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Title: **Maturation changes the excitability and effective connectivity of the frontal lobe: a developmental TMS-EEG study**

Short title: **Maturation of frontal lobe connectivity**

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ABSTRACT

The combination of transcranial magnetic stimulation with simultaneous electroencephalography (TMS-EEG) offers direct neurophysiological insight into excitability and connectivity within neural circuits. However, there have been few developmental TMS-EEG studies to date, and they all have focused on primary motor cortex stimulation. In the present study, we used navigated high-density TMS-EEG to investigate the maturation of the superior frontal cortex (dorsal premotor cortex (PMd)), which is involved in a broad range of motor and cognitive functions known develop with age. We demonstrated that reactivity to frontal cortex TMS decreases with development. We also showed that although frontal cortex TMS elicits an equally complex TEP waveform in all age groups, the statistically significant between-group differences in the topography of the TMS-evoked peaks and differences in current density maps suggest changes in effective connectivity of the right PMd with maturation. More generally, our results indicate that direct study of the brain's excitability and effective connectivity via TMS-EEG co-registration can also be applied to paediatric populations outside the primary motor cortex, and may provide useful information for developmental studies and studies on developmental neuropsychiatric disorders.

KEYWORDS: transcranial magnetic stimulation, electroencephalography, frontal cortex, child, adolescent, adult, connectivity

INTRODUCTION

The frontal lobe has a central role in emotional and social abilities and in a multitude of highest-order cognitive processes, such as executive function, attention and memory (Chayer and Freedman, 2001; Rosso et al., 2004; Stuss and Levine, 2002). The connections between the frontal lobes and other brain regions are abundant and often reciprocal, enabling the frontal cortex to wield control over other brain systems, in addition to receiving information (Stuss and Levine, 2002). It has even been suggested that modifications to frontal connectivity may be one of the critical factors in the evolution of human cognitive abilities (Sherwood et al., 2005).

The maturation of frontal lobe functions continues throughout childhood and adolescence (Anderson et al., 2001; Castel et al., 2011; Klenberg et al., 2001; Luciana and Nelson, 1998; Rosso et al., 2004), and is rooted in the protracted structural development of the frontal lobes (Giedd et al., 1999; Giedd, 2004; Gogtay et al., 2004; Sowell et al., 1999; Sowell et al., 2001; Sowell et al., 2003; Sowell et al., 2004a; Sowell et al., 2004b; Wu et al., 2014). Grey matter development in the frontal lobes follows an inverted U-shaped curve with an increase during preadolescence, followed by a decline during post-adolescence (Giedd et al., 1999; Sowell et al., 2004b). All major long-range association pathways (cingulum, superior longitudinal fasciculus, arcuate fasciculus, uncinated fasciculus and inferior fronto-occipital fasciculus) that connect the frontal lobes with other lobes undergo developmental changes in white matter microstructure and integrity (Asato et al., 2010; Chen et al., 2016; Eluvathingal et al., 2007; Lebel et al., 2008). Superficial white matter consisting of short association fibres also displays maturational changes within the frontal lobes (Oyefiade et al., 2018; Wu et al., 2014), and between the frontal and parietal lobes (Wierenga et al., 2016). These structural adjustments involve the reorganization of excitatory and inhibitory frontal circuits, which contribute to the refinement of cognitive functions during development (Duncan et al., 2010; Fillman et al., 2010; Hoftman and Lewis, 2011; Hoftman et al., 2017). The

functional maturation of the most prominent inhibitory neurotransmitter system – the GABAergic system - continues until the end of adolescence, and has distinct developmental profiles between different brain regions and types of interneurons (Kilb, 2012). These developmental alterations of the GABAergic system are paralleled by modifications in excitatory neurotransmission (Kilb, 2012).

Functional magnetic resonance imaging (fMRI) studies have revealed that the activation of brain regions involved in cognitive processing increases with development during cognitive tasks. Co-activation of brain regions related to cognitive functions also undergoes considerable development in task-relevant networks (Rubia, 2013). Resting-state fMRI (rs-fMRI) results have demonstrated that connectivity within resting state networks (RSN) involved in cognitive and emotional processes changes with maturation (Sole-Padulles et al., 2016). In general, the developmental modifications in RSN networks are characterized by a decrease in short-range connectivity and, conversely, an increase in long-range connectivity with development (Fair et al., 2007; Fair et al., 2009). Accordingly, electrophysiological studies have revealed increased coherence, i.e. a correlation of EEG activity between distal electrode placements, which is thought to be a measure of structural and functional connectivity (Cardenas et al., 2018; Kurth et al., 2013; Swingler et al., 2011; Tarokh and Carskadon, 2010; Tarokh et al., 2010), and increased coherence has also been associated with cognitive gains (Bell and Wolfe, 2007; Swingler et al., 2011; Tarokh et al., 2014). In line with the increased long-range connectivity with age, a recent EEG study (Kurth et al., 2017) demonstrated that sleep slow oscillations that quantify spontaneous brain network activity (Massimini et al., 2004) propagate across longer distances with increasing age, a finding that was suggested to indicate increased functional connectivity.

Although neuroimaging and electrophysiological studies have demonstrated increasing frontal functional connectivity with development, direct neurophysiological data on the maturation of human frontal connections are few. The combination of transcranial magnetic stimulation with simultaneous

electroencephalography (TMS-EEG) offers direct neurophysiological insight into connectivity within neural circuits. After a TMS pulse, the induced activation propagates from the site of stimulation to anatomically and functionally connected regions (Bestmann et al., 2004; Denslow et al., 2005), and the spread of the induced activity can be traced via the waveform and topography of the TMS-evoked potentials (TEPs) over the scalp, providing a direct measure of brain connectivity with millisecond temporal resolution (Ilmoniemi et al., 1997; Komssi et al., 2002; Kähkönen et al., 2004; Paus et al., 2001). The excellent temporal resolution of TMS-EEG allows sequential investigation of the spread of activation and contributes to defining the causal relationships in the connections across different cortical areas (Bortoletto et al., 2015; Ferreri and Rossini, 2013).

