Neural noise and cortical inhibition in schizophrenia

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ABSTRACT

Background: Neural information processing is subject to noise and this leads to variability in neural firing and behavior. Schizophrenia has been associated with both more variable motor control and impaired cortical inhibition, which is crucial for excitatory/inhibitory balance in neural commands.
Hypothesis: In this study, we hypothesized that impaired intracortical inhibition in motor cortex would contribute to task-related motor noise in schizophrenia.
Methods: We measured variability of force and of electromyographic (EMG) activity in upper limb and hand muscles during a visuomotor grip force-tracking paradigm in patients with schizophrenia (N = 25), in unaffected siblings (N = 17) and in healthy control participants (N = 25). Task-dependent primary motor cortex (M1) excitability and inhibition were assessed using transcranial magnetic stimulation (TMS).
Results: During force maintenance patients with schizophrenia showed increased variability in force and EMG, despite similar mean force and EMG magnitudes. Compared to healthy controls, patients with schizophrenia also showed increased M1 excitability and reduced cortical inhibition during grip-force tracking. EMG variability and force variability correlated negatively to cortical inhibition in patients with schizophrenia. EMG variability also correlated positively to negative symptoms. Siblings had similar variability and cortical inhibition compared to controls. Increased EMG and force variability indicate enhanced motor noise in schizophrenia, which relates to reduced motor cortex inhibition.
Conclusion: The findings suggest that excessive motor noise in schizophrenia may arise from an imbalance of M1 excitation/inhibition of GABAergic origin. Thus, higher motor noise may provide a useful marker of impaired cortical inhibition in schizophrenia.

Introduction

Sensorimotor impairments are common in schizophrenia and the study of their mechanisms can provide valuable pathophysiological insights into the disorder [1–3]. Recent studies showed that variability of motor control is increased in schizophrenia compared to controls, in execution of visually guided pointing tasks [4] and in visuomotor grip-force control tasks [5]. Consistent with this, altered or noisier electromyographic activity [6,7], as well as single motor unit activity [8], has also been reported in schizophrenia. However, the neural mechanisms underlying this increased variability remains unclear. Noise is a fundamental property of neural signaling [9,10] and is thought to contribute to behavioral (trial-to-trial) variability, whether in perception or action [11]. Motor noise has been characterized as signal-dependent noise in the motor system [12] and its signal-dependence most likely arises from the properties of the motoneuron pool (and its muscle fibers [13]). Motor noise is typically measured as behavioral and/or electromyography (EMG) variability [14].

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The signal-to-noise ratio in cortical signaling depends on the balance between excitatory and inhibitory neural activity, critical for cortical functioning [15,16]. In schizophrenia, there is growing evidence for an excitation/inhibition imbalance [17–20]. Imaging and genetic studies point to disturbed GABAergic (gamma-aminobutyric acid) neural functioning in schizophrenia [21–24]. Impaired functioning of GABA interneurons in schizophrenia has been linked to impaired neural oscillations and cognitive deficits [25]. In the motor cortex, GABAergic functioning can be assessed using double-pulse transcranial magnetic stimulation (TMS) to measure the short-latency intracortical inhibition (SICI) [26]. There is compelling evidence for reduced SICI in schizophrenia during rest [27–31] and more recent studies also showed reduced modulation of SICI during motor tasks [1,32]. Given the likely role of GABAergic inhibition in determining neural signal-to-noise ratio [16,33] and of behavioral studies showing increased variability (indicating increased neural noise) in schizophrenia [4,5,34] we hypothesized that reduced cortical inhibition would be related to enhanced motor noise in schizophrenia.

To test this, we performed novel analyses on data from a previous study [1]. To assess motor noise, we analyzed the variability of force during a visuomotor grip-force tracking task [5] as well as concurrent variability of EMG activity in forearm and hand muscles in patients with schizophrenia. These data were compared to those in healthy controls and siblings. We first predicted that higher motor noise in patients with schizophrenia should be reflected by increased variability of force and of EMG activity during steady hold. Secondly, we expected that (higher) variability in force and EMG activity would relate to reduced SICI in the group of patients with schizophrenia, reflecting GABAergic dysfunction and decreased signal-to-noise ratio. Finally, we analyzed whether EMG variability would relate to clinical symptomatology.

