Transcranial Magnetic Stimulation Evokes Giant Inhibitory Potentials in Children

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The electroencephalographic response to transcranial magnetic stimulation (TMS) recently has been established as a direct parameter of motor cortex excitability. Its N100 component was suggested to reflect an inhibitory response. We investigated influences of cerebral maturation on TMS-evoked N100 in 6- to 10-year-old healthy children. We used a forewarned reaction time (contingent negative variation) task to test the effects of response preparation and sensory attention on N100 amplitude. Single-pulse TMS of motor cortex at 105% motor threshold intensity evoked N100 amplitudes of more than $100\mu V$ in resting children (visible in single trials), which correlated negatively with age and positively with absolute stimulation intensity. During late contingent negative variation, which involves preactivation of the cortical structures necessary for a fast response, N100 amplitude was significantly reduced. We conclude that (1) N100 amplitude reduction during late contingent negative variation provides further evidence that TMS-evoked N100 reflects inhibitory processes, (2) response preparation and attention modulate N100, and (3) TMS-evoked N100 undergoes maturational changes and could serve to test cortical integrity and inhibitory function in children. Parallels between the inhibitory N100 after TMS (provoking massive synchronous excitation) and the inhibitory wave component of epileptic spike wave complexes are suggested.

The electroencephalographic (EEG) response to transcranial magnetic stimulation (TMS) has been established as a new approach to characterize reactivity and connectivity of the brain.1–4 The TMS-evoked potential was separated from the artifact caused directly by TMS-induced currents, the auditory-evoked potential (AEP) produced by the coil click, the somatosensory stimulation on the scalp, and reafferent proprioceptive input from muscle contraction.3–5 It was interpreted as a correlate of cortical excitability, which, in contrast with the compound motor-evoked potential (MEP), is able to separate cerebral from spinal cord or peripheral mechanisms.3

The TMS-evoked N100 component has been suggested to reflect inhibitory processes3; it was reduced immediately before movement onset compared with a relaxed resting condition. In paired pulse paradigms, inhibitory processes have been described with a peak 100 to 150msec after the conditioning stimulus in adults6–8; that is, when TMS-evoked N100 of the conditioning stimulus peaks.3

Inhibitory deficits are believed to play an important role in the pathophysiology of epilepsy,7 attention deficit hyperactivity disorder10,11 or migraine,12,13 to name but a few disorders that originate in childhood. However, in contrast with MEP,14,15 maturation of the TMS-evoked EEG response has not been studied in children so far, though maturation of the motor system is not completed until the late teenage years: The readiness potential changes its polarity from positive to negative,16–18 and the late component of contingent negative variation (late CNV, or lCNV) increases during childhood and adolescence in healthy subjects.19,20 During lCNV, the cortical areas involved in subsequent rapid processing of the imperative stimulus and response execution are supposed to be preactivated.21

This study sought to extend the findings of the TMS-evoked EEG response to the immature motor system of children. Furthermore, we tested the hypothesis that TMS-evoked N100 is an inhibitory potential that is reduced when cortex is preactivated.3 Therefore, we examined TMS-evoked N100 during resting conditions and during lCNV in 6- to 10-year-old children.

Subjects and Methods

Subjects

Seventeen right-handed (Edinburgh Handedness Inventory22), healthy children (10 girls, 7 boys) between 6.8 and
10.0 (mean age ± standard deviation, 8.8 ± 0.8) years old were examined. Seven right-handed, healthy young adults (three female and four male adults; aged 25.0 ± 1.8 years) served as the control group. Subjects were screened for visual impairments (corrected visus ≥ 0.8) and neurological or psychiatric diseases. An individual or a family history of epilepsy and an individual history of a convulsive attack of any type were exclusion criteria. No subject took any psychoactive drugs. All children were required a reliable motor threshold below or equal to 100% of maximum stimulator output (MSO; Magstim 200; Magstim, Wales, UK). The study was approved by the local ethics committee. All participants and the parents of all children provided written consent in accordance with the Declaration of Helsinki. One subject could not be included because of discomfort to TMS.

