

The neurodevelopmental trajectory of beta band oscillations: an OPM-MEG study

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Abstract

Neural oscillations mediate the coordination of activity within and between brain networks, supporting cognition and behaviour. How these processes develop throughout childhood is not only an important neuroscientific question but could also shed light on the mechanisms underlying neurological and psychiatric disorders. However, measuring the neurodevelopmental trajectory of oscillations has been hampered by confounds from instrumentation. In this paper, we investigate the suitability of a disruptive new imaging platform – Optically Pumped Magnetometer-based magnetoencephalography (OPM-MEG) – to study oscillations during brain development. We show how a unique 192-channel OPM-MEG device, which is adaptable to head size and robust to participant movement, can be used to collect high-fidelity electrophysiological data in individuals aged between 2 and 34 years. Data were collected during a somatosensory task, and we measured both stimulus-induced modulation of beta oscillations in sensory cortex, and whole-brain connectivity, showing that both modulate significantly with age. Moreover, we show that pan-spectral bursts of electrophysiological activity drive task-induced beta modulation, and that their probability of occurrence and spectral content change with age. Our results offer new insights into the developmental trajectory of beta oscillations and provide clear evidence that OPM-MEG is an ideal platform for studying electrophysiology in neurodevelopment.

eLife assessment

This study provides **important** evidence supporting the ability of a new type of neuroimaging, OPM-MEG system, to measure beta-band oscillation in sensorimotor tasks in 2-14 years old children and to demonstrate the corresponding development changes, since neuroimaging methods with high spatiotemporal resolution that could be used on small children are quite limited. The evidence supporting the conclusion is **compelling**. This work will be of interest to the neuroimaging and developmental science communities.

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Introduction

Neural oscillations are a fundamental component of brain function. They enable coordination of electrophysiological activity within and between neural assemblies and this underpins cognition and behaviour. Oscillations in the beta range (13-30 Hz) are typically associated with sensorimotor processes¹; they are prominent over the sensorimotor cortices, diminish in amplitude during sensory stimulation or motor execution (termed event related decrease, ERD), and increase in amplitude (above a baseline level) following stimulus cessation (this is most often termed the post-movement beta rebound (PMBR)² in relation to movement). Beta oscillations and their modulation by tasks are robustly measured phenomena and their critical importance is highlighted by studies showing abnormalities across a range of disorders – e.g. autism³, multiple sclerosis⁴, Parkinson's disease⁵ and Schizophrenia⁶. Despite this, little is known about the mechanistic role of beta oscillations, and most of what is known comes from studies applying non-invasive neuroimaging techniques to adult populations. Whilst the sensorimotor system changes little in adulthood, there are marked changes in childhood and a complete characterisation of the neurodevelopmental trajectory of beta oscillations, particularly how they underpin behavioural milestones, might offer a new understanding of their role in healthy and abnormal function.

Several studies have investigated how neural oscillations change with age: Gaetz et al.⁷ measured beta modulation during index finger movement, showing that the post-movement beta rebound (PMBR) was diminished in children compared to adults. Kurz et al.⁸ reported a similar effect when studying 11-19 year olds executing lower limb movement. Trevarrow et al.⁹ found an age related increase in the PMBR amplitude in healthy 9-15 year olds, and further that the decrease in beta power during movement execution did not modulate with age. Vakhtin et al.¹⁰ showed an increase in PMBR amplitude between adolescence and adulthood, and that this trajectory was abnormal in autism. All these studies probed beta responses to movement execution; in the case of tactile stimulation (i.e. sensory stimulation without movement) both task induced beta power loss, and the post stimulus rebound have been consistently observed in adults^{2,11-16}. Further, beta amplitude in sensory cortex has been related to attentional processes¹⁷ and is broadly thought to carry top down influence on primary areas¹⁸. However, there is less literature on how beta modulation changes with age during purely sensory tasks. A separate body of work has assessed neural oscillations in the absence of a task, demonstrating that there is a redistribution of oscillatory power across frequency bands as the brain matures. Specifically, low frequency activity tends to decrease, and high frequency activity increases with age¹⁸⁻²⁰. These changes are spatially specific, with increasing beta power most prominent in posterior parietal and occipital regions^{21,22}. Beta oscillations are also implicated in long range connectivity^{23,24} and previous studies have demonstrated increased

connectivity strength with age²⁵, particularly in attentional networks²⁶. In sum, there is accord between studies that show increases in task induced beta modulation and connectivity as well as a redistribution of spectral power, with increasing age.

Despite this progress, neurodevelopmental studies remain hindered by instrumental limitations. Neural oscillations can be measured non-invasively by either magnetoencephalography (MEG) or electroencephalography (EEG). MEG detects magnetic fields generated by neural currents, providing assessment of electrical activity with good spatial, and millisecond temporal precision. However, the sensors traditionally used for field detection operate at low temperature, necessitating the use of fixed ‘one-size-fits-all’ sensor arrays. Because the signal declines with the square of distance, smaller head size leads to a reduction in signal²⁷. In addition, movement relative to fixed sensors degrades data quality. These limitations mean scanning young children with traditional MEG systems/SQUIDS is challenging and this has meant that most MEG studies on neurodevelopment are limited to older children and adolescents. Similarly, there are challenges in EEG. EEG measures differences in electrical potential across the scalp. The electrode array adapts to head shape and moves with the head, making it ‘wearable’ and consequently usable from newborns to adults. However, the resistive properties of the skull distort signal topography, limiting spatial resolution. Moreover, this confound changes with age as the skull increases in thickness²⁸. EEG is also more susceptible to interference from muscles than MEG²⁹, particularly during movement. In sum, both EEG and MEG are limited; MEG is confounded by head size, EEG has poor spatial accuracy, and both are degraded by movement. However, in recent years, novel magnetic field sensors – Optically Pumped Magnetometers (OPMs) – have inspired a new generation of MEG system³⁰. OPMs are small, lightweight and have similar sensitivity to conventional MEG sensors but do not require cryogenics. This enables construction of a wearable MEG system³¹. Because sensors can be placed flexibly, the array can adapt to head size and provide good coverage regardless of age. Further, because sensors move with the head, movement is possible during a scan. OPM-MEG is, ostensibly, ideal for children; for example, Hill et al. showed the viability of OPM-MEG in a 2 year old³²; Feys et al. showed advantages for epileptic spike detection in children³³, and Corvilain et al. demonstrated utility even in the first weeks of life³⁴. However, no studies have yet used OPM-MEG in large groups to measure neurodevelopment.

In addition to instrumental limitations, most neurodevelopmental studies have used an approach to data analysis where signals are averaged over trials. This has led to the idea that sensory induced beta modulation comprises a drop in oscillatory amplitude during movement and a smooth increase on movement cessation. However, recent studies^{35–37} investigating unaveraged signals show that, rather than a smooth oscillation, the beta rhythm is, in part, driven by discrete punctate events, known as “bursts”. Bursts occur with a characteristic probability, which is altered by a task^{38,39}, and are not confined to the beta band but are pan-spectral, with components falling across many frequencies^{6,39}. There is also evidence that functional connectivity is driven by bursts that are coincident in time across spatially separate regions³⁹. Recent work using EEG has found that, even in children as young as 12 months, beta band activity is driven by bursts⁴⁰. Further work, also using EEG, investigated burst activity in infants (9 and 12 months) and adults during observed movement execution, with results showing stimulus induced decrease in burst rate at all ages, with the largest effects in adults⁴¹. These studies have changed the way that the research community thinks about beta oscillations⁴² and a full understanding of beta dynamics and their age dependence must be placed in the context of the burst model.

Here, we combine OPM-MEG with a burst analysis based on a Hidden Markov Model (HMM)^{39,43,44} to investigate beta dynamics. We aimed to scan a cohort of children and adults across a wide age range (upwards from 2 years old). Because of this, we implemented a passive somatosensory task which can be completed by anyone, regardless of age. Our study addresses two objectives: First, we test the veracity of a novel 192-channel triaxial OPM-MEG system for use

in paediatric populations, investigating its practicality in young children and assessing whether previously observed age-related changes in task-induced beta modulation and functional connectivity can be reliably measured using OPM-MEG. Second, we investigate how task-induced beta modulation in the sensorimotor cortices is related to the occurrence of pan-spectral bursts, and how the characteristics of those bursts change with age.

Results

Our OPM-MEG system comprised a maximum of 64 OPMs (QuSpin Inc., Colorado, USA) each capable of measuring magnetic field independently in three orthogonal orientations, meaning data were recorded using up to 192-channels. Sensors were mounted in 3D-printed helmets of differing size (Cerca Magnetics Ltd. Nottingham, UK), allowing adaptation to the participant's head (**Figure 1A**). The total weight of the helmet ranged from ~856 g (in the smallest case) to ~906 g (in the largest case). The system was integrated into a magnetically shielded room (MSR) equipped with an active field control system (see “coils” in **Figure 1A-B**; Cerca Magnetics Ltd. Nottingham, UK) which allowed reduction of background field to <1 nT. This was to ensure that participants were able to move during a scan without compromising sensor operation^{45,46}. A schematic of the system is shown in **Figure 1B**.