Methods

Participants

This study presents novel EMG and TMS analyses on the relation between task-related TMS measures and force/EMG variability from participants included in a previous study [1]. Twenty-five patients (SCZ; 7 females, 18 males, mean age±SD: 31±9y), fulfilling DSM-IV-R criteria for schizophrenia [35] were recruited at the University department (SHU) of Sainte-Anne Hospital, Paris, France. All patients were clinically stabilized and medicated with a constant dose of atypical antipsychotics for at least one month. Twenty-five healthy control participants (HC), age-, hand dominance- and gender-matched (age: 30±7y) were also recruited, as well as 17 non-psychotic siblings (SIB; 12 females, 5 males, age: 36 ± 10y; 2 siblings of SCZ group). An approximated intelligent quotient (aQI) was obtained (WAIS-III [36]) and participants with a score <80 were excluded. Three participants in each group were left-handed (Edinburg handedness inventory [37]), hence, 9 of the 67 subjects performed the visuomotor task with their non-dominant hand. All participants were assessed with the Diagnostic Interview for Genetic Studies v3.0 to ascertain the diagnosis in patients and to preclude axis 1 and 2 diagnosis in healthy control participants and siblings [38]. The study received ethical approval from the regional ethics committee (Ile de France VIII; Clinical Trials: NCT02826629) and all participants provided written informed consent.

Clinical assessments

Clinical symptomatology of patients was assessed using the Positive and Negative Syndrome Scale (PANSS [39]). PANSS subscores were calculated as follows: positive PANSS (sum of items P1 to P7), negative PANSS (sum of items N1 to N7), and disorganization (sum of items P2, N5, G10, G11). For complete data on clinical and neuropsychological assessments see Ref. [1].

Visuomotor grip force-tracking task

All participants performed a visuomotor grip force-tracking task with their right hand according to our previously published protocol [5]. Briefly, participants had to match a right-to-left scrolling line (target force) as accurately as possible with their grip force using a vertically moving cursor (instantaneous force feedback). Tracking-force, measured with the Power Grip Manipulandum (www.sensix.fr), was sampled at 1 kHz using a CED Power1401 and Spike2V6 (www.ced.co.uk). The target force followed a ramp-hold-and-release paradigm in each trial (pause = 3s; ramp = 2s; hold = 3s; release = instantaneous drop to baseline) at a target force level of 10% of maximum voluntary contraction (MVC).

EMG recordings and TMS

EMGs were recorded from 2 intrinsic (first dorsal interosseous, 1DI; abductor digiti minimi, ADM) and 2 extrinsic (flexor carpi radialis, FCR; extensor carpi radialis, ECR) hand muscles using surface electrodes (www.adinstruments.com). EMG signals were amplified with a CED 1902, and sampled at 1 kHz using a CED Power1401 under Spike2V6 (www.ced.co.uk). Transcranial Magnetic Stimulation (TMS) was applied over the cortical representation of the right 1DI (contralateral hemisphere) through a figure-of-eight coil (7 cm diameter) connected to two synchronized Magstim 200 units (www.magstim.com). Optimal coil position was defined as the stimulation site inducing the largest 1DI motor evoked potentials (i.e., MEPs>50 mV) at the lowest intensity. The neuronavigation system was used during the entire session and coil position was maintained at a maximum of ±5 mm and/or 5° shift from the target using default MRI scan (www.ant-neuro.com). TMS measures, such as resting motor threshold (rMT), task-related cortical excitability during HOLD phase (10%MVC; MEPs), and short-latency intracortical inhibition (SICI; conditioning stimulus at 80%rMT 2 ms prior the test pulse at 120%rMT [40]) have been previously described in detail [1].

Analysis of grip force control

Visuomotor force-tracking performance was analyzed using MatlabV9.1 (The MathWorks, Inc., Natick, MA, USA). Grip force was down-sampled to 100Hz and smoothed (20 ms sliding window). The following performance measures were extracted trial-by-trial for each participant: tracking precision (quantified as the root mean square *tracking error* (RMSe) between the target and the tracking-force during the ramp and hold periods); *onset* of force production and of force decrease (relative to the respective target); *release duration* (time taken to abruptly reduce the force from 75% to 25% of the target force).

For investigating task-related motor noise, the coefficient of variation (CV; standard deviation/mean) of tracking force (CV-GFT) was computed over a steady-state interval of 1s (i) during the pause between trials (minimal postural force while holding the manipulandum in the hand), and (ii) during the middle of the hold period at 10%MVC target force. This 1s analysis window thus captures motor noise (or its inverse: steadiness) during stationary force production. Any potential force (or EMG) fluctuations around the transition points (from ramp to hold, and from hold to release) have thus been excluded. Taking a less conservative 2s window gave similar results.

