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Original Article

Effects of a single session of cathodal transcranial direct current stimulation primed intermittent theta-burst stimulation on heart rate variability and cortical excitability measures

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ABSTRACT

Objectives: Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been used as neuromodulators in neuropsychiatric conditions. This study is aimed to find the effects of a single session of priming cathodal tDCS with intermittent theta-burst stimulation (iTBS) over left dorsolateral prefrontal cortex on heart rate variability (HRV) and cortical excitability parameters before and after perturbation.

Materials and Methods: The neuromodulatory techniques used in the study were Cathodal tDCS for 20 min followed by iTBS for 3 min on the left dorsolateral prefrontal cortex (DLPFC). HRV variables and TMS parameters were recorded before and after this intervention of combined neuromodulation in 31 healthy volunteers (20 males and 11 females; age range of 19–35 years with Mean ± SD = 24.2 ± 4.7 years).

Results: The results showed an overall increase in cortical excitability and parasympathetic dominance in healthy volunteers. Other measures of cortical excitability and HRV did not change significantly following single session of combined neuromodulation.

Conclusion: This study showed that there is an overall increase in cortical excitability and parasympathetic dominance in the cohort of healthy volunteers following a combination of neuromodulation involving cathodal tDCS followed by iTBS over left DLPFC. Future studies exploring the effects of other possible combinations with sham stimulation could be carried out to explore the utility of dual stimulation as add-on therapy in disorders.

Keywords: Transcranial magnetic stimulation, Transcranial direct current stimulation, Intermittent theta-burst stimulation, Heart rate variability, TMS measures of excitability

INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)[1,2] are being used to investigate and alter cortical excitability and plasticity in healthy individuals as well as patients with neurological and psychiatric disorders.[3] Recent evidence suggests that combining these stimulation protocols might be an important way to achieve optimal effects. This combinatory approach has been proved to be more effective than either

protocol alone in achieving optimal motor cortical plasticity based on metaplasticity effects,[4] as well as in driving clinical gains.[5-7] Further, studies have demonstrated that autonomic cardiovascular control through modulation of neurocardiac regulation could be influenced by electrical or magnetic stimulation.[8,9] While the motor cortical and clinical effects of dual stimulation are evident,[5-7] its effect on neurocardiac regulation which might be related to changes in excitability measures has not been well studied. We designed the current study with objectives of investigating the effects of priming rTMS with tDCS on cardiac autonomic control as assessed by heart rate variability (HRV) and motor cortical excitability measures using TMS. We hypothesise those changes in cortical excitability measures by these non-invasive brain stimulation (NIBS) techniques relate to the alterations in the cardiac autonomic measures of HRV. We selected the combination of NIBS based on earlier study[10] which investigated all possible combinations of tDCS (anodal/cathodal/sham) and TBS (both intermittent and continuous) and found cathodal tDCS and intermittent theta-burst stimulation (iTBS) had potential additive effects.

MATERIALS AND METHODS

The study was approved by the Institute Ethics Committee and accomplished in accord through the TMS Safety Guidelines and screened through TMS Adult Safety Screening.[11] A total of 31 healthy volunteers (20 males and 11 females; age range of 19–35 years with Mean ± SD = 24.2 ± 4.7 years) underwent this study. Before the experiment, all participants were explained about the procedure, and written informed consent was obtained. Subjects with a history of sleep disorder, cardiovascular problems, psychiatric illness, or neurological illnesses were excluded from the study. HRV was computed using the electrocardiography (ECG) recording with a telemetric BioHarness device (Zephyr Technologies) with a sampling rate of 1024 Hz. The participants were made to wear the BioHarness device (50 g, 50 mm width) after 5 min of rest and this device was attached round chest through elastic strap for 10 min ECG recording which is stored digitally to compute HRV measures using Lab Chart-7 (AD Instruments, Australia) software with an automatic program that allowed visual checking of the raw ECG and breathing signals. HRV was analyzed as per the guidelines of Taskforce Report.[12] It was ensured that subjects were breathing with normal respiratory rate of 12–15 breaths/min by recording the respiratory movements using chest belt attached to strain gauge apparatus. Artefact free 5 min ECG was analysed to obtain both time (standard deviation of normal-to-normal intervals [SDNN] and root mean square of standard deviation [RMSSD]) and frequency domain parameters (using Fast Fourier transformation, total power, low-frequency (LF) power and LF power expressed in normalised units (LF nu); high-frequency (HF) power and expressed as normalized units (HF nu); LF/HF ratio or sympathovagal balance [SVB]) of HRV.

