal power in M1, PMC and SMA as well as a time frequency representation of these grid points. Figure and caption of (**A**) adapted from Haverland et al., (2025), Figure 1A.

Movement rate was defined as the reciprocal of the time it took the participants to press all four buttons and was used as a measure of motor performance. We defined two measures for motor skill acquisition: Block-wise improvement, which was defined as the percentage increase in movement rate from the participants' first to their individual best block, and trial-wise improvement, which was defined as the percentage increase from one trial to the next trial. For block-wise improvement, we decided to use the individual best block rather than the last block to avoid potential fatigue effects that might have occurred especially in stroke survivors.

We decided to use MEG to capture the brain oscillations as it offers high spatial discrimination (Hämäläinen et al., 1993) and has been successfully used in several publications to detect high-gamma oscillations (Cheyne et al., 2008; Muthukumaraswamy, 2010; Bardouille & Bailey, 2019). The MRI data were used to calculate head models for the source reconstruction of the MEG data as well as the analysis of the integrity of the corticospinal tract in stroke survivors and control participants.

Custom-written MATLAB (R2021b, The MathWorks, Inc.) scripts and the Fieldtrip toolbox (Oostenveld et al., 2011) in MATLAB were used for preprocessing, frequency analysis, source analysis and cluster-based permutation statistics (Maris & Oostenveld, 2007; Maris, 2012) of the MEG data. The remaining statistical analyses were performed using R (R Core Team, 2022).

To get a representation of the oscillatory data at the source level, we used the dynamic imaging of coherent sources (DICS) beamforming method (Gross et al., 2001) with a time window of 0 to 0.6 s relative to the first button press and a frequency of 75 Hz ± 15 Hz frequency smoothing (Figure 1B). The result was baseline corrected using the time window of -1.6 to -1 s as noise estimate. For subsequent analyses, we used the power values of the participant-specific grid points with maximal power in the primary motor cortex (M1), premotor cortex (PMC), and the supplementary motor area (SMA) according to the brainnetome atlas (Fan et al., 2016). We further calculated a time-frequency representation of these grid points with maximal power in each of the regions.

We used different kinds of statistical models in the publication. For analyses on the trial level, linear mixed-effects models were well suited to account for non-independence in the data that got introduced into the dataset by including several trials from each participant. The advantage of doing analyses on the trial level was that no information got lost by averaging over participants. On the participant level we mostly used linear models or in one case cumulative link models, depending on the data structure.

Study 2: Differential effects of theta-gamma tACS on motor skill acquisition in young individuals and stroke survivors: A double-blind, randomized, sham-controlled study, Grigutsch et al.

The study cohort after application of the exclusion criteria consisted of 78 healthy, young participants and 20 survivors in the chronic phase after an ischemic stroke. The study was preregistered and performed double-blind, the assignment of experimental groups was pseudo-randomized. Participants performed a thumb movement task while undergoing tACS that targeted the motor cortex contralateral to the hand the participants performed the task with. For young participants, there were three experimental groups with different stimulation protocols: Stimulation with 75 Hz high-gamma oscillations coupled to the peak of 6 Hz theta oscillations (theta-gamma peak, TGP) as active condition, stimulation with 75 Hz high-gamma oscillations coupled to the trough of 6 Hz theta oscillations (theta-gamma trough, TGT) as active control condition and sham stimulation. For stroke survivors there were two groups, TGP and sham stimulation. The thumb movement task was closely adapted from the one used in Haverland et al., with small changes to account for the experimental setup and addition of a baseline block.

The primary outcome motor skill acquisition was defined as relative improvement in duration between the first and fourth button press (movement duration) between the baseline block and the block with the lowest mean movement duration. Thumb acceleration was measured with an accelerometer and the peak acceleration during each trail was calculated.

The difference in the primary outcome motor skill acquisition between stimulation conditions was assessed by two-tailed *t*-tests or Wilcoxon rank-sum tests as appropriate. Further analyses for the effects on movement duration and peak acceleration were investigated using linear mixed-effects models.

Additional analysis of the data of Haverland et al.: Theta-gamma phase-amplitude coupling and theta power during movement

In an analysis not included in the final publication, I analysed theta-gamma PAC in the MEG data of Haverland et al. using bicoherence (Shahbazi Avarvand et al., 2018; Bartz et al., 2019). For this analysis and the subsequent analysis of theta power, I first subtracted the event-related fields from the data to account for evoked theta activity. To increase the SNR of the data, I then performed a spatio-spectral decomposition (SSD) in the theta and gamma range and obtained a component with optimized SNR for each of the two frequency ranges by multiplying the resulting spatial filter with the time series (Nikulin et al., 2011; Haufe et al., 2014). Using the MATLAB function “data2bs_univar” (Shahbazi et al., 2014), I calculated the bispectra of the summed up components from 0 to 0.6 s in relation to the first button press for each participant and for visualization across all participants. I performed two-tailed *t*-tests to test for group

differences in bicoherence between 5 and 75 Hz. I further performed a beamforming analysis analogous to the analysis for high-gamma frequencies described above for the frequency 5 Hz ± 2 Hz frequency smoothing and extracted theta power values of the same grid points that were used for the high-gamma analyses (grid points with maximal high-gamma power in M1 and PMC). Wilcoxon rank-sum tests were performed to test for group differences in theta power.

Results

Study 1: Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors, Haverland et al.

All three groups improved in movement rate over the course of the six blocks of the task by a comparable margin. Mean movement rate averaged per participant was significantly lower in stroke survivors compared to control participants and lower in control participants compared to young participants. We detected similar group differences in high-gamma power in M1 and PMC, with stroke survivors having significantly lower high-gamma power than control participants and control participants having significantly lower high-gamma power than young participants.

The concurrence of the group differences in high-gamma power and movement rate suggested that the reduced movement rate might be related to the reduced high-gamma power in stroke survivors. We used two different analyses to test this hypothesis. In an analysis where we matched trials with the same movement rate and performing hand between stroke survivors and control participants, stroke survivors still had significantly less high-gamma power than control participants. When performing this analysis between young and control participants, the previously existing group difference was not significant anymore. A linear mixed-effects model with high-gamma power as dependent variable and group, movement rate and performing hand as fixed effects, however, did not show a significant effect of group.

Further analyses showed a significant positive effect of movement rate on high-gamma power in M1 and PMC on the trial and the participant level. In a whole brain cluster-permutation analysis, we showed that the relation between movement rate and high-gamma power is apparent in grid points in cortical motor regions contralateral to the performed movement, even without the preselection of grid points with maximal power.

When plotting group level time frequency spectrograms in the different groups, we noticed that a greater number of definable high-gamma activations (high-gamma peaks) could be seen in the groups with overall lower movement rate. We investigated this phenomenon and found that

the number of high-gamma peaks over the course of a trial depends on movement rate rather than group.

High-gamma peak frequency was significantly higher in young participants than in control participants but did not show a significant association with movement rate. Both trial-wise and block-wise improvement did not show an association with high-gamma power.

Study 2: Differential effects of theta-gamma tACS on motor skill acquisition in young individuals and stroke survivors: A double-blind, randomized, sham-controlled study, Grigutsch et al.

The primary outcome motor skill acquisition was not significantly different between the stimulation conditions in young participants, and condition did not show a significant effect on movement duration in a linear mixed-effects model in young participants. tACS therefore did not show a significant effect on movement duration or motor skill acquisition in young participants. In stroke survivors, participants in the TGP group exhibited significantly less motor skill acquisition than participants in the sham group. There was a significant effect of a condition x block interaction on movement duration with a steeper slope in the sham stimulation group in a linear mixed-effects model. This showed that participants in the TGP group improved less in movement duration over the course of the task.

In an analysis of the peak acceleration, a linear mixed-effects model showed a significant effect of stimulation condition on peak acceleration in young participants. Post-hoc tests revealed a significantly higher peak acceleration in the TGP and TGT groups compared to sham. There was no significant difference between TGP and TGT conditions. In stroke survivors, there was no significant effect of stimulation condition on peak acceleration.

Additional analysis of the data of Haverland et al.: Theta-gamma phase-amplitude coupling and theta power during movement

In an additional analysis that was not included in Haverland et al., I analysed the relationship between theta-gamma phase-amplitude coupling (PAC) and movement rate as well as improvement in movement rate. PAC was quantified using bicoherence. No notable amount of bicoherence between theta and gamma frequencies was observed visually (Figure 2A) and there was no significant difference between the participant groups in bicoherence between 5 Hz and 75 Hz after correction for multiple comparisons (Figure 2B, stroke/control: $t(19.5) = 1.7$, p value corrected for multiple comparisons (p_{cor}) = 0.103, control/young: $t(41.9) = -2.1$, p_{cor} = 0.0820, corrected for two comparisons). Due to these results, I did not investigate the relation between bicoherence and movement rate or improvement in movement rate.

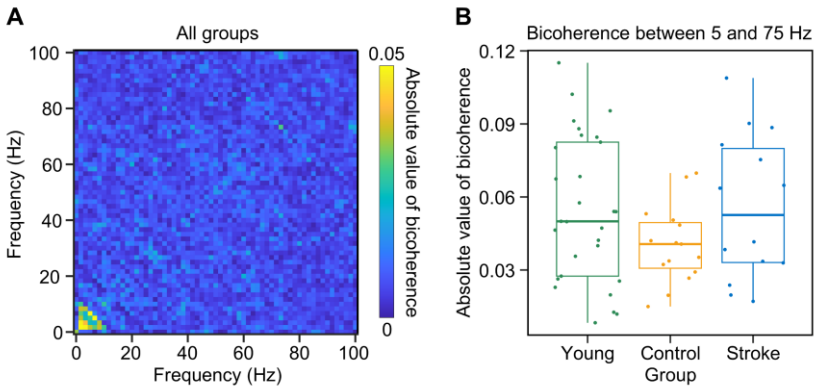

Figure 2 Theta-gamma PAC measured with bicoherence. (**A**) Absolute value of bicoherence between frequencies of 0 to 100 Hz in the data of all groups combined. To increase the SNR, one theta and one gamma component was identified by performing an SSD. There is no relevant bicoherence visible between theta and gamma frequencies. (**B**) Absolute value of bicoherence in the participant groups. There were no statistically significant group differences. Higher values of bicoherence in (**B**) than in (**A**) are due to calculation of bicoherence in single participants in (**B**) as opposed to in data from all participants combined in (**A**).

In light of the absent theta-gamma PAC, theta oscillations during the movement period were characterized to investigate potential underlying causes. Overlayed on a standard brain, theta power averaged over participants did not show a physiological pattern (Figure 3A). In time-frequency spectrograms averaged over participants of the grid point with maximal gamma power in the primary motor cortex contralateral to the movement, there was a short theta power increase around the onset of movement in every group (Figure 3C). Control participants showed significantly higher theta power during movement than young participants in both M1 and PMC (Figure 3B, $W = 435$, M1: $p_{cor} < 0.001$, $W = 435$, PMC: $p_{cor} < 0.001$, corrected for four comparisons).

