

# Abnormalities in cortical and transcallosal inhibitory mechanisms in subjects at high risk for alcohol dependence: a TMS study

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## ABSTRACT

Central nervous system (CNS) hyperexcitability and a resulting state of behavioral undercontrol are thought to underlie the vulnerability to early-onset alcohol dependence (AD). The aim of this study was to explore the differences in the functioning of cortical inhibitory systems, utilizing transcranial magnetic stimulation (TMS), in subjects at high risk (HR) and low risk (LR) for AD and to examine the relationship between CNS inhibition and behavioral undercontrol. Right-handed HR ( $n = 15$ ) and LR ( $n = 15$ ) subjects, matched for age, gender, height, weight and education, were assessed for psychopathology and family history of alcoholism using the Semi-Structured Assessment for the Genetics of Alcoholism and the Family Interview for Genetic Studies. Following single-pulse TMS, an electromyogram recorded from the right opponens pollicis muscle was used to measure the silent periods at different stimulus intensities. HR subjects had significantly shorter contralateral and ipsilateral (iSP) silent periods and a relatively higher prevalence of 'absent' iSP. They had significantly higher mean externalizing symptoms scores (ESS) than LR subjects, and there was a significant negative correlation between iSP duration and ESS. These preliminary findings suggest that HR subjects have relative impairments in corticocortical and transcallosal inhibitory mechanisms. The consequent state of CNS hyperexcitability may be etiologically linked to the excess of externalizing behaviors observed in this population, which is thought to be a predisposition to a higher risk of developing early-onset alcoholism.

**Keywords** Alcoholism, cortical inhibition, silent period, TMS, transcallosal conduction, vulnerability.

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## INTRODUCTION

Alcoholism is a common, etiologically complex disorder with significant genetic influence, usually manifest as part of a spectrum of disinhibitory disorders, which includes externalizing traits/disinhibitory syndromes such as attention deficit/hyperactivity disorder (ADHD), conduct disorder and adult antisocial behavior. It has been suggested that a heritable generalized disinhibitory complex, characterized by a state of central nervous system (CNS) hyperexcitability, might form the basic diathesis, with each disorder in this spectrum representing a variable expression of this general vulnerability (Haber, Jacob & Heath 2005; Porjesz *et al.* 2005).

The highest risks for developing alcoholism exists for individuals with a high family loading of alcoholism (specifically of the early-onset type) and display a cluster of disinhibited behavioral traits, usually evident in

childhood and persisting into adulthood (McGue *et al.* 2001). Aberrant electrophysiological characteristics have been reported in individuals at risk to develop alcohol dependence (AD) and related disinhibitory disorders. These include (1) spontaneous brain electrical activity, such as the increased beta power in the resting electroencephalogram (EEG) (Rangaswamy *et al.* 2004), and (2) neurocognitive markers of attentional processing, such as the reduced amplitude of the P300 component of the event-related potential (Hill 2004). These are hypothesized to reflect a state of CNS hyperexcitability resulting from an inherited homeostatic imbalance between the excitatory and inhibitory brain neurons, which represents a central vulnerability factor for developing AD (Porjesz *et al.* 2005).

Cortical inhibitory systems crucially modulate the balance between excitatory and inhibitory systems. Approximately 25–30% of the neurons in the primate

neocortex use gamma-aminobutyric acid (GABA) as their neurotransmitter, and these inhibitory neurons are important in influencing input-output properties and cortical reorganization and plasticity. There are two types of inhibitory postsynaptic potentials in the cerebral cortex: fast inhibition, mediated by ionotropic GABA<sub>A</sub> receptors, and slow inhibition, caused by metabotropic GABA<sub>B</sub> receptors. (Tamás *et al.* 2003).

These inhibitory systems can be evaluated non-invasively by transcranial magnetic stimulation (TMS) because of the ability of the TMS to stimulate cortical inhibitory and excitatory interneurons, in addition to the corticospinal output neurons, using paired-pulse or suprathreshold single-pulse TMS. A single suprathreshold TMS over the motor cortex (M1) suppresses voluntary muscle activation, recorded on an electromyogram (EMG), for up to 300 ms. This is termed the EMG silent period. Spinal mechanisms contribute to EMG suppression for the first 60 ms, but later effects are attributed to cortical inhibitory mechanisms. This silent period is thought to be mediated by GABA<sub>B</sub> receptors (Inghilleri *et al.* 1993; Kujirai *et al.* 1993; Siebner *et al.* 1998).