In healthy adults, TMS of the frontal cortex elicits a waveform showing several TEP components and lasting at least up to 300 ms (Massimini et al., 2005; Rogasch et al., 2014; Rogasch et al., 2015). Both the dorsolateral frontal cortex (Cash et al., 2016; Fitzgerald et al., 2008; Kähkönen et al., 2004; Lioumis et al., 2009; Rogasch et al., 2014) and superior frontal cortex or premotor area (Casarotto et al., 2011; Ferrarelli et al., 2008; Massimini et al., 2005; Zanon et al., 2013) have been targeted. Despite this methodological difference, a sequence containing deflections (named after their latency and polarity; N = negative, P = positive) at around 30 ms (P30), 40–50 ms (N45), 60 ms (P60), 100–120 ms (N100) and 160–190 ms (P180) is frequently reported in response to frontal cortex stimulation (Kähkönen et al., 2005a; Lioumis et al., 2009; Noda et al., 2016; Rogasch et al., 2014). In addition, some studies have found activity as early as at 10 ms (Massimini et al., 2005) and at around 20 ms (Lioumis et al., 2009; Massimini et al., 2005), and as late as at 280 ms (Massimini et al., 2005; Rogasch et al., 2014; Rogasch et al., 2015). These deflections are closely associated with neurotransmitter functioning and represent shifts in the inhibition–excitation balance in cortical circuits, allowing the estimation of cortical

inhibitory and excitatory functioning (Cash et al., 2016; Ferreri and Rossini, 2013; Rogasch and Fitzgerald, 2013).

There have been few TMS-EEG studies in children, and they have all described TEPs to motor cortex stimulation (Bender et al., 2005; D'Agati et al., 2014; Helfrich et al., 2012; Jarczok et al., 2016; Maatta et al., 2017). The results from these studies indicate that the TMS-evoked N100 component, the most prominent TEP after motor cortex stimulation, declines with maturation and could serve as a test of cortical inhibitory function in children (Bender et al., 2005; D'Agati et al., 2014; Helfrich et al., 2012). Moreover, these results demonstrate that interhemispheric signal propagation between motor cortices increases as a function of age (Jarczok et al., 2016; Maatta et al., 2017) and that the complexity of TEP morphology increases and signal spreading facilitates within ipsi- and contralateral cortices, reflecting developmental changes in motor cortex functional connectivity (Maatta et al., 2017). Furthermore, according to the results, motor cortex reactivity to TMS decreases with development (Maatta et al., 2017).

Exploring how frontal activation and connectivity develop with age can provide insight into why children and adults differ in complex cognitive functions (Stiles and Jernigan, 2010). Moreover, the characterization of frontal lobe development offers the promise of understanding the origins of developmental disorders, since the frontal lobe is the primary candidate for dysfunction in many neurological and psychiatric disorders that appear in childhood and adolescence (Gehricke et al., 2017; Lesh et al., 2011; Mitchell et al., 2009; Schubert et al., 2015; Solomon et al., 2014). Thus, it is of particular interest to understand how the frontal lobe and its connections change with development. Here, we addressed this question by using TMS-EEG co-registration to investigate the maturation of excitability and effective connectivity of the superior frontal cortex (dorsal premotor cortex (PMd)). The PMd was selected as a target because the spread of TMS-induced activity after stimulation of this region in adults has been well characterized using concurrent TMS and positron emission tomography (PET)

and fMRI recordings (Bestmann et al., 2005; Bestmann et al., 2008; Chouinard et al., 2003). Furthermore, the PMd is involved in a broad range of motor and cognitive functions (Genon et al., 2017) that develop with age. We hypothesized, based on the above-mentioned developmental motor cortex TMS-EEG studies, that we would find evidence of developmental changes in frontal cortex excitability, indexed by a larger TMS-evoked EEG response in children compared to adults, and that the TEP waveform would become more complex with brain maturation. We also hypothesized, based on previous structural and functional neuroimaging studies, that effective connectivity between the PMd and other brain regions increases with age, possibly reflecting the strengthening of long-range connections with development.

PARTICIPANTS AND METHODS

Participants

Altogether, 10 children (mean age 10.6 years, range 8.8 – 11.2 years), 11 adolescents (mean age 15.8. years, range 14.3 – 17 years) and 10 adults (mean age 29.3 years, range 22.3 – 45.3 years) participated in the study. There were five females in each age group. All participants were healthy and right-handed according to a revised and reduced version of the Waterloo Handedness Questionnaire that included 20 items (Steenhuis et al., 1990). The children were recruited from a population sample of children who participated in the Physical Activity and Nutrition in Children (PANIC) study at the Institute of Biomedicine, University of Eastern Finland (Eloranta et al., 2012). The adolescents were recruited from a middle school near the hospital, and the adults were students from the University of Eastern Finland and personnel of the TMS laboratory. The exclusion criteria were common contraindications to magnetic resonance imaging (MRI) and TMS (Rossi et al., 2009; Rossi et al., 2011).

All participants and the guardians of the children were informed about the nature of the study. After having received a detailed description of the procedure, the participants provided written informed consent. If the participant was under 15 years of age, a guardian also provided written informed consent. The Research Ethics Committee of the Hospital District of Northern Savo approved the study protocol (48/2010), and the study was carried out in accordance with the latest version of the Helsinki Declaration.

Study protocol

During the first examination visit, the participants were scanned with a 3.0 T MRI scanner (Philips Achieva X, Philips Healthcare, Eindhoven, The Netherlands). Structural 3D T1-weighted MR images were acquired (TR 8.07 ms, TE 3.7 ms, flip angle 8°, 1 x 1 x 1 mm3 resolution) for neuronavigation in TMS. An experienced neuroradiologist screened all the structural MR images before the TMS session.

TMS-EEG recording was carried out during the second visit. TMS was performed with an eXimia stimulator (Nexstim Plc., Helsinki, Finland) and a biphasic figure-of-eight coil combined with the eXimia navigation system, which enables continuous visualization of the stimulation site in relation to the individual cortical anatomic structure (3.2.2. research version) via a three-dimensional infrared Tracking Position Sensor Unit (Polaris, Northern Digital Inc., Waterloo, Canada). The individual reconstructed 3D brain surface was used for localization and targeting of the TMS. TMS pulses were administered to the right superior frontal cortex (Brodmann's area 6/8).

