Central Nervous System (CNS) disinhibition has been reported to underlie the vulnerability to alcohol dependence (AD) in individuals with a high-family loading of AD [1]. Maturational lag and defective myelination of particular brain regions, including the corpus callosum (CC), have been reported in these individuals [2]. Morphometric studies reported significantly smaller total CC, genu and isthmus areas in these individuals after controlling for age and intracranial area [3].

Conduction across the CC can be investigated using a Transcranial Magnetic Stimulation (TMS) parameter called Ipsilateral Silent Period (iSP). iSP is recorded by applying a suprathreshold cortical motor stimulus ipsilateral to a partially activated target muscle [4]. In patients with lesions of the posterior half of the trunk of CC or agenesis of the CC, the iSP is reduced or absent. iSP, therefore, represents the functional integrity of the transcallosal inhibitory/conduction mechanisms [5]. Abnormal transcallosal inhibition [6] and interhemispheric interactions have been reported in children with ADHD [7] using TMS.

We attempted to investigate transcallosal conduction in individuals at high-risk for alcohol dependence using single-pulse TMS. 'High risk' (HR) denoted alcohol-naïve offspring of early-onset alcohol-dependent fathers with two or more alcohol-dependent first-degree relatives and 'Low Risk' (LR) was defined as alcohol-naïve individuals without family history of AD or psychiatric disorders [8]. Right-handed, HR (n=31) and LR (n=27) subjects, aged 13 – 25 years, matched for age and gender, were assessed for psychopathology and family-history of AD, using the Semi-Structured Assessment for the Genetics of Alcoholism II (SSAGA II) [9] and the Family Interview for Genetic Studies [10]. Contraindications to TMS were ruled out [11]. Following single pulse stimulation at 100% stimulator output, iSP was recorded from the right First Dorsal Interosseus muscle, at maximal voluntary contraction [6] using auditory feedback [8]. 10–12 recordings were obtained with a 6 second interstimulus interval. iSP was considered to be present if there was at least a 70% reduction in background EMG activity following cortical stimulation and resumption of prestimulation EMG activity subsequently [6]. For each trial, the onset and offset of a silent period were manually defined, and the duration of a silent period was calculated as the difference in milliseconds of the onset of EMG silence and the return of EMG activity [6,8].

The Institute Ethics Committee approved the study. Written informed consent was obtained from all subjects and parents of subjects under 18 years of age.

Statistical Package for Social Sciences (SPSS, version 13.0) was used for analysis. iSP duration was reduced in HR subjects [mean ± SD=13. 18 ± 10. 72 milliseconds] as compared to LR subjects [mean ± SD=15. 11 ± 10. 50 milliseconds], though not statistically significant (t=0.47; P =0.649). In the summation of all iSP trials in HR and LR subjects, iSP was absent more often in the HR subjects (124 times out of 340 trials; 36.47%) as compared to the LR subjects (63 times out of 300 trials; 21%) and this was statistically significant (\(\chi^2=18.4; p< 0.0001\)).

Of the two output pathways from the primary motor cortex (M1) – corticospinal output and transcallosal output, the transcallosal output gives rise to inhibition of the contralateral M1 [4,5,12-14]. Transcallosal conduction can be measured either as iSP or as interhemispheric inhibition. Both have been shown to be absent in some patients with callosal lesions or agenesis of the CC, and are reported to involve transcallosal pathways [5,14,15]. Patients with agenesis or surgical lesions of the CC had delayed or absence of iSP [5,14,16]. iSP is reportedly preserved in patients with subcortical cerebrovascular lesions that interrupted the corticospinal tract but not CC [16]. In preschool children, who have yet to develop a functionally competent CC, iSP was absent [17]. In short, absence of iSP could indicate a defective conduction across or developmental delay or structural damage to CC. The greater absence of iSP in our alcohol-naïve HR group probably indicates defective conduction across CC, which could reflect a delay in development/maturation of the CC as compared to the age-matched LR group, and may underlie the vulnerability to AD.

Funding source
This study was funded by a research grant [NIMH/TMS/KM/040] from the Centre for Addiction Medicine, NIMHANS, Bangalore- 560029, India.

References