27 children (aged 2-13 years) and 26 adults (aged 21-34 years) took part in the study. All participants performed a task in which two stimulators (**Figure 1C**) delivered passive somatosensory stimulation to either the index or little finger of the right hand sequentially. Stimuli lasted 0.5 s, occurred every 3.5 s, and comprised three taps on the fingertip. This pattern of stimulation was repeated 42 times for both fingers. Throughout the experiment, participants could watch their favourite TV show. Following data preprocessing, high fidelity data were available in 27 children and 24 adults. Two datasets were excluded from further analysis as data quality was not sufficient to perform our Hidden Markov Model analysis (see Methods). We removed $19 \pm 12\%$ (mean $\pm$ standard deviation) of trials in children, and $9 \pm 5\%$ of trials in adults due to excessive interference. On average we had 160 ± 10 channels with high quality data available (note that not all sensors were available for every measurement – see also Discussion).

Beta band modulation with age

Figure 2 shows beta band modulation during the task for a single representative child (7 years old). Panel A shows the estimated brain anatomy (see Methods) with the locations of the largest beta modulation overlaid – contrasted between stimulus (0.3-0.8 s relative to stimulus onset) and rest (2.5-3 s) time windows. Data for index and little finger stimulation are overlaid in blue/green and red/yellow respectively. The largest effects fall in the sensorimotor cortices as expected. Panel B shows time frequency spectra depicting the temporal evolution of the amplitude of neural oscillations. Blue represents a decrease in oscillatory amplitude relative to baseline (2.5-3 s); yellow represents an increase. As expected, there is a reduction in beta amplitude during stimulation.

Group averaged beta dynamics are shown in **Figure 3**. Here, for visualisation, the children were split into three groups of 9: youngest (aged 2 – 6 years), middle (6 to 10 years), and oldest (10 to 13 years). Data were averaged within each group, and across all 24 adults (21 – 34 years) for comparison. The brain plots show group averaged pseudo-T statistical maps of stimulus induced beta band modulation. In all groups, a modulation peak appeared in the left sensorimotor cortex. We observed no significant difference in the location of peak beta modulation between index and little finger stimulation (see also Discussion). The time-frequency spectrograms (TFSSs) are also shown for each group. Here, we observe a drop in beta amplitude during stimulation for all 3

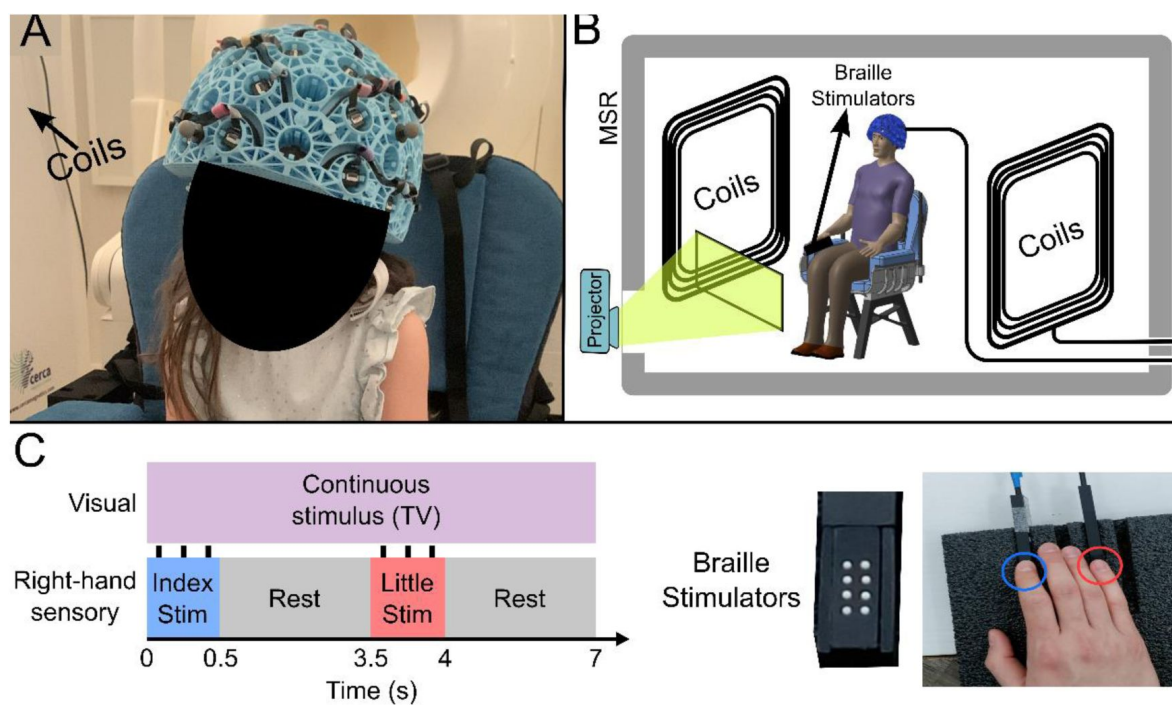


Figure 1

Experimental setup and beta band modulation during sensory task.

(A) 4-year-old child wearing an OPM-MEG helmet (consent and authorisation for publication was obtained). (B) Schematic diagram of the whole system inside the shielded room. (C) Schematic illustration of stimulus timings and a photo of the somatosensory stimulators. “Braille” stimulators each comprise 8 pins, which can be controlled independently; all 8 were used simultaneously to deliver the stimuli.

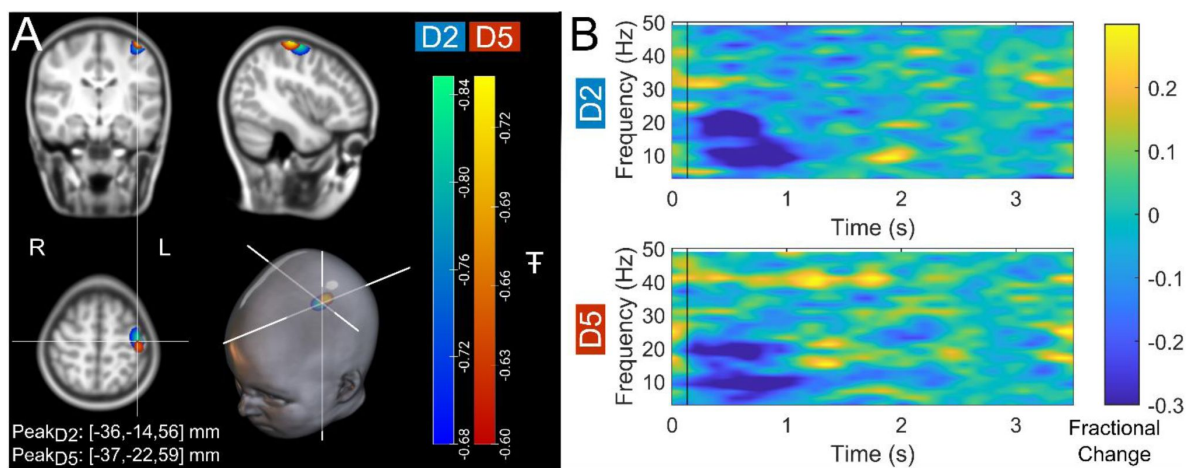


Figure 2

Data from a single participant (7 years old):

(A) Brain plots show slices through the left motor cortex, with a pseudo-T-statistical map of beta modulation. The blue/green peaks indicate locations of largest beta modulation during stimulation for index finger trials (digit 2/D2), while the red/yellow peaks show the little finger (digit 5/D5). (B) Time frequency spectra showing neural oscillatory amplitude modulation (fractional change in spectral amplitude relative to baseline measured in the 2.5-3 s window) for both fingers, using data extracted from the location of peak beta modulation (left sensorimotor cortex). Vertical lines indicate the time of the first braille stimulus. Note the beta amplitude reduction during stimulation, as expected.

groups, however this was most pronounced in adults and was weaker in younger children. For statistical analysis, we estimated the maximum difference in beta-band amplitude between stimulation (0.3-0.8 s) and post-stimulation (1-1.5 s) windows and plotted this as a function of age (**Figure 3B**). Here, Pearson correlation suggested a significant ($R^2 = 0.29$, $p = 4 \times 10^{-5}$) relationship. These data agree strongly with previous studies showing increased task induced beta modulation with age (though here we present a sensory, rather than motor task). However, they are acquired using a fundamentally new wearable technology, and in younger participants.

For completeness, the inset time course within each time-frequency plot shows the beamformer projected trial and subject averaged evoked response in sensorimotor cortex (estimated by trial averaging the beamformer projected data in the 4 Hz to 40 Hz band). Again, there is a neurodevelopmental effect (**Figures 3C** and **S1C**), with a significant increase in M50 amplitude with age in the little finger (see **Figure S1C**, $R^2 = 0.1$, $p = 0.023$) though this did not reach significance in the index finger ($R^2 = 0.04$, $p = 0.14$).