Contingent Negative Variation Task
We recorded 60 CNV trials using a visual warning stimulus S1 (a black exclamation mark on 11.5 × 10 cm white background [width × height], which was presented for 150 msec) and a visual imperative stimulus S2 (a black line drawing of a hand on 11.5 × 10 cm white background, which was presented for 150 msec) on a computer screen (black background) at 0.8 m distance. Intertrial intervals varied randomly from 7 to 11 seconds. Stimulus onset asynchrony between S1 and S2 was 3 seconds. In the 20 trials with TMS during ICNV (2.8 seconds after the onset of S1), S2 was delayed until 0.5 second after TMS (3.3 seconds after onset of S1) to avoid interference between processes related to TMS and to presentation of S2. Subjects were instructed to respond as fast as possible when S2 occurred by pressing a mouse button with the index finger of their nondominant left hand. ICNV amplitude was determined as the mean amplitude 200 msec before TMS in trials with magnetic stimulation.

Transcranial Magnetic Stimulation
Monophasic single-pulse TMS was applied using a Magstim 200 stimulator with a 9 cm diameter circular coil. The coil’s center was positioned over the vertex, and the coil was oriented tangentially to the skull on the right hemisphere so that the maximum MEP amplitude was produced in the left first dorsal interosseus muscle. The current flow within the coil was clockwise to stimulate the right motor cortex. The weight of the coil was carried by a tripod stand; the coil’s position relative to the subject’s head was fixed with tape, as well as an elastic band. An assistant assured manually that the position of head and coil remained constant during the recordings. Resting motor threshold (RMT) was determined as the lowest intensity that produced a MEP amplitude of at least 50 μV in at least 5 of 10 trials in the relaxed left first dorsal interosseal muscle. Relaxation was controlled by acoustic feedback and electromyogram (EMG) offline analysis. For TMS during the CNV task, intensity was set to 105% RMT to obtain reliable MEPs. When 105% RMT exceeded MSO (three subjects, RMT 96, 98, and 100% MSO), intensity was set to 100%. For both ethical and technical reasons, we refrained from applying stronger intensities. Because this analysis focused on intraindividual but not on between-subject comparisons, these subjects were not excluded (their inclusion did not crucially affect the presented results).

TMS was synchronized with the EEG recordings by TTL triggers (Gentask, Stim software package; Neuroscan, El Paso, TX): 20 magnetic stimulations were triggered during ICNV, and 20 stimulations were triggered randomly during the intertrial intervals (resting condition; see Fig 4). Stimulations during the resting condition and ICNV were randomly interleaved.

COMPARISONS BETWEEN ADULT SUBJECTS AND CHILDREN. Ten stimulations with 50% MSO were applied to adults and children to compare maturational effects at the same absolute intensity.

CONTROL CONDITION: PERIPHERAL MAGNETIC STIMULATION OF THE MEDIAN NERVE. For two subjects, the median nerve was stimulated magnetically on the left forearm at an intensity that produced a somatosensory sensation on the forearm subjectively superior to the sensation TMS had produced on the scalp.

Electromyographic Recordings
Surface EMG (compound muscle action potential) was recorded from the left first dorsal interosseus muscle with Ag-AgCl electrodes (impedances < 10 kΩ, filter 20–10,000 Hz; Toennies Neuroscreen; Jaeger-Toennies, Hoechberg, Germany). Epochs of 600 msec (180 msec baseline before and 420 msec after TMS) were analyzed offline: MEP interpeak amplitudes at rest and during ICNV were calculated. Rectified background EMG 180 msec before TMS was determined in addition to acoustic EMG feedback.

Electroencephalographic Recordings
We recorded continuous direct current EEG at a sampling rate of 500 Hz (Neuroscan Synamp; Neuroscan) against linked mastoid reference. An antialiasing, low-pass filter of 70 Hz and a 50 Hz notch filter were used. Recordings were taken at CP6’, CP5’, Cz, PO1’, PO2’, O1’, O2’, Oz, FP1’, FP10’, and FP9’ (extended international 10-20 system, minor deviations are indicated by ‘) by sintered Ag-AgCl disc electrodes (impedances < 5 kΩ). There was no electrode heating under the single-pulse conditions used. Deblooming with a sample-and-hold circuit was applied by a trigger from the magnetic stimulator to the EEG amplifier. CP6’ was chosen for most analyses because previous reports point toward a maximum of the TMS-evoked EEG response of motor cortex slightly posterior to and below C3/4 ipsilateral to TMS.