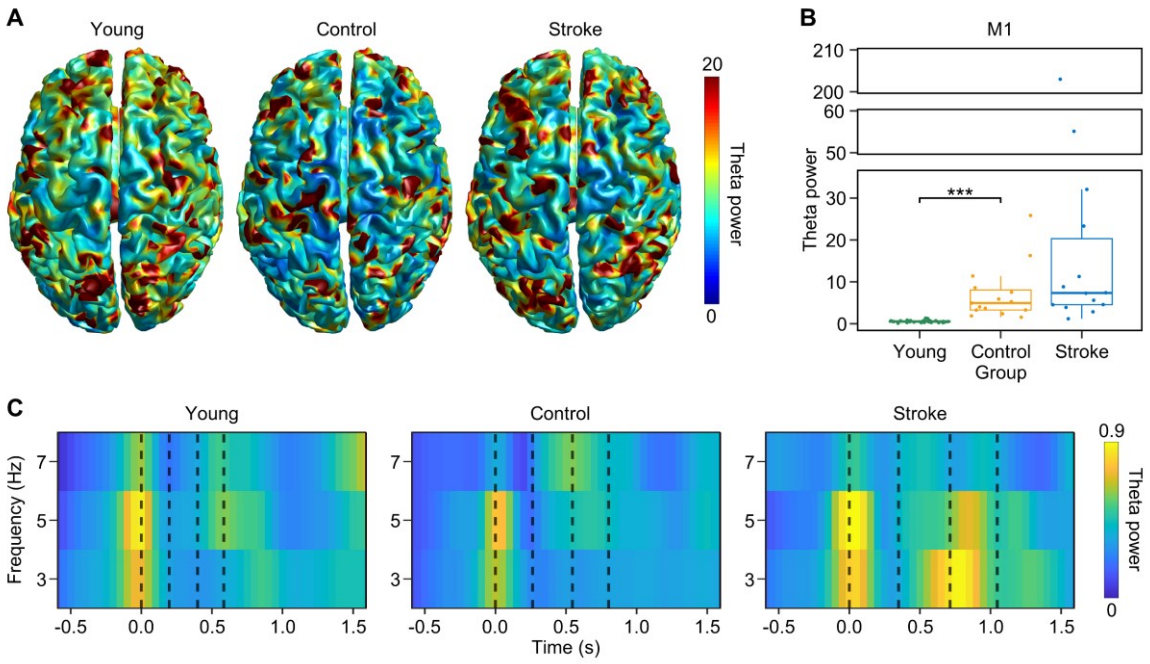

Figure 3 Theta power during movement. (**A**) Theta power during movement (0 – 0.6 s relative to the first button press) relative to baseline overlayed on a standard brain. (**B**) Group differences in theta power (0 – 0.6 s) in the grid point with maximal high-gamma power. Asterisks indicate significance. The difference between the control and stroke groups is not significant. The breaks in the y-axis were introduced to show two outliers in the stroke group. (**C**) Spectrograms of theta frequencies of the grid point with maximal high-gamma power in M1. Dotted lines indicate the average timepoints of the four button presses in the respective groups. Significance markers: ***$p < 0.001$

Discussion

In Haverland et al. we showed that high-gamma power relates to movement rate over three participant groups with differing motor performance levels. We further found that stroke survivors exhibited less high-gamma power than age-matched healthy control participants. This difference persisted after matching for movement rate, which hints at an additional role of stroke pathology in the reduction of high-gamma power. We did not find an association between high-gamma power and improvement in movement rate.

The association of high-gamma power and movement rate, a measure of motor performance, as well as the reduced high-gamma power in stroke survivors, suggest that increasing high-gamma power via non-invasive brain stimulation, for example tACS, could be a way to increase motor performance in stroke survivors. If it would be possible to increase motor performance in this way, high-gamma tACS could be used as a tool to help stroke survivors regain motor function, depending on the longevity of the effect.

Grigutsch et al. was inspired by the finding of increased thumb acceleration in young participants when undergoing TGP tACS compared to sham stimulation (Akkad et al., 2021). Taken together with the finding of Haverland et al. that high-gamma power is reduced after stroke,

we aimed to replicate the findings in young participants and investigate the effect of TGP tACS in stroke survivors. We were able to replicate the results of Akkad et al., showing that TGP tACS increased thumb acceleration in healthy, young participants compared to sham stimulation. Additionally, we were able to show a positive effect of TGT tACS on thumb acceleration as well. There was no effect of theta-gamma tACS on motor skill acquisition in young participants. As there was no difference between the effect of TGP and TGT on thumb acceleration, we interpreted the observed effects as effects of stimulation with the theta- or gamma oscillation rather than an effect of phase-specific PAC.

Interestingly, in stroke survivors, TGP tACS reduced general motor skill acquisition compared to sham stimulation while showing no effect on thumb acceleration. We hypothesized that tACS might have improved kinematic aspects of the movement while not improving other important factors for the execution of the task like coordination skills, which led to an overall worse outcome.

These results do not generate new evidence for the supporting role of theta-gamma PAC in motor skill acquisition. They rather suggest that high-gamma or theta tACS alone might be a promising approach to increase motor performance and motor skill acquisition. There is evidence that high-gamma tACS can improve different parameters of motor performance (Joundi et al., 2012; Santarnecchi et al., 2017; Guerra et al., 2018) and that it can improve motor skill acquisition (Nowak et al., 2017; Sugata et al., 2018; Bologna et al., 2019). Further studies are required to directly compare the effects of uncoupled theta and high-gamma tACS as well as theta-gamma tACS on motor performance and motor skill acquisition, especially after stroke, to untangle the different stimulation effects. The positive effect of the stimulation on thumb acceleration in young participants in Grigutsch et al. aligns well with the results of Haverland et al., which showed an association of high-gamma power and movement rate, a parameter that partly depends on thumb acceleration. The stimulation, however, did not show an effect on movement duration, which is directly linked to movement rate in this task. It therefore might be easier to detect oscillatory changes in more complex movements than to influence these complex movements in a significant way via tACS.

Overall, this suggests that the high-gamma component of the stimulation might be the reason for the increased thumb acceleration in Grigutsch et al., as was discussed in the publication. The question remains whether high-gamma tACS can amplify more complex movements and have a lasting positive effect on motor skill acquisition rather than just being able to increase individual kinematic parameters like thumb acceleration.

Theta-gamma phase-amplitude coupling and theta power during movement

Theta-gamma PAC describes the amplitude modulation of high-gamma oscillations dependent on the phase of a theta wave. It is primarily thought of as a mechanism in memory function (Friese et al., 2013; Lopes-dos-Santos et al., 2018; Daume et al., 2024) but has been described in the motor cortex (Canolty et al., 2006; Igarashi et al., 2013) and has been found to be associated with motor skill acquisition (Dürschmid et al., 2014). In the chronic phase after a stroke, theta-gamma PAC was described to be positively associated with motor recovery (Rustamov et al., 2022). Unfortunately, I was not able to detect a substantial amount of theta-gamma PAC in the data and was therefore not able to gain new insights into the mechanistic role of theta-gamma PAC in motor control. This was most likely due to difficulties I had with extracting theta oscillations from the data. Visually, the theta activation in the brain surface plots do not show a physiological pattern (Figure 3A) and even though the increase in theta power in control participants compared to young participants might suggest a physiological source of the theta oscillations, the unphysiological topographical pattern leads to the interpretation that the theta activity is obscured by artifacts. The underlying issue might be the short time window of interest that was used in this analysis due to the design of the motor task. The analysis time window of 600 ms only contains 2.4 to 4.2 cycles of a theta oscillation (for 4 to 7 Hz), which makes it difficult to record a clear theta activation. The solution to this problem could be the recording of brain oscillations during a longer movement to allow for a longer time window that catches more theta cycles and therefore allows for the reconstruction of a clearer theta activation with less artifact contamination. Future studies should further investigate the role of theta-gamma PAC after stroke to add to the understanding of oscillatory changes and the neurophysiology behind motor rehabilitation after stroke.

Conclusion

Taken together, we found a robust association between movement rate and high-gamma power in motor cortical areas in participant groups with differing motor performance levels. Stroke survivors exhibited less high-gamma power than healthy control participants, even when matched for movement rate. We did not find an association between high-gamma power and improvement in movement rate. These results led us to think of tACS with high-gamma frequencies as a promising approach to improve motor performance after stroke. In a follow-up tACS study we replicated results that showed that theta-gamma tACS improved thumb acceleration in healthy, young participants. It did not, however, improve thumb acceleration in stroke survivors and even deteriorated their ability to acquire a motor skill. Based on these studies, high-gamma tACS without cross-frequency coupling still seems to be a promising approach for the improvement of motor rehabilitation after stroke and should be further investigated in future studies.

2. Artikel: Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors

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Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors

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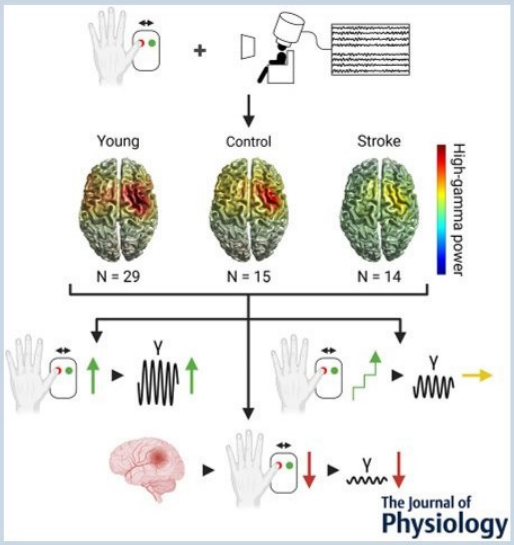

Abstract figure legend Magnetoencephalography data from stroke survivors, healthy, age-matched control participants and healthy young participants were measured during the execution of a thumb movement task. Movement-related high-gamma power was evident in all three groups with a maximum over motor cortical areas contralateral to the performed movement. High gamma power showed a strong positive relation to participants' movement rate (left), whereas no significant relation to motor skill acquisition was present (right). Stroke survivors showed reduced cortical high-gamma power mainly as a result of their reduced movement rate (middle).

B. C. Schwab and F. Quandt contributed equally to this work.

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DOI: 10.1113/JP286873

Abstract Motor cortical high-gamma oscillations (60–90 Hz) occur at movement onset and are spatially focused over the contralateral primary motor cortex. Although high-gamma oscillations are widely recognized for their significance in human motor control, their precise function on a cortical level remains elusive. Importantly, their relevance in human stroke pathophysiology is unknown. Because motor deficits are fundamental determinants of symptom burden after stroke, understanding the neurophysiological processes of motor coding could be an important step in improving stroke rehabilitation. We recorded magnetoencephalography data during a thumb movement rate task in 14 chronic stroke survivors, 15 age-matched control participants and 29 healthy young participants. Motor cortical high-gamma oscillations showed a strong relation with movement rate as trials with higher movement rate were associated with greater high-gamma power. Although stroke survivors showed reduced cortical high-gamma power, this reduction primarily reflected the scaling of high-gamma power with movement rate, yet after matching movement rate in stroke survivors and age-matched controls, the reduction of high-gamma power exceeded the effect of their decreased movement rate alone. Even though motor skill acquisition was evident in all three groups, it was not linked to high-gamma power. Our study quantifies high-gamma oscillations after stroke, revealing a reduction in movement-related high-gamma power. Moreover, we provide strong evidence for a pivotal role of motor cortical high-gamma oscillations in encoding movement rate.

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Key points

- Neural oscillations in the high-gamma frequency range (60–90 Hz) emerge in the human motor cortex during movement.
- The precise function of these oscillations in motor control remains unclear, and they have never been characterized in stroke survivors.
- In a magnetoencephalography study, we demonstrate that high-gamma oscillations in motor cortical areas scale with movement rate, and we further explore their temporal and spatial characteristics.
- Stroke survivors exhibit lower high-gamma power during movement than age-matched control participants, even after matching for movement rate.
- The results contribute to the understanding of the role of high-gamma oscillations in motor control and have important implications for neuromodulation in stroke rehabilitation.

Introduction

Gamma oscillations (25–140 Hz) have been found in various areas of the human brain (Buzsáki & Wang, 2012) and have been linked to neural communication (Misselhorn et al., 2019; Ni et al., 2016), as well as to a wide range of cognitive processes (Herrmann et al., 2004). At the onset of motor actions, spatially focused

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movement-related high-gamma oscillations (∼60–90 Hz) occur over the contralateral motor cortex (Miller et al., 2007), which have been shown to be prokinetic (Cheyne et al., 2008; Crone et al., 1998; Muthukumaraswamy, 2010; Pfurtscheller et al., 2003; Ulloa, 2021). High-gamma oscillations in motor cortical areas have been recorded from extracellular recordings, namely single- or multi-unit, local field potentials (LFPs) (Donoghue et al., 1998; Khorasani et al., 2016), electrocorticographic (ECoG) recordings (Crone et al., 1998; Hammer et al., 2016) and non-invasive magnetoencephalography (MEG) (Cheyne et al., 2008; Quandt et al., 2012) and electroencephalography (EEG) (Ball et al., 2008). In particular, invasive cortical recordings showed that high-gamma oscillations contain information that allows for decoding position, velocity and predominantly movement speed (Anderson et al., 2012; Hammer et al., 2016; Wang et al., 2017).