Functional connectivity in the beta band

Whole brain beta-band functional connectivity was estimated by calculating amplitude envelope correlation (AEC)⁴⁷ between (unaveraged) beta-band signals extracted from 78 cortical regions. **Figure 4A** shows connectome matrices averaged across participants in each of the four groups; each matrix element represents the strength of a connection between two brain regions. In the “glass brains”, the red lines show the 150 connections with the highest connectivity. In adults, the connectome is in strong agreement with those from previous studies^{25,48}, with prominent sensorimotor, posterior-parietal- and fronto-parietal connections. However, connectivity patterns in children differed in both strength and spatial signature, with the visual network showing the strongest connectivity. To statistically test the relationship between connectivity and age, we plotted global connectivity (i.e., the sum of all matrix elements) versus age (**Figure 4B**). Pearson correlation suggested a significant ($R^2 = 0.42$, $p = 2.67 \times 10^{-7}$) relationship with older participants having increased connectivity. We also probed how this relationship changes across brain regions: **Figure 4D** shows example scatter plots of node degree (i.e., how connected a specific region is to the rest of the brain) for two pairs of homologous frontal and occipital regions. Note that the gradient of the fit in the frontal regions (0.27 year^{-1} , $R^2 = 0.44$, $p = 1.2 \times 10^{-7}$ and 0.27 year^{-1} , $R^2 = 0.50$, $p = 5.8 \times 10^{-9}$) is much larger than that in the occipital regions (0.10 year^{-1} , $R^2 = 0.18$, $p = 2.0 \times 10^{-3}$, and 0.12 year^{-1} , $R^2 = 0.29$, $p = 4.2 \times 10^{-5}$). This is delineated for all brain regions in **Figure 4C**, where each region is coloured according to the gradient of the fit. The regions showing the largest change with age are frontal and parietal areas, with visual cortex demonstrating the smallest effect.

Burst interpretation of beta dynamics

To assess pan-spectral bursts, we applied a univariate, 3-state HMM to the broadband (1-48 Hz) electrophysiological signal extracted from the location of largest beta modulation. This enabled us to identify the times at which bursts occurred in sensorimotor cortex^{39,49}.

Figure 5A shows a raster plot of burst occurrence for all individual task trials in all participants. White represents time points and trials where bursts are occurring; black represents the absence of a burst. Participants are separated by the red lines and groups are separated by the blue lines. Burst absence is more likely in the time period during stimulation, indicating a task-induced decrease in burst-probability. **Figure 5B** shows group averaged burst-probability as a function of time. In all age groups, bursts were less likely during stimulation, though this modulation changes with age, with the younger group demonstrating the least pronounced effect. This is tested statistically in **Figure 5C** which shows a significant ($R^2 = 0.13$, $p = 8.9 \times 10^{-3}$ *) positive Pearson correlation between the modulation of burst probability and age. **Figure 5D** shows the association between beta amplitude and burst-probability modulation. Here the significant ($R^2 =$

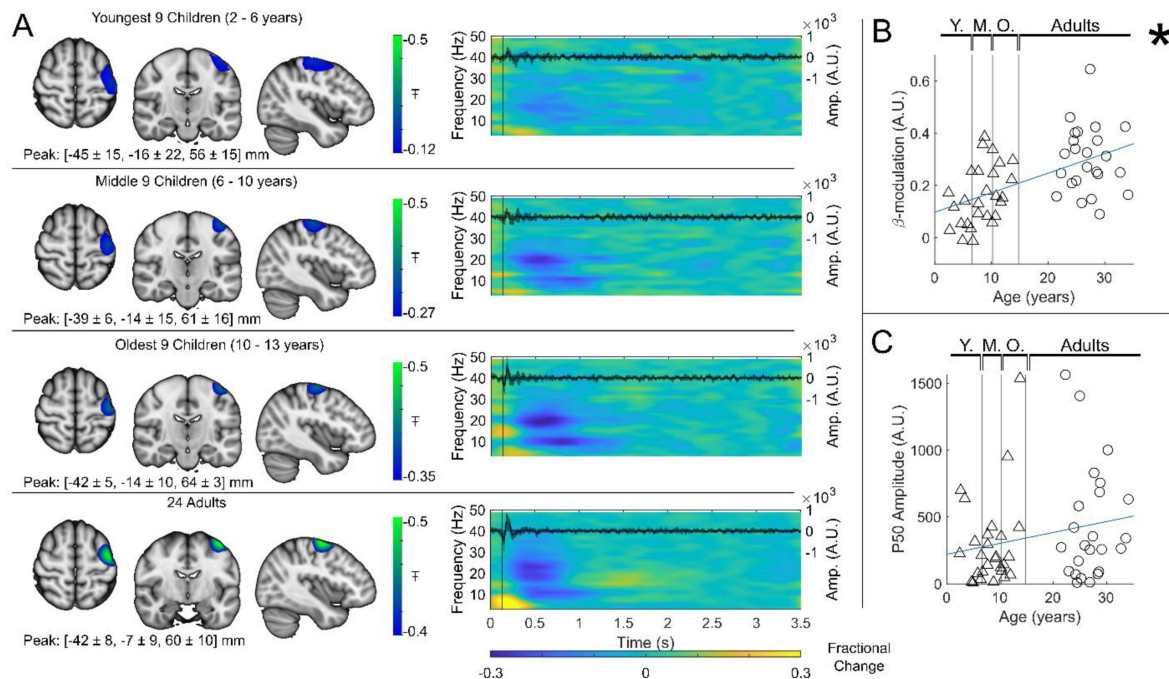


Figure 3

Beta band modulation with age:

(A) Brain plots show slices through the left motor cortex, with a pseudo-T-statistical map of beta modulation (blue/green) overlaid on the standard brain. Peak MNI coordinates are indicated for each subgroup. Time frequency spectrograms show modulation of the amplitude of neural oscillations (fractional change in spectral amplitude relative to the baseline measured in the 2.5-3 s window). Vertical lines indicate the time of the first braille stimulus. In all cases results were extracted from the location of peak beta desynchronisation (in the left sensorimotor cortex). Note the clear beta amplitude reduction during stimulation. The inset line plots show the 4-40 Hz trial averaged phase-locked evoked response, with the expected prominent deflections around 20 and 50 ms. (B) Maximum difference in beta-band amplitude (0.3-0.8 s window vs 1-1.5 s window) plotted as a function of age (i.e., each data point shows a different participant; triangles represent children, circles represent adults). Note significant correlation ($R^2 = 0.29$, $p = 0.00004^*$). (C) Amplitude of the P50 component of the evoked response plotted against age. There was no significant correlation ($R^2 = 0.04$, $p = 0.14$). All data here relate to the index finger stimulation; similar results are available for the little finger stimulation in Supplementary Information Section 1.

