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Dynamic causal modelling highlights the importance of decreased self-inhibition of the sensorimotor cortex in motor fatigability

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Abstract

Motor fatigability emerges when challenging motor tasks must be maintained over an extended period of time. It is frequently observed in everyday life and affects patients as well as healthy individuals. Motor fatigability can be measured using simple tasks like finger tapping at maximum speed for 30 s. This typically results in a rapid decrease of tapping frequency, a phenomenon called motor slowing. In a previous study (Bächinger et al, eLife, 8 (September), https://doi.org/10.7554/eLife.46750, 2019), we showed that motor slowing goes hand in hand with a gradual increase in blood oxygen level dependent signal in the primary sensorimotor cortex (SM1), supplementary motor area (SMA), and dorsal premotor cortex (PMd). It is unclear what drives the activity increase in SM1 caused by motor slowing and whether motor fatigability affects the dynamic interactions between SM1, SMA, and PMd. Here, we performed dynamic causal modelling (DCM) on data of 24 healthy young participants collected during functional magnetic resonance imaging to answer this question. The regions of interest (ROI) were defined based on the peak activation within SM1, SMA, and PMd. The model space consisted of bilateral connections between all ROI, with intrinsic self-modulation as inhibitory, and driving inputs set to premotor areas. Our findings revealed that motor slowing was associated with a significant reduction in SM1 self-inhibition, as uncovered by testing the maximum à posteriori against 0 ($t(23)=-4.51$, $p < 0.001$). Additionally, the model revealed a significant decrease in the driving input to premotor areas ($t(23) > 2.71$, $p < 0.05$) suggesting that structures other than cortical motor areas may contribute to motor fatigability.

Keywords Fatigue · Motor slowing · Functional MRI · Dynamic causal modelling · Motor areas · Premotor areas

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Introduction

Motor fatigue is a condition which is frequently experienced in everyday life. However, elevated fatigue is a key symptom of many neurological and neuropsychiatric disorders (Kluger et al. 2013; Manjaly et al. 2019). Despite its high prevalence in clinical and non-clinical settings, the mechanisms causing motor fatigue are still poorly understood. Here, we focus on one specific aspect of fatigue, called 'performance fatigability', which is defined as an objectively measurable decline in outcome parameters (Kluger et al. 2013). Performance fatigability can be studied using a simple finger-tapping paradigm: tapping as quickly as possible for 30 s is characterised by a significant decrease in tapping speed, which we refer to as 'motor slowing' (Bächinger et al. 2019). In this paradigm, the tapping speed reflects the objective outcome parameter and the reduction of tapping speed over time is a marker of fatigability. Motor slowing is

an interesting paradigm to investigate which brain mechanisms underpin fatigability because neuromuscular and spinal factors have been shown to play only a minor role in mediating the decline of tapping speed over time (Arias et al. 2015; Madrid et al. 2016, 2018; Madinabeitia-Mancebo et al. 2021).

In a recent study, we could show that motor slowing is associated with changes in the sensorimotor network and in the primary sensorimotor cortex in particular (SM1, Bächinger et al. 2019). Despite a decrease in tapping speed, blood-oxygen level dependent (BOLD) activation increased significantly over time in SM1, dorsal premotor cortex (PMd) and the supplementary motor area (SMA). Neurophysiological measurements revealed that motor slowing is linked to a decrease in inhibition, and specifically surround inhibition within SM1, which correlated with an increase in coactivation of agonistic-antagonistic muscle groups (Bächinger et al. 2019). These findings suggest that motor slowing is associated with the breakdown of inhibitory mechanisms in the primary motor cortex. This proposition is consistent with a population coding model of the primary motor cortex whereby local inhibition can shape the broadness of population tuning curves (Georgopoulos et al. 1986; Georgopoulos and Carpenter 2015): when surround inhibition is low, agonistic and antagonistic tuning curves are wider, resulting in a higher level of coactivation of involved and non-involved muscle groups.

It has been suggested that these local inhibitory mechanisms can be modulated by excitatory connections from other brain areas (Mahan and Georgopoulos 2013). In our previous motor slowing study, we proposed that projections from areas upstream of SM1 may have altered the observed change in inhibition in SM1 (Bächinger et al. 2019). Indeed, our functional magnetic resonance imaging (fMRI) results showed that motor slowing was also characterized by a significant activation increase in PMd and SMA. Both areas have been shown to be involved in modulating descending motor commands (see review Correia et al. 2022). It remains unclear, however, how PMd and SMA interact with SM1 while motor slowing arises, and how these areas contribute to shaping local inhibition in SM1.

To investigate premotor-motor interactions during motor slowing, we performed dynamic causal modelling (DCM) on the data from our previous study (Bächinger et al. 2019). Previously, we investigated which brain areas show a change in BOLD activation, but we did not analyse how these brain areas interact. By estimating effective connectivity through patterns of causal interaction, DCM can reveal directionality of neural interactions.