Signal Preprocessing
For the analysis of CNV, recordings 1 second before S1 served as baseline. The EEG-signal was low-pass filtered offline (20 Hz high cutoff, zero-phase Butterworth filter, slope 24 dB/octave) and segmented into epochs of 7.5 seconds (1 second before S1 to 3.5 seconds after S2). Artifacts were rejected by visual inspection. TMS artifacts made automatic artifact detection or ocular correction procedures impossible. Overall, less than one third of the trials had to be removed.

For the analysis of TMS-evoked potentials, a baseline
500 msec before TMS was applied; the EEG was segmented into intervals from 500 msec before to 500 msec after TMS. The timing of the event triggers was controlled for latency jitter (view function of Gentask Stim software package; Neuroscan). Data were low-pass filtered (same parameters as above), and artifacts were removed manually by visual inspection (less than 10% of trials had to be rejected).

Data Analysis
TMS-evoked N100 was determined as the highest negative peak at CP6 in the interval 80 to 200 msec after TMS. Visual inspection confirmed that there was only one prominent negative peak in this latency range. N100 amplitude was calculated as the mean amplitude in the time window 40 msec (±20 msec) around the N100 peak at CP6’. N100 latency was determined as the time from TMS to the peak maximum at CP6’. N100 was separated from the TMS-induced artifact and the “N100” that was produced when only the electrodes were stimulated on a glass head dummy, which was covered by a cloth soaked with water (simulating the impedances of skull and scalp, respectively) so that impedances of about 5 kΩ were yielded.

Linear regression analysis was used to determine the children’s stimulus–intensity slope for TMS-evoked N100 and its maturational development with increasing age. The development of RMT was also examined by linear regression.

The following further comparisons were performed (paired t tests). First, N100 amplitude at CP6’ and CP5’ was compared to test for lateralization. Second, N100 topography and amplitudes were compared with known topographies and amplitudes of AEP (produced by the coil click) and somatosensory-evoked potentials (produced by the haptic sensation on the scalp) to find out whether other evoked potentials apart from direct motor cortex activation by TMS could account for N100. Third, mean N100 amplitudes in trials with MEP amplitudes above and below the median were compared to elucidate influences of proprioceptive feedback on N100 and the EMG response to TMS. Fourth, influences of the CNV task were examined: N100 amplitude at CP6’ was tested for task influences by comparing TMS-evoked N100 at rest and during ICNV. Fifth, the difference between TMS-evoked N100 amplitude at rest and during ICNV was compared with ICNV amplitude to test whether a baseline shift could account for reduced N100 amplitudes during ICNV. Sixth, N100 amplitudes during the first and the second half of trials with TMS at rest (during the intertrial intervals) were compared in order to test for significant habituation/potentiation.

Results
Separation of N100 from Transcranial Magnetic Stimulation–Induced Artifacts
Figure 1 shows the differentiation of N100 from the TMS-induced artifact that remained in the recordings despite the deblocking device. The short sharp EEG artifact produced by the TMS pulse was transformed by the amplifier’s hardware and filter characteristics to a slightly delayed high-frequency oscillation with decreasing amplitude. The characteristics of the head dummy did not critically change the electromagnetic artifact. Mean N100 amplitude at CP6’ at 105% RMT for 6- to 10-year-old children was −130.6 ± 71.9 μV at rest (values are given mean ± standard deviation unless indicated otherwise). This value differed significantly from the “N100” amplitude when the electrodes were stimulated on a head dummy: 4.8 ± 0.9 μV (t = 7.8; p < 0.00001; N100 was absent).

We replicated that the EEG responses to left median nerve stimulation yielded no such prominent negativity in the N100 latency range (not shown).

Latencies and Topography of N100
Figure 2 shows the topography of TMS-evoked N100. N100 was significantly lateralized, as demonstrated by the difference of N100 amplitude at CP6’ versus CP5’: −37.7 ± 61.8 μV (t = 2.5; p = 0.02). Mean “N100” latency for 6- to 10-year-old children was 168 ± 12 msec at 105% RMT. Reduction of stimulation intensity to 50% MSO resulted in a decrease of mean “N100” latency to 147 ± 17 msec. In adults, N100 latency at 50% MSO was significantly shorter: 112 ± 23 msec (t = 4.9; p < 0.0001).