EMG analysis: muscular noise

We investigated task-related motor noise at the level of muscle activation by analyzing EMG variability of the four recorded muscles. First, EMGs were low-pass filtered at 40Hz [41]. Then, over the same interval of 1s (as for force), the CV of the EMG (CV-EMG) was computed trial-by-trial.

Statistical analysis

Statistical analysis was performed using Statistica10 (StatSoft, Inc., USA), involving Mann-Whitney U tests for assessing group differences in demographic and clinical outcomes. To assess task-related differences in group performance a general linear model repeated measures ANOVA with one GROUP factor (SCZ/SIB/HC) was used. For the analysis of variability, one between Group factor (SCZ/SIB/HC) and one within-group factor MUSCLE (1DI/ADM/FCR/ECR) were used. Fisher LSD post-hoc tests were applied (level of significance: $p < 0.05$). Pearson's correlations were used to probe the relation between EMG variability and force variability, and physiological markers, including previously acquired data on MEPs and short-latency intracortical inhibition (SICI) [1]. In the patient group, Spearman's rank-order correlation was used to assess relations between EMG variability and PANSS (positive, negative and disorganization subscales, i.e., non-parametric variables). The level of significance for correlation coefficients, corrected for three multiple comparisons, was set at 0.02 [42].

Results

Representative force and EMG data from a healthy control and a schizophrenia patient are shown in Fig. 1.

Variability of grip force data

For control purposes we first verified that there were no group differences in the amplitude of the grip force during rest or hold. The ANOVA showed indeed an absence of a Group effect (all p-values>0.63). CV of force during grip force-tracking (CV-GFT) during rest also did not differ between groups ($F(2,64) = 0.07$, $p = 0.93$). However, the ANOVA revealed a significant GROUP effect on CV-GFT ($F(2,64) = 5.23$, $p = 0.008$) during hold phase, with the SCZ group showing increased CV-GFT compared to HC (post-hoc; $p = 0.002$; Fig. 2A). The SIB group showed an intermediate level with a non-significant trend for higher of CV-GFT (post-hoc, SCZ vs., SIB, $p = 0.08$; SIB vs., HC, $p = 0.22$).

Variability of EMG activity

There were no significant differences in the mean amplitude of the EMGs in the four tested muscles (1DI, ADM, FCR, ECR) between groups, neither at rest ($F(2,64) = 0.56$, $p = 0.57$), nor during hold ($F(2,64) = 0.31$, $p = 0.74$). This confirmed that mean muscle activity was similar in all three groups. Furthermore, there were no GROUP differences in the EMG variability (CV-EMG) during rest in any muscle (ANOVA, $F(2,64) = 0.20$, $p = 0.82$). However, the ANOVA showed a significant GROUP effect on CV-EMG during hold ($F(2,64) = 9.97$, $p < 0.001$) and a significant MUSCLE effect ($F(3,192) = 3.84$, $p = 0.01$, Fig. 2B), but no interaction effect (GROUP*MUSCLE: $F(6,192) = 0.79$, $p = 0.58$). Post-hoc tests revealed that the SCZ group had significantly higher CV-EMG ($p < 0.001$) compared to HC and to SIB. SIB and HC showed no difference between their lower CV-EMGs (post-hoc, $p = 0.99$).

