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Cortical inhibition and primitive reflexes in remitted first-episode mania

Sir,

Primitive or developmental reflexes like glabellar tap and grasp reflexes are protective motor responses. They are normally present during early development and inhibited with brain maturation in later life. They resurface with cerebral dysfunction [1], often referred to as cortical release signs. Primitive reflexes may be present in healthy individuals, but they have a higher prevalence in psychotic disorders such as schizophrenia and bipolar disorder [2]. They are considered 'soft' neurological signs that by virtue of their 'endophenotype' status lend credence to the neurodevelopmental origins of these disorders [3].

Our understanding of the neural mechanisms of primitive reflexes is limited. There are structural neuroimaging correlates of 'soft' neurological signs in psychotic disorders [4] and healthy individuals [5]. However, these are not specific to primitive reflexes. Executive dysfunction, a marker of prefrontal cortical hypofunction is associated with primitive reflexes in schizophrenia [6]. The higher prevalence of primitive reflexes in patients with a range of brain disorders implicates a frontal lobe pathology, with impaired cortical inhibition [1,2]. Nevertheless, few studies have examined in vivo cortical inhibition and facilitation in relation to primitive reflexes.

In this report, we explore the association between the severity of primitive reflexes and motor cortical inhibition/facilitation, measured using Transcranial Magnetic Stimulation (TMS) in recently (<6-months) remitted (Young Mania Rating Scale [7] <8 for at least two months) patients with first-episode mania (FEM). We hypothesized a positive and negative correlation between primitive reflex severity and cortical facilitation and inhibition respectively. TMS and primitive reflexes data were available for 23 remitted FEM patients, 20 first-degree relatives (siblings and offspring) of patients with Bipolar I Disorder and 25 healthy subjects who were matched for age ($F = 1.8$; $P = 0.17$) and gender ($\chi^2 = 0.67$; $P = 0.7$). Ten (43.5%) patients in the FEM group were on a combination of mood stabilizers and antipsychotics; 13 (56.5%) were on antipsychotics alone. The mean chlorpromazine equivalent dose for the entire group was 227.26 ± 135.05 mg/day [8]. Primitive reflexes (glabellar tap, snout, grasp and sucking reflexes) were measured using the Neurological Evaluation Scale [9]. The institute ethics committee approved the study and all participants provided a written informed consent.

During the TMS experiment, pulses were delivered using a 70-mm figure-of-eight coil (MagPro R30 with MagOption; MagVenture, Farum, Denmark) positioned tangentially over the hand area of the left motor cortex. We located the hand area and determined the resting motor threshold (RMT) and stimulus intensity to elicit 1mV amplitude (SI_{1mV}) of motor evoked potentials (MEP) according to standard guidelines [10]. We obtained electromyography (EMG) recordings from the right first dorsal interosseous (FDI) and analyzed data using Signal-4 Software (Cambridge Electronic Devices, Cambridge, UK). Cortical silent period (CSP), defined as the time from the MEP offset to the return of any voluntary EMG-activity was measured in a tonically active right FDI by stimulating the left motor cortex with ten trials of 120% and 150% RMT each. Short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were estimated by delivering a subthreshold conditioning pulse 3 ms and 10 ms (respectively) before a suprathreshold test pulse (SI_{1mV}). Long interval intracortical inhibition (LICI) was estimated by delivering a suprathreshold conditioning pulse 100 ms before the suprathreshold test pulse. Separate recordings of MEP with the test pulse alone were also acquired. We acquired 20-pulses each of SICI, ICF, LICI, and test pulse MEP in random order with 6s intervals. SICI/LICI and ICF were expressed as the percentage of inhibition and facilitation, respectively, of the test-pulse following the conditioned stimulus.