We hypothesized that self-inhibition in SM1 would decrease during motor slowing. We further explored whether

motor slowing is associated with changes in effective connectivity between SM1, SMA, and PMd.

Methods

The data used in this manuscript has been published previously in Bächinger et al. 2019; experiment 6. The focus of the analysis in the previous publication was on changes in fMRI BOLD activation associated with motor slowing. Here, we re-analysed the data with an emphasis on network modelling with DCM. The behavioural task, fMRI preprocessing methods, and the general linear model (GLM) analysis of BOLD activity (i.e., parametric and block design-based analysis) is identical to Bächinger et al. 2019. We reiterate the relevant methods for the reader's convenience.

Participants

Of the 25 right-handed participants who took part in the experiment, 24 were included in the DCM analysis. The mean (SD) age was 23.8 (3.3) years and 50% were female. One participant was excluded because they did not show any motor slowing, but rather an increase in tapping speed, indicating that they did not perform the task as instructed. All participants were free of medication, had no history of neurological or psychiatric disease and were naïve to the purpose of the experiment. All experimental protocols were approved by the research ethics committee of the canton of Zurich (KEK-ZH 2015−0537) and participants gave written informed consent to the study.

Behavioural task and analysis

The experiment consisted of two different conditions: finger tapping for either 30 s (slowing condition) or 10 s (control condition), each followed by a 30 s break. Tapping was performed alternating between index and middle finger at maximum speed. Participants were informed about the condition prior to the start of tapping with a visual get-ready cue (randomly jittered between 2 and 3 s). The conditions were blocked within each fMRI run: One block was made up of four trials of the slowing condition, followed by four trials of the control condition, or vice versa. Each participant performed two fMRI runs consisting of two blocks each. This resulted in 16 trials per condition. The starting condition of the first run (slowing or control condition) was alternated across participants and the second run had a counterbalanced order in relation to the first run. Additionally, an implicit baseline of 20 s was measured after each block (Fig. 1A). Behavioural data was analysed as described previously (Bächinger et al. 2019). Tapping and break intervals were
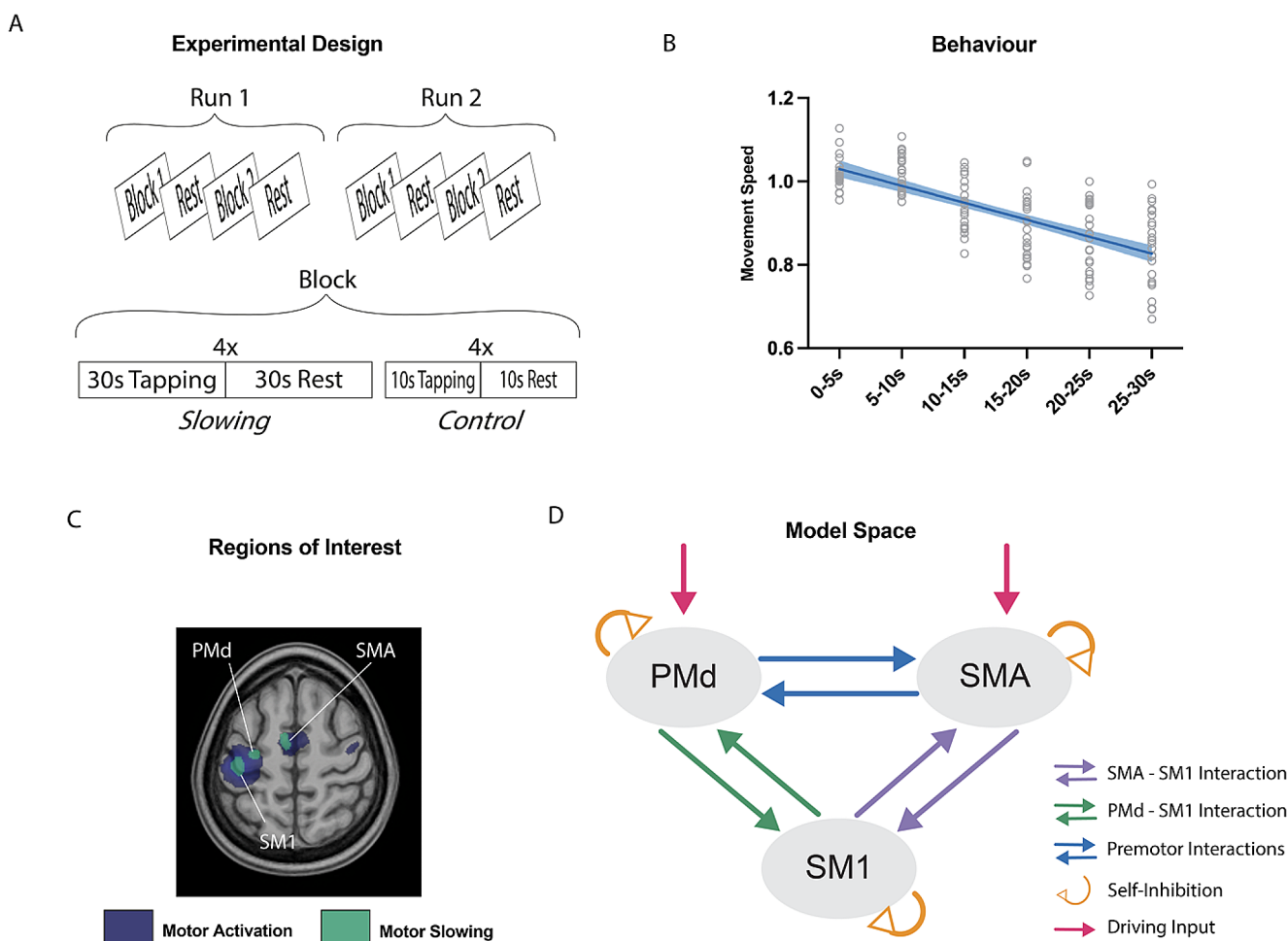
Fig. 1 (**A**) Experimental Design of fMRI study. 24 participants were either tapping for 30 s (slowing condition) or 10 s (control condition) during fMRI scanning. (**B**) Behavioural Results. Behavioural results showing a significant decrease in movement speed over 30 s of tapping. (**C**) fMRI activations, associated with either tapping itself (motor network, blue) or motor slowing (increasing activation with decreasing movement speed, green). Regions of interest where defined based on the closest individual activations of PMd, SMA, and SM1. (D) Schematic overview of the model space for DCM