TMS parameters were assessed using Mag-Venture TMS machine with MCF-B70 magnetic coil. The subjects were instructed to have their hair washed and keep the scalp oil free. EMG recording was used to quantify the TMS parameters. The right first dorsal interosseous (FDI) muscle representation on the motor homunculus was localised with the help of a 10–20 Electroencephalography system around middle of C3 and F3 imaginary line over left hemisphere. After localising the motor hotspot, single-pulse and paired-pulse paradigms were used for assessment of baseline motor cortical excitability, cortical silent period (CSP), and intracortical circuits. At resting state rest motor threshold (RMT defined as minimal intensity of TMS to generate small twitch of 50 μV motor evoked potential [MEP] in 5 out of 10 consecutive single-pulse stimuli) and MT1 (TMS intensity to generate MEP of 1 mV peak-to-peak amplitude), the single pulses delivered over the primary motor cortical area activating the FDI muscle were noted. Paired-pulse stimuli combinations were used to elicit Intracortical circuits such as: Long interval intracortical inhibition (LICI) – the conditioning stimulus (CS) and test stimulus (TS) were both suprathreshold intensity at MT1 separated by an interstimulus interval (ISI) of 100 ms; short-interval intracortical inhibition (SICI) – the CS was subthreshold intensity at 80%RMT and TS was suprathreshold intensity at MT1 with ISI of 3 ms between the two stimuli; intracortical facilitation (ICF) – the CS was subthreshold at 80% RMT and TS was suprathreshold intensity at MT1 (TMS intensity to generate MEP of 1 mV peak-to-peak amplitude). The ISI is 10 ms between the two stimuli; all these measures of intracortical circuits were carried out in the semi-random fashion of 15 such varied pulses to elicit various intracortical circuits (LICI, SICI, and ICF) separated by 5 s. The peak-to-peak amplitude of MEP with CS was calculated as a percentage of that of test pulse (MT1) alone. CSP – single pulse was given around MT1 with the subject made to contract the FDI by squeezing a ball. Due to on-going contraction of the muscle, TMS pulse resulted in a large MEP (usually above 1 mV) followed by suppression of background EMG activity, the length (average of 10 consecutive pulses with voluntary contraction) of which would provide CSP.[13] Then, these subjects underwent a session of cortical plasticity induction which was provided by a combination of cathodal-tDCS and iTBS. These protocols were administered as per established safety protocol with specified regulatory guidelines and stringent safety measures using standard equipment.[14] Stimulation parameters included tDCS (at 2 mA for 20 min with both ramp-up and down time of 30 s each with cathode was placed over left dorsolateral prefrontal cortex [DLPFC] and the anode was positioned above the right supraorbital region) and iTBS

protocol (consisted of 3 pulses at 50 Hz at 100% of RMT and such triplets in 5 Hz [theta] frequency with a 2 s stimulation and 8 s inter-train interval; 20 such trains over 192 s in the form of a total of 600 intermittent pulses). There was no time delay (except for taking out tDCS electrodes and setting magnetic coil on the scalp which took <1 min) between these two stimulation modalities. Adverse effects were assessed using a structured questionnaire[15] at the end of the session. The immediate effects of the tDCS-iTBS on TMS Parameters (paired pulse measures to elicit different intra cortical circuits: LICI, SICI, ICF, and cSP) and HRV measures were recorded and compared using paired "*t*" test.

RESULTS

These results are shown in [Table 1] (HRV measures and TMS parameters). In summary, there was decrease in the mean heart rate (HR); increase in time domain measures of HRV (SDNN, RMSSD), total, LF and HF powers and ICF. Overall, there was increase in parasympathetic activity following single session of neuromodulation as shown by an increase in time domain measures of HRV, total power as well as individual LF and HF powers, and a decrease in HR. TMS parameters showed an increase in ICF, which indicated enhanced N-methyl D-Aspartate-mediated glutamatergic neurotransmission.[16] Further, no change in other TMS parameters (SICI, LICI, and SP) suggests that dual stimulation protocol over DLPFC may alter the glutamatergic excitability without changing the motor cortical gamma-amino butyric acid (GABA) mediated inhibitory circuits such as measured by $GABA_A$-mediated SICI and $GABA_B$-mediated SP and LICI.[13,16]

Table 1: Comparison of time and frequency domain measures of HRV and TMS parameters in healthy volunteer before and after cathodal tDCS and iTBS perturbation.