Although high-gamma oscillations seem to play a crucial role in human motor control, they have so far never been quantified in stroke survivors. Because over 50% of all stroke survivors suffer from persistent hand-motor deficits (Pennati et al., 2020), understanding the neurophysiological processes of motor coding after stroke is key for the development of interventions to improve recovery and motor performance (Ward, 2011). Moreover, the study of human populations with impaired motor function may shed light on the general role of movement-related high-gamma oscillations. For example, if high-gamma oscillations purely reflect movement kinematics, they should be proportionally scaled down with impaired motor function. If high-gamma oscillations rather reflect the intent to move or the cognitive effort, they would be expected to be preserved or even enhanced with restricted motor function.

Here, we rigorously characterize the role of movement-related high-gamma oscillations in motor control and motor skill acquisition. We acquired a combined data set consisting of MEG data measured during a thumb movement task and anatomical and diffusion-weighted magnetic resonance imaging (MRI), as well as neurological tests from stroke survivors, healthy age-matched control participants and healthy young participants. We hypothesize that motor cortical high-gamma oscillations are tightly linked to movement rate as a measure of motor performance and explore their role in motor control in the chronic phase after stroke.

Methods

Ethical approval

The study was performed according to the *Declaration of Helsinki*, except for registration in a database, and all participants provided their written informed consent. The study was approved by the local ethics committee of the Medical Association of Hamburg (2021-10410-BO-ff).

Participants and assessment

Three different groups of individuals were recruited within the study: (i) 16 well-recovered stroke survivors; (ii) 18 healthy control participants age-matched to the stroke survivors; and (iii) 30 healthy young participants (aged 18–35 years). Stroke survivors, with a first-ever clinical ischemic stroke at least 6 months prior to inclusion, who experienced a deficit of the upper extremity for at least 24 h and showed a structural lesion on a clinical MRI or computer tomographic image were included in the study. Psychotropic medication was an exclusion criterion in all three groups. The number of recruited stroke survivors was based on prior comparable observational studies (Gerloff et al., 2006; Quandt et al., 2019). All participants were right-handed according to the Edinburgh Handedness Inventory. One healthy young participant and three age-matched older controls had to be excluded because they did not fulfil all inclusion criteria retrospectively (neurological conditions, handedness). Two-stroke survivors were excluded because of extensive artifacts in the MEG data as a result of metal implants. This resulted in 14 stroke survivors, 15 age-matched controls and 29 healthy young participants for the remainder of the study.

Multimodal imaging was obtained, consisting of MEG measurements during the execution of a motor task, as well as structural MR imaging. Standardized clinical testing was acquired in stroke and age-matched control participants by means of the Fugl-Meyer Assessment of the Upper Extremity (UEFM), Action Research Arm Test (ARAT), Nine Hole Peg Test (NHPT), Box and Block Test (BBT), whole hand grip force, key grip force, National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Mini-Mental State Examination (MMSE).

Motor task

Participants were seated comfortably in the MEG system in front of a screen with their performing arm fixated in a splint, next to a two-button response box (Current Designs, Philadelphia, PA, USA) that was placed in a position where the thumb of the participant could easily reach both buttons. The task consisted of alternately pressing the two buttons for a total of four button presses in reaction to a 'ready – steady – go' cue using the thumb while keeping the arm as relaxed as possible (Fig. 1*A*). During task execution, the participants were instructed to focus on a fixation cross that was displayed on the screen. The task was designed based on a study by Akkad

et al. (2021), which demonstrated an improvement in task performance in a similar thumb abduction task over time without a ceiling effect in a young cohort. Additionally, they reported an impact of theta-gamma transcranial alternating current stimulation (tACS) on task performance, making this type of task well-suited for investigating high-gamma activity. To increase the movement time for MEG analyses, we changed from a pure thumb abduction to a four-button press task.

First, participants performed 20 trials to familiarize themselves with the task. Afterwards, they were instructed to perform the task as fast as possible using standardized instructions. Each participant performed six measurement blocks with 40 trials each. After each trial, participants received feedback on their movement rate and the improvement relative to their mean movement rate in the current and the previous block. After each block, additional feedback was given in the form of a bar indicating the mean movement rate for each completed block. If participants pressed the button before the go-cue, took more than 1 s before initiating the first button press or pressed an incorrect order of buttons, an error message was displayed. The task was intentionally designed to prioritize speed over accuracy, with error trials excluded from further analysis.

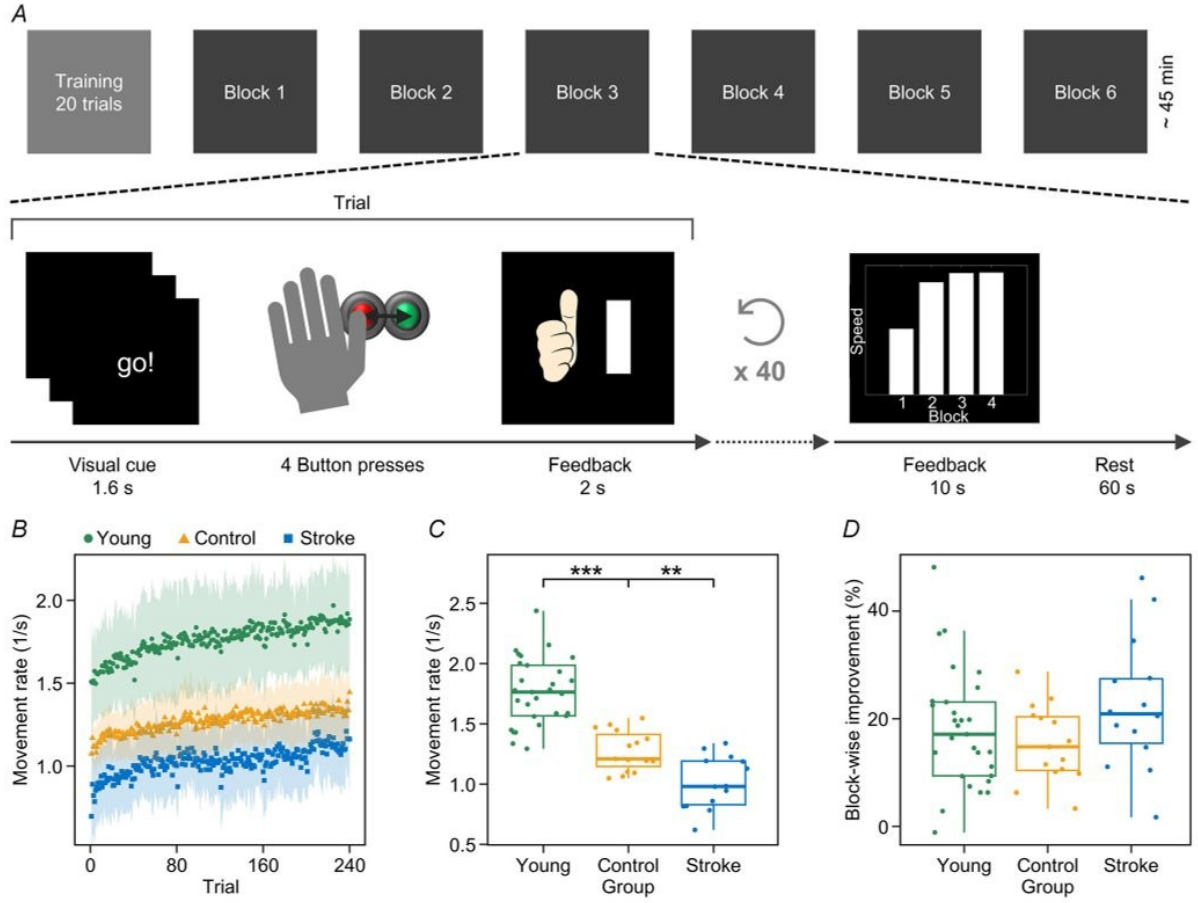

Figure 1. Motor task and behavioural data
A, the motor task contained one training block with 20 trials and six measurement blocks with 40 trials each. In each trial, participants had to perform four alternating button presses as fast as possible in response to a visual cue. They received feedback on their movement rate in each trial. Additional feedback showing the block mean of movement rate was given after each block. There was a 1 min rest period between blocks. *B*, movement rate for each trial averaged in each group. An increase in movement rate over the course of the trials was evident in all groups. Shaded areas indicate the SD. *C*, distribution of participant mean of movement rate. Asterisks indicate significant group differences. *D*, distribution of participant mean of block-wise improvement. Block-wise improvement represents the percentage improvement in movement rate from the first to the individual best block. There were no significant group differences in block-wise improvement. Significance markers: $^{**}P < 0.01$, $^{***}P < 0.001$.

There were differences in the experimental set-up between groups of young and control/stroke participants to account for behavioural differences and needs between these groups. Young participants performed the task with their left (non-dominant) hand, whereas stroke survivors used the hand contralateral to the lesioned hemisphere. The performing hand of age-matched control participants was chosen to match stroke survivors. Although, in the young group, lights in the measuring chamber were turned off, the light was kept on for stroke and older participants because they required additional light to feel comfortable. The size of the feedback bar (linear *vs*. sigmoidal increase) was adapted in the age-matched control group and in stroke survivors to account for expected differences in movement rate. The task was run in MATLAB, R2021b (The MathWorks, Inc., RRID:SCR_001622) using Psychtoolbox-3 (Kleiner et al., 2007) (RRID:SCR_002881).

Data acquisition

MEG data acquisition. MEG data were recorded with 275 axial gradiometers of a CTF-MEG system (CTF Systems, Coquitlam, BC, Canada) with a sampling rate of 1200 Hz. The head position was continuously measured, and participants were given instructions to help them return to their initial head position after each block of the task (Stolk et al., 2013). Electrooculogram (horizontal and vertical) and electrocardiogram were recorded via bipolar channels. Time points of button presses and visual stimuli were sent to the acquisition program via TTL (i.e. transistor-transistor-logic) triggers.

MRI data acquisition. MRI data were acquired from 11 out of 14 stroke survivors, all 15 control participants and 21 out of 29 young participants. The remaining participants did not consent to MR-imaging. We acquired T1-weighted images in all groups and T2-weighted and multishell diffusion-weighted images (DWI) in stroke and control participants using a 3 T Prisma MRI scanner (Siemens Healthineers, Erlangen, Germany) equipped with a 64 channel head coil. For anatomical imaging in stroke and control participants, a 3-D magnetization-prepared rapid gradient echo sequence [repetition time (TR) = 2500 ms, echo time (TE) = 2.15 ms, flip angle 8°, 288 coronal slices with a voxel size of 0.8 × 0.8 × 0.8 mm^3] was used. In young participants, the parameters of the sequence were slightly different (TR = 2300 ms, TE = 2.98 ms, flip angle 9°, 256 coronal slices with a voxel size of 1 × 1 × 1 mm^3). T2-weighted images were acquired by using a fluid-attenuated inversion recovery sequence (TR = 9210 ms, TE = 92 ms, TI = 2500 ms, flip angle 140°, 70 axial slices with a voxel size of 0.9 × 0.9 × 2.0 mm^3) for stroke lesion delineation. DWI was obtained by covering the whole brain with gradients ($b = 500$, 1000 and 2000 s mm^{-2}) applied along 96 non-collinear directions with the following sequence parameters: TR = 5000 ms, TE = 76 ms, slice thickness = 2 mm, in-plane resolution = 1 × 1 mm. For stroke survivor 14, the sequence parameters varied slightly: TR = 5000 ms, TE = 78 ms, slice thickness = 2 mm, in-plane resolution = 1 × 1 mm.