The navigation system also allows estimation of the TMS-evoked electric field, expressed in volts per metre (V/m), on the targeted cortical area. The stimulation intensity was based on the electric field on the targeted grey matter surface. We used a stimulation intensity of approximately 110–120 V/m, which in previous TMS-EEG studies has been shown to be effective in eliciting an EEG response in adults (Ferrarelli et al., 2008; Rosanova et al., 2009). Each participant underwent 300 TMS trials with

interstimulus intervals randomized between 1.5–1.7 s. The TMS system delivered trigger pulses that synchronized the TMS and EEG systems. EEG was recorded with a 60-channel TMS-compatible amplifier (Nextim Plc., Helsinki, Finland) continuously throughout the experiments with TMS-compatible Ag/AgCl-coated electrodes positioned according to the 10-10 International System. The ground and reference electrodes were positioned on the forehead. Skin/electrode impedance was set below 5 kΩ. Horizontal and vertical eye movements were detected by recording the electro-oculogram with two electrodes located to the left and right of the external canthi. In the EEG system, a sample-and-hold circuit was applied together with blocking of the amplifier input for 2 ms from the stimulus to avoid amplifier saturation. The data were recorded with a 1450 Hz sampling frequency and 16-bit precision. During the TMS session, the participants sat in an adjustable chair with a headrest that ensured a stable head position, and were instructed to keep their eyes open and to look at a fixation point on a screen in front of them. To mask coil-generated clicks, white noise (obtained from the waveform of the TMS click), which was digitized and processed to produce a continuous audio signal with specific time-varying frequencies (Massimini et al., 2005), was continuously delivered through earphones. The masking volume was adjusted until the participant reported that the TMS click was no longer audible.

Data analysis

Scalp-to-cortex distance

The scalp-to-cortex distance (SCD) was measured using navigation software as the peeling depth from the scalp to the target on the right superior frontal cortex (Brodmann's areas 6/8).

Visualization of stimulation sites

In order to visualize the locations of the stimulation sites of the participants, the individual MR images and thus stimulation target coordinates for each participant were spatially normalized to standard space

using SPM8 software running on MATLAB 7.4 (Mathworks Inc., Natick, MA, USA). Then, 90% confidence interval ellipsoids were fitted to the cluster of the individual stimulation targets. This was done by estimating the lengths and directions of the ellipsoid main axes based on the chi-square distribution using an in-house-written MATLAB script (Niskanen et al., 2010).

EEG

Offline data analysis was conducted with in-house-written scripts using MATLAB (version 2007b) and the freely available EEGLAB toolbox (Delorme and Makeig, 2004).

EEG data were divided into segments of 500 ms, including a 100-ms pre-stimulus baseline. EEG signals were bandpass filtered between 1 and 80 Hz, down-sampled from 1450 Hz to 725 Hz, and baseline corrected by using the 100 ms pre-stimulus time as the baseline. TMS-evoked EEG activity was visually inspected trial by trial in each channel and trials contaminated by muscle activity, eye movement or blinks were rejected. Following this procedure, all included trials were averaged for each channel and for each participant. The 15-ms interval immediately following the TMS pulse was excluded from the analyses. In this way, artefacts caused by the TMS-induced currents and the eventual TMS-evoked muscular scalp responses were avoided. Lastly, EEG was converted to the common average reference for the analyses.

The total EEG activity was first assessed using the global mean field power (GMFP), calculated as the root-mean-squared value of the EEG signal across all electrodes (Lehmann and Skrandies, 1980). For the analysis of evoked responses, averaged TEPs over all the included trials for each electrode and each participant were used, and semi-automatic amplitude/latency measurements of each TEP component were performed. Latency ranges used to calculate the TEPs were determined from the TEP waveform in

the vicinity of site of stimulation (mean of Fz and F2). The peaks were named after their latency and polarity (N = negative, P = positive).

Cortical source analysis of the TMS-evoked EEG activity

The current density on the cerebral cortex for the TEP components was estimated using minimum norm estimation (MNE; minimum-norm least-squares method) in Curry software (version 6.0.2, Compumedics Neuroscan Ltd., Charlotte, NC, USA) for illustrative purposes. This method was selected because it requires no a priori assumption about the nature of the source distribution (Hamalainen and Ilmoniemi, 1994) and has a relatively good (~5 mm) localization accuracy (Komssi et al., 2004).

An MR image from one individual in each age group was used in computations. A three-compartment boundary element model (BEM 6/8/9mm) and standard conductivity values were used (0.33 S/m for the brain and fluid, 0.0042 S/m for skull, and 0.33 S/m for skin). The digitized electrode positions were projected onto the scalp surface. The analysis was performed separately for each age group by using each group's grand average EEG data. The time points at which the current densities were calculated were obtained from the peaks in the GMFP. The cortical areas showing current maxima at each time point for each age group were anatomically identified by a neuroradiologist using the 3D surface model and MR images in three orthogonal directions.

Statistical analyses

Statistical analyses were computed with MATLAB and SPSS for Windows Version 22 (IBM Corporation, Somers, NY, USA). Differences between groups were defined as statistically significant if $p < 0.05$ and a trend if $p < 0.1$, and Bonferroni correction for multiple comparisons was applied when necessary for the number of age groups ($p < 0.05/3$) and also for the number of peaks in the TEP analyses ($p < 0.05/8$). The following assessments were performed:

1) Differences in SCD as well as differences in stimulation intensity (expressed both as V/m and as a percentage of the maximal stimulator output needed to evoke 110–120 V/m on the surface of the cortex) were assessed using one-way ANOVA, and the independent samples *t*-test was used for *post hoc* analysis.

2) Differences in GMFP between groups were assessed by performing a *t*-test at each time point in the 400-ms post-stimulus time interval. A GMFP area (15–400 ms post-stimulus) comparison was made with one-way ANOVA, and an independent samples *t*-test was used for *post hoc* analyses.

3) Developmental differences between age (in months), SCD, stimulation intensity expressed as the maximum stimulator output (MSO) and the GMFP area were assessed using two-tailed Pearson's correlation coefficients.