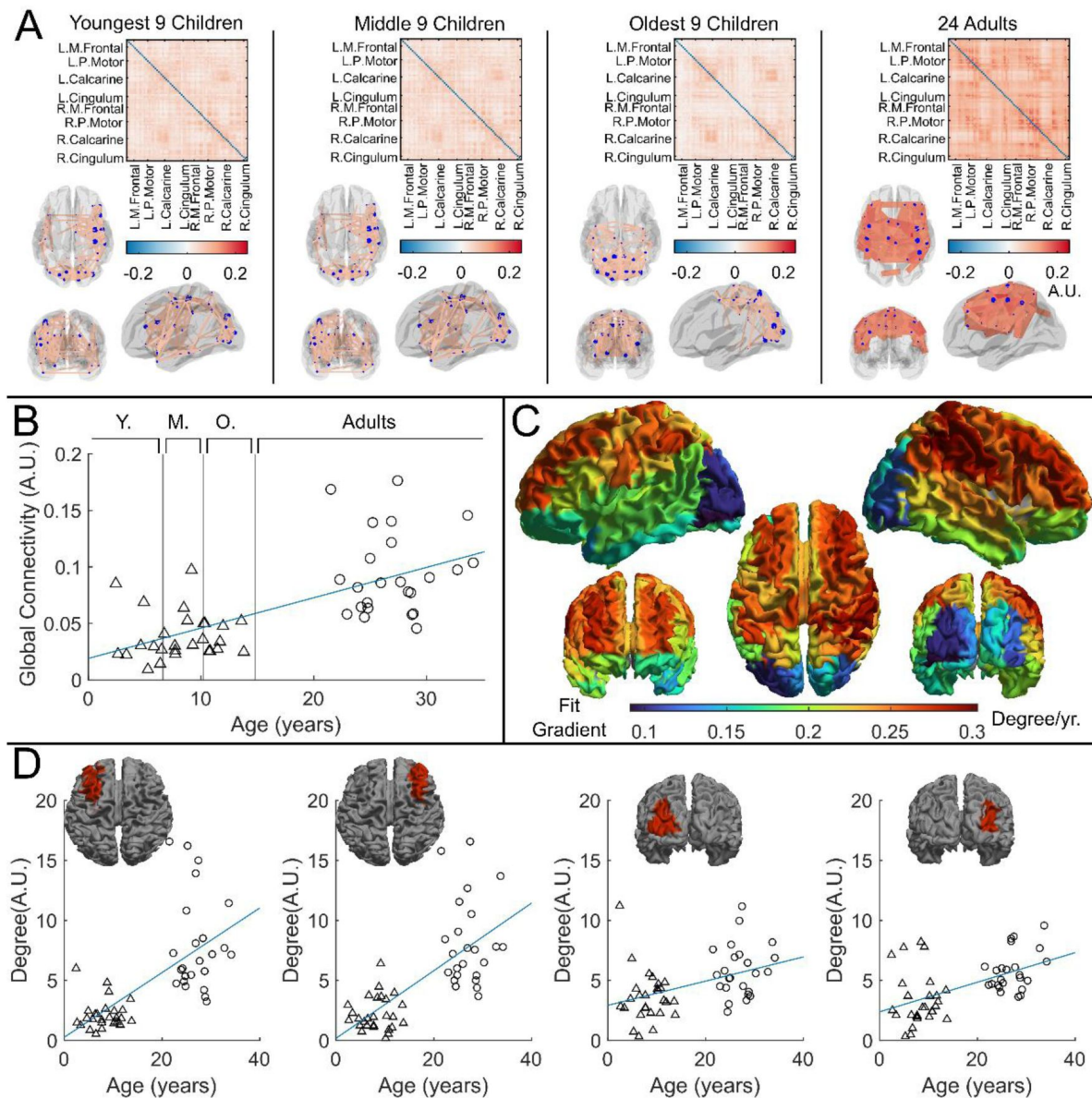


Figure 4

Functional connectivity – estimated using Amplitude Envelope Correlation (AEC) – varies with age.

(A) Connectivity matrices constructed using 78 regions of the AAL atlas and glass brains showing the strongest 150 connections (average across the group). AEC was estimated across the entire recording. (B) Global average connectivity increases significantly with age ($R^2 = 0.42$, $p = 2.67 \times 10^{-7}$). (C) Age-related changes in connectivity vary spatially. Brain plot shows the linear fit gradient of node degree (the sum across the rows of the connectivity matrices) against age. Node degree varies less in occipital regions while frontal regions become more strongly connected with increasing age. (D) Example plots show node degree against age for left and right frontal and occipital regions. Pearson correlation yielded (from left to right): ($R^2 = 0.44$, $p = 1.2 \times 10^{-7}$, $Degree = 0.27 \cdot age + 0.26$); ($R^2 = 0.50$, $p = 5.8 \times 10^{-9}$, $Degree = 0.28 \cdot age + 0.17$); ($R^2 = 0.18$, $p = 2.0 \times 10^{-3}$, $Degree = 0.10 \cdot age + 2.92$); ($R^2 = 0.29$, $p = 4.2 \times 10^{-5}$, $Degree = 0.12 \cdot age + 2.38$).

0.50, $p = 5.2 \times 10^{-9*}$) positive relationship supports a hypothesis that the observed change in task induced beta modulation with age (shown in **Figure 3**) is driven by changes in the modulation of burst probability. Interestingly, we saw no measurable change in the amplitude of bursts with age (See Supplementary Information section 2).

We estimated the spectral content of the bursts identified by the HMM. In **Figure 6A** the burst spectra are shown for all 4 participant groups. In adults, the spectral power diminishes with increasing frequency, with additional peaks in the alpha and beta band. In children, high frequencies are diminished, and low frequencies are elevated, compared to adults. This is also shown in **Figure 6B** where, for every frequency, we perform a linear fit to a scatter plot of spectral density versus age. Here, positive values indicate that spectral power increases with age; negative power means it decreases. The inset scatter plots show example age relationships at 3 Hz, 9 Hz, 21 Hz, and 37 Hz. We see a clear decrease in low-frequency spectral content and increasing high-frequency content, with age. Interestingly, spectral content in the alpha band appeared stable with no significant correlation with age. Similar trends for changes in frequency content with age were found for the non-burst states (See Supplementary Information section 3).

Discussion

There are few practical, non-invasive platforms capable of measuring brain function in children. Functional magnetic resonance imaging (fMRI) ⁵⁰ tracks brain activity with millimetre resolution, but the mechanism of detection is indirect (based on haemodynamics) with limited temporal precision. Participants must also lie immobile and are exposed to high acoustic noise; many children find this challenging and it is difficult to implement naturalistic experiments. Functional near infra-red spectroscopy (fNIRS) ⁵¹ provides a wearable platform which allows scanning of almost any participant during any conceivable experiment. However, fNIRS is also restricted to haemodynamic metrics; it has limited temporal resolution and spatial resolution is ~1 cm. EEG ⁵² measures electrophysiological activity in neural networks and thus offers millisecond temporal precision. It is also wearable, adaptable to any participant, and enables naturalistic experiments. However, spatial resolution is restricted due to the inhomogeneous conductivity profile of the head. This problem is exacerbated in young (<18 months) children due to additional inhomogeneities caused by the fontanelle, and in neurodevelopmental studies due to changing skull thickness. EEG is also highly susceptible to artefacts from electrical activity in muscles. Conventional MEG ⁵³ measures brain electrophysiology with both high spatial and temporal resolution, but is limited in performance and practicality due to the fixed nature of the sensor array. It follows that the technologies currently in use for neurodevelopmental assessment are limited by either practicality, performance, or both. OPM-MEG ostensibly offers the performance of MEG, with the practicality of fNIRS/EEG, making it attractive for use in children. Here, our primary aim was to test the feasibility of OPM-MEG for neurodevelopmental studies. Our results demonstrate we were able to scan children down to age 2 years, measuring high-fidelity electrophysiological signals and characterising the neurodevelopmental trajectory of beta oscillations. The fact that we were able to complete this study demonstrates the advantage of OPM-MEG over conventional-MEG, the latter being challenging to deploy across such a large age range.

System design for neurodevelopmental studies

We designed our system for lifespan compliance. Multiple sizes of helmet allowed us to select the best fitting size for any given participant. A statistical analysis (see Supplementary Information Section 4) showed no significant change in scalp-to-sensor distance with age, meaning sensors were not further away from the scalp in children (who tended to have a smaller head circumference) than they were in adults. Additional simulations suggested that, had our cohort been scanned in a single helmet size, sensor proximity would have been a confound. This is an important point which demonstrates the advantages of an adaptable OPM-MEG array over a static