HRV variables	Pre-intervention values (Mean±SE; *n*=31)	Post-intervention values (Mean±SE; *n*=31)	*P*-value
Heart rate mean (bpm)	84.67±2.28	76.41±2.44	<0.001
SDNN (ms)	60.70±4.50	76.59±5.97	<0.001
RMSSD (ms)	43.95±5.07	59.77±6.07	<0.001
Total power (ms^2)	3652.77±592.15	6474.05±1111.37	0.001
LF power (ms^2)	1146.02±177.96	2097.39±345.21	<0.001
HF power (ms^2)	989.58±216.47	1720.92±352.38	<0.01
LF power (nu)	57.25±2.82	55.81±3.17	0.67
HF power (nu)	42.02±2.60	42.04±2.80	0.99
LF/HF ratio (sympathovagal balance)	1.74±0.21	1.70±2.66	0.87
SICI (%)	51.58±5.05	66.30±10.81	0.13
LICI (%)	37.36±5.03	41.32±7.25	0.49
ICF (%)	133.32±13.28	162.76±19.17	0.01
CSP (ms)	97.66±12.80	93.10±14.19	0.50

HRV: Heart rate variability, TMS: Transcranial magnetic stimulation, tDCS: Transcranial direct current stimulation, iTBS: Intermittent theta-burst stimulation, SDRR: Standard deviation of RR intervals, RMSSD: Root mean square of standard deviation; LF: Low frequency, HF: High frequency, nu: Normalised units, SICI: Short interval intracortical inhibition, LICI: Long interval intracortical inhibition, ICF: Intracortical facilitation, CSP: Cortical silent period

DISCUSSION

Our study found increased SDNN, RMSSD, total, and HF powers of HRV measures indicating an increased parasympathetic tone similar to an increase in these components of HRV following the rTMS over DLPFC.[9] An earlier study revealed that rTMS could provoke fluctuations in the heartbeat[17] and tDCS increased vagal activity, a marker of parasympathetic activity, in the 15 min of prefrontal stimulation.[18] In our earlier report in patients with depression,[19] 10 days of rTMS sessions decreased the SVB. These changes could result in the improvement in clinical depression per se or indirect modulation of cardiac autonomic regulatory centres through DLPFC stimulation acting on limbic-hypothalamic-autonomic central circuits. A recent study also showed a similar increase in vagal activity following single sessions of TBS (intermittent, continuous, and sham) over the right fronto-temporal region.[20] Thus, the similar findings of vagal activation by a single session of dual stimulation could be indicating vagal facilitatory action of iTBS. However, further studies with other modes of combination of tDCS (anodal and sham) as well as TBS (continuous and sham) could explore further the effects of NIBS on neurocardiac regulation.

Our study found dual stimulation increased the ICF but no changes in other motor cortical circuits (SICI, LICI, and SP). Although there are no reports on the intracortical circuits by this combination on DLPFC, iTBS alone on primary motor cortex (M1) did not affect ICF.[21,22] On the other hand, anodal tDCS on M1 over 20 min increased the ICF[23] whereas a shorter duration of 10 min did not affect ICF.[24] Our findings have to be compared with the previous research targeting the M1, which revealed that cathodal tDCS reduced concentrations of glutamate[25] as well as reducing GABA in the prefrontal cortical regions using magnetic resonance spectroscopy.[26] Since we used dual stimulation on DLPFC, iTBS might have reversed the cathodal tDCS effect on glutamate (indicated by increased ICF) and nullified the effect on GABA (no changes in SICI, LICI, and SP).

Lack of sham or opposite combination of NIBS (anodal/+cTBS) in randomised order is a limitation; nonetheless, this study provides a promising lead to pursue further systematic research of investigating NIBS effects on autonomic and excitability measures. Our study observation supports possible parasympathetic dominance and increase

in glutamatergic cortical excitability following combination of NIBS perturbation (cathodal tDCS and iTBS) in healthy subjects. Replication and extension of these observations can pave way for the utility of dual stimulation techniques of the NIBS using cathodal tDCS and iTBS as an add-on therapy for patients with various neuropsychiatric conditions.

CONCLUSION

The results of this study indicated parasympathetic modulation of HRV measures and alterations of the cortical excitability in terms of increased ICF after the neuromodulation induced perturbation. The selective modulation of ICF and an overall parasympathetic enhancement produced by the chosen combination and other possible variations of this protocol need further exploration in larger cohorts and in certain neuropsychiatric conditions such as Depression, Parkinson's disease for exploring any diagnostic or therapeutic potential of such protocols.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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