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Capacity for cortical excitation is reduced in psychotic disorders: an investigation of the TMS-EMG cortical silent period

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Cover Letter

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c/o Schizophrenia Research Journal Office
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Dear Dr Mehta

Ms. Ref. No.: **SCHRES-D-21-00378**

Ms. Title: **Capacity for cortical excitation is reduced in psychotic disorders: an investigation of the TMS-EMG cortical silent period**

As requested, we have now included the final discussion paragraph with implications of our findings.

Thank you for your consideration and patience.

Sincerely,

Howells

Fleur M Howells

Ms. Ref. No.: **SCHRES-D-21-00378** Revision 2

Ms. Title: **Capacity for cortical excitation is reduced in psychotic disorders: an investigation of the TMS-EMG cortical silent period**

Comments from the Editor

Thank you for your submission. The manuscript appears to be missing a discussion and implications paragraph at the end. Please include that and resubmit.

Authors response

Apologies, we have inserted the following paragraph at the end of our manuscript.

"We found evidence of reduced glutamatergic excitatory motor cortical capacity in three groups of patients with differing psychotic disorders. Exciting the motor pathway further through single pulse TMS stimulation did not create the increased motor evoked amplitude seen in the healthy control group. The course of illness in psychosis may be characterised by initial hyper-glutamatergic states, seen during the prodromal period and acute psychosis, followed by a relative hypo-glutamatergic state (Natsubori et al. 2014;de la Fuente-Sandoval et al. 2011). Our neurophysiological findings suggest that there is a reduction in excitatory capacity of inter-cortical excitatory connections of layer 5 pyramidal neurons with chronic psychotic illness: this reduction is indicative of long term depression (LTD), that is limited capacity to long term potentiation (LTP) which requires strong inter-cortical connectivity of pyramidal neurons. The behavioural implications of this finding are that individuals with persistent psychosis will find it difficult to learn new motor activities which require activation of the motor cortex, which supports the promotion of physical activity in patients with chronic psychotic illnesses, to promote inter-cortical connectivity of layer 5 pyramidal neurons."

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Capacity for cortical excitation is reduced in psychotic disorders: an investigation of the TMS-EMG cortical silent period

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Keywords: bipolar disorder; bipolar I disorder with a history of psychosis (BIP); GABA; glutamate; methamphetamine; methamphetamine-induced psychotic disorder (MPD); schizophrenia (SCZ)

Abbreviations: SI - stimulation intensity; CSP - cortical silent period; TMS - transcranial magnetic stimulation; MEP - motor evoked potential; EMG - electromyography

The interplay of cortical excitability and inhibition is reported to be dysfunctional in psychotic disorders (Koshiyama et al. 2018;Overbeek et al. 2019) and associated with clinical symptomatology and cognitive deficits (Uhlhaas and Singer 2010;Gonzalez-Burgos et al. 2011;Taylor and Tso 2015). This dysfunctional interplay may reflect a core disturbance of glutamatergic mechanisms in psychosis, with hyper-glutamatergic activity in the prodrome and acute psychosis, and hypo-glutamatergic activity in states of chronic psychosis (Natsubori et al. 2014;de la Fuente-Sandoval et al. 2011). Whilst glutamate-mediated excitability varies with stage of psychosis, dysfunction in GABAergic-mediated inhibitory activity is suggested to persist through illness course (Taylor et al. 2019;Tanaka 2008;Lewis et al. 2012;McNally et al. 2013).

Pairing of transcranial magnetic stimulation (TMS) with electromyography (EMG) has been used to investigate capacity for cortical excitation and activation of $GABA_B$ receptor function: and is achieved by interrupting voluntary muscular contraction with a single TMS stimulation of the corresponding contralateral primary motor cortical area. The TMS pulse first accentuates the voluntary contraction (**Figure 1a**) by increasing cortical excitability of layer 5 pyramidal neurons, producing a motor evoked potential (MEP) (Pascual-Leone et al. 1998;Fitzgerald et al. 2002a), specifically enhanced activation of inter-cortical excitatory connections (Ziemann 2004;Douglas and Martin 2004). MEP amplitude may reflect the capacity for long term potentiation (LTP), and a reduction in amplitude may reflect long term depression (LTD) within the corticospinal tract (Dickins et al. 2017;Mehta et al. 2019). MEP evoked by TMS stimulation in patients with schizophrenia suggest facilitation of LTP early in the course of illness, but deficits after multiple psychotic episodes (Hasan et al. 2011;Hasan et al. 2015;Wobrock et al. 2008), associated with cognitive deficits in chronic illness (Salavati et al. 2015).