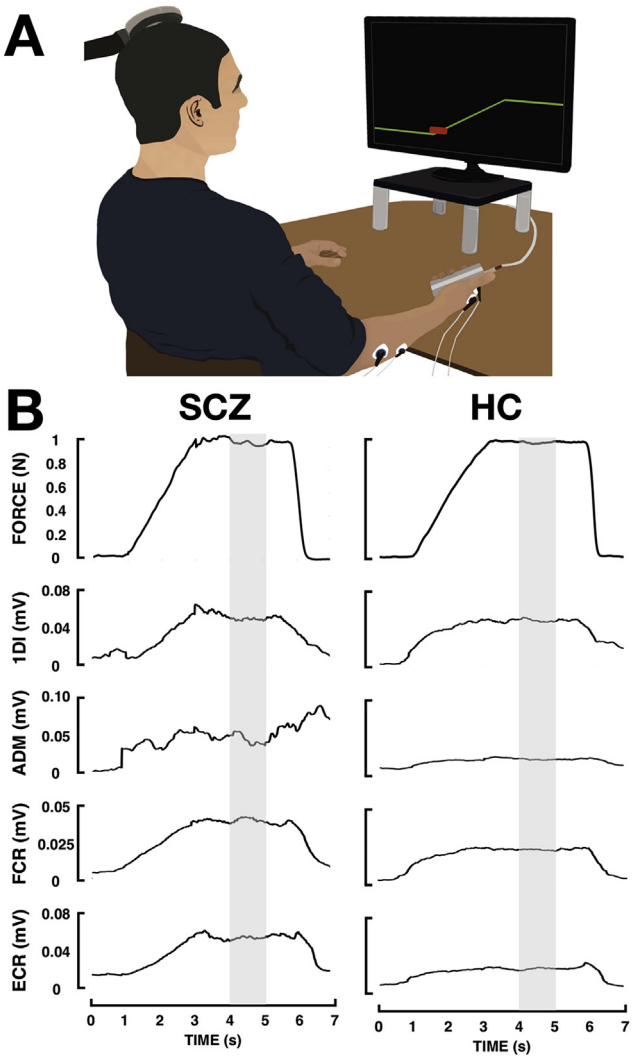

Fig. 1. Single participant example of grip force tracking, including EMGs. A. Visuomotor grip force-tracking set-up. Participants had to match a right-to-left scrolling line (target force) as accurately as possible with their grip force using a vertically moving cursor (instantaneous force feedback). **B.** Task-related force and EMGs (averaged over 48 trials). From top to bottom: user tracking-force (solid line); EMG of first dorsal interosseous (1DI); abductor digiti minimi (ADM); flexor carpi radialis (FCR) and extensor carpi radialis (ECR). Note: steady-state force and EMG activity was assessed in the 1s grey window during the hold period.

Relation between force and EMG variability

Variability of grip force (CV-GFT) during hold correlated positively with variability in muscle activity (CV-EMG) within the SCZ group (Pearson's correlation: $r = 0.57$, $p < 0.001$). A similar correlation was also seen across all participants ($r = 0.41$, $p < 0.001$).

Relation between EMG variability and visuomotor task performance

In order to study the behavioral impact of EMG variability we investigated the correlation of CV-EMG and visuomotor task performance, i.e., how accurate participants are to match the target force (root mean square error). We found a significant positive correlation between CV-EMG and accuracy of force tracking across all participants (Pearson's correlation, $r = 0.42$, $p = 0.001$), and also within the SCZ group ($r = 0.48$, $p = 0.02$). Thus, this positive correlation indicates that higher EMG variability was related to increased tracking error.

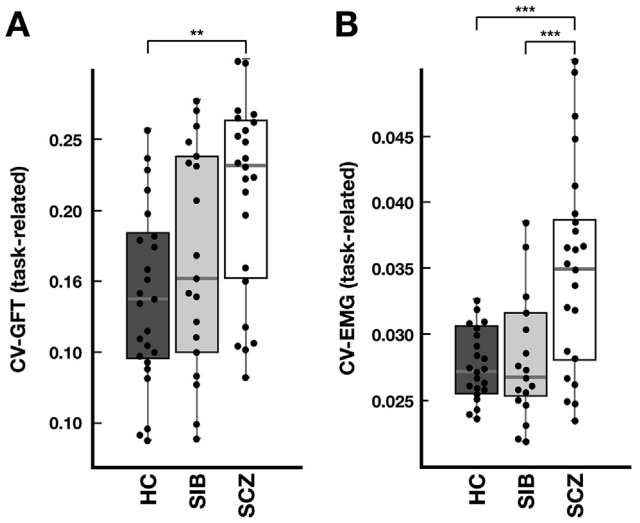

Fig. 2. Behavioral and muscular variability (noise) during grip force tracking. A. Behavioral variability between healthy control participants (HC; in dark), non-psychotic siblings (SIB; in grey) and patients with schizophrenia (SCZ; in white): CV of grip force-tracking (CV-GFT) during the hold period (10%MVC target force). Compared to HC, CV was significantly increased in SCZ patients ($p = 0.008$). SIB with higher and intermediate results showed a trend for an increase in CV compared to HC ($p = 0.08$). **B**. Muscular variability between groups: CV of EMG activity (CV-EMG) during the hold period recorded in two intrinsic (first dorsal interosseous, abductor digiti minimi) and two extrinsic (flexor carpi radialis, extensor carpi radialis) hand muscles. The CV-EMG represents the average CV across these four muscles. Compared to HC and SIB, patients with SCZ showed a significantly increased CV-EMG ($p < 0.001$). Asterisks indicate: ** = $p < 0.01$, *** = $p < 0.001$.