Data analysis

Clinical and behavioural data. For UEFM, MMSE, ARAT, NHPT and BBT, we used the absolute test scores of the performing hand (UEFM: range 0–66, MMSE: range 0–30, ARAT: range 0–57, NHPT: pegs s^{-1}, BBT: blocks min^{-1}). The whole hand grip force and key grip force scores of the performing hand were divided by the scores of the non-performing hand to obtain a ratio score. Within the motor task, the movement rate was defined as the reciprocal of the time between the first and the fourth button press in each trial. Improvement was defined in two different ways:

(i) On a trial level as the percentage increase in movement rate from the current to the next trial:

$$\text{Trial–wise improvement} = \frac{\text{movement rate in the next trial} - \text{movement rate in the current trial}}{\text{movement rate in the current trial}} \times 100\% \quad (1)$$

(ii) Across blocks as the change from first block to best block:

$$\text{Block–wise improvement} = \frac{\text{movement rate in the best block} - \text{movement rate in the first block}}{\text{movement rate in the first block}} \times 100\% \quad (2)$$

We chose to compare the first and best blocks to circumvent the influence of potential fatigue effects in some patients. Fatigue effects may have led to suboptimal performance in the last blocks.

Processing of the MEG data. Data analysis was conducted using the software package FieldTrip (Oostenveld et al., 2011) (RRID:SCR_004849) in MATLAB. MEG data were bandpass filtered from 1 to 120 Hz and bandstop filtered at 49–51 Hz and 99–101 Hz (to eliminate the line noise artifact and its first harmonic) using a fourth-order Butterworth filter. Data were segmented into trials from −3.2 s before, up to +3.5 s after the time point of the first button press (0 s). Artifacts were carefully removed by a combination of visual artifact rejection, as well as an independent component analysis, in which components representing eyeblinks, cardiac activity or muscle artifacts were removed from the data. Error trials, trials in which participants took more than 3 s to complete all four button presses, as well as trials in which the movement duration (time from first to fourth button press) deviated more than three scaled absolute deviations from the individual block median, were excluded, leaving on average 205.5 ± 16 (mean ± SD) trials per participant in the young group (5960 trials in total), 191.5 ± 25.8 trials per participant in the stroke group (2681 trials in total) and 205.6 ± 14.6 trials per participant in the control group (3084 trials in total).

Source space activity was estimated using the dynamic imaging of coherent sources (DICS) beamforming method (Gross et al., 2001) with regularization ($\lambda = 5\%$). Head models, giving a geometrical description of the head, were computed based on individual T1-weighted MRIs (21 young participants, 11 stroke survivors and 15 control participants) or based on the Colin27 Average Brain (Holmes et al., 1998) (eight young participants, three stroke survivors) using the single-shell method (Nolte, 2003). Source models, specifying the location of the sources in the brain volume, consisted of a regularly spaced 8 mm, 3-D grid warped on the individual or standard head model, respectively. At each location, a projection matrix describing signal propagation to the MEG sensors (the leadfield matrix) was computed. Time-frequency averaged cross-spectral density matrices for the movement period (0 to 0.6 s) and baseline period (−1.6 to −1 s) at 75 Hz with ± 15 Hz frequency smoothing (17 Slepian tapers) were computed and source space activity was estimated at each grid point. To noise-normalize source power, the difference of power in the movement period and baseline period was divided by the power in the baseline period for each trial in each participant. Thus, the baseline served as the noise estimate. Brain regions were identified by masking the source representation with the Brainnetome atlas (Fan et al., 2016). For each participant, the grid point with maximal power in the primary motor cortex (M1, regions A4hf, A4ul, A4ll, A4t and A4tl), premotor cortex (PMC, regions A6vl, A6cvl, A6dl and A6cdl) and supplementary motor area (SMA and region A6m) contralateral to their performing hand was detected. The power values of these grid points were used for further analyses.

To obtain a time-frequency representation of virtual channels, we computed real-valued DICS filters at 75 ± 15 Hz frequency smoothing for the periods 0 to 1.5 s (task period) and −1.6 to −0.1 s (baseline period) and multiplied the filters of the grid points with maximal power in each region with the time-series data. In the resulting source level time-series data, we estimated power in the range 60–90 Hz (steps of 2 Hz and 0.05 s, 0.25 s moving time window, five Slepian tapers, resulting in ±12 Hz frequency smoothing). We identified the high-gamma peak frequency for each participant by averaging the data within the time interval from 0 to 0.6 s over trials and determined the frequency with the highest power value.

To quantify the number of peaks in participant-level frequency-averaged time courses, MEG data were locked to the first, second, third and fourth button press, respectively. Time-frequency representation of virtual channels was obtained as described above. Peaks in the high-gamma frequency band (60–90 Hz) were detected using the findpeaks function in MATLAB, within the time interval of −0.1 s with respect to the corresponding button press to the next button press. For the fourth button press, the detection window spanned from −0.1 s to the button press time plus the interval between the first and second button presses. Peaks were defined by a minimum width of 0.04 s and a high-gamma power at least 1% higher than the neighbouring time points.

Processing of the MRI data

Fractional anisotropy of the corticospinal tract. Preprocessing and reconstruction of MRIs were performed using QSIPrep, version 0.16.1 (Cieslak et al., 2021), which is based on Nipype, version 1.8.5 (Gorgolewski et al., 2011) (RRID:SCR_002502). Individual fractional anisotropy (FA) maps were computed on the preprocessed DWI imaged using MRTrix3 (Tournier et al., 2019) (RRID:SCR_006971) function 'dwi2tensor' and 'tensor2metric'. The maps were registered on a FA template in MNI space (FMRIB58_FA standard space image https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FMRIB58_FA) using 'antsregistration' (ANTs 2.4.0) (Avants et al., 2009) (RRID:SCR_004757). A corticospinal tract (CST) template mask from the mesencephalon to the cerebral penduncle (MNI co-ordinates $z = -25$ to $z = -20$) was used to compute tract-related mean FA (for details refer to the original publication [Schulz et al., 2017]).

Mean CST-FA values of the hemisphere contralateral to the performing hand (affected hemisphere in stroke survivors) were divided by the mean CST-FA values of the hemisphere ipsilateral to the performing hand to obtain ratio scores.

Statistical analysis

Statistical analysis was performed in R, version 4.1.3 (R Core Team, 2022) (RRID:SCR_001905).

Group differences. Differences in stroke survivor characteristics (Table 1), movement rate (Section: Improvement in movement rate), block-wise improvement (Section: Improvement in movement rate), CST-FA (Section: Clinical scores and structural imaging), high-gamma power (Section: Movement-related high-gamma power) and high-gamma peak frequency (Section: High-gamma peak frequency) were assessed using two-tailed t tests and Wilcoxon rank-sum tests as appropriate.

High-gamma power compared to baseline. Two-tailed paired t tests were calculated in each source grid point comparing participants' average high gamma power during the movement period (0 to 0.6 s) and baseline period (−1.6 to −1 s) and corrected for multiple comparisons via a cluster-based permutation analysis (Maris, 2012; Maris & Oostenveld, 2007) with 1000 randomizations and a threshold for clustering of $\alpha = 0.01$. Data from participants performing the task with the right hand were flipped across hemispheres prior to the analysis.

Modelling the association of high-gamma power and behavioural data. To assess the association between high-gamma power and movement rate (Section: Relation of high-gamma power and movement rate) and high-gamma power and trial-wise improvement (controlling for movement rate), linear mixed-effects models were calculated across groups for each motor region (M1 and PMC) on a trial-based level. Group was added as an interaction term and performing hand as a fixed effect. Non-significant interaction terms were described and then removed from the model. Models included random slopes for movement rate and random intercepts for participants. To ensure homoscedasticity and linearity of the residuals, high-gamma power was transformed to log(100 + high-gamma power). The constant 100 was added to the high-gamma power to avoid negative arguments of the log function.

The analysis was repeated not only on a trial-based level, but also on averaged activity across all trials of each participant, leading to one robust value per participant with low noise. To assess the association between high-gamma power and movement rate and high-gamma power and block-wise improvement (controlling for movement rate in block 1), linear regression models were calculated across groups for each motor region. Group and performing hand were included as fixed effects. These analyses were extended to the time series at each grid point in source space to map the topographical distribution of these relationships. To correct for multiple comparisons, we conducted a cluster-based permutation analysis (Maris, 2012; Maris & Oostenveld, 2007) with 1000 randomizations. The assignment of high-gamma power to the variable of interest was shuffled while keeping the assignment of the group and performing hand-fixed. Data at single grid points were selected at $\alpha = 0.01$. We compared the summed t values of the variable of interest within each cluster to the distribution of summed t values from the randomizations to compute the final P value.

The association of high-gamma power with clinical scores, CST-FA and high-gamma peak frequency was similarly analysed using linear regression models for each motor region.

High-gamma power matched for movement rate. To evaluate whether group differences in high-gamma power are solely a result of differences in movement rate or also because of an effect of group, we matched each trial of each stroke survivor to a trial with the same movement rate (±1%) of a control participant performing the task with the same hand, as well as each trial, of each young participant to a trial of a control participant. Trials were then averaged within the participants and the group difference was assessed with a one-tailed t tests with the alternative hypothesis being that stroke survivors have less high-gamma power than control participants and that control participants have less high-gamma power than young participants. Given the random selection of trials in the matching process, we performed the analysis 1000 times and used the median P value as the indicator of significance.

Number of high-gamma peaks. We modelled the dependent variable number of high-gamma peaks with independent variables group, movement rate and performing hand using cumulative link models (CLM, ordinal package) with a flexible logit link function for the regions M1 and PMC.

Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality, proportional odds assumption held true in the CLMs. In linear mixed-effects models and CLMs, significance was obtained by likelihood ratio tests of the full model against a reduced model without the effect in question. In the case of multiple comparisons, P values were corrected accordingly using the false discovery rate.

Table 1. Clinical and demographic data of stroke survivors.

ID	Sex	Age	Lesion side	TAS (months)	Stroke location	MRS	NIHSS	UEFM	ARAT	Grip force	KG force	NHPT	BBT
1	F	70	L	52	TC, CR	1	0	65	57	1.11	1.16	0.39	50
2	F	79	R	8	TC, CR, CI	3	2	46	44	0.09	0.60	0.08	26
3	M	74	R	153	BG, CI, CR	2	1	50	54	0.51	0.60	0.20	33
4	F	71	R	52	BG	1	1	63	57	0.97	1.07	0.35	43
5	F	74	R	43	PLCI	1	0	60	56	0.89	0.80	0.38	47
6	F	43	L	38	PLCI	0	0	66	57	1.59	1.26	0.60	82
7	F	73	L	39	MED	1	1	58	56	0.92	0.88	0.31	49
8	M	65	L	9	BG	1	0	66	57	0.93	1.28	0.45	71
9	M	61	R	9	PLCI	1	0	66	56	0.89	1.12	0.32	39
10	M	58	L	6	CR	1	0	64	57	1.05	1.00	0.41	52
11	M	57	L	51	MED	1	2	63	53	0.98	1.14	0.38	55
12	F	67	R	129	PO	0	0	64	57	0.97	1.40	0.41	58
13	M	62	R	9	CR	1	1	60	54	0.68	0.90	0.23	35
14	M	61	R	16	PRE	1	0	64	54	0.69	0.75	0.33	48
stroke	F: 7	65.4		45.6		1.1	0.6	61.1***	54.9**	0.88	1.00	0.35*	49.1**
SD stroke		9.3		45.3		0.7	0.8	6.1	3.5	0.33	0.25	0.12	14.7
control	F: 7	64.5				0	0	65.7	56.9	1.18	0.97	0.44	65.9
SD control		8.4				0	0	0.7	0.5	0.7	0.09	0.06	7.7

*$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$, statistical test of stroke against control group. Values of MRS, NIHSS, UEFM, ARAT, NHPT (pegs s^{-1}) and BBT (blocks min^{-1}) are absolute test scores of the affected hand (performing hand in control participants). Values of grip force and key grip force are ratios between the affected and not affected hand in stroke survivors and performing and not performing hand in control participants.

BG, basal ganglia; CI, capsula interna; CR, corona radiata; KG, key grip; MED, media infarct; PLCI, posterior limb of the capsula interna; PO, pons; PRE, precentral gyrus; TAS, time after stroke; TC, thalamocapsular.