TMS, applied over the M1 during contralateral voluntary target muscle contraction, elicits a motor evoked potential (MEP) followed by a temporary suppression of EMG activity, termed the contralateral silent period (cSP). For cSP durations longer than about 100 ms, the resumption of EMG activity is thought to depend on the recovery of motor cortical excitability from GABAergic inhibition following TMS pulse (Chen, Lozano & Ashby 1999).

An ipsilateral silent period (iSP) can be obtained by a suprathreshold cortical motor stimulus applied ipsilaterally to the partially activated target muscle, which results in the transient cessation of EMG activity (Ferber *et al.* 1992). The iSP is thought to be a specific marker of transcallosal motor inhibition, mediated by transcallosal fibers and inhibitory GABA interneurons affecting the neuronal network between the primary M1 layer III contralateral to stimulation—the projection site of transcallosal motor fibers—and cortex layer V, the origin of the pyramidal tract. The iSP is mediated by the mid-body of the corpus callosum (Borojerdi, Diefenbach & Ferber 1996; Meyer, Roricht & Woiciechowsky 1998) and is considered to reflect the functional integrity of the transcallosal fibers connecting corresponding motor cortices.

Changes in cortical inhibition occur in many neurological and psychiatric disorders, and TMS has been used to investigate hyperexcitability states. Deficient intracortical inhibition (shorter latency and duration of iSP, but not cSP) has been found in drug-naïve patients with ADHD, which improved after administration of methyphenidate (Moll *et al.* 2000; Buchmann *et al.*, 2006).

The resting motor threshold (RMT), the basic unit of TMS dosing and an index of cortical excitability, reaches adult levels by 13 years of age, suggesting that maturity of the corticospinal motor pathway that controls the intrinsic hand muscles is electrophysiologically complete before 13 years of age (Nezu *et al.* 1997). Early evidence suggests that the cSP increases almost linearly in childhood and reaches adult levels by early adolescence and that there is no difference in right-handed iSP with increasing age (Garvey *et al.* 2003). A previous study on the ontogeny of ipsilateral corticospinal projections using TMS concluded that the maturation of both corticospinal and transcallosal pathways is almost complete by 10 years of age (Müller, Kass-Iliyya & Reitz 1997).

In this study, we examined the evidence for the hypothesized CNS hyperexcitability (Porjesz *et al.* 2005) in subjects at high risk (HR) for developing AD in comparison with low-risk (LR) healthy subjects matched for age, sex, handedness, education and anthropometry (height and weight). In the light of evidence cited earlier, we restricted the sample to adolescents over the age of 12 years and young adults. Using single-pulse suprathreshold TMS, we compared the cSP and iSP between HR and LR subjects. We hypothesized that the HR subjects would have significantly reduced the durations of cSP and iSP (which are potential indicators of a hyperexcited state of the CNS). Also, we predicted that the HR subjects would have greater externalizing symptoms scores (ESS) (behavioral manifestations of hyperexcited CNS) than the LR subjects.

## MATERIALS AND METHODS

Fifteen 'HR' male offspring (age range of 12–25 years) of treatment-seeking patients with AD [Diagnostic and Statistical Manual of Mental Disorders/Fourth Edition (DSM-IV)] (American Psychiatric Association 1994) and 15 'LR' control subjects (age- and sex-matched offspring of volunteers) were recruited for the study. 'HR' in this study was defined to denote an alcohol-naïve offspring of early-onset (having developed dependence before 25 years of age) alcohol-dependent fathers with two or more alcohol-dependent first-degree relatives. 'LR' was defined as alcohol-naïve individuals with an absence of family history of AD in any of the first-degree relatives.