Relation between measures of variability and cortical excitability/ inhibition

Patients had similar MEPs at rest compared to controls (Table 1). However, during force-tracking at 10%MVC patients had significantly increased MEPs compared to HC (see Ref. [1]).

MEP amplitude during Hold correlated positively with CV-EMG across all participants ($r = 0.47$, $p < 0.001$) but not in the SCZ group alone ($r = 0.30$, $p = 0.18$).

Regarding cortical inhibition (SICI), we found a GROUP effect ($F(2,64) = 5.77$, $p = 0.005$) with significantly reduced SICI in patients with SCZ compared to HC and SIB groups (SCZ vs. HC, $p = 0.005$; SCZ vs. SIB, $p = 0.006$; Fig. 3A). We also found that SICI correlated negatively with CV-EMG across all participants (Fig. 3B, CV-EMG, $r = -0.38$, $p = 0.002$). Importantly, this correlation was also observed within the SCZ group ($r = -0.53$, $p = 0.006$).

MEP amplitude (in 1D1) did not correlate with force variability (CV-GFT; $r = 0.05$, $p = 0.71$), and SICI showed a non-significant trend for a negative correlation with CV-GFT across all participants ($r = -0.29$, $p = 0.02$) and within the SCZ group according to the corrected level of significance ($r = -0.44$, $p = 0.03$).

Relation between EMG variability and clinical scores

CV-EMG during hold correlated positively with negative symptoms in PANSS ($r = 0.55$, $p = 0.005$, corrected for multiple comparisons). Thus, patients with greater EMG variability had increased negative symptoms. No other correlation reached level of corrected significance (all p-values >0.12). Note: none of our measures were correlated with chlorpromazine equivalences (all p-values>0.31).

Discussion

In this study, we showed increased task-related grip force variability and higher EMG variability in patients with schizophrenia, indicating enhanced motor noise. This increase in motor noise, likely due to a less coordinated neural firing patterns in the motor system, correlated with reduced cortical inhibition, such that schizophrenia patients with decreased inhibition had higher levels of task-related (behavioral and muscular) noise.

Motor noise and its likely neural origin

Neural noise in the motor system is thought to primarily arise from the properties of the motoneuron pool [13]. Here we found both increased force and EMG variability, pointing to enhanced motor noise during the 1s period of steady force production (active hold). The two measures of variability (EMG and force) correlated closely as can be expected, given their causal relation during static force production. In a neurodevelopmental perspective, motor noise has also been found in autism spectrum disorder [43], a disorder associated with abnormal maturation of cortical inhibitory interneurons, and in developmental dyslexia [44].

As hypothesized, we found that the increased motor noise in patients with schizophrenia was, at least partly, related to reduced cortical inhibition (SICI). SICI is a measure of GABA-A receptor-mediated inhibition in cortical inhibitory interneurons [45]. Our data suggest a role of such GABAergic interneurons during steady maintenance of an ongoing voluntary muscle contraction. GABA interneurons also contribute to cortical gamma oscillations via inhibition of multiple pyramidal neurons, resulting in a more coordinated firing pattern of pyramidal neurons [46]. In line with this, recordings in non-human primates revealed that bicuculline (a GABA antagonist) injection reduced the signal-to-noise ratio in cortical interneurons as well as in pyramidal neurons, as demonstrated by loss of task-modulated tuning [47]. We therefore speculate that SICI, reflecting GABA-A interneuron mechanisms, could promote coordinated firing of corticospinal neurons in motor cortex and thus, leads to less variability in EMG and force recordings, i.e., reduced neural noise.

Furthermore, SICI tested during isometric muscle contraction of less than 40%MVC has been found to be of similar magnitude as compared to rest [48] and has been shown to be increased in tasks requiring coordination between fingers [49]. Translated to our set-up (power-grip at 10%MVC), SICI would not be expected to contribute to maintenance of the level of force but is likely more related to the level of M1 excitability [50]. Our data are also in agreement with studies showing that cortical inhibition increases temporal precision [51], improves the gain of neuronal responses [52], and enhances, as shown computationally, the signal to noise ratio of neural information processing [16]. Hence, we consider that, besides the motoneuron pool, dysregulation of cortical inhibition is another potential source of motor noise, particularly enhanced in schizophrenia.