Immediately after the MEP, the contraction is interrupted by a period of 'silence'(**Figure 1a**). This period, the cortical silent period (CSP), may reflect the activation of $GABA_B$ receptors which hyperpolarize layer 5 pyramidal neurons (Inghilleri et al. 1993;McCormick 1989;Werhahn et al. 1999). CSP duration increases then plateaus with increasing TMS stimulation intensity, from 120ms to 300ms, reflecting enhanced $GABA_B$ receptor activity, which leads to an extended hyperpolarization of pyramidal neurons (McCormick 1989;Saisanen et al. 2008;Kimiskidis et al. 2005).

Findings on CSP duration in schizophrenia are inconsistent: longer duration is reported in drug naïve (Tang et al. 2014), first-episode (Hasan et al. 2012), and chronically-ill (Soubasi et al. 2010) patients, while non-medicated individuals have reported shorter CSP durations (Frantseva et al. 2008). Antipsychotic medications may lengthen CSP duration (Frantseva et al. 2008;Daskalakis et al. 2008;Kaster et al. 2015;Frank et al. 2014; Ustohal et al. 2017). Lack of resolution may be related to varying stimulation intensities (SIs) and protocol use across different laboratories (Wobrock et al. 2009;Strube et al. 2014).

The exact relationship between level 5 pyramidal glutamatergic pyramidal excitation and $GABA_B$ inhibition when using the TMS-EMG cortical silent period paradigm is uncertain (Saisanen et al. 2008;Orth and

Rothwell 2004;Kim et al. 2005). Limited studies in schizophrenia report on both MEP amplitude and CSP duration. Wobrock et al (2010) found MEP amplitude was enhanced with no change in CSP duration in first episode schizophrenia, while Fitzgerald et al (2002b) found CSP duration was reduced with no difference in MEP amplitude in chronic schizophrenia.

Studies of CSP are largely confined to a diagnosis of schizophrenia, and it is uncertain whether reported changes in CSP are limited to SCZ or shared by other disorders with psychotic features. In bipolar I disorder, there is evidence of facilitation in MEP amplitude with a reduction in CSP duration (Levinson et al. 2007), but a second study found no difference in CSP duration in either currently euthymic or manic patients with bipolar I disorder (Ruiz-Veguilla et al. 2016). No studies have yet investigated these parameters in substance-induced psychotic disorders (e.g. methamphetamine-induced psychotic disorder(MPD)). In addiction, studies are also limited, where evidence of CSP duration lengthening has been reported in cocaine-dependence (Gjini et al. 2012), associated with a positive psychotic symptom, namely paranoia (Boutros et al. 2005).

To address uncertainty regarding CSP measures in schizophrenia we applied a rigorous protocol which included three diagnoses where psychosis is prominent: SCZ, bipolar I disorder with a history of psychosis (BIP), and MPD. Our TMS-EMG protocol investigated dominant and non-dominant motor cortices, with graded SIs: resting motor threshold and supra-threshold stimulation intensities (RMT: 100%, 120%, 140%). See **Supplement 1** for study methodology and characteristics of our study population.

Our findings support a reduction in layer 5 pyramidal neuron cortical excitability, i.e. hypo-glutamatergic activity, in our patient groups. As patient groups reported a significant reduction in MEP amplitude for the *right motor cortex serving the non-dominant hand* (**Figure 1c**): 100RMT ($H_{3,87}$=19.98, p=0.00020) was reduced in SCZ (p=0.0088) and BIP (p=0.00016); 120RMT ($H_{3,82}$=18.42, p=0.00040) was reduced in all patient groups (SCZ p=0.028; BIP p=0.00063; MPD p=0.015); and 140RMT ($H_{3,69}$=20.17, p=0.0002) was reduced in all patient groups (SCZ p=0.029; BIP p=0.0077; MPD p=0.00046). These findings suggest that ability to enhance motor cortical excitatory capacity in layer 5 pyramidal neurons is limited in psychotic disorders, suggesting a reduction in inter-cortical excitation of glutamatergic pyramidal neurons, which may limit processes of LTP (Dickins et al. 2017;Mehta et al. 2019).