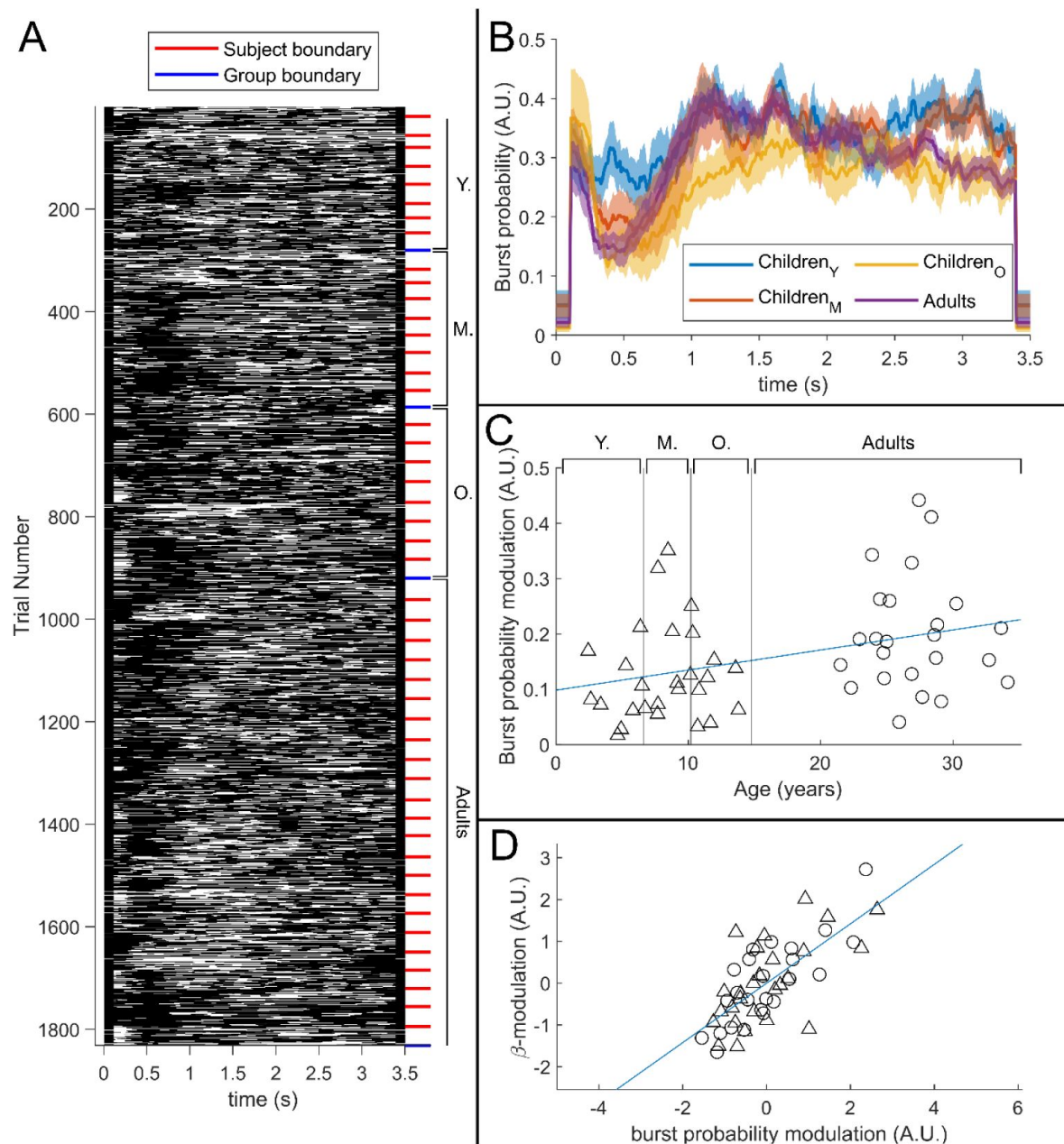


Figure 5

The relationship between beta-band amplitude modulation and pan-spectral burst probability.

(A) Raster plot showing burst occurrence (white) as a function of time for all trials and participants combined (participants sorted by increasing age). (B) Trial averaged burst probability time-courses across the four participant groups. Shaded areas indicate the standard error. (C) Stimulus-to post-stimulus modulation of burst probability (0.3-0.8 s vs 1-1.5 s) plotted against age. Note significant ($R^2 = 0.13$, $p = 0.0089^*$) positive correlation. (D) Beta amplitude modulation plotted against burst probability. Note again significant correlation ($R^2 = 0.5$, $p = 5.2 \times 10^{-9}^*$). Values for both measures were z-transformed within the Children and Adult group respectively to mitigate the age confound. Triangles and circles denote Children and Adults respectively.

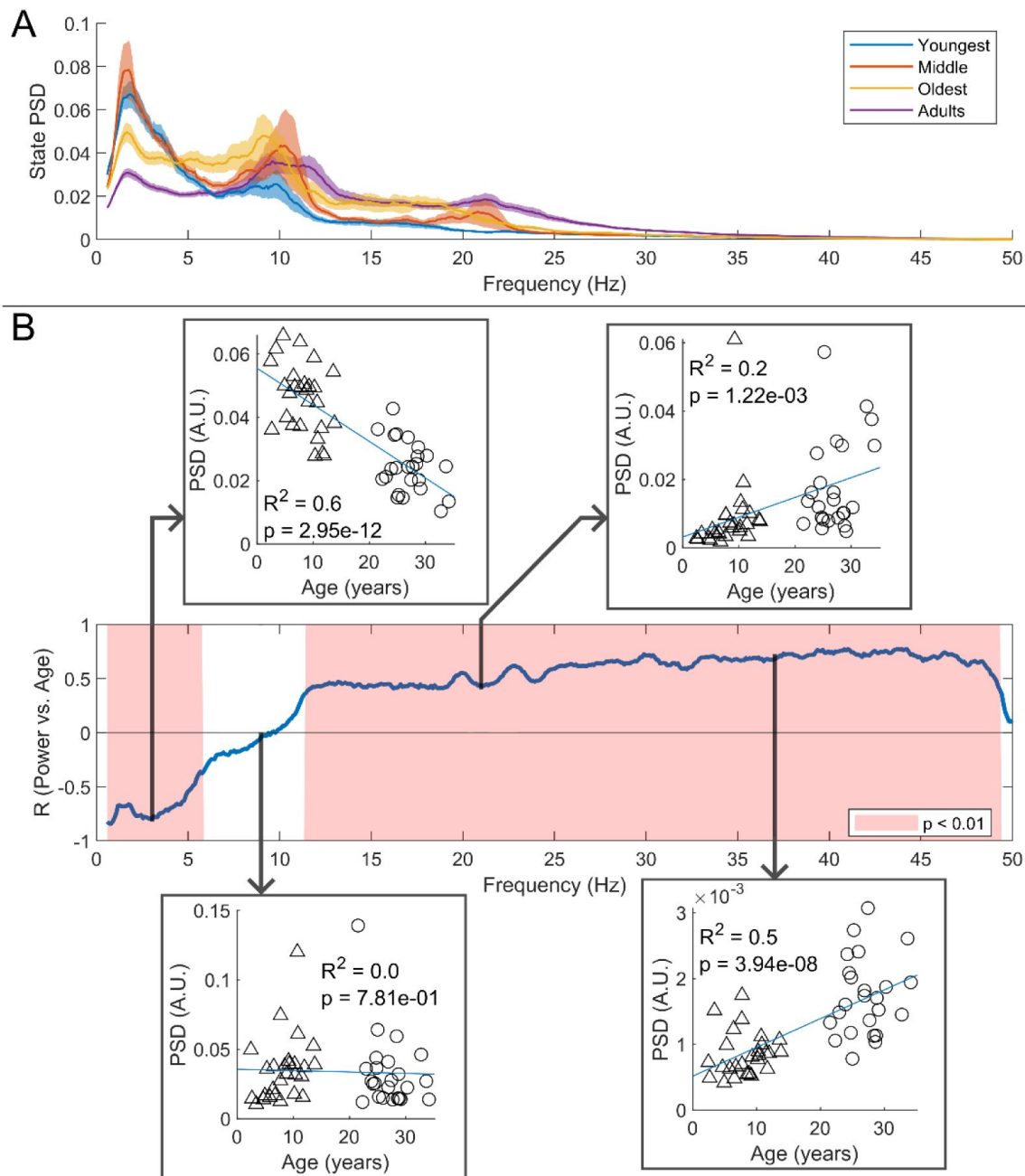


Figure 6

Spectral content of the burst state varies with age.

(A) Average burst-state spectra across groups. Shaded areas indicate standard error on the group mean. (B) Pearson correlation coefficient for the PSD values in (A) against age across all frequency values. Red shaded areas indicate $p < 0.01$ (uncorrected). The four inset plots show example scatters of PSD values with age at selected frequencies (3 Hz, 9 Hz, 21 Hz, and 37 Hz). Low-frequency spectral content decreases with age while high-frequency content increases. No significant correlation was observed in the high theta and alpha bands.

array. Relatedly, it is noteworthy that an analysis of beta burst amplitude showed no measurable modulation with subject age (Supplementary Information Section 2); this (indirectly) suggests we are not losing sensitivity in the youngest volunteers (if we were this would presumably result in lower amplitude bursts in children). The helmets themselves were relatively lightweight, ranging from ~856 g (in the smallest case) to ~906 g (in the largest case). While this is heavier than, for example, a child's bicycle helmet (the average weight of which is ~300-350 g) they were well tolerated by our cohort. Heat from the sensors (which require elevated temperature to maintain operation in the spin exchange relaxation free regime⁵⁴) was controlled via both convection (with air being able to flow through the helmet lattice) and an insulating material cap worn under the helmet by all participants (See **Figure 1A**). Together, these ensured that participants remained comfortable throughout data recording.

Whilst the helmet allows sensors to move with the head, sensor operation is perturbed by background fields (e.g., if a sensor rotates in a uniform background field, or translates in a field gradient, it will see a changing field which can obfuscate brain activity and, in some cases, stop the sensors working³¹). For this reason, our system also employed active field control⁴⁶ which enabled us to reduce the field to a level where sensors work reliably, even in the presence of head movements. This meant that, although we did not encourage our participants to move, they were completely unrestrained. The sensors themselves are also robust to head motion, as every sensor is a self-contained unit connected to its own control electronics by a cable that can accommodate rapid and uncontrolled movement. One limitation of the current study is that practical limitations prevented us from quantitatively tracking the extent to which children (and adults) moved their head during a scan. Anecdotally however, experimenters present in the room during scans reported several instances where children moved, for example to speak to their parents who were also in the room. Such levels of movement could not be tolerated in conventional MEG or MRI and so this again demonstrates the advantages afforded by OPM-MEG.

There were two other design features which helped ensure our system was optimal for children. Firstly, a challenge when imaging children is the proximity of the brain to the scalp; the brain-scalp separation is ~15 mm in adults but can be as little as ~5 mm in children. Previous work⁵⁵ has shown that, when using radially oriented magnetic field measurements, a combination of finite sampling and brain proximity leads to inhomogeneous coverage (i.e. spatial aliasing). Here, our system was designed with triaxial sensors which helps to prevent this confound (we also note that triaxial sensors enable improved noise rejection^{56,57}). Secondly, our system was housed in a large MSR which allowed children to be accompanied by a parent and experimenter throughout the scan. These features led to a system that enables acquisition of high-quality MEG data and is also well tolerated.