divided into 10 s bins and movement speed was normalised to the average speed of the control condition per participant. This normalised movement speed was subjected to a linear mixed effects model with the fixed factor *time* (i.e., time bins) and the random factor *participant*. Motor slowing was defined as a significant main effect of *time* (Fig. 1B).

fMRI acquisition and preprocessing

fMRI scans were acquired with a Philips Ingenia 3T whole body scanner. Prior to the functional runs, high resolution T1-weighted anatomical scans were acquired (voxel size = 1 mm^3, 160 sagittal slices, matrix size = 240 × 240, TR/TE = 8.3/3.9 ms). These anatomical scans were used for functional image registration and normalisation. During the behavioural runs 360 volumes were acquired in each run (voxel size = 2.75 × 2.75 × 3.3 mm^3, matrix size = 128 × 128,

TR/TE = 2500/35 ms, flip angle = 82 degrees, 40 slices acquired in interleaved order for full brain coverage). Preprocessing was performed using SPM12 (Wellcome Trust) with default parameters.

First, functional images were realigned to the average functional image. Then, the anatomical image was segmented, of which a transformation to MNI space was obtained, and the structural image was skull stripped. The functional images were co-registered to the anatomical image using normalised mutual information, and to MNI space through the forward transformation. The normalised images (2 × 2 × 2 mm^3) were spatially smoothed with an 8 mm isotropic Gaussian kernel at full-width-half maximum.

fMRI data analysis

fMRI analyses were also performed in SPM12. The first-level model of each participant consisted of a general linear model. The GLM design matrix included four regressors of interest: tapping, parametric modulation of tapping, recovery, and parametric modulation of recovery. The tapping regressor represented the time periods when the participant was tapping. The recovery reflects the 30 s rest condition after a tapping trial. The parametric modulation regressor consisted of a linear increase over the tapping periods (reflecting the increase in motor slowing) or a linear increase over the recovery period after a 30 s tapping trial (but not a 10 s tapping trial). The linear increase was the same across all participants and did not depend on the participant's performance. Importantly, the parametric modulation regressor was orthogonalized with respect to the tapping regressor. Note that the 30 s slowing condition and the 10 s control condition were modelled together in each regressor. For the parametric modulator, the slowing condition consisted of a linear increase in six bins of 5 s, and the control condition was made up of a linear increase in two bins of 5 s. Regressors of no interest in the GLM consisted of get-ready periods and six head movement parameters (translation and rotation along the x, y, and z-axis). All regressors except the six head movement parameters were convolved with a canonical hemodynamic response function. The two regressors of interest were contrasted against the implicit baseline and were then subjected to a second-level random-effects analysis across participants. The second level analysis was a single one-sample t-test contrasting the regressors of interest against zero. P-values smaller than 0.05 family-wise error (FWE) corrected for multiple comparisons were considered statistically significant. Localisation of functional clusters was aided by the anatomy toolbox (Eickhoff et al. 2005).