Results

Participants

Fourteen stroke survivors (mean ± SD age = 65.4 ± 9.3 years, seven females, eight with a lesion of the right hemisphere, performing hand: 8 × left hand, 6 × right hand), 15 age-matched control participants (age = 64.5 ± 8.4 years, seven females, performing hand: 10 × left hand, 5 × right hand) and 29 young participants (age = 25.4 ± 4.6 years, 13 females) passed the inclusion criteria. Stroke survivors and control participants showed no signs of cognitive impairment according to the MMSE (stroke: mean 28.9 points, range 27–30 points; control: mean 29.7 points, range 28–30 points).

Clinical scores and structural imaging

Stroke survivors mostly showed only mild impairment of the upper extremity (mean UEFM = 61.1) (Table 1), with a significant difference between stroke and control participants in UEFM, ARAT, NHPT and BBT (UEFM: $W = 30.5$, $P < 0.001$, ARAT: $W = 51.0$, $P = 0.004$, NHPT: $t_{18.9} = -2.7$, $P = 0.016$, BBT: $t_{19.2} = -3.8$, $P = 0.001$) but no significant difference in whole hand ($W = 64.0$, $P = 0.077$) and key grip force ratio ($t_{15.8} = 0.4$, $P = 0.688$). CST-FA values were not significantly different between stroke and control participants ($t_{22.8} = 1.1$, $P = 0.269$) (Fig. 2*B*) when measured inferior to the level of the stroke lesion.

Improvement in movement rate

On average, stroke survivors had a significantly lower movement rate than control participants ($t_{24.3} = -3.6$, $P_{cor} = 0.001$; corrected for two comparisons) (Fig. 1*C*), and control participants had a significantly lower movement rate than young participants ($t_{40.8} = -7.4$, $P_{cor} < 0.001$; corrected for two comparisons). All three groups improved their average movement rate from block 1 to block 6 (stroke survivors: $t_{12} = -4.7$, $P_{cor} < 0.001$, control participants: $t_{14} = -6.9$, $P_{cor} < 0.001$, young participants: $t_{28} = -8.9$, $P_{cor} < 0.001$; corrected for three comparisons) (Fig. 1*B*). Comparing the first and the individual best block, stroke survivors increased their average movement rate by 22.6 ± 12.2 % (mean ± SD), control participants by 15.3 ± 7.1 % and young participants by 18.0 ± 10.9 %. Block-wise improvement showed no significant differences between the three groups, even without correction for multiple comparisons (stroke/control: $t_{20.5} = 1.9$, $P = 0.066$, control/young: $t_{39.6} = -1.0$, $P = 0.332$) (Fig. 1*D*).

Movement-related high-gamma power

We observed an increase in high-gamma power during the movement period (0–0.6 s, 60–90 Hz) relative to baseline with a maximum over the contralateral motor cortices (Fig. 3*A*). The increase of high-gamma power during movement was significant compared to baseline in each group (stroke survivors: $P_{cor} = 0.006$, control participants: $P_{cor} = 0.003$, young participants: $P_{cor} = 0.003$; corrected for three comparisons). The increase in high-gamma power occurred with movement onset and was most pronounced in M1 and PMC (Fig. 3*D*), prompting us to focus further analysis on these regions. Stroke survivors had significantly lower high-gamma power than control participants in the grid point with maximal power in regions M1 and PMC (M1: $t_{18.9} = -2.2$, $P_{cor} = 0.037$, PMC: $t_{19.4} = -2.3$, $P_{cor} = 0.037$; corrected for four comparisons) (Fig. 3*B*) and control participants had significantly lower high-gamma power than young participants (M1: $t_{34.4} = -2.3$, $P_{cor} = 0.037$, PMC: $t_{30.1} = -2.9$, $P_{cor} = 0.032$; corrected for four comparisons). When matching performance (movement rate) and handedness in stroke survivors and age-matched

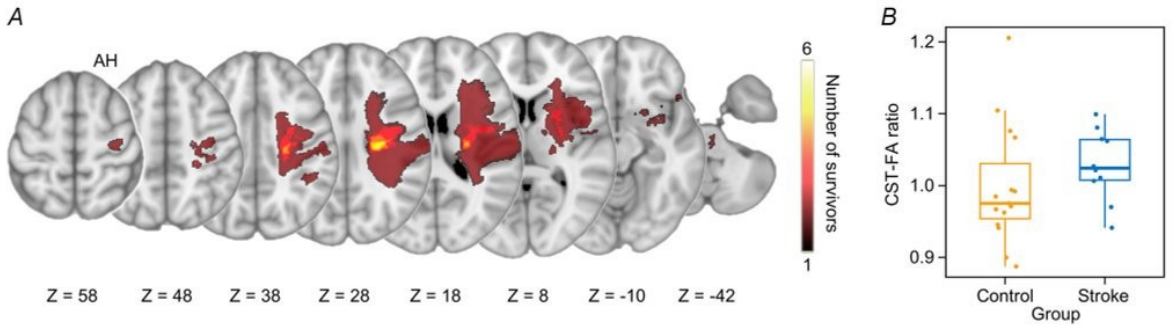

Figure 2. Stroke survivor characteristics
A, stroke lesions of the 10 survivors with available MRI lesion data, overlayed on a T1-weighted image in MNI standard space. Colour indicates the number of stroke survivors with a lesion at the voxel. Left-hemispheric lesions were flipped to the right hemisphere. *B*, distribution of CST-FA ratios. There was no significant group difference.

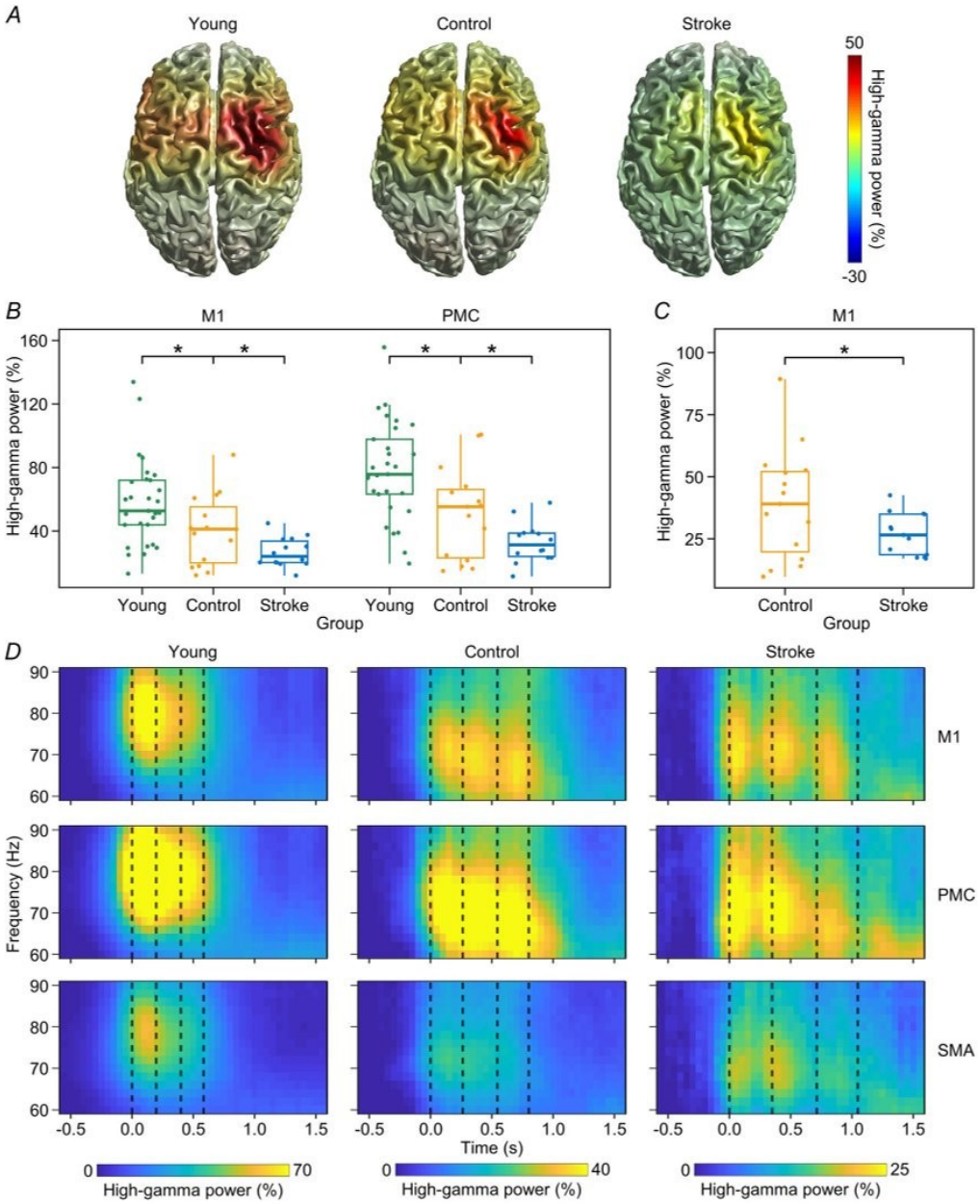

Figure 3. Characteristics of high-gamma power
A, group mean high-gamma power (0–0.6 s, 60–90 Hz) overlayed on a standard brain. The colour indicates the percentage increase in high-gamma power compared to the baseline. The activity of participants that performed the task with the right hand was flipped across hemispheres. High-gamma activity is evident mainly in motor regions contralateral to movement. *B*, distribution of participant mean high-gamma power in M1 and PMC. Asterisks indicate significant group differences. *C*, group difference (control participants *vs*. stroke survivors) in high-gamma power when matched for movement rate and performing hand. Boxplots and dots show the mean high-gamma power of each participant over 1000 repetitions of the matching process. *D*, group-level time-frequency spectrograms. The time point of the first button press corresponds to 0 s. Dotted lines indicate the average time points of button presses. Note the different scaling of the colour bars in the different groups. High-gamma power in M1 and PMC was much more prominent than in SMA, we therefore excluded SMA from further analysis. Significance marker: $^*P < 0.05$.

Table 2. Linear mixed-effects models of high-gamma power and movement rate.

		Model summary			Model comparison		
DV	IVs	Estimate	SE	*t*	χ^2	d.f.	*P*
Log(100 + HGP M1)	*Fixed effects*						
	Movement rate	0.16	0.04	3.8	12.6	1	**<0.001**
	Group				1.7	2	0.42
	Group (stroke)	−0.04	0.05	−0.9			
	Group (young)	0.02	0.05	0.5			
	Performing hand (*r*)	−0.01	0.05	−0.3			
	Random effects	**Variance**	**SD**				
	Participant (intercept)	0.07	0.26				
	Movement rate (slope)	0.05	0.23				
Log(100 + HGP PMC)	*Fixed effects*						
	Movement rate	0.17	0.04	4.1	14.2	1	**<0.001**
	Group				3.5	2	0.17
	Group (stroke)	−0.07	0.06	−1.2			
	Group (young)	0.05	0.06	0.9			
	Performing hand (*r*)	−0.05	0.06	−0.8			
	Random effects	**Variance**	**SD**				
	Participant (intercept)	0.09	0.30				
	Movement rate (slope)	0.05	0.22				

Performing hand indicates the effect of the right hand in comparison to the left hand, group indicates the effect of the respective group in comparison to the control group. Model comparison against a reduced model without the fixed effect in question. *P* values are uncorrected for multiple comparisons. Significant *P* values are highlighted in bold.
DV, dependent variable; d.f., degrees of freedom; HGP, high-gamma power; IVs, independent variables.

controls (trials in each group 1206.0 ± 2.7; mean ± SD), stroke survivors still had a significantly lower high-gamma power than control participants in both motor regions (M1: $t_{20.2} = -1.9$, $P_{cor} = 0.0383$, PMC: $t_{18.9} = -2.1$, $P_{cor} = 0.0383$; corrected for two comparisons) (Fig. 3*C*). However, when including all data and accounting for movement rate as a covariate in a linear mixed-effects model, no significant group effect was observed (M1: $P = 0.422$, PMC: $P = 0.173$). The group difference in high-gamma power between young and control participants was not significantly different anymore after matching for movement rate, even without correction for multiple comparisons (trials in each group: 1470.9 ± 2.1, M1: $t_{22.7} = -0.7$, $P = 0.239$, PMC: $t_{18.9} = -1.1$, $P = 0.144$).