4) In statistical analysis of TEPs, a linear mixed-effects model was used. The channels were divided into 15 regions (see Fig. 1 for further details). For analysis, we created variables to determine the regions: three in the anteroposterior (AP) direction (1 = frontal, 2 = central and 3 = parieto-occipital) and five in the mediolateral (LAT) direction (1 = left lateral, 2 = left mediolateral, 3 = medial, 4 = right mediolateral, 5 = right lateral). The baseline-to-peak amplitude of peaks of interest was used as a dependent variable, the participant was determined as a random factor, and the group, AP and LAT as fixed factors. The main effect of group and the interaction between group x AP x LAT were tested independently for each of the TEPs, and the results were Bonferroni corrected according to the number of peaks. *Post hoc* analyses were run to determine the source of statistically significant interactions between group x AP X LAT. Before the *post hoc* analysis, we combined the variables group (children/adolescents/adults) with AP and LAT (15 regions). Thereafter, a linear mixed model was run with GROUP_AP_LAT as fixed factors and the peak of interest as the dependent variable. For TEP analyses, only results indicating statistically significant differences between the groups are reported.

5) As SCD was expected to differ between the age groups (Maatta et al., 2017), we wanted also to evaluate whether SCD had a significant influence on the possible between-group differences in GMFP area or in TEP amplitudes or topographical distribution. To this end, we performed GMFP area comparison with univariate analysis of variance using SCD as a covariate, and the LMM analysis of TEPs were repeated with SCD as a covariate.

6) The TEP latencies were analysed as the mean latency in the region where the mean response was largest in amplitude in each group. One-way ANOVA and independent samples *t*-tests were used for between-group comparisons.

RESULTS

General indices

The examinations were well tolerated and no side effects were observed. No abnormalities were found in MRI or EEG.

Results from the visualization of stimulation sites indicate that the location of the stimulation target was comparable among all participants (Fig. 2), and according to visual inspection, this site corresponds to the rostral and dorsal part (PMd/prefrontal border) of the PMd (Genon et al., 2017).

SCD at the site of stimulation differed statistically between the groups ($F = 14.745$, $p = 0.000$), and was statistically significantly shorter in children compared with adults ($p = 0.000$) and adolescents ($p = 0.012$). SCD correlated with age ($r = 0.638$, $p = 0.000$).

The electric field induced on the frontal cortex was compared *post hoc* between the age groups to ensure that the stimulation intensities were equal ($F = 2.821$, $p = 0.077$, mean in adults 116 V/m, in adolescents

115 V/m, in children 119 V/m). The stimulation intensity, expressed as a percentage of the MSO needed to elicit an electric field of 110–120 V/m, on the other hand, differed statistically significantly between the groups (F = 9.424, $p = 0.001$), being significantly lower in children (51% MSO, SD 4.9) and adolescents (48% MSO, SD 6.9) than in adults (60% MSO, SD 6.4) ($p = 0.001$ and $p = 0.012$, respectively). The stimulation intensity expressed as a percentage of MSO correlated statistically significantly with age (r = 0.562, $p = 0.001$). However, when we ran a partial correlation controlled for SCD, the correlation no longer remained statistically significant (r = 0.343, $p = 0.179$).

TMS-EEG results

Effects of age on GMFP

GMFP showed a significant decline with age. Groups-wise differences as a function of time are presented in Figure 3. The mean area of GMFP (15–400 ms post-stimulus) differed between the groups (F = 6.967, $p = 0.004$), being significantly larger in children than in adolescents ($p = 0.047$) and in adults ($p = 0.003$). GMFP area correlated significantly with age (r = -0.384, $p = 0.033$).

Effects of age on TEP waveform

Upon visual inspection, there were eight peaks in the TEP waveform at the site of stimulation in all age groups (Fig 4a). Group-wise mean amplitudes and latencies for each peak, as well as the location of the amplitude maximum for each peak, are presented in Table 1. The topographic distribution of the peaks is presented in Figure 4b. The mean amplitude did not differ significantly between the age groups for any component, except for the P180 (F = 6.73, $p = 0.032$).

Peak 1 - P20

The topography of P20 differed statistically significantly between the groups (F = 6.307, $p = 0.000$). However, no between-group differences were found in the *post hoc* analysis for the interaction between group, AP and LAT. The P20 latency differed statistically significantly between the groups (F = 9.079, $p = 0.008$), being significantly longer in children compared with adults and adolescents ($p = 0.003$ in both comparisons).

Peak 2 - N 30

The topography of this negativity differed statistically significantly between the groups (F = 6.399, $p = 0.000$). However, no between-group differences were found in the *post hoc* analysis for the interaction between group, AP and LAT. The N30 latency did not differ between the groups.

Peak 3 - P40

The topography of this negativity differed statistically significantly between the groups (F = 4.668, $p = 0.000$). However, no significant between-group differences were found in the *post hoc* analysis for the interaction between group, AP and LAT. The P40 latency did not differ between the groups.

Peak 4 - N45

The topography of this negativity differed significantly between the groups (F = 3.711, $p = 0.000$). However, no significant between-group differences were found in the *post hoc* analysis for the interaction between group, AP and LAT. The N45 latency did not differ between the groups.

Peak 5 - P60

The topography of this peak differed significantly between the groups (F = 4.010, $p = 0.000$). However, no between-group differences were found in the *post hoc* analysis for the interaction between group, AP and LAT. The P60 latency did not differ between the groups.

Peak 6 - N100

Although the mean amplitude of the response did not differ between the three groups, there were topographical differences in the distribution of this peak ($F = 5.428$, $p = 0.000$).

The *post hoc* analysis for the interaction between group, AP and LAT showed that the response in children was significantly larger than that in adolescents centrally in the right lateral electrodes ($p = 0.021$). The N100 latency differed significantly between the groups ($F = 10.477$, $p = 0.000$). These differences stemmed from the longer latency in adults compared with children and adolescents ($p = 0.002$ and $p = 0.001$, respectively).

