Reduced Cortical Inhibition in Violent Offenders: A Study with Transcranial Magnetic Stimulation

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Key Words

Violent offenders · Intracortical inhibition · Intracortical facilitation · Transcranial magnetic stimulation

Abstract

Background: Aggression and violent behaviour are often regarded as a threat to society. Therefore, understanding violent behaviour has high social relevance. We performed a study with transcranial magnetic stimulation on a sample of violent offenders in order to measure cortical inhibition in the motor neuron system that is part of the frontal cortex. **Methods:** To investigate intracortical inhibition and intracortical facilitation, we conducted paired-pulse stimulation according to the technique of Kujirai and his group (see Method). The investigation sample comprised 62 right-handers: 32 prisoners who had committed severe violent crimes and 30 controls with no history of violence. All subjects were male and matched for age. **Results:** Using the paired-pulse paradigm with interstimulus intervals (ISI) of 1–15 ms, a reduced cortical inhibition (ISI: 3 ms) was found in the left cortex of violent offenders compared with control subjects. **Conclusions:** These findings corroborate the hypothesis of inhibition deficits and frontal cortex dysfunction in violent offenders when compared with non-violent control subjects.

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Introduction

Aggression is often regarded as a threat to society. However, Filley et al. [1] suggested that both aggression and cooperation are genetically encoded behaviours that are essential for survival. Therefore, it is reasonable to make a distinction between adaptive and maladaptive aggressive behaviour as well as between violence and aggression. Human aggression and violence are major social problems. Whereas aggression represents intentional activities that inflict bodily or mental harm on others, violence has been defined as an aggressive act that causes physical injury [1, 2]. Thus, aggression may be a valid behaviour because it may serve an adaptive purpose, and it may also occur without bodily damage. In contrast, violence is a subtype of aggression which is characterized by the unwarranted infliction of physical harm. It is particularly this unwarranted maladaptive subtype of aggression which poses a threat to society. This study refers to violent aggression defined as an abiding ‘overt and intentional physically aggressive behaviour against another person’, as suggested by Citrome and Volavka [2] and adopted by expert consent [1].

Genetic and prenatal factors – like fetal environment, obstetric complications, rearing environment, biological factors and psychiatric disorders such as substance abuse,

psychosis, depression and personality disorders – can predispose subjects to maladaptive aggressive behaviour [2]. Even though the exact interplay of the variables involved is uncertain, there is no doubt that human aggression is at least partly determined by genetic factors [3]. In particular twin and adoption studies [4] and studies on the link between chromosomal disorders like the XYY genotype or the Klinefelter syndrome [5] have demonstrated a substantial genetic influence on the development of violent behaviour. Moreover, studies of knockout mouse models suggest that targeted disruption of single genes like 5-HTTLPR, MAOA or NOS1 [6] can induce aggressiveness in male mice. Admittedly, the situation in human life appears to be much more complicated. There is a growing body of literature indicating a complex interplay between genes and environmental conditions [7].

Studies linking the neurobiological basis to violent behaviour are primarily based on research regarding changes in brain structure and neurophysiology, using neuroimaging or electrophysiological techniques. Based on these studies, two functional systems are linked to violent behaviour in particular: the limbic system [8] and the frontal lobes [9]. For example, hypothalamic activation has been found to be associated with aggression in domestic violence perpetrators [10]; these findings are consistent with those by Blair [11] and Gobrogge et al. [12], who described that anterior hypothalamic regulation was involved in neurobiological processes linked to aggressive behaviour.

In a positron emission tomography study evaluating responses to the probe *meta*-chlorophenylpiperazine, decrements in the lateral medial and orbital frontal cortices were found at baseline in men with a history of physical aggression and in the orbitofrontal cortex of both men and women with a history of physical aggression [13]. Regarding frontal lobe dysfunction, the orbitofrontal cortex has been identified as a mediator of the inhibition or regulation of aggressive behaviour. Orbitofrontal damage, especially when bilateral, has frequently been linked to behavioural changes including violence [14]. Patients with similar orbitofrontal injuries have been found to display antisocial personality traits like impulsivity, disinhibition and lack of empathy [15].