The Semi-Structured Assessment for Genetics of Alcoholism-II (SSAGA-II)—adult version (Bucholz *et al.* 1994) was used to rule out any lifetime psychiatric disorder (other than AD) in fathers of HR subjects and to rule out any lifetime psychiatric diagnosis (including AD) in both parents of LR as well as in mothers of HR subjects. The fathers in both groups were also assessed for externalizing symptoms, as detailed further. Having a high externalizing symptom count was not a cause for

exclusion. Family history of psychiatric disorders in first-degree relatives of both HR and LR subjects was gathered using the Family Interview for Genetic Studies (Maxwell 1992) from three or more adult informants in the family. None of the HR subjects had a family history of psychiatric disorder (other than AD) in their first-degree relatives. None of the LR subjects had a family history of psychiatric disorder (psychoses, anxiety disorder, affective disorder, obsessive-compulsive disorder, Tourette's syndrome or AD) in their first-degree relatives.

The subjects were then assessed using the SSAGA-II (child, adolescent or adult versions as indicated) for externalizing symptoms (attention deficit, hyperactivity, impulsivity, conduct and oppositional-defiant symptoms) and to rule out any other syndromal psychiatric diagnoses (psychoses, anxiety disorder, affective disorder, obsessive-compulsive disorder or Tourette's syndrome). The SSAGA items pertaining to inattention, hyperactivity, impulsivity and conduct symptoms were added to calculate the ESS.

An experienced neurologist ruled out any neurological disorder, mental retardation or history of significant head injury, as these were specific exclusion criteria. Contra-indications to TMS were also ruled out (Wassermann 1998). All subjects were right-handed as assessed by Annett's Questionnaire (Annett 1967).

The Institute Ethics Committee approved the study, and written informed consent was obtained from all the participants and parents of subjects under 18 years of age. The procedure was conducted in accordance with the Declaration of Helsinki.

TMS was performed using a figure-of-eight coil connected to a MagStim 200 stimulator (Magstim Co. Ltd, Whitland, UK). The coil was held over the vertex with the handle pointing backwards at an angle of approximately 45° to the midline, such that the induced current was in a posterior–anterior direction perpendicular to the motor strip. The optimal positions from the left M1 that evoked MEP from the right opponens pollicis (OP) muscle was defined as the point of optimal excitability (POE). The POE of the left OP (right M1) was also defined for locating the point of stimulation for iSP. EMG was recorded from the right OP using disposable disk electrodes placed in a tendon-belly arrangement. The RMT was determined to the nearest 1% of the stimulator output (SO) and was the minimum intensity required to evoke MEPs of  $\geq 50 \mu\text{V}$  in at least 5 out of 10 trials. cSP was determined using the SO of 110, 130 and 150% of RMT, and iSP using stimulus intensities of 75 and 100% of the SO. The contraction of OP was obtained by asking the subject to oppose the thumb toward the tip of the little finger against a resistance placed on the palmar surface of the proximal phalanx of the thumb. Several practice sessions were conducted and the feedback of his maximal voluntary

contraction was given by the audio output of the EMG activity. Twelve trials were obtained at each stimulus intensity, with 6-second interstimulus intervals to avoid muscle fatigue. Only the trials in which the subject was able to produce maximum voluntary contraction were accumulated. A silent period (cSP and iSP) was deemed to be present if there was a cessation of the ongoing background EMG activity. 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 latencies (ms) of the onset of EMG silence and the return of EMG activity (Chen 2000; Buchmann *et al.* 2006).

To enhance the study prospects to detect TMS abnormalities in HR subjects for AD, the statistical tests examined the status (presence or absence), as well as the duration, of silent periods, with each being treated as an independent observation. Comparison was made between HR and LR groups for the durations of cSP and iSP at each stimulus intensity. Statistical analyses were performed using the Statistical Package for Social Sciences (version 11.0) (SPSS Inc., Chicago, IL). The group comparison was done using the independent samples *t*-test, and the association between risk status and absent silent period was examined using the  $\chi^2$  test. The relationship between the silent periods and ESS was examined using the Pearson's correlation test.

## RESULTS

The HR group did not differ from the LR group in terms of age, height, weight and education. They had significantly higher ESS than LR subjects (Table 1). Two of the 15 HR subjects satisfied the criteria for syndromal ADHD. The fathers of the HR subjects had higher ESS than the fathers of the LR subjects.