Dynamic causal modelling

To investigate the changes in effective (directed) connectivity with motor slowing, we performed DCM (Friston et al. 2003) using SPM12. In short, dynamic causal models are generative models that aim to capture directed interactions among brain regions or states based on à priori hypotheses. In DCM, changes in brain states over time are modelled in the form of a state-space equation:

$$\dot{x} = \left(A + \sum\nolimits_{j=1}^{m} u_j B^{(j)} \right) x + Cu \quad \#(1)$$

In this equation, x is the state vector representing the current neuronal state and $\dot{x}$ refers to the change in the neuronal state over time. The matrix A represents the underlying endogenous or intrinsic connectivity with fixed weights defined by the model, whereas $B^{(j)}$ reflects the weights of task-dependent modulations of connectivity, driven by external modulatory inputs u_j. C represents the weights for direct inputs, characterising the extrinsic driving input u directly influences brain regions.

In the scope of this study, the matrix A represents the endogenous connectivity of the motor system (i.e., bidirectional connectivity between SM1, PMd, and SMA; see also *regions of interests*). The term $u_j B^{(j)}$ characterises the strength of the modulatory changes that occur due to motor slowing, which are modelled as a linear increase reflecting motor slowing. The final term Cu, describes the external driving input to the (pre-)motor system, modelled here as a constant input from prefrontal areas to either PMd, SMA, or both.

Regions of interest, endogenous connectivity, and its modulation

As a hypothesis driven method, DCM requires a neurobiologically-plausible model of connectivity to be defined à priori. We therefore selected regions of interest which were associated with motor slowing. Specifically, we previously found that activity (pFWE < 0.05) of the left SM1, left PMd, and bilateral SMA (Bächinger et al. 2019) were inversely correlated with motor slowing of the right hand: All these regions showed an activation increase with decreasing tapping speed. Based on this finding, we investigated here whether motor slowing is associated with changes in premotor-motor interactions. To that end we built several DCMs incorporating PMC, SMA, and SM1 (i.e., the three areas directly associated with motor slowing).

We extracted the BOLD signal time-series of our Effect of Interest from 4 mm radius spheres centred on the following three regions of interest: SM1, PMd, and SMA. The Effect of Interest consisted of our four regressors of interest (tapping, parametric modulation of tapping, recovery, parametric modulation of recovery). All regions of interest were defined by taking the coordinates from the group-level analysis (Supplementary Material 1) and then extracting the closest peak-level activation on the single subject level.

The endogenous connectivity matrix (matrix A in Equation (1)) was defined by previous anatomical studies: Specifically, we assumed that all regions are connected bidirectionally based on previous anatomical findings (Luppino et al. 1993; Rouiller et al. 1994; Michely et al. 2015). Also, all included regions were assumed to be self-modulatory. Self-modulations were chosen to represent two-state models, which model two neuronal populations, an excitatory and an inhibitory, per region. In these two-state models, connections between two areas A and B are assumed to

be excitatory and connection within each area A or B are modelled as being self-inhibitory (Marreiros et al. 2008; see Supplementary Material 2 for more detailed information). The model thus aims to explain changes in BOLD signal via the interplay of excitatory and inhibitory dynamics within and across regions, thereby incorporating current knowledge of the cortical microcircuit in which functional neuronal dynamics arise from an interplay between excitatory pyramidal cells (which are mainly glutamatergic) and inhibitory interneurons (which are mainly GABAergic, McColgan et al. 2020; Douglas and Martin 2004). As such, the two-state model is biologically more plausible and closer to the underlying anatomy of the human cortical microcircuit than single-state models (McColgan et al. 2020).

The extrinsic regressor (term u in Equation (1)) that modulates connectivity of the network (term B in Equation (1)) reflected the effect of motor slowing. In the scope of this study, motor slowing was simplified as a linear change over time, as represented by the parametric modulation (see section *fMRI data analysis*) which served as input for this analysis. The driving input to the model was assumed to be a constant input from prefrontal areas (Michely et al. 2015).

Model space and model families

As our main interest was to test whether self-inhibition of SM1 is crucial to explaining modulation of connectivity during motor slowing, we split the model space into model families with and without self-inhibition of SM1. Further, we wanted to investigate whether the premotor areas (SMA, PMd or both) shape the self-inhibition in SM1. Therefore, we set up multiple model families: (1) The top-down model family (in accordance with our main hypothesis outlined in the introduction), in which connections from SMA to SM1 and from PMd to SM1 were modulated. (2) The bottom-up model family, to verify whether our hypothesis may be inversed, meaning self-inhibition of SM1 may modulate SMA and PMd in a bottom-up fashion. In this model family, connections from SM1 to SMA and from SM1 to PMd were modulated. (3) The selective premotor model family, to test whether one premotor area is much more strongly involved in modulations of motor slowing: only SM1-SMA or SM1-PMd connections were modulated in these models. (4) The null model family. In this model family, none of the connections between any of the premotor areas and SM1 were modulated.