Many studies have related lesions or underdevelopment of the prefrontal cortex [15] to inefficiency of inhibitory control. Therefore, we investigated the primary motor cortex regarding inhibitory control by transcranial magnetic stimulation (TMS). TMS is a non-invasive method used to examine cortical function and to study the activation of brain regions based on the ability of a

magnetic field to penetrate skull and brain meninges, subsequently inducing neuronal depolarization and the generation of action potentials [16]. Single- and paired-pulse TMS is differentiated on the basis of the stimulation type. One of the main areas of TMS application is the investigation of cortical excitability, which is mediated by neurochemical and synaptic processes in the neurons affected by TMS. Paired-pulse TMS studies subsequently reported that excitability of the motor cortex was changed by stimulation of contralateral cortical areas [17, 18].

Decreased motor inhibition has been shown to be correlated with a variety of behavioural dysfunctions such as impulsivity in attention deficit/hyperactivity disorder (ADHD) patients [19] and other neuropsychiatric disorders including epilepsy, dystonia and Parkinson's disease. On a different level of investigation within the neurobiological domain, we propose that differences in inhibitory control can be found between people with and people without a history of violence. We presume that an association with frontal cortex dysfunction measured by TMS can be found in violent offenders because inhibitory control of prepotent action is vital for appropriate behaviour in general and for the regulation of violence in particular.

In this study, we hypothesized that impaired cortical inhibition is present in the investigated group of violent law offenders. In order to examine our hypothesis, we investigated a sample of 62 subjects: 32 prisoners who had committed violent crimes and 30 controls with no history of violence.

Subjects and Methods

Subjects

The study was performed on 62 subjects, of which 32 were offenders sentenced to prison for violent crimes and 30 were controls. All subjects included were right-handed and medication and drug free. Subjects with current axis I disorders according to the DSM-IV were not included. Only participants who gave written informed consent after oral and written explanation about the aims of the investigation were enrolled.

The 32 adult male volunteers had been referred to the Institute of Forensic Psychiatry at Saarland University in Homburg, Germany, by legal authorities for forensic examination. The subjects were assigned to the violent group according to personal police records and recently committed crimes on the basis of careful evaluation of all available documents. This way, only subjects with habitual aggressive and violent behaviour were included in the violent group. The controls had no history of violence. The violent offences comprised homicide (32.5%) and assaults (67.5%). The mean age $\pm$ SD of the violent offenders was 35.5 ± 14.4 years.

The current study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

The crucial factor in recruiting violent offenders who were under detention was their willingness to participate in the study and give informed consent. By contrast, controls had no criminal record. They were matched with the subjects of the violent group according to their age, their mean age being 30.4 ± 7.7 years.

Exclusion criteria were absence of sufficient linguistic skills in German, inability to read or mental retardation. Subjects with a low intelligence ($IQ < 85$) were not included in the study. All subjects were without any DSM-IV axis I diagnosis and showed a clean drug screening at the time of testing. Further exclusion criteria were any history of neurological events such as brain injury or any kind of vascular, inflammatory or degenerative brain disturbance (e.g. meningitis, encephalitis in childhood, developmental or degenerative disorder). Psychometric and explorative testing was performed by an experienced psychiatrist.

Method

TMS utilizes the principle of electromagnetic induction by the discharge of very strong currents over a short period of time which flow through a copper wire coil. A rapid time-varying magnetic field is induced by an impulse of approximately 270 μ s. When the coil is held to the head of a subject, the magnetic field pulse induces a weak current parallel to the plane of the coil in the adjacent second conductor, the brain.

