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# Does the EEG response to single pulse transcranial magnetic stimulation (TMS) represent a model for epileptic spike-wave complexes?

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## Introduction:

The electroencephalographic (EEG) response to transcranial magnetic stimulation (TMS) has recently been established as a new direct parameter of motor cortex excitability [1-2]. Its N100 component has been suggested to reflect an inhibitory response because it was found to be diminished during movement execution [2].

## Methods:

We have employed TMS in a sample of 6-10-year-old healthy children in order to investigate the influences of cerebral maturation on the N100 component. We used a visual forewarned reaction time (contingent negative variation - CNV) task with 3s stimulus onset asynchrony to test the effect of response preparation and sensory attention on N100 amplitude by comparison of 20 stimulations at rest and 20 stimulations during late CNV (see figure 1). TMS (9cm circular coil) of the right motor cortex at rest and during late CNV were randomly intercalated in the recorded 60 trials [3]. TMS was performed with relaxed left first dorsal interosseal muscle (FDI) and with 20% pre-contraction to determine cortical silent period.

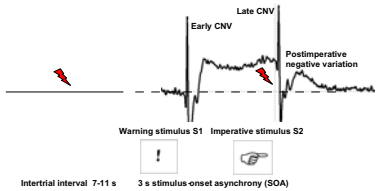


**Fig. 1:**
**The experimental setup of transcranial magnetic stimulation during the contingent negative variation task:**
A visual warning stimulus S1 indicated that 3 s later a visual target stimulus S2 would occur which required a fast unilateral button press with the left hand. A schematic CNV-waveform is given, illustrating CNV components (early and late CNV as well as postimperative negative variation). The vertical dashed line indicates when S2 is presented, negativity is up. Random transcranial magnetic stimulations (indicated by a flash) during the intertrial interval were randomly interspersed with transcranial magnetic stimulations during late CNV (2.8 s post S1). In trials with TMS during late CNV presentation of S2 was delayed until 500 ms after TMS in order to avoid interferences between the TMS-evoked potential and presentation of S2.

## Results:

Single pulse TMS of the motor cortex at rest evoked a large N100 amplitude of more than 100µV in children at 105% motor threshold intensity at the site of its maximum (CP6 130.6 +/- 71.9µV), which could be well separated from TMS-induced artifacts where N100 was absent (see figure 2). TMS-evoked N100 could also not be explained by auditory evoked activity of the coil click, nor the somatosensory evoked potential of the scalp sensation or reafferent input from the muscle twitch in the left FDI, judging from amplitudes, topography, ipsilateral lateralization (see figure 3) and independence from MEP-amplitudes [2]. TMS-evoked N100 amplitude correlated negatively with age and positively with absolute stimulation intensity (see figures 4 and 5). Adult control subjects did not present these giant N100 amplitudes even with suprathreshold TMS application (see figure 4). During late CNV, which is thought to involve a preactivation of the cortical structures necessary for a fast reaction to the imperative stimulus, N100 amplitude was significantly reduced (11.7 +/- 11.0 µV; t=4.4; p<0.001; see figure 6). N100 showed a significant potentiation throughout the recordings even though intervals between successive TMS applications exceeded 5s. Cortical silent period (CSP) correlated significantly with N100 amplitude in trials with 20% FDI precontraction even after controlling for absolute stimulation intensity (r'=0.56, p=0.04).

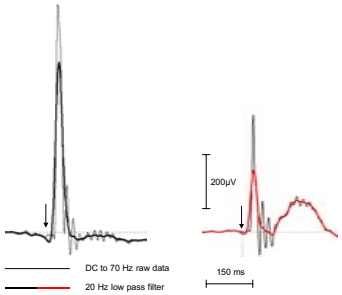


**Fig. 2:**
**EEG response to TMS (right, 74% maximum stimulator output) in contrast to the artifact induced by TMS when the electrodes were stimulated on a head dummy (left, electrode impedances were also about 5kOhm, 100% maximum stimulator output, same scaling, same electrode CP6').**
The response shown at the right was recorded at CP6 in one child. Negativity is up. The arrows indicate TMS application. Please note that the N100 component from about 100ms on was not distorted by the TMS artifact and that 20 Hz low-pass filtering eliminated only artifactual high frequency oscillations without affecting TMS-evoked N100. The EEG artifact produced by the short TMS pulse was transformed by the amplifiers anti-aliasing filter settings (70 Hz low-pass filter and 50 Hz notch filter) to a rapidly decreasing high frequency oscillation. The deblocking device (sample-and-hold-circuit) introduced a short delay after TMS but was not sufficient to eliminate the TMS-induced artifact.

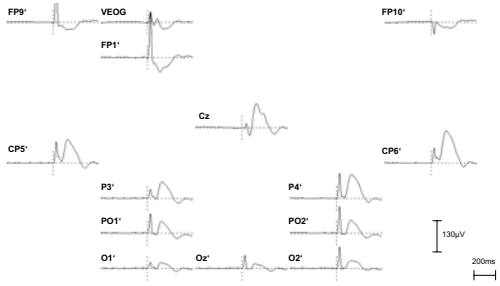


**Fig. 3:**
**Topography of the EEG response (grand average) to TMS at 105% motor threshold for all healthy 6.8-10.0 year-old children (linked mastoid reference).**
Left electrodes have odd numbers. Please note the lateralization ipsilateral to the side of the stimulation (right), the centroparietal negative maximum and the fronto-polar positivity. EOG did not influence the presented results. The vertical dashed line indicates when TMS occurred.