In contrast, no correlation was found between EMG or force variability and MEP amplitude during hold. This suggests that M1 excitability does not seem to contribute directly to generation of EMG or force variability. During motor tasks, M1 excitability can be modulated by input from other prefrontal [53] and premotor areas [54], and we have previously shown that these areas can be over-activated in patients with schizophrenia compared to controls [32]. Enhanced premotor activity may then contribute to increased M1 excitability. Furthermore, hyperfocusing of attention has also been posited to play a role in enhanced task-dependent M1 excitability in schizophrenia [1,55]. Taken together, these elements suggest that the degree of intracortical inhibition, rather than M1

Table 1
Task-related recordings of force and EMG activity for the three groups: patients with schizophrenia (SCZ), healthy control participants (HC) and siblings (SIB).

Task-related recordings	SCZ Group (N = 25) Mean ± SD		HC Group (N = 25) Mean ± SD		SIB Group (N = 17) Mean ± SD	
	REST	HOLD	REST	HOLD	REST	HOLD
Grip-Force Tracking						
Mean grip force (NU)	0.09 ±0.04	1.01 ±0.03	0.07 ±0.03	1.00 ±0.02	0.06 ±0.02	1.01 ±0.03
Grip force tracking variability (CV-GFT)	0.06± 0.01	0.21 ±0.08	0.06 ±0.01	0.14 ±0.06	0.06 ±0.01	0.17 ±0.07
EMG Activity						
Mean EMG Activity (mV)	0.004 ±0.003	0.018 ±0.007	0.003 ±0.002	0.017 ±0.010	0.004 ±0.002	0.016 ±0.008
EMG variability (CV-EMG)	0.07 ±0.03	0.035 ±0.008	0.07 ±0.02	0.028 ±0.003	0.07 ±0.04	0.028 ±0.005
TMS measures						
Resting motor threshold (RMT)	54% ±11	x	53% ±11	x	51% ±8	x
% of stimulator output (%SO)	x	64% ±12	x	64% ±13	x	61% ±10
Cortical Excitability MEPs	2.81 mV ±1.60	1.83(NU) ±0.54	2.96 mV ±1.41	1.43(NU) ±0.37	2.89 mV ±1.43	1.51(NU) ±0.54
SICI (%reduction)	37 ±18	30 ±15	50 ±17	38 ±14	47 ±19	39 ±15

Mean measures (mean ± SD) of performance in grip-force tracking (mean grip force, grip-force tracking variability), electromyographic activity recordings (mean EMG activity, EMG variability) and motor evoked potentials (MEPs) for unconditioned and conditioned stimulus and short-latency intracortical inhibition (SICI) were obtained during Rest and Hold phases. Resting motor threshold (RMT) was calculated at rest and 120% of the RMT was applied during task.

excitability, is a key feature in generating motor noise in schizophrenia. More generally, excitation/inhibition imbalance, here observed in M1 through measured SICI, might not be restricted to the motor system. A lower signal-to-noise ratio might affect larger networks and tentatively contribute to altered functional network connectivity in schizophrenia [56].

Clinical relevance

Task-related variability of EMG activity was correlated with negative symptoms. Negative symptoms are similarly thought to stem from a functional and anatomical imbalance of brain networks [57], suggesting a potential link between cortical neural noise and symptoms of decreased volition and negative mood, though we cannot exclude other alterations in motor behavior [58]. This raises the intriguing question of a relationship between negative symptoms and neural noise. One hypothesis is that both phenomena would have a common grounding in GABAergic interneuron dysfunction. Although we did not find a relation between SICI and negative PANSS symptoms, SICI has previously been shown to be reduced in patients with depression [59] and is enhanced with anti-depressant therapy [60]. This was interpreted in the context of a close relationship between GABA and serotonergic activity [60]. Furthermore, the serotonergic system has been reported to be involved in persons with prominent negative symptoms in schizophrenia [61,62].