The HR subjects had significantly shorter cSP at 130 and 150% SO, as well as shorter iSP at 100 and 75% SO, than the LR subjects. Compared with LR subjects, a significantly larger proportion of the HR subjects failed to manifest iSP at each stimulus intensity (Table 2).

Subjects with absent iSP at 75% SO also had significantly higher ESS ( $16.4 \pm 10.3$ ) than in those who displayed iSP ( $11.2 \pm 7.8$ ,  $P < 0.0001$ ).

## DISCUSSION

In this study, HR subjects had significantly shorter cSP (indicating reduced intracortical inhibition) and iSP (indicating reduced interhemispheric, transcallosal inhibition) in comparison with LR subjects. Also, silent periods were more frequently absent in HR subjects at 75 and 100% SO (Fig. 1). HR subjects had significantly higher mean ESS than LR subjects, and there was a significant negative correlation between iSP duration and ESS.

**Table 1** Differences in Clinical variables between HR and LR groups.

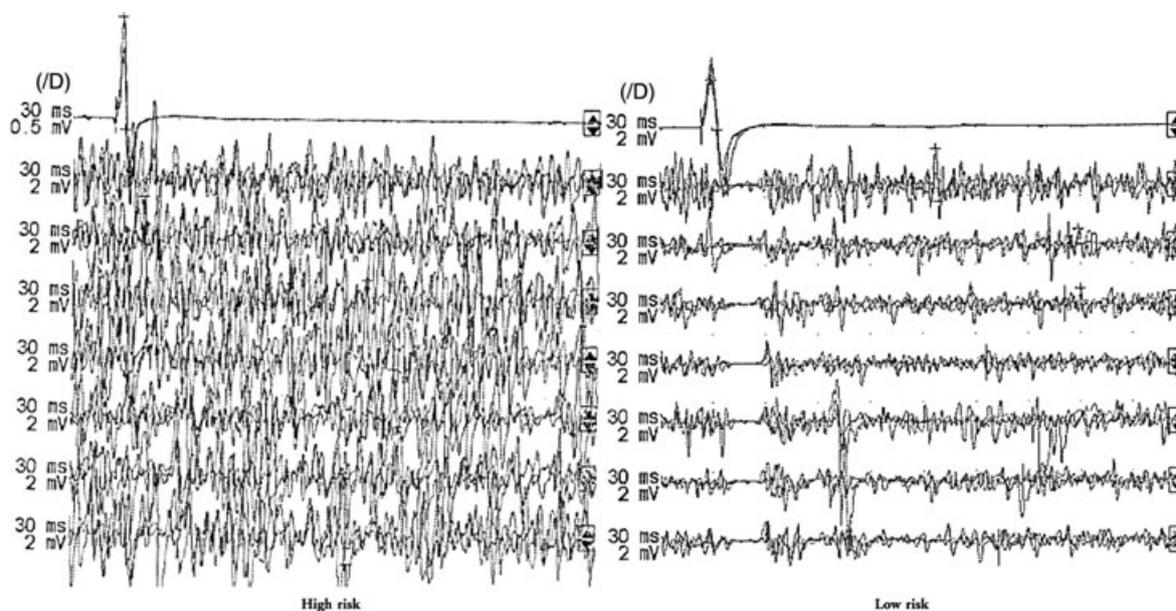
	HR	LR	<i>t</i>	<i>P</i>
Age (years)	20.53 ± 4.22			
Height (cm)	166.6 ± 8.2	168.9 ± 9.5	0.7	0.5
Weight (kg)	62.4 ± 15.7	65.4 ± 17.4	0.5	0.6
Education (years)	13.3 ± 4.3	15.0 ± 5.0	1.0	0.3
ESS	20.3 ± 7.9	6.40 ± 3.4	21.5	<0.001
Fathers' age at developing dependence	15.33 ± 2.32	–		
Father's ESS	17.47 ± 5.91	2.00 ± 1.60		<0.001

ESS = externalizing symptoms score; HR = high risk; LR = low risk.