As mentioned, our main interest was to determine the necessity of self-inhibition in SM1, which is why these 4 model families were further specified as either having self-inhibition of SM1 modulated or not. This resulted in 8 model families: Top-down models without self-inhibition of SM1 (36 models, Fig. 2A), bottom-up models without self-inhibition of SM1 (36 models, Fig. 2B), selective premotor models without self-inhibition of SM1 (12 models, Fig. 2C),
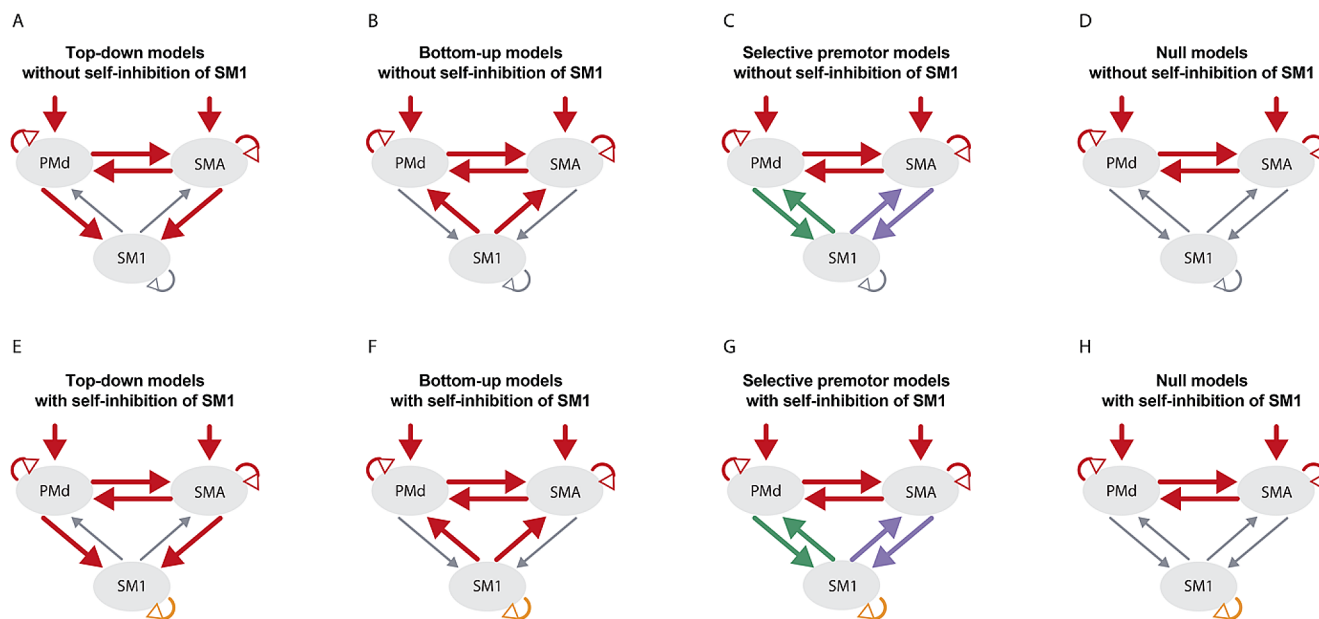

Fig. 2 Model Families. One model family consisted of several models differing in which connections were modulated. The connections that may have been modulated within one model family are marked in red. The selective premotor models (C and G) either had modulations of the SMA-SM1 (purple) or the PMd-SM1 (green) interactions, but not both in the same model. The premotor interaction (SMA to PMd and PMd to SMA) were always modelled together. The driving input was set either to PMd, SMA, or both. Self-inhibition of SMA and PMd were only modulated in combination with a modulated connection with SM1. However, for model families A and E, the premotor-motor connections were also modulated without self-inhibition of the corresponding premotor area. Self-inhibition of SM1 (orange) was assumed in all models of model families E-H

null models without self-inhibition of SM1 (6 models, Fig. 2D), top-down models with self-inhibition of SM1 (36 models, Fig. 2E), bottom-up models with self-inhibition of SM1 (36 models, Fig. 2F), selective premotor models with self-inhibition of SM1 (12 models, Fig. 2G), null models with self-inhibition of SM1 (6 models, Fig. 2H).

In all model families, the models were set up (i) with and without modulation of premotor interactions between SMA and PMd (Fig. 1D, blue), and (ii) with the driving input set to either PMd, SMA, or both (Fig. 1D, red). The main modulations of the selective premotor model family were either a bidirectional modulation of SM1-SMA (Fig. 1D, purple) or SM1-PMd (Fig. 1D, green). In both cases, the involved premotor area was modelled with self-inhibition (Fig. 1D, orange). The top-down and bottom-up model family differed in whether the connections SM1-PMd, SM1-SMA, or both were modulated, with or without self-inhibition of the involved premotor area. All in all, the model space consisted of 180 models, split into 8 model families. A list of all the models can be found in Supplementary Material 3.