For each subject, the optimal coil position – defined as the stimulation site that produced the largest magnetically evoked potential (MEP) at moderately suprathreshold intensities in the resting right-hand first dorsal interosseus muscle (FDI) – was determined by moving the coil in 0.5-cm steps over the presumed left motor cortex areas. The coil was held tangentially to the head with the handle pointing backwards and at an angle of 45° lateral to the midline. This ensured that the induced current pointed forwards and was perpendicular to the central sulcus, which is optimal for producing transsynaptic activation of corticospinal neurons. The resting motor threshold (RMT), expressed as a percentage of the maximum stimulator output, was defined as the lowest intensity that produced an MEP of $>50 \mu$ V in 5 out of 10 trials in the relaxed FDI [20]. The measurements were performed by an experienced investigator controlled by another experienced investigator and corrected for outliers and extreme values.

When the induced current flowing parallel to the brain surface is sufficient, depolarization of neuronal membranes occurs, and hence an action potential is generated. Thereby, preferentially, interneuronal elements that are oriented horizontally to the surface of the brain are activated [21]. TMS is thought to predominantly activate pyramidal cells transsynaptically via excitatory interneuronal elements [21–24]. By this technique, two magnetic stimuli are delivered in close sequence to the same cortical spot through a single stimulation coil [25]. The first, the conditioning pulse (CP), is a subthreshold pulse and is considered to condition the response to the second, the test stimulus (TS), which is a suprathreshold stimulus and follows within a time period of several milliseconds. The MEP obtained depends on the intensity of the CP, the interval between the stimuli (interstimulus interval, ISI) and the intensity of the TS [26]. Different circuits are recruited by varying intensities of CP and TS. At an ISI of 1–15 ms, short intracortical inhibition (SICI) and short intracortical facilitation (SICF) may be studied. In our study, MEP after an ISI of 1, 3 and 5 ms were accepted to indicate inhibition, and MEP after an ISI of 7, 9, 11, 13 and 15 ms to indicate facilitation.

TMS was applied with a Medtronic MagPro X100 Stimulator with MagOption (Medtronic, Denmark). A figure-of-eight coil with a diameter of 65 mm was placed at the skull above the supposed hand area of the motor cortex. Surface electromyography was recorded from the contralateral FDI with a standard electromyographic amplifier (Medtronic Keypoint 4; recording software: Medtronic Keypoint V 5.01). The bandwidth of the filters was set to 1 Hz and 10 kHz, respectively. The optimal position of the coil was determined by moving the coil by 0.5-cm steps until an optimal MEP could be registered. RMT and active motor thresholds (AMT) were determined according to the protocol by Kujirai et al. [25]. Briefly, the RMT was the minimal stimulus intensity which was required to produce motor potentials of more than 50 μ V peak-to-peak amplitude in 50% of the test pulses. The AMT was determined in analogy with the RMT, while the subject tonically distended a dynamometer with 10–20% of the maximum power. Recruitment curves were determined by increasing stimulus intensity in steps of 10% beginning from subthreshold intensities up to maximum stimulus output at 100%. Paired-pulse stimulation was performed according to the technique of Kujirai et al. [25]. The subthreshold CP was set at 80% of the RMT and was followed by a suprathreshold TS. TMS was adjusted to produce a mean MEP of 0.5–1.2 mV peak-to-peak amplitude when unconditioned (uMEP). The ISI were set between 1 and 15 ms at steps of 2 ms. At each ISI, 8 trials (MEP) were averaged. The time between two measurements was at least 5 sec to avoid secondary effects, such as potentiation. Peak-to-peak amplitudes of these conditioned MEPs (cMEP) were set in relation to an MEP elicited by the mean of 8 test pulses without any conditioning prepulse (uMEP). Data are presented as relative amplitudes of the uMEP (relative amplitude: cMEP/uMEP). Care was taken to relax the subjects and to avoid any movements of the extremities during recordings. Each MEP was checked optically to ensure that the FDI was completely relaxed. Recordings were carefully controlled. Therefore, the amplitudes were visually controlled for any abnormalities throughout the measurement. Doing this, only those subjects were included in the data analysis who were sufficiently relaxed and cooperative during measurement.