Relation of high-gamma power, structure and clinical scores

High-gamma power in stroke survivors from either motor region was not significantly related to the structural integrity of the CST (CST-FA) (M1: $P = 0.634$, PMC: $P = 0.454$). Furthermore, there was no significant relation between high-gamma power in either motor region and residual motor function assessed by clinical scores (UEFM: M1: $P = 0.738$, PMC: $P = 0.468$; ARAT: M1: $P = 0.0852$, PMC: $P = 0.318$; NHPT: M1: $P = 0.872$, PMC: $P = 0.587$; BBT: M1: $P = 0.799$, PMC: $P = 0.555$; grip force: M1: $P = 0.807$, PMC: $P = 0.975$; key grip force: M1: $P = 0.818$, PMC: $P = 0.843$).

Relation of high-gamma power and movement rate

We computed linear mixed-effects models to assess the relationship between high-gamma power and movement rate, including an interaction term between the fixed effects movement rate and group. As this interaction was non-significant (M1: $P = 0.338$, PMC: $P = 0.615$), it was removed from the final model. Interaction plots for the different groups (Fig. 4*B*) are derived from the initial model that included the interaction, whereas all further analyses are based on the models without the interaction term.

Movement rate significantly related to high-gamma power in linear mixed-effects models across all groups in both motor regions, as trials with higher movement rate were associated with greater high-gamma power (M1: $P_{cor} < 0.001$, PMC: $P_{cor} < 0.001$; corrected for two comparisons) (Fig. 4*A* and Table 2). To investigate

whether a single group drove the effect of movement rate, we plotted the relationship between high-gamma power and movement rate in each group individually (Fig. 4*B*), which showed a positive association of high-gamma power and movement-rate in each group. Further evidence for the positive relation between high-gamma power and movement rate is provided by participant-level analyses across all groups. In those linear models, the same significant positive relation between movement rate and high-gamma power was evident (M1: $P_{cor} = 0.00816$, PMC: $P_{cor} = 0.00816$; corrected for two comparisons) (Fig. 4*C* and Table 3). This participant-level linear model was sufficiently stable to be computed in any region of the brain, even if the overall level of high-gamma power was low. Thus, to further infer on the spatial distribution of the association of high-gamma power and movement rate, we modelled the relationship for activity at each grid point. The positive relation was apparent even without the preselection of the grid point with maximal power in motor regions. Importantly, the significant cluster only covered motor areas with a particular focus on the contralateral hand knob ($P = 0.048$) (Fig. 4*D*).

High-gamma peak frequency

High-gamma peak frequency significantly differed between young (M1: $\tilde{f}_{\text{peak}} = 79.4$ Hz) and control participants (M1: $\tilde{f}_{\text{peak}} = 70.7$ Hz), with significantly lower high-gamma peak frequency in the older controls (M1: $W = 46.5$, $P_{cor} < 0.001$, PMC: $W = 55.0$, $P_{cor} = 0.001$; corrected for four comparisons) (Fig. 5). High-gamma peak frequency was not significantly different between stroke survivors (M1: $\tilde{f}_{\text{peak}} = 71.9$ Hz)

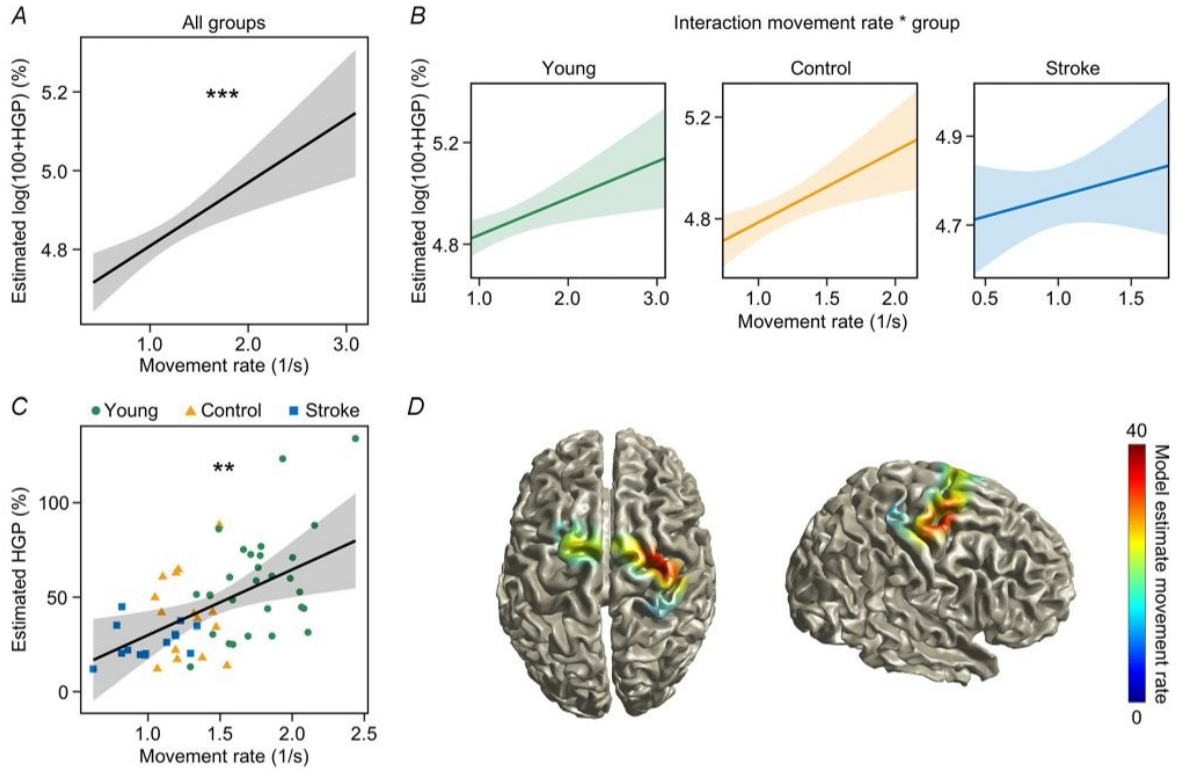

Figure 4. Relation between high-gamma power in M1 and movement rate
A, effect plot of the fixed effect movement rate in a trial-level linear mixed-effects model across groups for the relation between movement rate and high-gamma power. *B*, effect plots of the interaction between movement rate and group in trial-level mixed-effects models for the relation between movement rate and high-gamma power. For each group individually, the direction of the relation is positive. The plots are limited to actual ranges of movement rates in the respective groups. *C*, effect plot of the fixed effect movement rate in a participant-level linear regression model across groups for the relation between movement rate and high-gamma power. *D*, resulting cluster of a grid point-wise analysis for the relation of movement rate and high-gamma power. For activity in each grid point in the brain, a linear model between movement rate and high-gamma power was computed and results were tested for significance with a cluster-based permutation analysis. The colour indicates the model estimates of movement rate. Asterisks indicate the significance of the effect movement rate. HGP: high-gamma power. Significance markers: $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 3. Linear regression models of high-gamma power and movement rate.

		Model summary				Whole model		
DV	IVs	Estimate	SE	*t*	*P*	*F*	d.f.	*P*
HGP M1	Movement rate	34.7	12.4	2.8	**0.007**	7.1	4, 53	**<0.001**
	Group (stroke)	−4.3	8.8	−0.5	0.63			
	Group (young)	4.0	10.5	0.4	0.71			
	Performing hand (*r*)	−5.6	8.5	−0.7	0.51			
HGP PMC	Movement rate	40.0	14.5	2.7	**0.008**	10.2	4, 53	**<0.001**
	Group (stroke)	−7.0	10.3	−0.7	0.50			
	Group (young)	15.0	12.2	1.2	0.23			
	Performing hand (*r*)	−11.9	9.9	−1.2	0.24			

Performing hand indicates the effect of the right hand in comparison to the left hand, group indicates the effect of the respective group in comparison to the control group. *P* values are uncorrected for multiple comparisons. Significant P values are highlighted in bold.
d.f., degrees of freedom; DV, dependent variable; HGP, high-gamma power; IVs, independent variables.

and control participants (M1: $W = 107.0$, $P_{cor} = 0.947$, PMC: $W = 100.5$, $P_{cor} = 0.947$; corrected for four comparisons). Linear regression models across groups showed no significant relation between movement rate and high-gamma peak frequency even without correction for multiple comparisons (M1: $P = 0.147$, PMC: $P = 0.0663$).

Number of high-gamma peaks

High-gamma power time courses revealed differences in high-gamma power evolution over time between the three groups (Fig. 6*A* and *B*). After correction for multiple comparisons, there were no significant group differences in the number of high gamma peaks during task execution (control/young: M1: $W = 276.5$, $P_{cor} = 0.141$, PMC: $W = 274.5$, $P_{cor} = 0.141$; stroke/control: M1: $W = 138.5$, $P_{cor} = 0.141$, PMC: $W = 149$, $P_{cor} = 0.141$). When modelling the number of high-gamma peaks as a function of group and movement rate, we observed a significant effect of movement rate (M1: $P_{cor} = 0.0172$, PMC: $P_{cor} = 0.0315$; corrected for two comparisons) (Fig. 6*C* and Table 4), but not group (M1: $P_{cor} = 0.759$, PMC: $P_{cor} = 0.759$; corrected for two comparisons). Hence, participants with faster movement rate had a significantly higher probability of having fewer high-gamma peaks. Specifically, in M1, if the movement rate was greater than 1.95 s^{-1} (corresponding to ∼7.8 presses s^{-1}), the probability was highest that the participants would exhibit only one high-gamma peak. In contrast, if the movement rate was below 1.17 s^{-1} (corresponding to ∼4.7 presses s^{-1}), the probability was highest that the participant would exhibit one individual high-gamma peak for each button press.

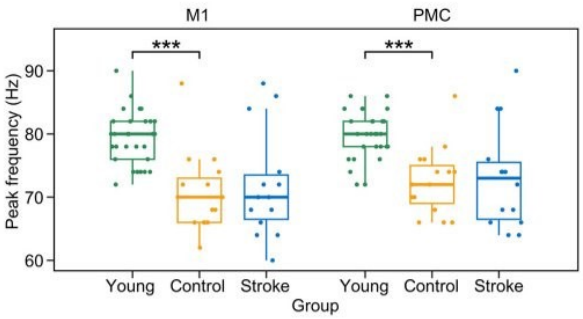

Figure 5. Characteristics of high-gamma peak frequency
Distribution of participant's mean high-gamma peak frequency. Asterisks indicate significant group differences. Significance marker: ***$P < 0.001$.

Relation of high-gamma power and improvement

Neither improvement across trials, defined as the percentage increase in movement rate from the current to the next trial (trial-wise improvement), nor improvement across blocks, defined as the change from first block to best block (block-wise improvement) showed a significant association with high-gamma power (trial-wise: M1: $P = 0.775$, PMC: $P = 0.480$; block-wise: M1: $P = 0.132$, PMC: $P = 0.383$). In line, a cluster-based permutation analysis, modelling the association of activity in each grid point separately, showed no significant relation between high-gamma power and block-wise improvement.

Discussion

Our study characterizes cortical high-gamma oscillations at differing performance levels across age groups and

in stroke survivors. We have demonstrated that a faster movement rate is robustly related to increased cortical high-gamma power over motor areas during movement onset. By contrast, improvement in performance did not significantly relate to high-gamma power. Moreover, with lower movement rates, we observed distinct high-gamma peaks for each movement, whereas, in faster movements, high-gamma activation became smeared over time. Even though movement rate showed the strongest association with high-gamma power, a difference in high-gamma power between the stroke and the control cohort persisted even after matching for movement rate.