Model selection and statistical analysis

To identify the most likely model family given the data, we used random-effects family-level Bayesian model selection (Penny et al. 2004; Stephan et al. 2009). As the model selection did not reveal decisive evidence for a single winning model family (family exceedance probabilities < 0.95, Fig. 3), all models across all model families were averaged
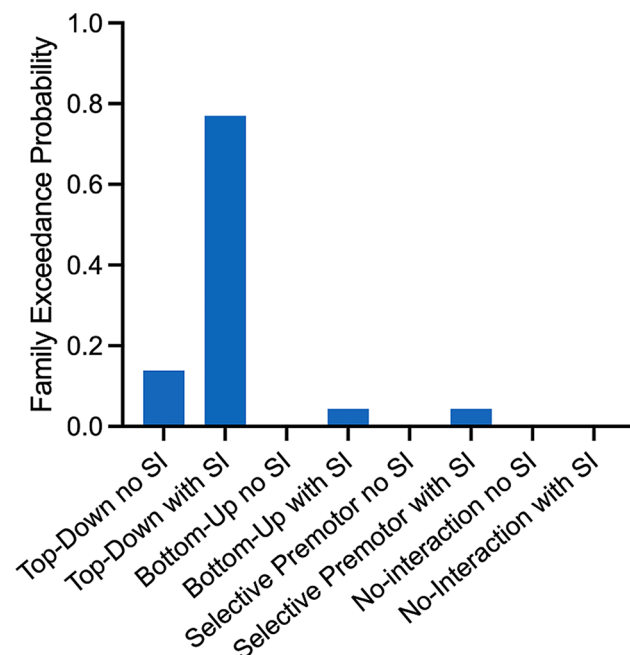
Fig. 3 Exceedance probabilities of random-effects Bayesian model selection for defining winning model family. No model family reached the evidence threshold (> 0.95)

through Bayesian model averaging (BMA) with an Occam's window of 0.05 to inspect the model parameters. These BMA parameter estimates were then subjected to two further analyses (Stephan et al. 2010). First, to identify the connections which were significantly modulated by motor slowing across participants, a group level post-hoc analysis on the maximum-à-posteriori (MAP) of the matrix B was performed using Bonferroni-corrected t-tests. Secondly, a stepwise linear regression was performed to identify which of these modulated connections were directly associated with individual differences in motor slowing as quantified by the behavioural data. The regression model tested whether behavioural changes in tapping speed can be explained by the MAPs of the modulated connections.

Results

With DCM, we investigated if motor slowing is associated with changes in effective connectivity in the motor network. We first ran family-wise random-effects Bayesian model selection (Penny et al. 2010), which revealed the highest probability for the top-down model family with self-inhibition of SM1. The variance explained by the models of this model family is on average 31.2% (see Supplementary Material 4 for variance explained per participant). However, evidence for this model family was not decisive, as the exceedance/posterior probability was < 0.95 (Fig. 3). Therefore, we performed Bayesian model averaging across the whole model space. The variance explained by models in the Occam's window, which are the ones that were averaged, can be found in Supplementary Material 5. The BMA revealed that motor slowing was accompanied by decreased connectivity in driving inputs to PMd and SMA, decreased connectivity from PMd to SM1, and decreased self-inhibition of SMA, as well as SM1. An increase in connectivity was found bidirectionally between PMd and SMA, bidirectionally between SMA and SM1, unidirectionally from SM1 to PMd, and for self-inhibition of PMd (Fig. 4).

To identify which of these connections were significantly modulated during motor slowing, we tested the maximum-à-posteriori estimates against 0 (one-sample t-test with Bonferroni correction). Significant modulation was only found for the decrease of self-inhibition of SM1 (t(23) = -4.51, $p < 0.001$, Bonferroni corrected) and the decrease in driving inputs to the premotor areas (t(23) > 2.71, $p < 0.05$, Bonferroni corrected, Fig. 4). There was a trend that effective connectivity from SMA to SM1 increased with motor slowing but this effect did not survive Bonferroni correction (t(23) = 2.27, $p = 0.033$).

In an additional analysis, we tested whether any changes in effective connectivity were directly associated with the