Ultimately, we obtained usable data in 27/27 children and 24/26 adults. Our findings support previous neurodevelopmental studies^{7,9,25} and in this way validate OPM-MEG by showing substantial equivalence to the established state-of-the-art. Importantly however, most prior studies of neurodevelopmental trajectory in MEG were carried out in older children – for example Kurz et al.⁸ showed a similar effect in 11-19 year olds; Trevarrow et al.⁹ employed a cohort of 9-15 year olds and our own previous work also scanned a cohort of 9-15 year olds²⁶. In the present study, we were able to successfully scan children from age 2 years and there are no fundamental reasons why we could not have scanned even younger participants. There are important reasons for moving to younger participants: from a neuroscientific viewpoint, many critical milestones in development occur in the first few years (even months) of life – such as learning to walk and talk. If we can use OPM-MEG technology to measure the brain activities that underpin these developmental milestones, this would offer a new understanding of brain function. Moreover, many disorders strike in the first years of life – for example autism can be diagnosed in children as young as two years and epilepsy has a high incidence in children, including in the neonatal and infant period⁵⁸. In those where seizures cannot be controlled by drugs, surgery (which can be informed by MEG assessment) is often a viable option for treatment;

the younger the patient, the more successful the outcome⁵⁹. For these reasons, the development of a platform that enables the assessment of brain electrophysiology, with high spatiotemporal precision, in young people is a significant step and one that has potential to impact multiple areas.

Although the system was successful, there are some limitations to the present design which should be mentioned. Firstly, the range of available helmets was limited, and future studies may aim to use more sizes (or flexible helmets) to better accommodate variation in head size and shape. Also, even the lightweight helmet used here may be too heavy for younger participants; whilst in general it was well tolerated, some of the young participants commented that it was heavy. This indicates that further optimisation of weight is needed if we want to move towards younger (< 2 years) participants. (Note that this is possible since, whilst the total weight is ~900 g, the combined sensor weight is just 250g.) Similarly, here the warmth generated by the sensors was controlled by convection and insulation. However, for systems with a higher channel count, where more heat may be generated, active cooling (e.g., air forced through the helmet) may be required. Further, here magnetic field control (key to ensuring participants were unconstrained) was only available over a region encompassing the head whilst participants were seated (i.e., participants had to be sat in a chair for the scanner to work). However, in future studies, it may be desirable to accommodate different positions (e.g. participants seated on the floor or lying down) and a greater range of motion (e.g., crawling or walking). This may be possible with newly developing coil technology⁶⁰.

Neuroscientific insights

In addition to demonstrating a new platform for neurodevelopmental investigation, our study also provides insights into coordinated brain activity and its maturation with age. Beta oscillations are thought to mediate top-down influence on primary cortices, with regions of high beta amplitude being inhibited (for a review see Barone and Rossiter¹). Whilst most evidence is based on studies of movement, there is significant supporting evidence from somatosensory studies in adults; for example Bauer et al.⁶¹ showed that, when one attends to events relating to the left hand, a relative decrease in beta amplitude is seen in the contralateral (right) sensory cortex and an increase in ipsilateral cortex – suggesting the brain is inhibiting the sensory representation of the non-relevant hand. Given this strong link to attentional mechanisms and top-down processing, it is unsurprising that beta oscillations are not fully developed in children, and consequently change with age.

The burst model of beta dynamics is relatively new, yet significant evidence already shows that the neurophysiological signal is driven by punctate bursts of pan-spectral activity, whose probability of occurrence changes depending on the task phase. Our study provides some of the first evidence (see also Rayson et al.⁴¹) that neurodevelopmental changes in the amplitude of task induced beta modulation can also be explained by the burst model. Specifically, we showed that task induced modulation of burst probability changes significantly as a function of age, suggesting bursts in somatosensory cortex are less likely to occur during stimulation of older participants compared to younger participants. We also showed that the “classical” beta band modulation exhibited a significant linear relationship with burst-probability modulation. In addition, when bursts occur in younger participants, they tend to have different spectral properties. Specifically, younger participants have increased low-frequency activity and decreased high frequency activity, compared to adults. It is likely that a combination of the change in burst probability with age, and the change in dominant frequency (away from the canonical beta band) drives the observation from previous studies of changing beta modulation with age. Interestingly, we found no significant modulation of (broadband) burst amplitude with age. These findings are in good agreement with a recent paper which used EEG to probe burst modulation during observed movements in babies and adults⁴¹.

Our connectivity finding is also of note, showing a significant increase in functional connectivity with age. This is in good agreement with previous literature – for example Schäfer et al.²⁵ showed quantitatively similar data in conventional MEG, albeit again by scanning older children (ages 6 and up). Here we also showed that connectivity changes with age are most prominent in the frontal and parietal areas, and weakest in the visual cortex. It makes intuitive sense that the largest changes in connectivity over the age range studied should occur in the parietal and frontal regions – these regions are typically associated with both cognitive and attentional networks and are implicated in the networks that develop most between childhood and adulthood. Here, we observed a relative lack of age-related change in the visual regions; this could relate to the nature of the task – recall that all volunteers watched their favourite TV show and so the visual regions were being stimulated throughout, driving coordinated network activity in occipital cortex. The visual system is also early to mature compared to frontal cortex.

We failed to see a significant difference in the spatial location of the cortical representations of the index and little finger; there are three potential reasons for this. First, the system was not designed to look for such a difference – sensors were sparsely distributed to achieve whole head coverage (rather than packed over sensory cortex to achieve the best spatial resolution in one area⁶²). Second, our “pseudo-MRI” approach to head modelling (see Methods) is less accurate than acquisition of participant-specific MRIs, and so may mask subtle spatial differences. Third, we used a relatively straightforward technique for modelling magnetic fields generated by the brain (a single shell forward model). Although MEG is much less susceptible to conductivity inhomogeneity of the head than EEG, the forward model may still be impacted by the small head profile. This may diminish spatial resolution and future studies might look to implement more complex models based on e.g. finite element modelling⁶³. Finally, previous work⁶⁴ suggested that, for a motor paradigm in adults, only the beta rebound, and not the power reduction during stimulation, mapped motortopically. This may also be the case for purely sensory stimulation. Nevertheless, it remains the case that by placing sensors closer to the scalp, OPM-MEG should offer improved spatial resolution in children and adults; this should be the topic of future work.

Finally, this was the first study of its kind using OPM-MEG, and consequently aspects of the study design could have been improved. Firstly, the task was designed for children; it was kept short while maximising the number of trials (to maximise signal to noise ratio). However, the classical view of beta modulation includes a PMBR which takes ~10 s to reach baseline following task cessation^{2,65,66}. Our short trial duration therefore doesn't allow the rebound to return to baseline between trials, and so conflates PMBR with rest. Consequently, we cannot differentiate the neural generators of the task induced beta power decrease and the PMBR; whilst this helped ensure a short, child friendly task, future studies should aim to use longer rest windows to independently assess which of the two processes is driving age related changes. Secondly, here we chose to use passive (sensory) stimulation. This helped ensure compliance with the task in subjects of all ages and prevented confounds of e.g. reaction time, force, speed and duration of movement which would be more likely in a motor task.^{65,66} However, there are many other systems to choose and whether the findings here regarding beta bursts and the changes with age also extend to other brain networks remains an open question. Thirdly, we lost more trials in children than we did in adults ($19 \pm 12\%$ compared to $9 \pm 5\%$) and this ostensibly implies a greater signal to noise ratio in adults compared to children which could help drive the effects observed. To test this, we ran a second analysis in which data were removed to equalise the final trial counts in the two groups (see Supplementary Information Section 5). These additional analyses resulted in no change to our conclusions. Finally, the number of sensors available varied across participants – this was mainly for pragmatic purposes (the system was experimental and not all OPMs were available for every recording). Whilst we always ensured good coverage of sensorimotor cortex, and tried to optimise whole brain coverage as much as we could, the system is likely to have diminished sensitivity around the temporal cortex, and this may explain why there was relatively little change in connectivity with age in those regions. In future, the inclusion of more sensors, particularly around the cheekbone would be a natural extension.

Conclusion

Characterising how neural oscillations change with age is a key step towards understanding the developmental trajectory of coordinated brain function, and the deviation of that trajectory in disorders. However, limitations of conventional, non-invasive approaches to measuring electrophysiology have led to confounds when scanning children. Here, we have demonstrated a new platform for neurodevelopmental assessment. Using OPM-MEG, we have been able to provide evidence – supported by previous studies – that shows both task-induced beta modulation and whole brain functional connectivity increase with age. In addition, we have shown that the classically observed beta power drop during stimulation can be explained by a lower burst probability, and that modulation of burst probability changes with age. We further showed that the frequency content of bursts changes with age. Our results offer new insights into the developmental trajectory of beta oscillations and provide clear evidence that OPM-MEG is an ideal platform to study electrophysiology in neurodevelopment.