Primitive reflexes were elicited only in the remitted FEM group ($n = 8$). The glabellar tap was the only primitive reflex elicited. There were no significant between-group differences in SICI ($F = 1.2$; $P = 0.29$), LICI ($F = 1.3$; $P = 0.27$), ICF ($F = 1.5$; $P = 0.23$) and CSP elicited with 120% ($F = 1.2$; $P = 0.29$) and 150% RMT ($F = 0.55$; $P = 0.58$) stimuli. Since the distribution of the total primitive reflex score was ordinal (0 = absent; 1 = mild; 2 = marked), we used Kendall's Tau correlation to examine its association with cortical inhibition/facilitation in the remitted FEM group. Age ($Tau = -0.29$; $P = 0.1$) and chlorpromazine equivalent dose ($Tau = -0.01$; $P = 0.9$) were not significantly correlated with primitive reflexes. None of the cortical inhibition/facilitation measures demonstrated a significant correlation with chlorpromazine equivalent dose (all P values > 0.1). Independent *t*-test to compare cortical inhibition/facilitation between FEM patients on antipsychotics alone ($n = 13$) and those on a combination of mood stabilizers and antipsychotics ($n = 11$) revealed no significant difference (all P values > 0.19).

Primitive reflexes had a significant negative correlation with both measures of CSP (see Fig. 1), which remained significant after Bonferroni correction for multiple testing ($P < 0.01$). There were no significant correlations between primitive reflexes and ICF ($Tau = 0.35$; $P = 0.053$), SICI ($Tau = -0.32$; $P = 0.07$), and LICI ($Tau = -0.21$; $P = 0.23$).

We demonstrate a significant negative association between CSP and primitive reflexes in remitted FEM. The severity of primitive

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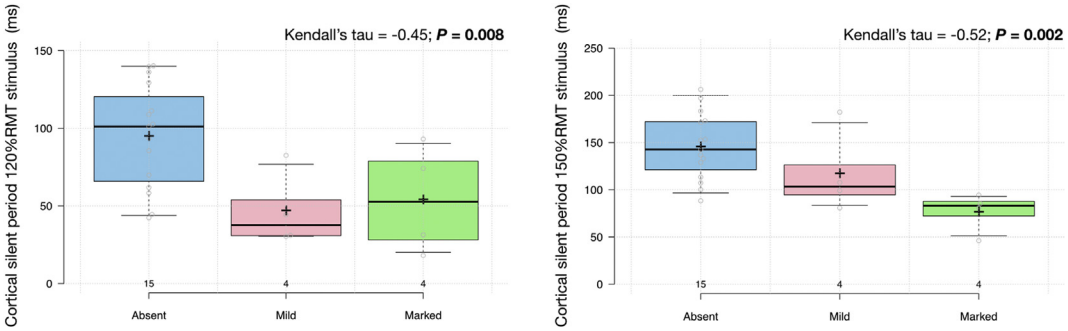

Fig. 1. Box plots representing the cortical silent period (in milliseconds) among remitted first episode mania patients with absent, mild and marked primitive reflexes. Center lines show the medians; box limits indicate the 25th and 75th percentiles as determined by R software; whiskers extend to 5th and 95th percentiles, outliers are represented by dots; crosses represent sample means; data points are plotted as open circles; n = 15, 4, and 4 are sample points.

reflexes was not associated with age or antipsychotic dose. Neither the cumulative antipsychotic dose nor the use of mood stabilizers had a significant association with TMS cortical measures. CSP has been considered a marker of $GABA_B$ receptor-mediated cortical inhibition [10]. Therefore, a longer silent period is indicative of a stronger inhibitory tone of the motor cortex. These findings are in keeping with our hypothesis that poorer cortical inhibition would be associated with marked primitive reflexes.

To the best of our knowledge, this is the first demonstration of an association between primitive reflexes and diminished in vivo measurement of cortical $GABA_B$ receptor-mediated inhibitory processes. CSP perhaps reflects the frontal inhibitory tone that regulates lower brain centers and therefore can be studied as a neuromarker of behavioral disinhibition, thus improving the study of brain-behavior correlates in psychiatric disorders. None of the first-degree relatives demonstrated primitive reflexes. One possible reason could be that most of them were beyond the age of developing mania (mean age ~28 years).

Interestingly, the direction of the association between primitive reflexes and the other inhibitory (SICI/LICI) and facilitatory (ICF) parameters was also in keeping with our proposed hypothesis, albeit not reaching statistical significance. Future studies may aim to replicate these preliminary observations in larger samples to refine the neurophysiological markers of frontal disinhibition. Such efforts will play a substantial role in understanding neuropsychiatric symptoms characterized by poor frontal regulation [11], as well as track changes with treatment [12].

Conflicts of interest

UMM is one of the Associate Editors at Schizophrenia Research and receives honorarium from Elsevier for this service. None of the other authors have any conflict of interest to report.

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