In MPD this reduction was limited to supra-threshold SIs, and we found duration of illness was negatively associated with MEP amplitude at the highest SI applied ($MPD_RMC140RMT$ $R_{Spearman's(n=14)}$=-0.74, p=0.0022, **Figure 1f**). This suggests a progressive decline in excitatory capacity in MPD, active neurodegeneration which has previously been suggested (Howells et al., 2014). In our study, we suggest that there is a progressive pruning of pyramidal neuron dendritic arborizations, a consequence of hyper-glutamatergic and toxic glutamate states associated with methamphetamine abuse (Hsieh et al., 2014), and this would account for the lack of difference at threshold SI and negative association at the highest SI with duration of illness.

The lack of difference in MEP amplitudes of the *left motor cortex serving the dominant hand* (**Figure 1b**) may simply be related to the practice and control required by the dominant hand (Priori et al. 1999;Reid and Serrien 2012), through plastic processes which serve to refine motor activity (Li et al. 2017), with enhanced connectivity via supplementary motor cortex inputs and basal ganglia (Scholz et al. 2000). We suggest researchers who are investigating innate motor cortical function should investigate both hemispheres.

We did not find differences in CSP duration (**Figure 1d&e**), which is considered a measure of $GABA_B$ receptor activation within cortical layer 5 (Inghilleri et al. 1993;McCormick 1989;Werhahn et al. 1999): this is contrary to some schizophrenia research papers, but aligns with others (Wobrock et al. 2010).

We also explored the potential interaction with medication (**Supplement 2**), and associations with deficits in a EEG proxy for thalamo-cortical connectivity, which we previously reported in this cohort (Howells et al., 2018; **Supplement 3**).

We found evidence of reduced glutamatergic excitatory motor cortical capacity in three groups of patients with differing psychotic disorders. Exciting the motor pathway further through single pulse TMS stimulation did not create the increased motor evoked amplitude seen in the healthy control group. The course of illness in psychosis may be characterised by initial hyper-glutamatergic states, seen during the prodromal period and acute psychosis, followed by a relative hypo-glutamatergic state (Natsubori et al. 2014;de la Fuente-Sandoval et al. 2011). Our neurophysiological findings suggest that there is a reduction in excitatory capacity of inter-cortical excitatory connections of layer 5 pyramidal neurons with chronic psychotic illness: this reduction is indicative of long term depression (LTD), that is limited capacity to long term potentiation (LTP) which requires strong inter-cortical connectivity of pyramidal neurons. The behavioural implications of this finding are that individuals with persistent psychosis will find it difficult to learn new motor activities which require activation of the motor cortex, which supports the promotion of physical activity in patients with chronic psychotic illnesses, to promote inter-cortical connectivity of layer 5 pyramidal neurons.

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Figure Legend

Figure 1a) Root mean-squared average of 10 electromyography (EMG) abductor pollicis brevis (APB) records, 200ms prior to, and 400ms post transcranial magnetic (TMS) stimulation. Participants held 40% contractile force on a pinch gauge, activating the abductor pollicis brevis (APB), this contractile activity is evident during the pre-stimulus baseline (mV). From the time of TMS stimulus and onset of motor evoked potential (MEP) there is a latency period, the latency to MEP (ms). The amplitude of the MEP shows the muscular activity evoked by TMS stimulation (mV). This is followed by the forced inhibition of contractile capacity of the APB, this duration is the cortical silent period (CSP, ms). The end of the CSP shows the return of voluntary contraction of the APB. **b & c)** MEP amplitudes produced from single pulse transcranial magnetic stimulation preceding the cortical silent period, for three stimulation intensities, resting motor threshold (100RMT) and supra-threshold stimulation intensities of 120% (120RMT) and 140% (140RMT). **b)** Left motor cortex MEP amplitudes reported no group differences. **c)** Right motor cortex MEP amplitudes were reduced in the psychotic groups when compared with CON, at *100RMT for SCZ and BIP, at $^{\#}$120RMT and $^{\#}$140RMT for SCZ, BIP, and MPD. **d & e)** CSP duration produced from single pulse transcranial magnetic stimulation, for three stimulation intensities, resting motor threshold (100RMT) and supra-threshold stimulation intensities of 120% (120RMT) and 140% (140RMT), data are reported as median with interquartile range, whiskers include non-outlier range. **d)** Left motor cortex and **e)** right motor cortex (RMC) CSP durations showed no group differences. **f)** At 140RMT RMC MEP amplitudes of MPD correlated negatively with duration of illness. CON - healthy controls; SCZ - schizophrenia; BIP - bipolar I disorder with a history of psychosis; MPD - methamphetamine-induced psychotic disorder.