Fig. 4 BMA model results. Arrows with triangle heads represent (self-)inhibitory connectivity, the other arrows represent facilitatory connectivity. Increase in connectivity or self-inhibition with increasing motor slowing are shown in red, decrease in connectivity or self-inhibition with increasing motor slowing are shown in blue. The arrows towards PMd and SMA reflect the constant driving input over the whole tapping period. $p < 0.05$ uncorrected, $*p < 0.05$ Bonferroni corrected
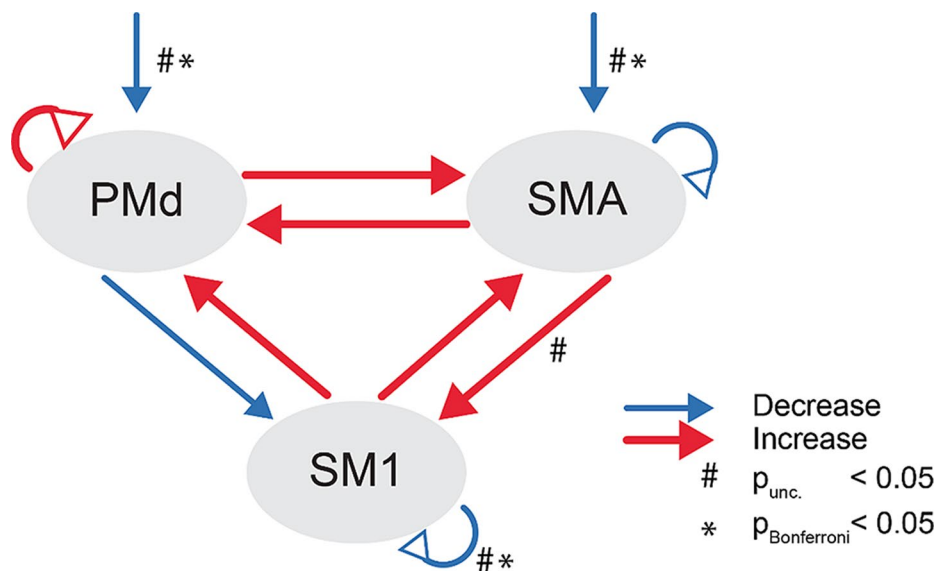
behavioural effects of motor slowing. In a stepwise linear regression analysis, we found that stronger connectivity from SMA to SM1 and from SM1 to SMA were linearly associated with more motor slowing (adjusted $R^2 = 0.514$; $p < 0.01$). However, partial residual analysis revealed that these associations could have been driven by outlier values (Supplementary Material 6).

Discussion

High motor fatigability, as reflected by the phenomenon of motor slowing, is characterised by increased activity within the cortical sensorimotor network. This observation is somewhat paradoxical, since higher cortical BOLD activity has been associated with higher tapping speed when tested in a non-fatigued state (Rao et al. 1996; Schlaug et al. 1996; Sadato et al. 1997; Jäncke et al. 1998b; Jäncke, Peters, Jäncke et al. 1998a, b; Deiber et al. 1999; Agnew et al. 2004; Lutz et al. 2004). Here, we used DCM to test how motor slowing modulates the interaction between PMd, SMA, and SM1. Our main result shows that motor slowing was characterised by a significant decrease of (i) SM1 self-inhibition, and (ii) excitatory driving inputs to both premotor areas (SMA and PMd). We further observed an increase in SMA to SM1 connectivity at a trend level.

DCM revealed that self-inhibition of SM1 decreased during motor slowing. Interestingly, the driving inputs to the premotor areas decreased significantly, while interactions between premotor and motor areas only reached trend level significance for a connectivity increase from SMA to SM1. This suggests that the release of self-inhibition in SM1 is the major contributor to the increase in BOLD activity typically observed during motor slowing. While it is well known that

BOLD signal increases with motor fatigue (Post et al. 2009; Van Duinen et al. 2007; Liu et al. 2003; Benwell et al. 2007), to the best of our knowledge, this is the first time such an increase in BOLD has been directly linked to the decrease in inhibition in SM1 *during* a fatiguing task. As such, our finding further complements a larger body of neurophysiological research showing that intracortical inhibition is reduced when measured directly *after* a fatiguing task (Bächinger et al. 2019; Benwell et al. 2006; Maruyama et al. 2006; Hunter et al. 2016; Latella et al. 2020). We thus extend our previous findings by showing that a linear decrease in self-inhibition of SM1 significantly contributes to the rise of BOLD signal *during* motor slowing.

While other fatiguing paradigms may share supraspinal mechanisms such as reduced intracortical inhibition, the underlying processes inducing this reduction may be different. In fatiguing protocols using sustained maximal or submaximal contraction, a decrease in voluntary drive parallels the development of fatigue (Post et al. 2009; Smith et al. 2007; Gandevia et al. 1996; Schillings et al. 2003; Søgaard et al. 2006; Todd et al. 2003). This is in contrast to the motor slowing paradigm, in which the voluntary drive was not decreased despite a clear drop in movement speed (Madrid et al. 2018). Similarly, from pre to post motor slowing, a reduction in force-generating capacity of the exercised muscles could not be shown (Rodrigues et al. 2009; Madrid et al. 2018), whereas, in other protocols, peripheral or muscle fatigue is a fundamental aspect. Motor slowing has however been associated with an increase in coactivation of agonistic-antagonistic muscle groups (Bächinger et al. 2019; Rodrigues et al. 2009), leading to the assumption that the 'slowing' is a result of imprecise coordination of muscular activation patterns rather than peripheral fatigue. Hence, the self-inhibitory changes may mainly reflect local interactions