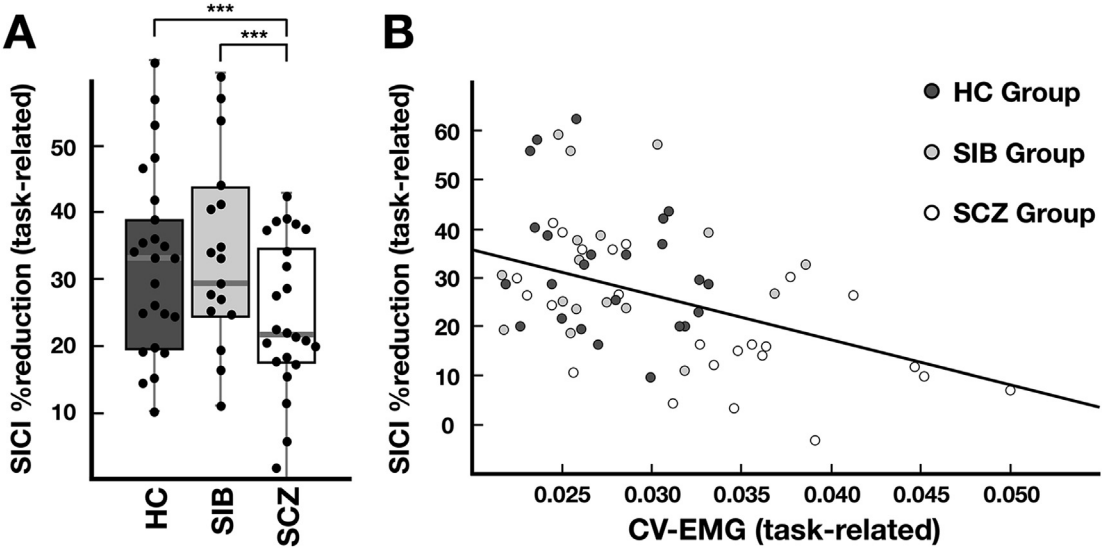

Fig. 3. Cortical inhibition. A. Task-related short-latency intracortical inhibition (SICI) between healthy controls (HC; in dark), non-psychotic siblings (SIB; in grey) and patients with schizophrenia (SCZ; in white). Patients showed significantly reduced SICI during hold compared to HC and SIB (SCZ vs. HC, $p = 0.005$; SCZ vs. SIB, $p = 0.006$). **B**. Significant correlation across all participants between SICI and EMG variability (CV-EMG) during hold ($r = -0.38$, $p = 0.002$).

Siblings showed an intermediate noise-related task performance, i.e. a non-significant trend to higher force variability than healthy control participants, but a trend for lower variability than patients with schizophrenia. However, their general task performance (tracking error) was similar to the control group and they did not significantly differ from control participants in EMG variability. Siblings also showed intermediate values of MEP amplitude, but normal values in cortical inhibition. Thus, their motor noise levels tended to be in-between those of the control group and the schizophrenia group. This is consistent with siblings carrying a genetic risk for (minor) cortical abnormalities that are expressed in a weak but present noise-related motor deficit [63].

Study limitations

SICI can vary depending on intensity of a conditioning stimulus and a more complete account of SICI dysfunction in schizophrenia could be provided by using a conditioning protocol [64]. Our findings reflect increased neural noise in medically stabilized patients with schizophrenia. Replication would be needed to establish whether the obtained results hold in more acute patients, e.g., in first-episode schizophrenia patients.

Conclusion

The findings show a concomitant increase of task-related motor noise measured in grip force and in EMG activity together with reduced cortical inhibition in schizophrenia. Patients with higher motor noise had smallest levels of SICI. This provides evidence of increased neural noise in the motor system in schizophrenia. This also suggests that impaired GABA-ergic function induces an imbalance of cortical excitation/inhibition, which acts as an underlying mechanism for increased behavioral and muscular variability.

CRediT authorship contribution statement

Loïc Carment: Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft. **Lucile Dupin:** Investigation, Methodology, Software, Writing - review & editing. **Laura Guedj:** Investigation, Methodology, Writing - review & editing. **Maxime Térémetz:** Investigation, Methodology, Writing - review & editing. **Macarena Cuenca:** Investigation, Methodology, Writing - review & editing. **Marie-Odile Krebs:** Conceptualization, Funding acquisition, Writing - review & editing. **Isabelle Amado:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing. **Marc A. Maier:** Conceptualization, Funding acquisition, Supervision, Writing - original draft. **Påvel G. Lindberg:** Conceptualization, Funding acquisition, Supervision, Project administration, Writing - original draft.

Declaration of competing interest

The authors declare that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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