Figure 1

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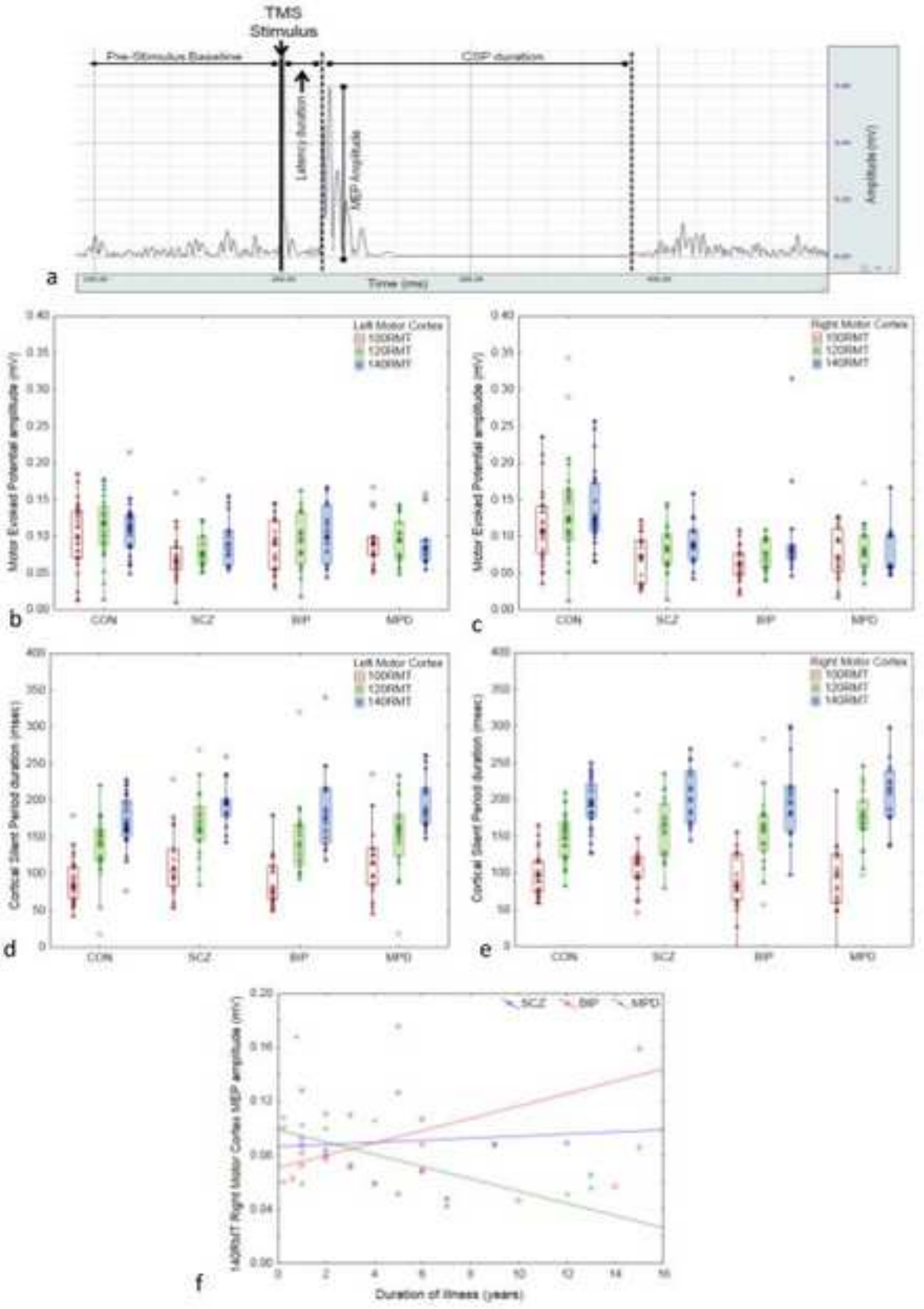

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Conflict of interest

Authors declare no conflict in interest related to the present paper.

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Contributors

FMH designed the study, conducted the statistical analysis, and is the primary author. FMH with JH set-up the testing protocol and collected the data. JH extracted and processed the EMG data for analysis. HT conducted the clinical interviews (SCID-I) and administered the clinical scales. DSB provided substantial editorial input. All authors contributed to revisions and approved the final submission.

Supplement 1

Supplement 2

Supplement 3