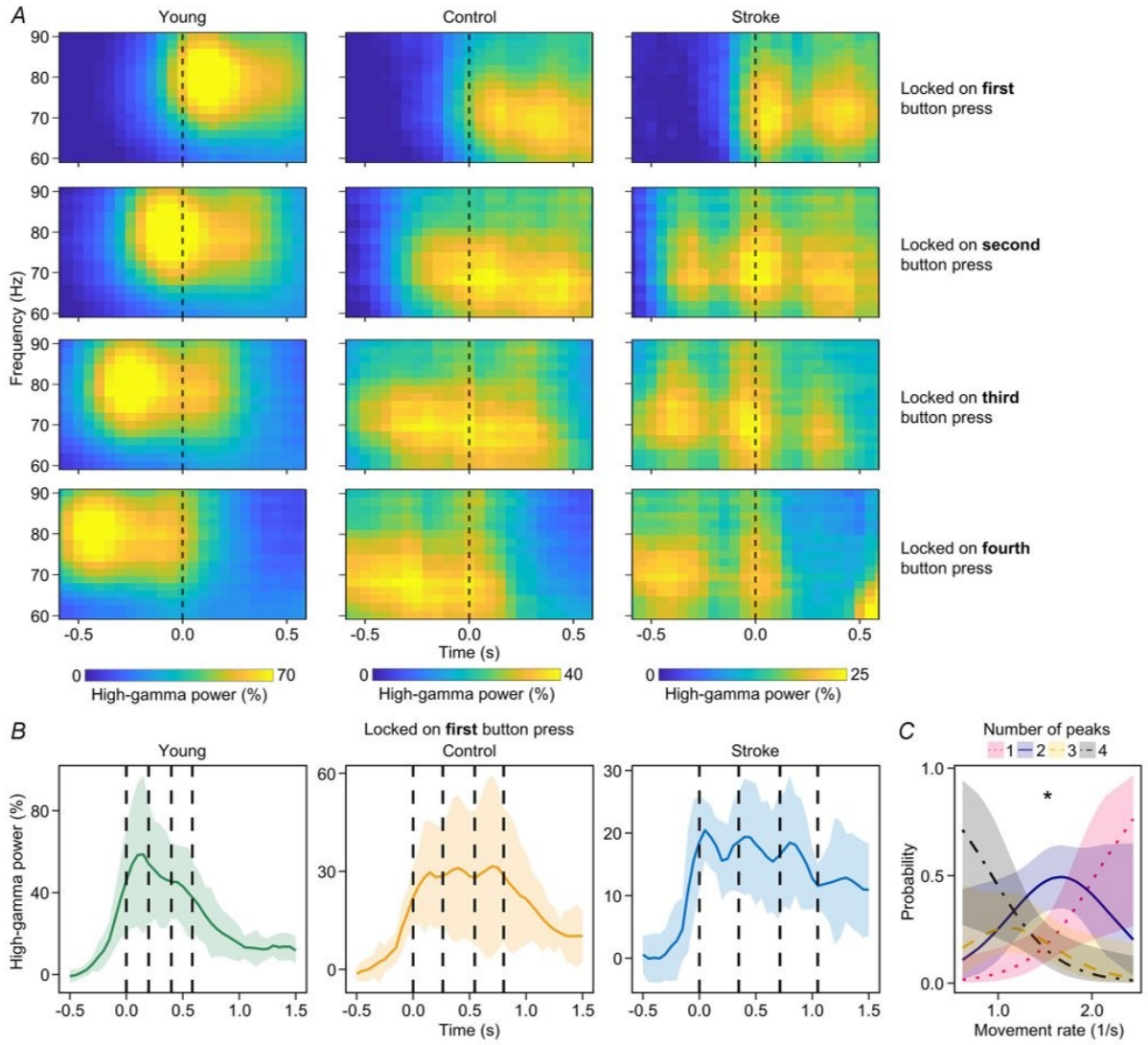

Figure 6. High-gamma power time course in M1
A, group-level time-frequency spectrograms locked on each individual button press. Time zero corresponds to the time point of the respective button press. In stroke survivors, one high-gamma peak is visible around each button press. In the young and control group, the peaks tend to be blurred. *B*, group-level high-gamma power time courses, locked on the first button press. Dotted lines indicate the average time points of button presses. Shaded areas indicate median absolute deviation. *C*, effect plot of the independent variable movement rate in a cumulative link model that models the relationship between number of high-gamma peaks, movement rate and group with participant-level data from all three groups combined. The effect of movement rate was significant compared to a reduced model, the effect of group was not significant (not shown). The data shown are from the grid point with maximal power in M1. Significance markers: $^*P < 0.05$.

Table 4. Cumulative link models of the number of high-gamma peaks, movement rate and group

		Model summary			Model comparison		
DV	IVs	Estimate	SE	*z*	χ^2	d.f.	*P*
nPeaks M1	Movement rate	−2.91	1.15	−2.5	6.9	1	**0.009**
	Group				0.6	2	0.76
	Group (stroke)	0.45	0.76	0.6			
	Group (young)	0.51	0.90	0.6			
	Performing hand (*r*)	−0.18	0.73	−0.2			
nPeaks PMC	Movement rate	−2.39	1.14	−2.1	4.6	1	**0.03**
	Group				1.8	2	0.42
	Group (stroke)	1.00	0.79	1.3			
	Group (young)	−0.06	0.92	−0.1			
	Performing hand (*r*)	0.19	0.74	0.3			

Performing hand indicates the effect of the right hand in comparison to the left hand, group indicates the effect of the respective group in comparison to the control group. Model comparison against a reduced model without the fixed effect in question. *P* values are uncorrected for multiple comparisons. Significant P values are highlighted in bold.
d.f., degrees of freedom; DV, dependent variable; IVs, independent variables; nPeaks, number of high-gamma peaks.

Decreased cortical high-gamma power in stroke survivors

In humans, studies on movement-related high-gamma oscillations are restricted. Most reports on high-gamma oscillations have utilized invasive ECoG recordings, which are typically not available in stroke survivors. Scalp EEG, which can be measured easily in stroke survivors, can smear the focal high-gamma oscillations as a result of spatial blurring at the skull. MEG recordings, however, offer the opportunity to measure motor cortical high-gamma oscillations non-invasively and with high spatial precision in survivors with stroke pathology. In line with the literature in healthy cohorts, we observed high-gamma oscillations in chronic stroke survivors at the onset of contralateral movements, located over the primary motor cortex and premotor cortices. We observed that chronic stroke survivors, even though they exhibited largely very mild hand motor impairment, showed less cortical high-gamma power compared to age-matched controls. This difference even remained significant after matching for movement rate. However, this group effect was only apparent when controlling for variability, suggesting that, although a difference exists, it can be challenging to detect amidst the variability in movement rates. These results are paralleled by an existing study in rodents, in which the peri-infarct cortex of mice after stroke showed a deficit in low-gamma power under anaesthesia (Hazime et al., 2021). The disproportional decrease of high-gamma power in stroke survivors supports the notion that high-gamma power may not purely reflect movement kinematics. This is further supported by findings of significant high-gamma power in motor imagery (Fischer et al., 2017; Miller et al., 2010). The decrease in high-gamma power was not related to clinical motor function scores or structural integrity of the corticospinal tract when measured inferior to the level of the stroke lesion. The lack of a significant relationship between high-gamma power and structural integrity of the CST in stroke survivors might possibly be a result of the low number of survivors on whom we were able to acquire MRIs rather than the actual lack of a relationship, as corticospinal connectivity is related to motor impairment after stroke (Urbin et al., 2021). Furthermore, differences in FA at more superior locations of the CST may exist, potentially accounting for the observed differences in high-gamma power.

Topological organization of high-gamma oscillations

High-gamma oscillations are more spatially focused compared to lower frequencies (Crone et al., 1998) and better aligned with somatotopy (Miller et al., 2007; Quandt et al., 2012). In comparison, modulation of beta activity (13–30 Hz) may reflect a more general, widespread activation signal during and after movement with only limited specificity for the limb component that was moved (Pfurtscheller et al., 2003). In simple motor tasks, high-gamma oscillations have been described to be localized to M1 (Cheyne et al., 2008; Crone et al., 1998; Miller et al., 2007). With complex tasks, a more widespread cortical area is recruited (Donoghue & Sanes, 1994), consisting of PMd and PMv as part of the network for hand motor control (Chouinard & Paus, 2006; Rizzolatti et al., 2002). PMC is connected with both the arm area of the primary motor cortex and the spinal cord (Dum & Strick, 1991) and is considered to be involved

in connecting external cues with forthcoming movement (Chouinard & Paus, 2006). A reason for the observed elevated high-gamma power levels in PMC might be that our task is required to constantly maximize motor performance. It may have thus involved a more complex network, including PMC, compared to simpler tasks such as finger abductions or fist clenching.

The role of high-gamma oscillations in motor control

High-gamma oscillations are considered to be prokinetic in nature and have been shown to strongly synchronize during active but not passive movements (Brücke et al., 2012; Liu et al., 2008; Muthukumaraswamy, 2010). At the onset of movement, in addition to the motor cortex, the basal ganglia and thalamus exhibit gamma-band oscillations (Androulidakis et al., 2007; Blenkinsop et al., 2017; Kempf et al., 2009; Muthukumaraswamy, 2011). Invasive recordings from the basal ganglia in patients with deep brain stimulation (Anzak et al., 2012; Brücke et al., 2012; Fischer et al., 2017; Joundi, Brittain, et al., 2012; Lofredi et al., 2018) revealed that movement-related high-gamma power from the contralateral subthalamic nucleus and globus pallidus interna increased with movement amplitude, movement velocity and force production, stressing its potential significance in movement coding. Also, links to behaviour have been established in movement disorders, in which less high-gamma power in the contralateral subthalamic nucleus is associated with higher symptom severity in Parkinson's disease (PD) (Lofredi et al., 2018). Similarly, PD patients in the dopamine-depleted state show pathologically impaired movements and less high-gamma power (Anzak et al., 2012; Joundi, Brittain, et al., 2012). In line, dopaminergic medication, as a prokinetic drug, leads to increased high-gamma power in PD patients (Litvak et al., 2012). Furthermore, patients suffering from hyperkinetic movements, such as medication-induced dyskinesias, present with pronounced high-gamma power (Swann et al., 2016). Recent studies have examined the subcortical-cortical communication in the gamma band and found that fast reaction times were preceded by enhanced subcortical spike to cortical gamma phase coupling (Fischer et al., 2020), underlining the role of gamma activity within the subcortical–cortical network for motor performance. In cortical invasive recordings, high-gamma oscillations up to very high frequencies (600–1000 Hz) contained decoding information on position, velocity and predominantly movement speed (Hammer et al., 2016). Single-unit activity in M1 is thought to mainly tune direction, whereas larger neural populations, as reflected by LFPs, appear to represent movement speed (Anderson et al., 2012; Mehring et al., 2003; Wang et al., 2017). Here, for the first time using non-invasive recording in humans, we demonstrate a clear association of cortical high-gamma power (60–90 Hz) and movement rate across three groups with differing levels of movement rate.

Time course of high-gamma oscillations

High-gamma oscillations have been shown to be most pronounced around movement onset, subsiding over the course of movement even when force production is maintained (Muthukumaraswamy, 2010). With repetitive movements, a distinct burst of high-gamma power has been described, with a tendency for individual gamma bursts to blur at a movement frequency of 3 Hz (Muthukumaraswamy, 2010). In line, we showed that the observed intersubject difference in high-gamma peaks was driven by differences in movement rate, where with faster movements individual peaks blurred and the probability to exhibit only one high-gamma peak increased. This contrasts with observations for power at lower frequencies: beta-band power modulations have still been observed at a movement frequency of 4 Hz (Toma et al., 2002). Hence, for faster repeating movements, high-gamma oscillations may code the overall motor action rather than every single movement separately. In addition, there has been evidence that high-gamma oscillations seem to also encode cognitive processes rather than purely active contraction of muscles (Isabella et al., 2021).