**Table 2** Differences in cSP and iSP between HR and LR groups.

	HR	LR	<i>t</i>	<i>P</i>
Mean cSP at 130% SO (ms)	113.2 ± 48.1	126.3 ± 40.0	2.8	0.005
Mean cSP at 150% SO (ms)	148.0 ± 37.0	156.0 ± 37.2	2.1	0.039
Mean iSP at 100% SO (ms)	13.4 ± 10.4	15.7 ± 8.2	2.3	0.02
Absent iSP at 100% SO	28.3% (51 out of 180 trials)	14.4% (26 out of 180 trials)	$\chi^2 = 10.3$	<0.001
Absent iSP at 75% SO	45.2% (61 out of 135 trials)	30.3% (41 out of 135 trials)	$\chi^2 = 6.3$	<0.01

cSP = contralateral silent period; HR = high risk; iSP = ipsilateral silent period; LR = low risk; SO = stimulator output.

**Figure 1** iSP at 100% stimulator output. The figure shows a sample electromyogram recording depicting absent iSP in a high-risk individual as compared with an age-matched low-risk individual. iSP = ipsilateral silent period

These findings suggest that alcohol-naïve offspring of early-onset alcoholics appear to have impaired cortical inhibition. The magnitude of this impairment bears a negative relationship to the spectrum of disinhibitory behavior traits, which have been documented to increase the susceptibility to early onset of alcohol use and dependence (McGue *et al.* 2001).

The cSP is a neurophysiological indicator of cortical inhibition (Lang *et al.* 2006), and its duration reflects the

integrity of cortical inhibitory mechanisms, probably mediated through GABA<sub>B</sub> receptors (Werhahn *et al.* 1999). Treatment with pregabalin (GABA analog), vigabatrin (irreversible inhibitor of GABA transaminase) and tiagabine (GABA reuptake inhibitor) increase the duration of the cSP, further suggesting that this inhibitory process is GABA dependent (Lang *et al.* 2006).

Alcohol consumption increases the duration of TMS-induced cSP, presumably by enhancing intracortical

inhibition and suppressing intracortical facilitation by potentiating GABA receptor-mediated currents (Ziemann, Lonnecker & Paulus 1995). Arguably, the heightened reinforcement that HR individuals experience upon consumption of alcohol (Schuckit & Smith 2006) may be a function of this enhanced cortical inhibition.

Studies suggest that the behavioral and cognitive effects of ethanol are mediated, at least in part, by enhanced GABAergic neurotransmission via the allosteric potentiation of postsynaptic GABA<sub>A</sub> receptors that mediate fast synaptic inhibition in the mammalian CNS. GABA<sub>B</sub> (metabotropic) receptors mediate the slow synaptic inhibitory response of GABA transmission (Solis & Nicoll 1992). Most GABAergic synapses contain both presynaptic and postsynaptic GABA<sub>B</sub> receptors. Presynaptic GABA<sub>B</sub> receptors function as autoreceptors, and their activation inhibits GABA<sub>A</sub> inhibitory postsynaptic currents (IPSCs), whereas postsynaptic GABA<sub>B</sub> receptors are primarily coupled to the activation of a potassium conductance (Misgeld, Bijak & Jarolimek 1995). Although ethanol has little direct effect on the GABA<sub>B</sub> receptor response (Roberto *et al.* 2003), blockade of the GABA<sub>B</sub> receptor has been shown to increase ethanol potentiation of the GABA<sub>A</sub> response (Wan *et al.* 1996).

Inhibition of GABA<sub>B</sub> receptor function enhances the ethanol-mediated potentiation of distal GABA<sub>A</sub> IPSCs in inbred long-sleep (LS), but not in inbred short-sleep (SS), mice (Proctor *et al.* 2006). LS and SS lines of mice differ markedly in their genetic sensitivity to alcohol, and LS mice derive far greater reinforcement from ethanol (Proctor *et al.* 2006). GABA<sub>B</sub> receptor activity may thus play a role in regulating behavioral sensitivity to ethanol. The observed decreased cortical inhibition in the HR group may perhaps point to an underlying impairment of GABA<sub>B</sub> activity, which is likely to render them more susceptible to the reinforcing effects of alcohol.