Statistics

The statistical analyses were performed by SPSS version 17. All tests were two-tailed with a level of significance at $\alpha = 0.05$. Dependent variables were age, RMT, AMT, SICI (ISI: 3 ms) and SICF (ISI: 7 ms) in the left hemisphere. The independent variable was group membership. Subjects were classified into the group of violent offenders or controls by individual violent history and violent crimes committed. To test the assumption of normal distribution of the dependent variables, the Kolmogorov-Smirnov test was performed. As the normality assumption was violated, the non-parametric Mann-Whitney U test was performed.

Power calculations for the independent two-sample t test were used to analyse RMT and AMT differences between the groups and to compare group differences in SICI and SICF. To compare inhibition and facilitation between the groups, statistical analysis (ANOVA) was performed on two blocks of variables: mean value over log-transformed MEP after the ISI of 1, 3 and 5 ms (inhibition), and mean value over log-transformed MEP after the ISI of 7, 9, 11, 13 and 15 ms (facilitation). Considering the explorative character of the following study, we refrained from further statistic analysis and did not adjust for multiple comparisons.

Fig. 1. Mean relative amplitude and SE over transformed MEP after ISI of 1 and 3 ms (inhibition). Controls: $M = 1.08$, $SD = 1.54$, $SE = 0.28$. Violent offenders: $M = 1.26$, $SD = 1.30$, $SE = 0.23$, $F(60) = 1.183$, $p = 0.281$ (ANOVA on log-transformed values).

Fig. 2. Mean relative amplitude and SE over transformed MEP after ISI of 7, 9, 11, 13 and 15 ms (facilitation). Controls: $M = 6.63$, $SD = 1.54$, $SE = 0.28$. Violent offenders: $M = 6.8$, $SD = 4.34$, $SE = 0.77$, $F(60) = 0.016$, $p = 0.899$ (ANOVA on log-transformed values).

Results

There was no significant age difference between violent offenders and controls [$T(48.17) = -1.77$; $p = 0.082$]. The mean relative amplitude of the RMT was 47.53 ± 5.89 in the group of violent offenders and 46.96 ± 7.58 in the control group. For the AMT, the mean relative amplitude was 40.94 ± 5.08 in the group of violent offenders and 39.96 ± 6.6 in the control group. Neither at the AMT (AMT: $Z = -1.404$; $p = 0.160$) nor at the RMT [RMT: $T(58) = -0.325$; $p = 0.746$] significant differences were found.

There was no significant correlation between age and RMT, neither in the controls ($r = 0.298$; $p = 0.124$) nor in the group of violent offenders ($r = 0.014$; $p = 0.939$). Similar results were found regarding age and AMT: there was no significant correlation between age and AMT in the controls ($r = 0.270$; $p = 0.165$), nor in the group of violent offenders ($r = 0.023$; $p = 0.901$).

Regarding cortical excitability, differences between the group of violent offenders and controls were found by the paired-pulse protocol (table 1). The relative MEP increased with longer ISI and displayed a sigmoidal curve in both groups. The lowest relative amplitudes (<1) were found in short ISI (1–5 ms) of paired-pulse curves, reflecting SICI. SICF, corresponding to relative amplitudes

>1 , occurred at ISI of >5 ms and reached maximum values at the 15-ms ISI. The group of violent offenders generally showed higher mean relative amplitudes at each ISI compared with controls.

With an inhibitory ISI of 3 ms, there were significantly higher MEP ratios in the group of violent offenders (MEP ratio of 65% in the group of violent offenders vs. 56% in controls; $p = 0.021$; for details see table 1). But according to these results, there was no significant difference between the groups concerning overall inhibition [$F(60) = 1.183$; $p = 0.281$] (fig. 1), nor was there a significant difference in facilitation [$F(60) = 0.016$; $p = 0.899$] (fig. 2).