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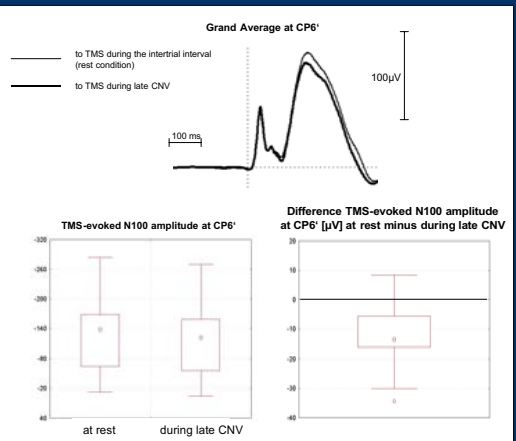


**Fig. 6:**
**Top: Grand averages (n = 17 children) of TMS-evoked N100 at CP6 for the rest (TMS during the intertrial interval) and the late CNV condition.**
The vertical dashed line indicates when TMS occurred. The small peak between the TMS-induced artifact (first negative peak) and the TMS-evoked N100 (third broad negative peak) could represent a small N45/55 [1-3] which is shadowed in our recordings by the TMS-induced artifact (see figure 2).
**Bottom: Box-plots** illustrating the small (left) but intraindividually highly consistent (right) decrease in N100 amplitude decrease during late CNV. The box-plots are shown with the same specifications as in figure 6.

## Conclusions:

1.) N100 amplitude reduction during late CNV provides further evidence that TMS-evoked N100 is an inhibitory surface-negative potential which could be caused by inhibitory post-synaptic potentials from deeper cortical layers. Parallels between the inhibitory N100 after TMS (provoking a massive synchronous excitation) and the wave-component of the typical epileptic spike-wave complex (also representing massive synchronous neuronal action - spike - leading to an inhibitory response via the nucleus reticularis thalami-wave) are tentatively suggested because the long latency of TMS-evoked N100 makes a cortico-thalamo - cortical loop more likely than long-lasting inhibitory postsynaptic potentials within the cortex. TMS-evoked N100 could represent a model of epilepsy research which can be applied directly to humans, opening up a lot of new possibilities.
2.) Response preparation and attention modulates N100, N100 therefore appears to be a more sensitive, independent parameter for cortical excitability than the compound motor evoked potential and seems suitable for the analysis of more complex cognitive processes.
3.) TMS-evoked N100 could be a valuable tool to test cortical integrity and / or inhibitory function in children because children show a much larger N100 amplitude at motor threshold intensity than adults. N100 maturation may reflect pruning processes of inhibitory interneurons.

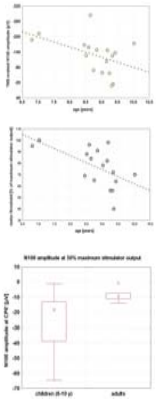

**Fig. 4:**

**Left: Scatterplots illustrating the pronounced age-dependent decrease in TMS-evoked N100 amplitude at 105% motor threshold (top) and the decrease of motor threshold with increasing age (middle).**
When motor threshold and TMS-evoked N100 amplitude values of adult subjects are taken into consideration (motor threshold 40-50% of the maximum Magstim 200 output and TMS-evoked N100 amplitude 10-30µV [1-3]; see also the box plots on the bottom), the notion of a decrease of motor threshold and TMS-evoked N100 amplitude at near motor threshold intensities through school age is furthermore strongly supported. The decrease of TMS-evoked N100 amplitude at the same intensity relative to motor threshold with increasing age is one of the main results of this study.

**Bottom: Box plots illustrating the differences in TMS-evoked N100 amplitude for 6.8 to 10.0 year-old children and young adult subjects at 50% maximum stimulator output.**
The median is indicated within the box, the box represents the quartiles, the whiskers outline the range except for outliers which are indicated separately by points.

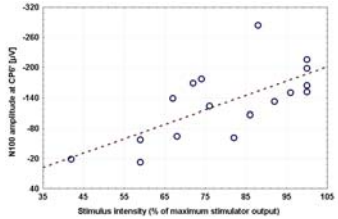


***Fig. 5:***
**Scatterplot illustrating stimulus-intensity dependence of TMS-evoked N100 at CP6.**
On the abscissa, absolute stimulator output values are given. Please note that except for 3 subjects where this would have exceeded the maximum stimulator output (intensity was set to 100% maximum stimulator output), for all subjects the applied intensity was adjusted to 105% of resting motor threshold (same relative but not absolute stimulus intensity).

## References:

[1] Komssi S, Kahkonen S, Ilmoniemi RJ. The effect of stimulus intensity on brain responses evoked by transcranial magnetic stimulation. Hum Brain Mapp 2004; 21: 154-64.
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[3] Bender S,Basseler K, Sebastian I, Resch F, Kammer T, Oelkers-Ax R, Weisbrod M. Electroencephalographic response to transcranial magnetic stimulation in children: Evidence for giant inhibitory potentials. Ann Neurol. 2005; 58: 58-67.