Maturation of N100
Effects of age on N100 amplitude. The steep regression slope when N100 amplitude was predicted by age (Fig 3) almost reached significance within our limited age range (r = 0.47; p = 0.056; regression slope, 41.4 ± 20.0 μV/year [mean ± standard error]; the positive value indicates a decrease of the negative N100 potential).

Effects of age on resting motor threshold. RMT also decreased significantly with increasing age (see Fig 3). The regression slope was −12.3 ± 4.4% per year (mean ± standard error) in the children’s group (r = 0.58; p = 0.01). The children’s mean RMT was 76.7 ± 17.2%; the adults’ mean RMT was 49.1 ± 12.1%.

Stimulus-intensity dependence. The stimulus-intensity slope for N100 amplitude was −2.8 ± 0.8 μV per percentage point of MSO (mean ± standard error; r = 0.69; p = 0.002; see Fig 3) for 6- to 10-year-old children. The negative slope indicates an increase of the negative surface potential. Intrainsidividual stimulus-intensity dependence is also illustrated in Figure 3.

Effects of age versus absolute stimulus intensity. After correcting for different absolute stimulation intensities, the correlation between age and TMS-evoked N100 amplitude disappeared (partial correlation r’ = 0.12; p = 0.67). However, when adults and children were stimulated by the same absolute intensity (50%
MSO), mean N100 amplitude at CP6 at rest was $8.7 \pm 4.1 \mu V$ for adults and $26.1 \pm 20.1 \mu V$ for children ($t = 2.2; p = 0.035$).

**Effects of the Contingent Negative Variation Task**
Mean ICNv amplitude was small but significant in 6-to 10-year-old children: $-5.0 \pm 8.6\mu V$ at Cz ($t = 2.4; p = 0.03$), and $-2.6 \pm 4.8\mu V$ at CP6' ($t = 2.2; p = 0.04$). For N100 amplitude reduction during ICNv, see Figure 4 and the Table. Though the effect was small regarding absolute average N100 amplitude, it was found reliably in the intraindividual comparisons.

N100 amplitude difference at CP6' between TMS at rest and during ICNv was significantly larger than ICNv: $-9.1 \pm 12.2\mu V$ ($t = 3.1; p = 0.008$). The correlation between mean individual ICNv amplitudes and the mean individual decreases in TMS-evoked N100 amplitude was not significant ($r = 0.05; p = 0.85$).

**Comparisons of Motor-Evoked Potential Amplitude and Transcranial Magnetic Stimulation–Evoked N100 Amplitude**
See the Table for MEP amplitudes at rest and during ICNv. There was no significant correlation between mean MEP amplitude and mean TMS-evoked N100 amplitude at CP6' ($r = 0.09; p = 0.74$), nor was there a significant correlation between rectified pre-TMS EMG and N100 amplitude ($r = 0.1; p = 0.7$). The difference of N100 amplitude at CP6' between trials with MEP amplitudes above and below the median was $3.8 \pm 15.6\mu V$ ($t = 1.0; p = 0.33$).

**Habituation/Potentiation**
Mean N100 amplitude at CP6' for the first and second halves of the trials were $-125.1 \pm 70.2\mu V$ and $-136.1 \pm 73.8\mu V$, respectively. The difference was $-11.0 \pm 11.6\mu V$ ($t = 3.9; p = 0.001$; Fig 5).

**Discussion**
**Methodological Issues: Origin of Transcranial Magnetic Stimulation–Evoked N100**
Children aged 6 to 10 years had giant, TMS-evoked, N100 amplitudes of more than 100\mu V at 105% RMT. N100 could be easily distinguished visually in single trials. Its topography, lateralized ipsilaterally to the side of stimulation with a centroparietal negative maximum and frontopolar positivity, was in clear...
agreement with an origin in the stimulated ipsilateral motor cortex\(^2\) (see Fig 2), though the time-course of the potential at centroparietal and frontopolar sites was not perfectly “mirrored.”

The TMS-evoked N100 could be well separated from the electromagnetically induced artifact or artifacts produced by coil vibration (see Fig 1) using a common direct current amplifier. We could not assess the early components of the TMS-evoked potential\(^3\) because of insufficient deblocking of the TMS-induced artifact, though in grand averages a peak that could correspond to N452–4 (see Fig 4) appeared. The TMS-induced artifact, but not TMS-evoked N100, showed considerable variability and was strongly influenced by the relative position of the coil with respect to electrodes and cables.