In order to control for any effect of severity of violence, we also compared the subgroups of violent offenders who had committed homicide (group 1: murder, $n = 8$; group 2: manslaughter, $n = 4$) with the subgroups of offenders with assaults (group 3: bodily harm, $n = 10$; group 4: grievous bodily harm, $n = 10$) regarding SICI and SICF. There were no differences between the groups for any ISI [ISI 1 ms: $F(3) = 1.43$, $p = 0.255$; ISI 3 ms: $F(3) = 1.46$, $p = 0.246$; ISI 5 ms: $F(3) = 0.924$, $p = 0.442$; ISI 7 ms: $F(3) = 1.03$, $p = 0.393$; ISI 9 ms: $F(3) = 0.911$, $p = 0.448$; ISI 11 ms: $F(3) = 0.926$, $p = 0.441$; ISI 13 ms: $F(3) = 1.14$, $p = 0.351$; ISI 15 ms: $F(3) = 1.41$, $p = 0.260$].

Table 1. TMS paired-pulse stimulation

ppTMS	Violent offenders	Controls	Statistic
<i>SICI ISI</i>			
1 ms	0.61 ± 0.77	0.50 ± 0.74	T(60) = -0.542, p = 0.590 ^b
3 ms	0.65 ± 0.65	0.58 ± 0.86	Z = -2.310, p = 0.021 ^a
5 ms	1.1 ± 0.73	0.94 ± 0.72	T(60) = -0.631, p = 0.530 ^b
<i>SICF ISI</i>			
7 ms	1.24 ± 0.76	1.30 ± 0.66	T(60) = -0.631, p = 0.772 ^b
9 ms	1.35 ± 0.80	1.36 ± 0.77	T(60) = 0.060, p = 0.952 ^b
11 ms	1.45 ± 0.91	1.39 ± 0.82	T(60) = -0.292, p = 0.772 ^b
13 ms	1.49 ± 1.17	1.37 ± 0.83	T(60) = -0.460, p = 0.647 ^b
15 ms	1.31 ± 1.08	1.25 ± 0.77	T(60) = -0.213, p = 0.832 ^b

The table shows mean relative amplitude values ± SD for several ISI. ppTMS = Paired-pulse TMS.

^a Non-parametric Mann-Whitney U test.

^b t test of two independent samples.

Beside this result, no further statistically relevant difference concerning the values at the individual ISI was found, neither for inhibition nor for facilitation of the left hemisphere.

Discussion

As far as we know, the present study is the first to examine violent behaviour by means of TMS. The study is a pilot study investigating the neurobiological correlates of maladaptive impulsive behaviour in humans who were under detention for their maladaptive impulsive behaviours.

As expected, no significant difference in RMT was found, which could be seen as a sign of normal basic axonal or neuronal excitability in subjects with aggressive behaviour [27]. The main result of the present study is that the subjects belonging to the group of violent offenders demonstrated significantly increased relative MEP amplitudes evoked by paired-pulse TMS at the inhibitory ISI of 3 ms compared with control subjects. No significant differences at the facilitatory ISI of 7 or 9 ms could be detected between the study groups. These findings reflect reduced SICI but equivalent SICF in violent offenders compared with non-violent controls.

In the present study, we found reduced intracortical inhibition in a sample of adult violent offenders com-

pared with controls using paired-pulse TMS. The findings are similar to those from a recent study by our research group investigating intracortical inhibition in a sample of adult ADHD patients [19]. In line with a preliminary report on adults with ADHD [27], we found a significant reduction of intracortical inhibition but no significant increase in cortical facilitation in the ADHD sample. One explanation for the similarity of the results could be the common factor of impulsivity found in ADHD patients as well as in violent law offenders.