within SM1. Thus, our findings of decreased self-inhibition in SM1 are in line with electrophysiological measurements also in other fatiguing paradigms, even though motor slowing is thought to result from supraspinal mechanisms, whereas in other fatiguing paradigms, muscle fatigue is an important factor. We further found that the driving input to the cortical premotor areas decreases during motor slowing. Despite this finding being consistent with the reduction in tapping speed, the decrease in facilitatory input makes it unlikely that influences from other areas drive the high activity in SM1, PMd, and SMA. This is interesting because the driving input to premotor areas seems to play a more important role for motor slowing than premotor-primary motor interactions. Where these driving inputs originate has yet to be defined, but basal ganglia or the cerebellum via the thalamus are likely candidates based on previous research (Liu et al. 2003; Van Duinen et al. 2007; Post et al. 2009; Hou et al. 2016; Bächinger et al. 2019). The cerebellum is particularly interesting, as it has been found to be involved in the continuous monitoring of movement rates, as well as in regulating movement rhythmicity via the brain stem, basal ganglia, and thalamus (Scott 2004; Bastian 2006; Pisotta and Molinari 2014; Therrien and Bastian 2019).

Concerning premotor-motor interactions, we found a trend-level increase in effective connectivity from SMA to SM1 with motor slowing, and the stepwise linear regression analysis hinted that stronger effective connectivity between SMA and SM1 was associated with more slowing on an individual level. SMA is known for its importance of controlling internally generated movements through projections to M1 (Samuel 1997; Konoike and Nakamura 2020). In this regard, SMA has not only been linked to the temporal sequencing of movements (Tanji 2001), but also to rhythm production itself (Konoike and Nakamura 2020). Increased SMA activity has been proposed to be related to the elevated difficulty in motor control (Kawashima et al. 1999). In other fatiguing paradigms, SMA has been linked to effort perception (Zénon, et al. 2014; Sharples et al. 2016; Emanuel et al. 2021), with modulation of SMA leading to changes in perceived effort. However, even though interactions between premotor and primary sensorimotor cortex might contribute to motor slowing to some extents, our study revealed only weak evidence for this hypothesis, and it seems likely that other, more complex neuronal interactions with a larger network may underlie the observed behavioural outcome.

In summary, these results revealed additional evidence supporting the hypothesis that motor slowing is associated with a release of inhibition in SM1. Additionally, the driving input coming from other (motor) areas is essential for explaining the network modulations occurring during motor slowing.

Limitations

A principal limitation of DCM is that interpretations can only be made for the investigated model space. The regions included in the analysis were chosen, because they showed an increase in BOLD signal with motor slowing. Therefore, the interpretation of our results is limited to interactions between PMd, SMA, and SM1. We chose the excitatory driving input to represent unspecific projections from upstream regions to the premotor areas. We took this decision because our previous work revealed that, even though subcortical areas are activated during the motor slowing task, their activity changed only insignificantly over time. As such it remains an open question which area(s) might cause the observed increase of BOLD activity within the cortical motor network and the field will probably have to develop new approaches for addressing this question.

We applied BMA since there was no winning model family. BMA offers the advantage that it estimates the parameters for all plausible candidate models, thereby accounting for uncertainty about both (i) the model parameters and (ii) the underlying true model. The final parameter estimates are obtained according to the posterior probabilities of the associated models. This has several advantages compared to single-model selection (Hinne et al. 2020) including that BMA is rather robust against model misspecification and that it has been shown to result in optimal predictions because it better mitigates errors which are introduced as the 'true' model cannot always be found. The conclusions we draw from our analysis do not propose a specific winning model of effective connectivity between premotor areas and sensorimotor cortex. Instead, we identified specific model parameters which changed significantly across all models with motor slowing.

Conclusion

Our DCM analysis indicates that a reduction in self-inhibition of SM1 explains the increase in BOLD activation that occurs during motor slowing, even though it is not directly associated with the behavioural decrease in movement speed. Furthermore, we show that premotor-motor interactions are only moderately modulated by motor slowing, but that the driving input to the cortical motor network appears to increase. This finding emphasizes that processes upstream of the premotor-motor areas contribute to the changes occurring in the cortical sensorimotor network when fatigability increases during fast finger tapping and future research has to identify the neurobiological substrate of this effect.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00429-

Data availability The datasets analysed during the current study will be made available on the ETH research collection.

Declarations

Ethics approval This study was approved by the research ethics committee of the canton of Zurich (KEK-ZH 2015 − 0537) and was conducted in accordance with the Declaration of Helsinki.

Consent to participate All participants gave written informed consent before participating in this study.

Consent to publish The authors affirm that human research participants provided informed consent for publication of anonymised data.

Competing interests The authors declare no competing interests.

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