Peak 7 - P180

The mean amplitude of P180 differed significantly between the age groups ($F = 6.733$, $p = 0.032$). P180 was significantly larger in children compared with adults ($p = 0.003$). There was also a trend of the response in children being larger compared to that in adolescents ($p = 0.057$). Significant topographic differences in P180 distribution were found between these groups ($F = 26.342$, $p = 0.000$). In the *post hoc* analysis for the interaction between group, AP and LAT, significant regional differences between children and adults were found frontally in the left mediolateral region ($p = 0.038$), centrally ($p = 0.0049$) and parieto-occipitally in the midline ($p = 0.001$) and in the right mediolateral region ($p = 0.017$). Furthermore, there was a trend of the response in children being larger frontally in the left mediolateral region compared to adolescents ($p = 0.078$). The P180 latency did not differ between the groups.

Peak 8 - N280

The topography of this peak differed significantly between the groups ($F = 8.814$, $p = 0.000$). However, no between-group differences were found in the *post hoc* analysis for the interaction between group, AP

and LAT. The N280 latency differed significantly between the groups (F = 5.816, p = 0.008). *Post hoc* analyses revealed that this difference stemmed from the significantly longer latency in children compared with adolescents (p = 0.007).

SCD and TMS-EEG

SCD did not have significant impact on the GMP area analysis. Univariate analysis of variance with SCD as a co-variate demonstrated that GMFP area differed significantly between the groups (F=6.909, p=0.004). In post hoc analyses, GMFP in children was significantly larger than that in adults (p=0.006) and in adolescents (p=0.010).

In the LMM analysis of TEPs with SCD as a covariate, only P180 (peak 7) was influenced by SCD. The between-group difference in P180 amplitude remained significant with minor changes in F and p values (F=6.200, p=0.048). P180 remained significantly larger in children compared with adults (p=0.006), and contrary to the original LMM analysis without SCD, also the difference between children and adolescents reached significance (p=0.028 vs. p= 0.057). No other changes were observed in relation to SCD.

Sources computed using minimum norm estimation (MNE)

Figure 5 presents the estimated current densities of the maximal activity in each component and group, illustrating the differences between groups. Visual inspection of activation showed differences between children, adolescents and adults in the response to right superior frontal cortex stimulation (the term ipsilateral refers to the right hemisphere and contralateral to the left hemisphere).

In adults, the current maxima (reflecting the maximum neuronal activity) shifted from the site of stimulation to the contralateral medial post central gyrus (19 ms), the contralateral premotor cortex (30 ms), the ipsilateral laterobasal occipital cortex (37 ms), the ipsilateral paracentral lobulus and

simultaneously the prefrontal cortex (46 ms), and the contralateral occipital cortex (62 ms), and thereafter located in the ipsilateral paracentral lobulus (99 ms, 199 ms, and 298 ms). It is noteworthy that at 46 ms and 62 ms, adults also showed strong activation in the contralateral inferior parietal lobe. In adolescents, the current maxima moved to ipsilateral prefrontal and parietal association cortices (19 ms), ipsilateral (28 ms) and contralateral (39 ms) lateral sensory cortices, then to the ipsilateral medial sensory cortex (50 ms), the ipsilateral prefrontal cortex (70 ms) and the ipsilateral precuneus (97 ms), and thereafter to the contralateral (182 ms) and ipsilateral paracentral (294 ms) lobuli. Children displayed current maxima that at 19 ms located in the ipsilateral prefrontal cortex in the vicinity of the site of stimulation, and then shifted to the contralateral premotor cortex (32 ms), followed by the contralateral medial primary sensory (44 ms) and primary motor (57 ms) and ipsilateral primary sensory (77 ms) cortices. Thereafter, the current maxima moved to the ipsilateral medial primary sensory cortex/paracentral lobule (102 ms), the ipsilateral medial premotor cortex (172 ms) and finally the ipsilateral associative auditory cortex (282 ms).

DISCUSSION

Main findings

The results of this study describe, for the first time, the age-related differences in connectivity of the right PMd cortex using TMS-EEG in children, adolescents and adults. We demonstrated that in children, the reactivity to frontal cortex TMS is stronger than in adults, as indexed by larger-amplitude TMS-evoked activity, particularly in the late part of the TEP. We also showed that frontal cortex TMS elicits an equally complex TEP waveform in all age groups. Moreover, according to our results, the topographical

distribution of TEPs and the topography of TMS-elicited current maximum at different time points evolve with brain maturation, indicating developmental differences in effective connectivity.

Global mean field power

GMFP is an indicator of global cerebral activation in response to an external perturbation and also provides information on the functional connectivity of the stimulated area. In this study, TMS elicited a larger GMFP response in children compared to adults, with the responses in adolescents lying between those of children and adults. This finding is consistent with the results of our previous study using suprathreshold TMS to of the motor cortex (Maatta et al., 2017), as well as with the results of other developmental TMS-EEG (Bender et al., 2005; Jarczok et al., 2016) and EEG studies (Matousek and Petersen, 1973; Tarokh and Carskadon, 2010; Whitford et al., 2007) demonstrating higher TEP amplitudes and EEG power in children and adolescents than in adults. With development, EEG shows a similar curvilinear decline to grey matter volume, and it has therefore been suggested that the smaller EEG responses in adults may be associated with grey matter loss in the pre- and peripubescent period (Whitford et al., 2007). Interestingly, the results of the present study suggested that the developmental differences in SCD may not have a substantial influence on developmental differences in TMS-EEG amplitude and topography. Before strong conclusions can be made, however, it must be noted that SCD was measured at one site only (the site of stimulation). As there may be a considerable with-in subject variance in SCD at different cortical regions, our current data can only be considered as a rough estimate on the impact of SCD on EEG.

GMFP also provides information on the excitation–inhibition status of the stimulated networks (Ferreri et al., 2011a). For example, experimental procedures that increase cortical excitability, such as anodal transcranial direct current stimulation (tDCS), also increase GMFP (Romero Lauro et al., 2014).

Furthermore, in a time window related to inhibitory activity (45–130 ms), inhibitory paradigms such as 1 Hz TMS increase GMFP (Casula et al., 2014). Thus, in addition to developmental differences in brain structure, age-related differences in the excitation–inhibition balance (Saisanen et al., 2018) may also account for the enhanced GMFP in children, as previously demonstrated for physiological aging (Ferreri et al., 2017).