No white noise was used to mask the coil click\(^4\) because of its arousing effects (blurring task condition effects) and because children would not have tolerated the additional stress. However, N100 could not be explained by an AEP after the coil click\(^5\) because AEPs show a less lateralized topography,\(^29\) much lower amplitudes especially at central leads in children, and shorter N1 latencies.\(^29\)–\(^32\)

The influence of proprioceptive reafferences was small: We replicated that TMS-evoked N100 amplitude did not correlate with MEP amplitudes of the target muscle.\(^3\)\(^,\)\(^4\) This suggested that MEP and TMS-evoked N100 are two independent parameters.

The somatosensory-evoked potentials resulting from the haptic sensation on the scalp would have produced a potential lateralized contralaterally to the side of stimulation\(^3\)\(^,\)\(^4\) with much lower amplitudes.\(^33\) This is in concordance with a control stimulation of the median nerve yielding much lower amplitudes in the N100 latency range (AEP, somatosensory-evoked potentials, proprioceptive reafferences).\(^3\)\(^,\)\(^34\)

Moreover, known stimulus-intensity dependencies for these sensory-evoked potentials are far less pronounced than in our data.\(^35\)–\(^39\)

Stimulus-Intensity Dependence and Maturation

TMS-evoked N100 amplitude depended strongly on the intensity of stimulation. Contradictory previous results in adults\(^2\)–\(^4\) could be attributed to smaller N100 amplitudes in adult subjects and lower absolute stimulus intensities used.

TMS-evoked N100 amplitude decreased with increasing age in the narrow age range examined (see Fig 3). When TMS-evoked N100 amplitude values of adults are considered,\(^2\)–\(^4\) a decrease of N100 amplitude through school age is further supported. This age-related decrease might be attributed not only to maturational effects, but mainly to an age-related decrease of RMT\(^14\)\(^,\)\(^40\)–\(^42\) and the different absolute stimulus intensities applied. The comparison of N100 amplitude at the same absolute intensity between children and adults showed also true maturational differences. The effect appears too large for a simple increase in skull thickness when compared with the development of other evoked potentials such as auditory N1.\(^30\)–\(^32\) Latency shortening with increasing age is a well-known
Effects of Attention and Motor Preparation during Late Contingent Negative Variation

The children’s ICNV amplitude was small but significant. TMS-evoked N100 amplitude was reduced during motor preparation and stimulus anticipation during ICNV when the cortex was preactivated. This clearly points toward N100 as inhibitory potential. Inhibitory processes in deep cortical layers produce surface-negative potentials.

The random sequence of TMS during intertrial intervals and ICNV avoided systematic confounding effects of external conditions on N100 results.

Fig 3. Scatterplots illustrating the age-dependent decrease of transcranial magnetic stimulation (TMS)-evoked N100 amplitude, the decrease of motor threshold with increasing age, and interindividual and intrasubjectual stimulus-intensity dependence of TMS-evoked N100 at CP6. (Top left) Maturation of TMS-evoked N100 at CP6 at an intensity of 105% resting motor threshold (RMT; r = 0.47; p = 0.056). Values in adults further support an age-related amplitude decrease. (Top right) RMT (percentage of maximum stimulator output [MSO]) as a function of age (r = 0.58; p = 0.01). (Bottom left) Stimulus-intensity dependence of TMS-evoked N100. On the abcissa, absolute stimulator output values are given. Note that except for three subjects (100% MSO), the applied intensity was adjusted to 105% RMT (same relative but not absolute stimulus intensity; r = 0.69; p = 0.002). (Bottom right) The TMS-evoked potential at CP6 is shown at 40, 50, 60, and 70% MSO (57, 71, 86, and 100% RMT) for a representative child. Between-subject stimulus-intensity dependence was not accidentally produced by interindividual variability. The arrow indicates TMS application. Note that TMS-evoked N100 showed a more pronounced stimulus-intensity dependence than the TMS-induced artifact, which, in contrast with TMS-evoked N100 amplitude, showed considerable variability (see Fig 2).