Methods

Participants and Experiment

The study received ethical approval from the University of Nottingham Research Ethics Committee and written consent was obtained from the parents of each participant. Consent and authorisation for publication of **Figure 1A** [↗](#) were also obtained.

The paradigm comprised tactile stimulation of the tips of the index and little fingers using two braille stimulators (METEC, Germany) (See **Figure 1C** [↗](#)). Each stimulator comprised 8 independently controlled pins which could be raised or lowered to tap the participant's finger. A single trial comprised approximately 0.5 s of stimulation during which the finger was tapped 3 times using all 8 pins. Pins were up for 82ms during each 'tap' and down for 82ms between 'taps'. This was followed by 3 s rest. The finger stimulated (index or little) was alternated between trials. There was a total of 42 trials for each finger, meaning the experiment lasted a total of 294 s. Throughout the experiment, participants watched a television program of their choice (presented via projection onto a screen in the MSR, using a View Sonic PX748-4K projector at 60Hz refresh rate). All children were accompanied by a parent and one experimenter throughout their visit.

Data collection and co-registration

The sensor array comprised 64 triaxial OPMs (QuSpin Inc, Colorado, USA, Zero Field Magnetometer, Third Generation) which enabled a maximum of 192 measurements of magnetic field around the scalp (192-channels). The OPMs could be mounted in one of four 3D-printed helmets of different sizes (Cerca Magnetics Ltd., Nottingham, UK); this affords (approximate) whole-head coverage and adaptation to the participants head size. All participants wore a thin aerogel cap underneath the helmet to control heat from the sensors (which operate with elevated temperature). The system is housed in a magnetically shielded room (MSR) equipped with degaussing coils [67](#) [↗](#) and active magnetic field control [46](#) [↗](#) (Cerca Magnetics Ltd., Nottingham, UK). Prior to data collection, the MSR was demagnetised and the magnetic field compensation coils energised (using currents based on previously obtained field maps. This procedure, which results in a background field of ~ 0.6 nT [68](#) [↗](#), is important to enable free head motion during a scan [69](#) [↗](#). All OPMs were equipped with on-board coils which were used for sensor calibration. MEG data were collected at a sampling rate of 1,200 Hz (16-bit precision) using a National Instruments (NI, Texas, USA) data acquisition system interfaced with LabVIEW (NI).

Following data collection, two 3D digitisations of the participant's head, with and without the OPM helmet, were generated using a 3D structured light metrology scanner (Einscan H, SHINING 3D, Hangzhou, China). Participants wore a swimming cap to flatten hair during the 'head-only' scan. The head-only digitisation was used to measure head size and shape, and an age-matched T1-weighted template MRI scan was selected from a database⁷⁰ and warped to fit the digitisation, using FLIRT in FSL^{71,72}. This procedure resulted in a "pseudo-MRI" which provided an approximation of the subject's brain anatomy. Sensor locations and orientations relative to this anatomy were found by aligning it to the digitisation of the participant wearing the sensor helmet, and adding the known geometry of the sensor locations and orientations within the helmet^{73–75}. This was done using MeshLab⁷⁶.

MEG Data Preprocessing

We used a preprocessing pipeline described previously⁷⁵. Briefly, broken or excessively noisy channels were identified by manual visual inspection of channel power spectra; any channels that were either excessively noisy, or had zero amplitude, were removed. Automatic trial rejection was implemented with trials containing abnormally high variance (exceeding 3 standard deviations from the mean) removed. All experimental trials were also inspected visually by an experienced MEG scientist, to exclude trials with large spikes/drifts that were missed by the automatic approach. In the adult group, there was a significant overlap between automatically and manually detected bad trials (0.7+1.6 trials were only detected manually). In the children 10.0 +9.4 trials were only detected manually). Notch filters at the powerline frequency (50 Hz) and 2 harmonics, and a 1-150 Hz band pass filter, were applied. Finally, eye blink and cardiac artefacts were removed using ICA (implemented in FieldTrip⁷⁷) and homogeneous field correction (HFC) was applied to reduce interference⁷⁸.

Source Reconstruction and Beta-Modulation

For source estimation, we used a LCMV beamformer spatial filter⁷⁹. For all analyses, covariance matrices were generated using data acquired throughout the whole experiment (excluding bad channels and trials). Covariance matrices were regularised using the Tikhonov method with a regularisation parameter equal to 5% of the maximum eigenvalue of the unregularized matrix. The forward model was based on a single shell volumetric conductor⁸⁰.

To construct the **Pseudo-T statistical images**, data were filtered to the beta-band (13-30 Hz) and narrow band data covariance matrixes generated. Voxels were placed on both an isotropic 4-mm grid covering the whole brain, and a 1-mm grid covering the contralateral sensorimotor regions. For each voxel, we contrasted power in active (0.3-0.8 s) and control (2.5-3 s) time windows to generate images showing the spatial signature of beta band modulation. Separate images were derived for index and little finger trials.

To generate **time frequency spectra**, we used broad-band (1-150 Hz) data and covariance matrices. The beamformer was used to produce a time course of neural activity (termed a "virtual electrode") at the voxel with maximum beta-band modulation (identified from the 1-mm resolution pseudo-T-statistical images). The resulting beamformer-projected broad-band data were frequency filtered into a set of overlapping bands, and a Hilbert transform used to derive the analytic signal for each band. The absolute value of this was computed to give the envelope of oscillatory amplitude (termed the Hilbert envelope). This was averaged across trials, concatenated in frequency, baseline corrected and normalised yielding a time frequency spectrogram showing relative change in spectral power (from baseline) as a function of time and frequency. To generate the **evoked response**, the broadband (4-40 Hz) beamformer projected data (for the same location in sensorimotor cortex) were simply averaged across trials. To quantify the magnitude of **beta-modulation**, we filtered the virtual electrode to the beta band, calculated the Hilbert envelope, averaged across trials and computed time courses of amplitude change relative to baseline (2.5-3s). The beta modulation index (β_{mod}) was calculated using the equation $\beta_{mod} = (\beta_{Post} - \beta_{Stim})/\beta_{Baseline}$.

where β_{Stim} , β_{Post} , and $\beta_{Baseline}$ are the average Hilbert-envelope-derived amplitudes in the stimulus (0.3-0.8s), post-stimulus (1-1.5s) and baseline (2.5-3s) windows, respectively. To calculate the **evoked response amplitude**, we measured the amplitude of the evoked response at 50 ms post stimulation (the M50). These values (derived for every participant) were plotted against age and a relationship assessed via Pearson correlation.

Functional Connectivity Analysis

To measure functional connectivity, we first parcellated the brain into distinct regions. To this end, estimated brain anatomies were co-registered to the MNI standard brain using FSL FLIRT ^{71,72} and divided into 78 cortical regions according to the Automated Anatomical Labelling (AAL) atlas ⁸¹⁻⁸³. Virtual electrode time courses were generated at the centre of mass of each of these 78 regions, and the beta band Hilbert envelope derived. We then computed Amplitude Envelope Correlation (AEC) as an estimate of functional connectivity between all possible pairs of AAL regions ^{24,47}. Prior to AEC, we applied pairwise orthogonalisation to reduce source leakage ^{84,85}. This resulted in a single connectome matrix per participant. We estimated “Global Connectivity” as the mean connectivity value across all off-diagonal elements in the connectome matrix. This was plotted against age and the relationship assessed using Pearson correlation. To visualise the spatial variation in age-related connectivity changes, we also estimated the correlation between node degree (i.e., the column-wise sum of connectome matrix elements) and age, for each of the 78 AAL regions.

Beta Bursts and Hidden Markov Modelling

To estimate beta burst timings we employed a three-state, time-delay embedded univariate HMM ⁴⁴. This method has been described extensively in previously papers ^{39,49}. Briefly, virtual electrode time series were frequency filtered 1-48 Hz. The HMM was used to divide this time course into three “states” each depicting repeating patterns of activity with similar temporospectral signatures. The output was three time courses representing the likelihood of each state being active as a function of time. These were binarized (using a threshold of 2/3) and used to generate measures of the probability of state occurrence as a function of time in a single trial. The state whose probability of occurrence modulated most with the task was defined as the “burst state”. We estimated age-related changes in burst probability modulation and the relationship between burst probability modulation and classical beta-modulation (see above) using Pearson correlation. Further, we investigated the spectral content of the burst state and its modulation with age using multi-taper estimation of the power spectral density (PSD) ⁴⁴. Having derived the spectral content of the burst state we used Pearson correlation to measure how the PSD magnitude, for every frequency, changes with age.

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Conflicts of interest

V.S. is the founding director of QuSpin, a commercial entity selling OPM magnetometers. J.O. and C.D. are employees of QuSpin. E.B. and M.J.B. are directors of Cerca Magnetics Limited, a spin-out company whose aim is to commercialise aspects of OPM-MEG technology. E.B., M.J.B., R.B., N.H. and R.H. hold founding equity in Cerca Magnetics Limited. HS, FW, and TH are employees of Cerca Magnetics Limited.