Waveform

In adults, TMS of the right superior frontal cortex elicited a sequence of eight components with altering polarity when recorded at the site of stimulation, i.e. positivities at around 20 ms, 40 ms, 60 ms and 190 ms, and negativities at around 32 ms, 50 ms, 100 ms and 300 ms. Contrary to our hypothesis, an equally complex EEG response was also evoked in children and adolescents at the site of stimulation, although the latencies and topography of the components differed between the groups. The waveform recorded in the participants of our study shows resembles the sequence of P13-N18-P30-N45-P60-N100-P180-N280 components elicited by TMS of the adult motor cortex (Ferreri et al., 2011a), and is consistent with the findings of previous frontal cortex TMS studies (Kähkönen et al., 2005a; Lioumis et al., 2009; Massimini et al., 2005; Noda et al., 2016; Rogasch et al., 2014). We did not find amplitude differences in early TEPs between the age groups, and only a minor difference in the early part of GMFP, but the late P180 was significantly larger in children than in adults, and there was also a trend of the response in children being larger compared to adolescents. Accordingly, major differences in GMFP between children and adults were seen in the P180 latency range and later on.

The mechanisms underlying the generation of each TEP peak have not been fully elucidated. In general, evidence from motor cortex TMS-EEG studies suggests that the peaks within the first 30 ms reflect excitatory neurotransmission (Ferreri et al., 2011a; Mäki and Ilmoniemi, 2010), whereas later peaks

reflect inhibitory neurotransmission, mediated by $GABA_A$ (40–50 ms) and $GABA_B$ (~100 ms) receptors (Ferreri et al., 2011a; Premoli et al., 2014). Regarding the TEPs following frontal cortex stimulation, a recent paired-pulse TMS-EEG (ppTMS-EEG) study demonstrated that the frontally elicited P60 was suppressed by short-interval intracortical inhibition (SICI) and enhanced by intracortical facilitation (ICF), suggesting that this peak is modulated by $GABA_A$ inhibitory and glutaminergic excitatory activity (Cash et al., 2016). Other ppTMS-EEG studies have suggested that activity in the time interval of 50–100 ms after frontal cortex stimulation may relate to GABAB inhibitory activity, and that the frontal N100 may represent $GABA_B$-related cortical inhibition (Fitzgerald et al., 2009; Rogasch et al., 2015). A TMS-EEG study using short-latency afferent inhibition (SAI) has also linked the GABAergic-mediated inhibition in P60 and N100 also to cholinergic activity (Ferreri et al., 2011c).

The mechanisms contributing to the generation of TEP components occurring after 100 ms post-stimulus are more ambiguous. Despite the fact that pharmacological TMS-EEG studies have failed to demonstrate a direct link between P180 and specific neurotransmitter functions (Premoli et al., 2014), the long latency and wide distribution of the P180 component have been linked to the activity of reverberant cortico-cortical as well as cortico-subcortical circuits driven by $GABA_B$ neurotransmission in the motor cortex (Ferreri et al., 2011b). This component appears to be sensitive to age-dependent modulation, since in motor cortex TMS-EEG studies, it has differed in both amplitude and spatial distribution between young and elderly adults, and these differences have been linked to age-related changes in $GABA_B$ receptor-mediated inhibition (Ferreri et al., 2017; Opie et al., 2018). P180 in frontal cortex TMS is modulated by long latency intracortical inhibition (LICI), which was recently demonstrated to also represent $GABA_B$-receptor activity in the frontal cortices (Salavati et al., 2017). Following these lines of interpretation, the increased P180 in children in response to frontal cortex stimulation may reflect developmental differences in $GABA_B$ergic neurotransmission and/or in frontal cortico-subcortical-cortical loops (for

example, through the thalamus (McFarland and Haber, 2002)). It is well know that the functional maturation of the GABAergic system continues until the end of adolescence (Kilb, 2012), and the $GABA_B$ hypothesis for the increased P180 in children is in line with the results from previous motor cortex TMS studies suggesting stronger inhibition in children compared to adults (Bender et al., 2005; Maatta et al., 2017; Saisanen et al., 2018). The functional significance of the suggested increase in inhibition in children remains uncertain. In a recent TMS and magnetic resonance spectroscopy study in adults (Greenhouse and King, 2017), more excitable corticospinal pathways were associated with higher GABA concentrations in the motor cortex. These higher GABA concentrations were suggested to indicate a homeostatic mechanism, since more excitable pathways may require a larger inhibitory neurotransmitter reservoir (Greenhouse and King, 2017). Similarly, in a recent TMS-EEG study in healthy adults, poorer performance in the attention task was related to larger N100 amplitudes, indicating more pronounced $GABA_B$ergic inhibition. This was hypothesized to result from a more excitable cortex that needs more inhibition to maintain its balance (Kaarre et al., 2018). Neuroplasticity is heightened during periods of brain development (Ismail et al., 2017), and developmental changes in both glutamatergic and GABAergic mechanisms are thought to underlie the experience-dependent plasticity of cortical circuits (Murphy et al., 2005). Thus, one possible explanation behind the stronger $GABA_B$ergic activity in children compared with adults could be related to maintaining the right balance between excitation and inhibition in the developing brain. However, it should be noted that neural artefacts such as auditory responses may also contribute to the TEP components in this latency range (Rogasch et al., 2014; ter Braack et al., 2015), and as long as the neuropharmacology of P180 remains unclear, caution must be taken in interpreting these findings.

The equal number of TEP peaks in all age groups after frontal cortex TMS is an interesting contradiction to our previous results on TEPs following motor cortex stimulation, where maturation associated with

increased complexity of the TEP waveform (Maatta et al., 2017). It is not certain which physiological properties of the stimulated network determine the number of generated TEP peaks. However, it has been shown that restricted propagation elicits a waveform with less TEP components (Massimini et al., 2005). It has also been shown that repetitive TMS (rTMS) over the primary motor cortex modulates a network encompassing a smaller number of brain regions compared to rTMS over the dorsal premotor cortex, and many of the regions activated after rTMS of the primary motor cortex are confined to the cortical and subcortical motor system (Chouinard et al., 2003). Thus, in addition to methodological differences between the current study and the motor cortex TMS-EEG study (Maatta et al., 2017), one plausible mechanism that may explain the discrepancy in the TEP waveform configuration between the two studies may relate to differences in the connectivity profile and its development between premotor and motor cortices.