However, similar findings have been reported in studies concerning psychiatric disorders associated with impulsive behaviour or prefrontal dysfunction [28, 29]. For example, motor deficit is a known feature in patients with schizophrenia both with and without medication [30, 31]. There are also findings of reduced cortical inhibition in a large sample of medicated first-episode patients with limited exposure to antipsychotic medication [31], supporting the hypothesis that inhibitory intracortical deficits may be part of the schizophrenic pathophysiology [32, 33]. Additionally, reduced SICI has been found in neuropsychiatric disorders like unipolar depression [28], obsessive-compulsive disorder [34] and Tourette's syndrome [35]. These findings indicate that reduced SICI is not specific for any disorder but seems to reflect a dysfunction of frontal cortical circuits independent of the diagnostic entity.

SICI and SICF appear to be caused by activation of separate circuits [36] represented by inhibitory interneurons or inhibitory connections between cortical output cells [37] and facilitatory interactions, partly in the motor cortex, at or upstream from corticospinal neurons [36]. CP in the paired-pulse stimulation technique are thought to activate inhibitory interneurons within the motor system including projections onto corticospinal neurons [25]. Several neural transmission systems like GABAergic, dopaminergic and glutamatergic systems appear to play an important role in these mechanisms. This follows from studies showing that medication that enhances GABAergic activity increases the degree of intracortical inhibition and decreases intracortical facilitation evoked by paired TMS stimuli [38–40]. Also, dopaminergic drugs have been shown to enhance intracortical inhibition in normal subjects [41, 20], and glutamatergic drugs have been shown to increase intracortical inhibition and decrease facilitation [42, 43]. It might be concluded from these findings that violent behaviour is associated with dysfunctions in the abovementioned circuits.

In general, our results suggest that TMS, and particularly the paired-pulse technique, is a useful tool to inves-

tigate the neurological correlates of violent behaviour. It uses motor cortex excitability, which allows studying intracortical circuits [25, 36, 44] and displays little inter- and intraindividual variability [45]. In this study, we used stimulation of the frontal motor cortex, which resulted in motor evoked potentials that could be measured directly at the FDI. Thus, we were able to control the correct position of the coil for each stimulation. In contrast to TMS of non-motor cortical regions there was, therefore, no need for an additional neuroimaging procedure to monitor the position of the coil [46].

Violent crimes are often committed by men. Therefore, we focussed the study on a male group. Nevertheless, further studies should also investigate violent females, above all to compare female violent offenders with male violent offenders. Altogether, violent offenders are a particular investigational group. Therefore, our sample size was relatively small and there are several limitations inherent in this study. There were differences between the types of violent acts for which the criminal offenders had been prosecuted. This heterogeneity has to be taken into account because differences in inhibitory control and facilitation between the various subgroups of violent offenders were lost by averaging over the subjects. However, we found no differences between offenders who had committed assaults that might be regarded as having a correlation with severity of violence. The results indicate that

in our study sample, there is no correlation between severity of violence and measurements of cortical inhibition and facilitation.

Also, a selection bias should be taken into account as the violent offender sample consisted only of persons who had been referred to the institute for forensic examination. Furthermore, the patients came from a wide range of sociodemographic backgrounds. Psychosocial factors are either preceding or associated with offensive activity (e.g. socioeconomic status and education) and, following offensive activity (e.g. stress of imprisonment), may also be associated with differences in brain function. Further studies could investigate more homogeneous groups, for example differentiated by developmental varieties of delinquency and violence. Another interesting approach in future research would be the comparison between subjects showing reactive and instrumental violence, or the correlation of cortical inhibition and facilitation with behavioural personality variables of violent behaviour such as impulsivity.

However, the findings corroborate the hypothesis of inhibition deficits in the population investigated. Further studies are needed to confirm and to further define these excitatory phenomena in order to gain greater insight into the aetiology of aggressive behaviour and to generate useful endophenotypes.

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