Mean MEP amplitude during ICNV was significantly larger than at rest (previous findings in adults had not always reached significance). EMG (increased MEP amplitude during ICNV) and the cortical response to TMS (decreased N100 amplitude) were again dissociated. EMG preactivation did not differ for the rest and ICNV conditions; therefore, changes in MEP amplitude were not likely to be caused by task-induced differences in muscle precontraction.

N100 amplitude reduction during ICNV could not be explained by effects of ICNV on other evoked potential components: Probe stimuli during CNV have been shown to increase the N1/P3 complex so that effects of CNV on AEPs, somatosensory-, or proprioceptive-evoked potentials would have resulted.
Fig 4. (A) Experimental setup. A schematic contingent negative variation (CNV) waveform is given. The vertical dashed line indicates presentation of S2; transcranial magnetic stimulations (TMSs; indicated by a flash) during the intertrial interval were randomly interspersed with stimulations during late CNV (ICNV; 2.8 seconds after S1). (B) Grand averages (n = 17 children) of TMS-evoked N100 at CP6' for the resting (TMS during the intertrial interval) and the ICNV condition. The vertical dashed line indicates TMS. Note that the small peak between the TMS-induced artifact (first negative peak) and the TMS-evoked N100 (third broad negative peak) may represent a small N45/55, which is shadowed in our recordings by the TMS-induced artifact (see Fig 1). (C) Scatterplot illustrating the highly consistent (in 15/17 children) decrease in TMS-evoked N100 amplitude during ICNV (although it was small with respect to absolute N100 amplitude). Note that for only 2 of 17 children (7.0 and 8.5 years old) equal or greater N100 amplitudes were found during ICNV.
in an increase of N100 amplitude and in a different biphasic waveform (N1/P3). However, the established differences corresponded in their time course to the waveform of the TMS-evoked N100 at rest.

TMS-evoked N100 appears sensitive to changes in attention and motor preparation and may prove to be a promising tool to investigate cortical activity in cognitive tasks. Nikulin and colleagues\(^3\) recently described that a visual stimulus influenced N100 amplitude.

**Habituation/Potentiation**

There was a significant potentiation of N100 amplitude during the recording session, although intervals between subsequent TMS exceeded 5 seconds. Low-frequency TMS exerts inhibitory effects on the cortex\(^4\)\(^9\)\(^-\)\(^5\)\(^1\); however, no influences on MEP amplitudes\(^4\)\(^2\) have been described for frequencies less than 0.2Hz.

**Explicatory Mechanisms**

The TMS-evoked N100 component could result from inhibitory cortical interneurons directly excited by TMS\(^3\); however, even for long-lasting IPSP\(^3\)\(^,\)\(^5\)\(^2\), the long peak latency is difficult to explain.

Transcranial magnetic stimulation produces a sudden synchronized neuronal discharge that in this respect is similar to an epileptic spike. To prevent a sudden synchronized discharge from generalization, intracortical, as well as thalamocortical, inhibitory mechanisms are activated via the thalamic reticular nucleus as established in animal models\(^5\)\(^3\)\(^,\)\(^5\)\(^4\), producing typical spike wave complexes in the EEG.\(^4\)\(^4\)\(^,\)\(^5\)\(^5\)\(^,\)\(^5\)\(^6\)

Therefore, TMS-evoked N100 could be interpreted as “wave” response to an externally generated “spike.” It might provide an in vivo model to assess thalamocortical inhibitory processes in human subjects.

During ICNv, the GABAergic cells in the thalamic reticular nucleus are inhibited,\(^2\)\(^1\) thus N100 may be reduced during ICNv because this inhibition decreases the effect of synchronized corticothalamic input. This hypothetical model needs confirmation by further research.

**Conclusion**

In summary, we found an easily distinguishable TMS-evoked N100 amplitude by near–motor threshold stimulation in 6- to 10-year-old children, which correlated with absolute rather than relative stimulus intensity and showed age-dependent maturation. TMS-evoked N100 was independent from MEP amplitudes and showed significant potentiation throughout a trial block. During ICNv (cortical preactivation), TMS-evoked N100 was significantly reduced, pointing toward a surface-negative inhibitory potential. TMS-evoked N100 may be a valuable tool to investigate inhibitory functioning in children.

This work was supported by the Medical Young Investigator Award of the Medical Faculty of the University of Heidelberg (S.B.).

We thank Professor H.-M. Meinck for providing technical support and Dr S. Zimmermann for editing the manuscript for fluency in English.

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