Effective connectivity

Even though the morphology of the waveform in the younger age groups appeared to be relatively similar to that in adults at the site of stimulation, the spread of activity, as indicated by statistically significant between-group differences in the topography of the peaks and differences in current density maps, suggest marked changes in effective connectivity of the right PMd with maturation. These are possibly secondary to developmental differences in structural connectivity and excitatory and inhibitory activity.

Anatomically, in adults, the PMd is reciprocally connected with ipsilateral (Dum and Strick, 2005; Lu et al., 1994; Wise et al., 1997; Yeo et al., 2013) and contralateral (Marconi et al., 2003) cortical motor areas, especially the primary motor cortex, parietal cortex and contralateral PMd. By performing a connectivity-based parcellation using a meta-analytics approach, the adult right PMd was recently divided into subregions that are functionally coupled with several brain regions, including the bilateral prefrontal

cortex, intraparietal sulcus (IPS), inferior parietal regions, superior parietal lobule (SPL), insula, right putamen and right visual cortex, and which are integrated into the motor network (Genon et al., 2017). It is not currently known how these subregions and their connectivity change with development.

By combining rTMS with PET and fMRI, it has been shown that in adults, stimulating the PMd while the subject is at rest affects activity in putatively interconnected motor structures, including the contralateral PMd and bilateral supplementary motor area (SMA). Other activated areas were the frontal and parietal association cortices, as well as putative bilateral auditory cortex and subcortical structures, including the thalamus (Bestmann et al., 2005; Bestmann et al., 2008; Chouinard et al., 2003).

We evaluated the spread of TMS-evoked neural activation using MNE, which is suggested to be useful for the localization of poorly known activity distributions and for tracking activity changes between brain areas as a function of time (Komssi et al., 2004). In our adult participants, after stimulation of the right PMd, current maxima (reflecting the centre of neuronal activity) were seen 19 ms post-stimulus in the medial post central gyrus contralateral to the site of stimulation, from where it travelled to the contralateral premotor cortex, ipsilateral laterobasal occipital cortex, ipsilateral paracentral lobulus and prefrontal cortex, contralateral occipital cortex and, at around 100 ms and thereafter, remained in the ipsilateral paracentral lobulus. It is noteworthy that at 46 ms and at 62 ms, adults also showed strong activation in the contralateral inferior parietal lobe. These results are similar to those obtained from PET and fMRI studies, where rTMS targeted to the left PMd evoked activity in the premotor and sensory-motor areas and contralateral inferior parietal regions (Bestmann et al., 2005; Bestmann et al., 2008; Chouinard et al., 2003). In addition, in our study, activation was seen in prefrontal and occipital areas, which is in line with a recently proposed functional connectivity profile of the right PMd (Genon et al., 2017). Because of the better temporal resolution of EEG compared to other brain imaging methods, our

results add to the findings of previous studies by also providing information on the temporal order of the spread of activation from the PMd to connected brain regions.

In the younger age groups, the pattern of activation differed, which may reflect an age-related rearrangement in cortico-cortical effective connectivity. Interestingly, the differences were most pronounced within the first 100 ms post-stimulus and were evident between all three age groups. In children, the current maxima persisted longer than in the other age groups in the vicinity of the site of stimulation and in its contralateral counterpart, possibly reverberating there. Thereafter, the current maxima mainly localized in sensorimotor regions with some spread of activation to prefrontal cortex within the first 100 ms post-stimulus, suggesting a strong neural circuit between the PMd and interconnected sensory-motor regions. In adolescents, the current maxima were also mainly localized in sensory-motor regions, but the spread of activation to prefrontal cortex and precuneus was also seen. Intriguingly, at around 50-60 ms adults showed relatively strong activation in the contralateral inferior parietal lobe, which is a multimodal integration cortex (Igelstrom and Graziano, 2017; Zhang and Li, 2014) and known to mature late (Fjell et al., 2015; Hill et al., 2010). The spread of activation to this region was not seen in the younger age groups. These findings are supported by studies using structural and functional neuroimaging methods. It has been demonstrated that functional networks purported to subserve lower-level sensory and motor systems are in place relatively early (de Bie et al., 2012), whereas connectivity within networks involved in complex cognitive functions progressively develops throughout childhood and adolescence (Sole-Padulles et al., 2016). For example, increasing fronto-parietal functional connectivity, in addition to changes in white matter structure, has been suggested as a mechanism underlying developmental increases in attentional and working memory capacity (Edin et al., 2007; Klarborg et al., 2013; Klingberg et al., 2002; Mabbott et al., 2006). Furthermore, in the executive control network, in an RSN involved in response flexibility and decision making (Seeley et al., 2007),

an age-related increase in connectivity in the inferior parietal lobule has been seen (Sole-Padulles et al., 2016).

Notably, in all age groups, the current maxima were localized in the paracentral lobulus at around 180 ms. The paracentral lobulus includes parts from both the frontal and parietal lobes. This region has been suggested to be related the cognitive control of sensorimotor functions (Zhang et al., 2015), and to be a part of a long-range association limbic–motor pathway (Rizzo et al., 2018). Synaptic activity in the limbic circuits is tightly regulated by a relatively small population of GABA inhibitory neurons (Prager et al., 2016) previously suggested to be involved in P180 genesis (Ferreri et al., 2011c; Salavati et al., 2017).