Effects of high-gamma peak frequency

The range of motor high-gamma oscillations has been reported to be variable across studies, ranging from 75–100 Hz (Crone et al., 1998) to 60–90 Hz (Muthukumaraswamy, 2010) and up to 55–375 Hz (Anzak et al., 2012). In the hippocampal CA1 region, studies have described a slow-, mid- and fast-frequency gamma band. It remains unclear whether distinct high-gamma bands encode separate forms of motor processing. Over the lifespan, the high-gamma frequency range has been reported to vary depending on age with an increase from the very young child to adulthood (Cheyne et al., 2014; Johnson et al., 2020). Here, we observe a decrease of the high-gamma peak frequency with age, with the peak frequency being significantly lower in the older controls (79.4 Hz *vs.* 70.7 Hz). These findings are in contrast to a previous study, which found no association between high-gamma peak frequency and age in a large cohort with a simple motor task (Bardouille & Bailey, 2019). The reason for the differences might be the different analysis methods or discrepancies in motor tasks. Intra-participant gamma peak frequency has been reported to be consistent over recording sessions, over hemispheres

and for movement of the same body part with differing movement vigour (Brücke et al., 2012; Cheyne & Ferrari, 2013; Lofredi et al., 2018). Also, in our study, high-gamma peak frequency did not significantly change with varying movement rates.

The role of high-gamma power in motor skill acquisition

Recent work suggested that motor-related high-gamma oscillations may also be relevant for motor learning and plasticity (Akkad et al., 2021; Guerra et al., 2020; Nowak et al., 2018) and that motor skill acquisition is dependent on changes in local circuitry within M1 (Kida et al., 2023; Kolasinski et al., 2019). Some studies have shown an increase in motor performance (faster reaction times, learning of movement parameters) after high-gamma tACS (Bologna et al., 2019; Guerra et al., 2018; Joundi, Jenkinson, et al., 2012; Santarnecchi et al., 2017; Spooner & Wilson, 2023; Sugata et al., 2018). Furthermore, a study analysing transcranial magnetic stimulation-induced intracortical inhibition reported a decrease in intracortical inhibition after high-gamma tACS, correlating with improved motor learning scores (Nowak et al., 2017). In our study, the level of motor skill acquisition was similar in stroke survivors compared to young and age-matched control participants. Hence, there seems to be potential for further rehabilitation to improve motor skills even in a cohort of mildly impaired stroke survivors. We investigated the relationship between high-gamma power and improvement in movement rate over time and did not find a significant association. Our recent study applying theta-gamma tACS in young participants and stroke survivors (Grigutsch et al., 2024) is in line with this finding, whereas, in healthy participants, thumb acceleration was increased by theta-gamma tACS, the overall motor skill acquisition was not affected. In stroke survivors, theta-gamma tACS even deteriorated overall motor skill acquisition. Our findings suggest that high-gamma power does at least not strongly relate to motor skill acquisition in this thumb movement task.

Limitations

Several limitations should be considered for this study. First, the sample size of stroke survivors was limited. It is therefore possible that we missed findings because of restricted statistical power. Second, most stroke survivors exhibited only mild impairment, limiting generalizability to more severely impaired stroke survivors. Nevertheless, we were able to show a highly robust relationship between movement rate and high-gamma power and significant group differences between stroke and control participants. The observed group differences in high-gamma power, however, were subtle and became evident only when accounting for variability in movement rate, suggesting that these findings might vary in other cohorts or under different conditions. Third, because we specifically investigated thumb movements, the generalizability to the movement of other parts of the upper extremity is unknown. Still, high-gamma oscillations are elicited by movements of different body parts in a similar manner (Crone et al., 1998; Miller et al., 2007; Muthukumaraswamy, 2010), which suggests that our findings may potentially generalize to other movement paradigms. Fourth, our task was not explicitly designed to investigate the blurring of high-gamma bursts at higher movement rates. However, we consider this finding significant and consider that it opens avenues for future research into this phenomenon. Finally, we found no association between high-gamma power and motor skill acquisition, although it is important to note that our study misses any evaluation of long-term effects neglecting the learning-performance distinction (Kantak & Winstein, 2012). We, therefore, are only able to draw conclusions on short-term motor skill acquisition.

Conclusions

In conclusion, characterizing cortical movement-related high-gamma oscillations, we found a strong positive relationship between movement rate and high-gamma oscillations within the motor network. We quantified high-gamma oscillations in stroke survivors with motor impairment, revealing a reduction in movement-related high-gamma power mostly because of the reduced movement rate of stroke survivors. We suggest that enhancing cortical high-gamma activity through neuromodulation could potentially serve as a therapeutic approach to improve motor performance in stroke survivors.

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Additional information

Data availability statement

The data that support the findings of this study are available at GitHub using the following link: https://github.com/xeni-lab/high-gamma-in-stroke.

Competing interests

The authors declare that they have no competing interests.

Author contributions

B.H., L.S.T., C.J.S., B.C.S. and F.Q. were responsible for the conception or design of the work. B.H., L.S.T., S.W., C.J.S., L.F., R.O., J.F., G.S., F.L.H., C.G., R.S., T.R.S., B.C.S. and F.Q. were responsible for the acquisition, analysis or interpretation of data for the work. B.H., L.S.T., S.W., C.J.S., L.F., R.O., J.F., G.S., F.L.H., C.G., R.S., T.R.S., B.C.S. and F.Q. were responsible for drafting the work or revising it critically for important intellectual content.

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Keywords

finger movement, high-gamma oscillations, magnetoencephalography, MEG, movement-related high-gamma synchronization, stroke

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History

Translational perspective

The neurophysiological processes of motor coding are still incompletely understood. In particular, high-gamma oscillations during movement are mainly studied using invasive recordings because non-invasive electroencephalography can often not fully detect local high-gamma oscillations (60–90 Hz). However, invasive recordings in healthy participants or stroke survivors are rare. We therefore recorded magnetoencephalography data during a thumb movement task in chronic stroke survivors, age-matched control participants and healthy young participants. High-gamma oscillations were localized in motor cortical areas and strongly related to movement rate across all three groups. Stroke survivors showed reduced cortical high-gamma power compared to age-matched control participants, even after matching for movement rate. Our results highlight the relevance of high-gamma oscillations for fast finger movements, which are important in stroke rehabilitation. Reduced high-gamma oscillations during slower movements suggest that movement rate could be enhanced with neuromodulation which boosts high-gamma oscillations; for example, using brain stimulation or pharmacological interventions. Specifically, transcranial alternating current stimulation (tACS) in the high-gamma range may promote high-gamma oscillations and enhance movement rate in stroke survivors.

3. Zusammenfassung

High-gamma oscillations (60 – 90 Hz) in cortical motor areas play a prokinetic role in the motor system. They have never been quantified in stroke survivors. Theta-gamma phase amplitude coupling (PAC) has been shown to influence motor skill acquisition and might be an important mechanism in motor rehabilitation after stroke. In a magnetoencephalography study, we found a robust positive association between motor cortical high-gamma power and movement rate as measure of motor performance in stroke survivors, age-matched control participants and young participants. Stroke survivors showed less high-gamma power than control participants, even after matching for movement rate. We were not able to detect relevant theta-gamma PAC in the data. In a follow-up transcrancial alternating current stimulation (tACS) study, young participants showed an increase in thumb acceleration during theta-gamma tACS compared to sham. Stroke survivors exhibited a decreased amount of motor skill acquisition during theta-gamma stimulation compared to sham. These results do not support the use of theta-gamma tACS to improve motor rehabilitation after stroke. High-gamma tACS, however, should be further investigated to test its effectiveness in improving motor rehabilitation.

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Oszillationen im hohen Gamma Bereich (60 - 90 Hz) in kortikalen motorischen Arealen haben eine prokinetische Rolle im motorischen System. Sie wurden nach einem Schlaganfall noch nie quantifiziert. Theta-Gamma Phasen-Amplituden-Kopplung (PAC) beeinflusst den Erwerb motorischer Fähigkeiten und könnte daher ein wichtiger Mechanismus in der motorischen Rehabilitation nach einem Schlaganfall sein. In einer Magnetoenzephalographie-Studie fanden wir einen robusten positiven Zusammenhang zwischen der Power von hohen Gamma-Oszillationen im Motorkortex und der Bewegungsrate als Maß für die motorische Leistung bei Schlaganfallüberlebenden, alters-angepassten Kontrollprobanden und jungen Probanden. Schlaganfallüberlebende zeigten eine geringere Power hoher Gamma-Oszillationen als Kontrollprobanden, selbst nach Korrektur für die Bewegungsrate. Wir konnten keine relevante Theta-Gamma-PAC in den Daten finden. In einer Folgestudie mit transkranieller Wechselstromstimulation (tACS) zeigten junge Probanden eine Zunahme der Daumenbeschleunigung während Theta-Gamma tACS im Vergleich zur Scheinstimulation. Schlaganfallüberlebende zeigten während der Theta-Gamma-Stimulation im Vergleich zur Scheinstimulation einen geringeren Erwerb motorischer Fähigkeiten. Diese Ergebnisse sprechen nicht für den Einsatz von Theta-Gamma-TACS zur Verbesserung der motorischen Rehabilitation nach einem Schlaganfall. tACS mit hohen Gamma-Oszillationen sollte jedoch weiter in Bezug auf Wirksamkeit zur Verbesserung der motorischen Rehabilitation untersucht werden.

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5. Abkürzungsverzeichnis

DICS: Dynamic imaging of coherent sources

M1: Primary motor cortex

MEG: Magnetoencephalography

MRI: Magnetic resonance imaging

PAC: Phase-amplitude coupling

PMC: Premotor cortex

SMA: Supplementary motor area

SNR: Signal-to-noise ratio

SSD: Spatio-spectral decomposition

tACS: Transcranial alternating current stimulation

TGP: Theta-gamma peak

TGT: Theta-gamma trough

6. Abbildungsverzeichnis

Figure 1A was adapted without changes from *"*Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors*"* by Haverland et al., 2025, The Journal of Physiology, Volume 603, 873-893. The figure caption was adapted without changes.

7. Erklärung des Eigenanteils

I am the first author of the publication ‘Human cortical high-gamma power scales with movement rate in healthy participants and stroke survivors’ (Haverland et al., 2025). The fundamental structure of this study was planned by Bettina Schwab and Fanny Quandt, apart from that I was involved in every step of the experimental process. Together with another doctoral candidate, Lena Timmsen, I wrote the script for the motor task based on the task used in Akkad et al. (2021) and adapted it to the specific needs of our MEG setup. We recruited the participants with help from Karin Reimann for the young participant group, performed the MEG measurements with help from Christiane Reißmann and raised the clinical scores in all participants. Afterwards, Lena Timmsen and I performed the preprocessing of the MEG data. I performed further data analysis including time-frequency analysis, source reconstruction, cluster-based nonparametrical statistical tests, calculating group differences with statistical tests and modeling of data relations with linear models, linear mixed-effects models and cumulative link models alone under supervision of Fanny Quandt and Bettina Schwab. I wrote the first draft of the publication, created the figures, and revised the manuscript according to the feedback of the co-authors. I further am a co-author of the publication ‘Differential effects of theta-gamma tACS on motor skill acquisition in young individuals and stroke survivors: A double-blind, randomized, sham-controlled study‘ (Grigutsch et al., 2024), where I helped adjusting the motor task to the experimental setup, was involved in the data analysis and data interpretation and revised the first draft of the manuscript. Finally, I wrote the summarized presentation of the publications and performed additional analyses regarding theta-gamma phase-amplitude coupling and theta power.

8. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe, insbesondere ohne entgeltliche Hilfe von Vermittlungs- und Beratungsdiensten, verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe. Das gilt insbesondere auch für alle Informationen aus Internetquellen.

Soweit beim Verfassen der Dissertation KI-basierte Tools („Chatbots“) verwendet wurden, versichere ich ausdrücklich, den daraus generierten Anteil deutlich kenntlich gemacht zu haben. Die „Stellungnahme des Präsidiums der Deutschen Forschungsgemeinschaft (DFG) zum Einfluss generativer Modelle für die Text- und Bilderstellung auf die Wissenschaften und das Förderhandeln der DFG“ aus September 2023 wurde dabei beachtet.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich damit einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Datum Unterschrift

9. Danksagung

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