GABA<sub>B</sub> receptors may play a crucial role in the generation of another endophenotype of alcoholism, the low-voltage alpha EEG in abstinent alcoholics and their non-alcoholic first-degree relatives that is thought to be a trait variable involved in the susceptibility to alcoholism (Porjesz *et al.* 2002). A recent study found evidence of an association between the alpha low-voltage EEG phenotype and exon 7 substitution polymorphism of the gene encoding the human GABA<sub>B</sub> receptor in normal subjects. Likewise, the exon 7 polymorphism showed a highly significant association with parietotemporal EEG coherence, suggesting that GABA<sub>B</sub> receptors may play a crucial role in the synchronization of EEG oscillations (Winterer *et al.* 2003).

The reduced ability to manifest iSP had a significantly inverse relationship with higher ESS in the HR subjects. These findings are consistent with an earlier study that reported shorter duration and latencies of iSP in subjects

with ADHD compared with normal controls. A maturational delay of transcallosal fiber tracts has been postulated as the underlying pathophysiological factor of altered iSP latency and duration in children with ADHD (Buchmann *et al.* 2006).

Because ipsilateral conduction deficits are a function of the integrity of the corpus callosum (Meyer *et al.* 1998), the inability to generate iSP probably represents deficient transcallosal conduction. Abnormalities of the corpus callosum have been reported in several morphometric studies of children with ADHD (Hill 2004), conduct and antisocial personality disorder (Raine *et al.* 2003), conditions known to increase vulnerability to alcoholism. The ipsilateral conduction deficits observed in the HR subjects in the current study and the increased occurrence of externalizing behaviors in subjects with absent iSP may indicate the existence of a possible dysfunction in the corpus callosum in individuals with vulnerability to alcoholism.

Interestingly, we have recently reported the finding of reduced volumes of the genu and isthmus of the corpus callosum in subjects at HR for AD (defined similarly as in this study), compared with LR subjects, using structural magnetic resonance imaging (MRI) (Venkatasubramanian *et al.* 2007). The corpus callosum is one of the last structures to mature in a developing brain (Keshavan *et al.* 2002), and this maturation occurs by myelination. Delayed brain maturation is hypothesized to be the mechanism for some of the deficits, such as brain volume deficits, reduced P300 amplitude and increased body sway, which appear to differentiate children of alcoholics (HR) from LR children (Hill 2004; Benegal *et al.* 2006). The iSP is a putative electrophysiological marker of callosal myelination (Buchmann *et al.* 2006) and the inability to generate iSP in our HR group could also be a function of delayed or defective maturation of the corpus callosum relative to the LR group.

Some strengths of the study methodology were the: (1) examination of non-alcohol dependent HR and LR subjects; (2) matching subjects and controls for age, sex, handedness, anthropometry (height and weight) and education; and (3) ensuring the alcohol-naïve status of mothers of all the subjects, which excluded the potential confounding effects of alcohol toxicity on perinatal brain development. Additional use of paired-pulse TMS to investigate the GABA<sub>A</sub>-mediated contribution to the cortical inhibitory tone and the oscilloscopic measures of the maximum force of OP contraction would have added to the methodological rigor of the study; however, we were limited by the hardware available to us. The age range in our sample, 12–25 years, spans an extensive developmental period of the human brain, during which there are significant morphologic changes that may be expected to result in different maturational trajectories

for the two groups. However, we were guided in our choice of age range by the existing literature, which suggests that the maturation of both corticospinal pathways and transcallosal pathways is almost complete by around 10 years of age.

To the best of our knowledge, this is the first study to describe conduction abnormalities using TMS in subjects at HR for AD. These preliminary findings indicate the presence of impaired intracortical inhibition, which is possibly related to reduced GABA<sub>B</sub> function, as well as the existence of a possible dysfunction in the transcallosal conduction in individuals with a vulnerability to alcoholism. Future studies with a larger sample size using both TMS as well as imaging techniques (structural and functional MRI) with repeated measures across the developmental span in the same cohort of HR subjects for alcoholism are needed to validate the current findings.

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