At 282 ms, children demonstrated activation at the ipsilateral secondary auditory cortices. The spread of activation to these regions was not seen in adolescents or adults. By combining rTMS with fMRI, it has been shown that in adults, stimulating the PMd affects also activity in bilateral auditory cortex, presumably due to the auditory stimulation caused by the TMS coil click (Bestmann et al., 2005). The confounding effect of auditory evoked activity can be significantly reduced by noise masking, which was used in our study (ter Braack et al., 2015). One possible explanation for the finding that only children demonstrated activity in the auditory cortex may thus be that the noise masking was more efficient in the older age groups, resulting in stronger auditory-evoked activity in children compared with other groups. Also age-related differences in auditory processing, for example in the auditory habituation, between children and adults (Karhu et al., 1997; Muenssinger et al., 2013), and mechanisms connected with developmental differences in auditory attention could have affected this finding. The alternative explanation to our finding stems from the age-related re-arrangement of cortico-subcortical connectivity. Notably, in children, subcortical areas are more strongly connected with primary sensory and association areas than in adults (Supekar et al., 2009). As functionally related brain systems emerge during development in childhood and adolescence, this over-connectivity is followed by pruning, which rewires

connectivity (Uddin et al., 2010). TMS-evoked EEG activity at around 280 ms is suggested to be related to the activity of reverberant cortico-cortical as well as cortico-subcortical circuits driven by $GABA_B$ergic neurotransmission (Ferreri et al., 2011b). The finding that only children demonstrated activity in the auditory cortex may thus be mediated by developmental differences in the organizational patterns of functional cortico-subcortical networks.

Strengths and limitations

In order to maximize the accuracy and reliability of our results, we used advanced methodologies such as high-density EEG and neuronavigation. Furthermore, the number of trials was high, thus minimizing the effect of coincidental errors in the TEP waveform. In addition, we calibrated TMS intensity based on the estimated electric field on the targeted cortex, instead of relying on the conventionally used percentage of MSO. This was done to ensure that the PMd was stimulated at comparable intensities in each participant, despite developmental differences in SCD and neuroanatomy. However, a disadvantage of this method is that it does not take the possibly different excitability of the PMd in different phases of development into account. It is known that the motor threshold is higher in children compared to adults, suggesting increasing motor cortex reactivity with maturation (Garvey et al., 2003; Maatta et al., 2017; Moll et al., 1999; Nezu et al., 1997; Pitcher et al., 2015; Saisanen et al., 2017). In adults, studies investigating the relationship of excitability between different cortical areas have demonstrated that the motor and visual cortex react differently to TMS, with no correlation between them (Boroojerdi et al., 2002; Gerwig et al., 2003; Stewart et al., 2001). Similarly, in adults, the reactivity to TMS differs between the motor and prefrontal cortex, but there is an association between these reactivities (Kähkönen et al., 2004; Kähkönen et al., 2005b). Currently, there are no data on the relationship between reactivities to TMS in different brain regions in children. Given this reasoning and the fact that the SCD increases

significantly with maturation, we propose that the use of electric field-based estimation of stimulation intensity is a valid method in developmental TMS-EEG studies when stimulating outside the primary motor cortex. Of note is, that developmental differences in SCD did not explain the amplitude differences and topographical differences in TMS-EEG responses.

In addition, there are some other limitations that need to be considered when interpreting the findings. First, our study lacked exploration of the behavioural significance of the electrophysiological findings. Future work using a combination of TMS-EEG measures and neuropsychological tests should be conducted to fill this gap. Second, the use of a cross-sectional design limited our ability to capture within-individual changes in TEPs across development. Though it is likely that our findings are representative of general developmental trends in neural activation in response to PMd stimulation, prospective longitudinal studies are necessary to elucidate the developmental changes within the same individuals across time. Third, our sample size was relatively small and precluded an analysis of gender differences, which are known to influence brain development (Giedd et al., 2012)**.** However, despite the small group sizes, we found statistically significant changes in cortical excitability and connectivity between different age groups. These changes should be further examined in a larger population.

CONCLUSION

In conclusion, this is the first time that maturational changes in excitability and effective connectivity of the frontal lobe have been investigated using concurrent TMS-EEG. We confirmed and extended previous evidence of developmental changes in effective connectivity by showing that the propagation of TMS-evoked activity diverges in different phases of development. Furthermore, we showed that normal development leads to changes in frontal cortical excitability. More generally, our results

demonstrate that direct study of the brain's excitability and effective connectivity via TMS-EEG co-registration can be applied to paediatric populations, and may provide useful information for developmental studies and for studies on developmental neuropsychiatric disorders. Finally, larger and longitudinal studies in the future will enable better characterization of the developmental pathways at the individual level.

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Figure legends

Figure 1. 60 EEG channels were used in the analyses when exploring the topography of the TEP peaks. The channels were divided into fifteen regions according to their anteroposterior (AP; 1 = frontal, 2 = central and 3 = parieto-occipital) and mediolateral (ML; 1 = left lateral, 2 = left mediolateral, 3 = medial, 4 = right mediolateral, 5 = right lateral) location.

Figure 2. The locations of the individual stimulation sites in adults (black dots), adolescents (blue dots) and children (red dots) and their corresponding 90% confidence interval ellipsoid (green area).

Figure 3. TMS-evoked electrical activity presented as GMFP in children, adolescents, and adults. Statistically significant differences between groups are presented in the lower panel in black.

Figure 4. TEP waveform and topography after right superior frontal cortex stimulation.

A) In upper panel, grand average of the EEG responses presented as butterfly plots in time window -100–400 ms. The mean of electrodes Fz and F2 (site of stimulation) is indicated in red. Zero corresponds to the TMS pulse.

B) Topography of the TEP peaks in adults (19 ms, 30ms, 37ms , 46 ms, 62 ms, 99 ms, 199 ms, and 298 ms), in adolescents (19 ms, 28 ms , 39 ms, 50 ms, 70 ms, 97 ms, 182 ms, and 294 ms) and in children (19 ms, 32 ms, 44 ms, 57 ms, 77 ms, 102 ms, 172 ms, and 282 ms). The time points at which scalp distribution maps were calculated were obtained from the peaks in the GMFP. All voltage scales are optimized for each group and component.

Figure 5. Estimated current densities in each group, calculated using MNE and plotted on the cortical surface. The time points at which the current densities were calculated were obtained from the peaks in the GMFP. The results were auto-scaled and thresholded at 50% of maximum to maximum. CDR=current density reconstruction.