Supplementary Information

Section 1: Beta modulation with stimulation of the little finger

Figure 3 [↗](#) shows beta modulation as a function of age, following tactile stimulation of the index finger. The same methods were used to generate equivalent responses during trials in which the little finger received stimulation. This is shown in **Figure S1** [↗](#), which supports the conclusions drawn in the main manuscript. Again, a significant variation of beta modulation with age is observed.

Section 2: burst amplitude does not correlate with age

Our manuscript shows a significant correlation between beta modulation and burst probability (**Figure 5D** [↗](#)) – implying that the stimulus related drop in beta amplitude occurs because bursts are less likely to occur during this window. Further, we showed significant age-related changes in both beta amplitude modulation and burst probability, leading to a conclusion that the age dependence of beta modulation was caused by changes in the likelihood of bursts (i.e. bursts are less likely to ‘switch off’ during sensory stimulation, in children). Here we extend these analyses to test whether burst amplitude also changes significantly with age. We reasoned that if burst amplitude remained the same in children and adults, this would not only suggest that beta modulation is driven solely by burst probability (distinct from children having lower amplitude bursts), but also show directly that the beta effects we see are not attributable to a lack of sensitivity in younger people.

We took the (unnormalized) beamformer projected electrophysiological time series from sensorimotor cortex and filtered them 5–48 Hz. (The motivation for the large band was because bursts are known to be pan-spectral and have lower frequency content in Children – this band captures most of the range of burst frequencies highlighted in our spectra.) We then extracted the timings of the bursts, and for each burst took the maximum projected signal amplitude. These values were averaged across all bursts in an individual subject and plotted for all subjects against age.

Results (see **Figure S2** [↗](#)) showed that the amplitude of the beta bursts showed no significant age-related modulation ($R^2 = 0.01$, $p = 0.48$ for the index finger (Panel A) and $R^2 = 0.01$, $p = 0.57$ for the little finger (Panel B)). This is distinct from both burst probability and task-induced beta modulation. This adds weight to the argument that the diminished beta modulation in children is not caused by a lack of sensitivity to the MEG signal and supports the conclusion that burst probability is the primary driver of age-related changes in beta oscillations.

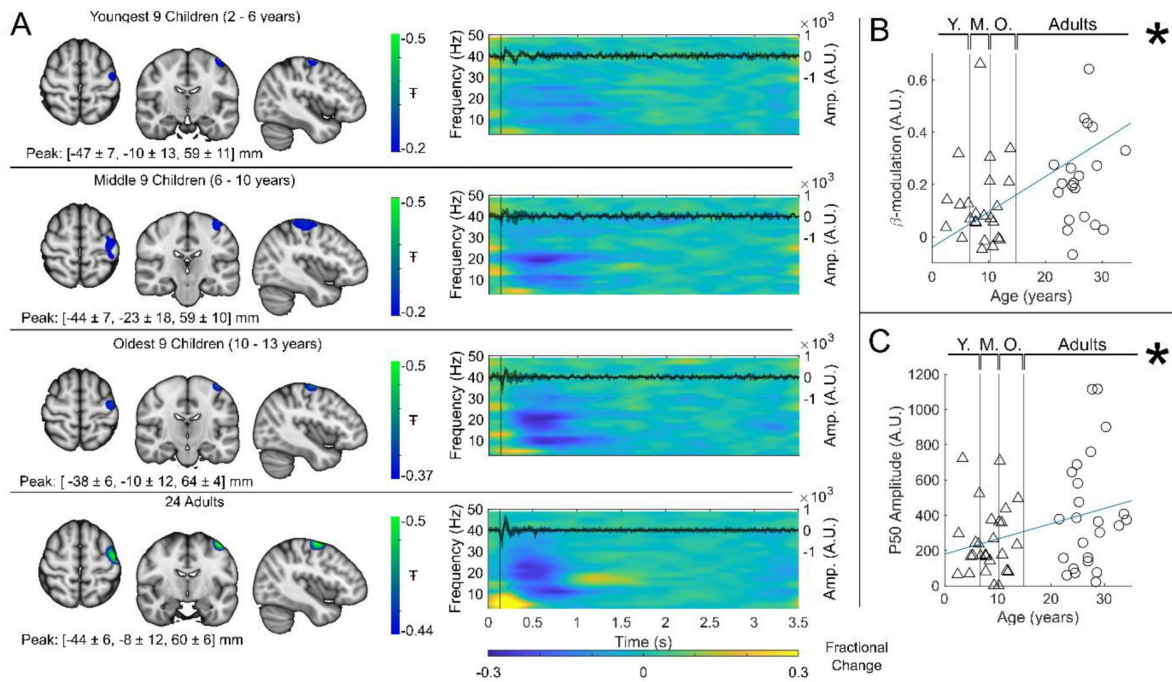


Figure S1

Equivalent to **Figure 3** in the main manuscript but derived for little finger (rather than index finger) stimulation. Beta modulation showed a significant increase with age ($R^2 = 0.23$, $p = 0.0003$). The P50 Amplitude showed a weak but significant increase with age ($R^2 = 0.1$, $p = 0.023$).

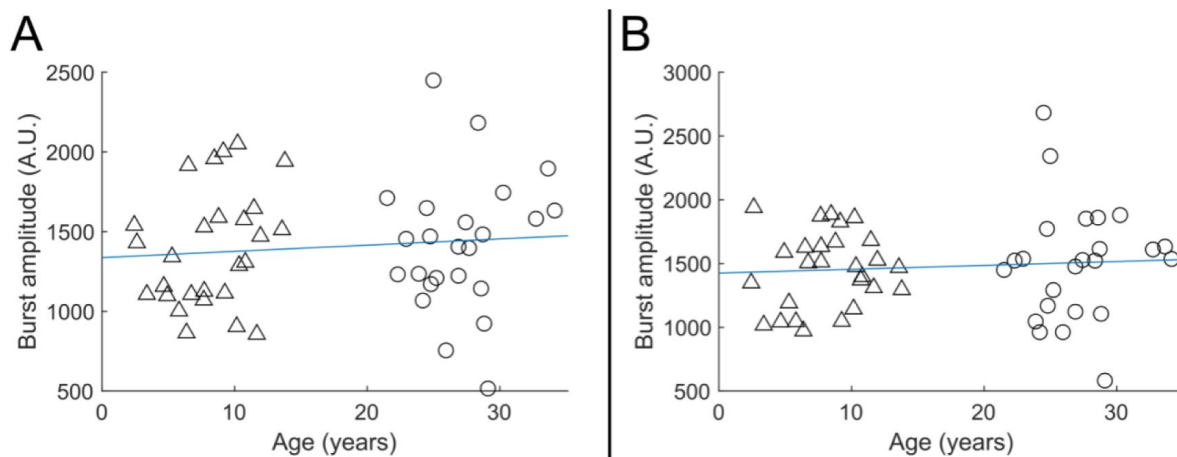


Figure S2

Beta burst amplitude as a function of age; A) shows index finger stimulation trials ($R^2 = 0.01$, $p = 0.48$); B shows little finger stimulation trials ($R^2 = 0.01$, $p = 0.57$). In both cases there was no significant modulation of burst amplitude with age.

Section 3: Burst spectra in the non-burst states

Figure 6 [in the main manuscript](#) shows the frequency spectrum of the HMM-derived burst state. Here we show equivalent spectra for the non-burst states. As shown, even in the non-burst states, a change in spectrum is observed with children exhibiting less high-frequency and more low-frequency activity.

Section 4: Proximity of sensors to the head

For an ideal wearable MEG system, the distance between the sensors and the scalp surface (sensor proximity) would be the same regardless of age (and head shape/size), ensuring maximum sensitivity in all subjects. To test how our system performed in this regard, we undertook analyses to compute scalp-to-sensor distances. This was done in two ways:

1. **Real distances in our adaptable system:** We took the co-registered OPM sensor locations and computed the Euclidean distance from the centre of the sensitive volume (i.e. the centre of the vapour cell) to the closest point on the scalp surface. This was measured independently for all sensors, and an average across sensors was calculated. We repeated this for all participants (recall participants wore helmets of varying size and this adaptability should help minimise any relationship between sensor proximity and age).
2. **Simulated distances for a non-adaptable system:** Here, the aim was to see how proximity might have changed with age, had only a single helmet size been used. We first identified the single example subject with the largest head (scanned wearing the largest helmet) and extracted the scalp-to-sensor distances as above. For all other subjects, we used a rigid body transform to co-register their brain to that of the example subject (placing their head (virtually) inside the largest helmet). Proximity was then calculated as above and an average across sensors calculated. This was repeated for all participants.

In both analyses, sensor proximity was plotted against age and significant relationships probed using Pearson correlation.

In addition, we also wanted to probe the relationship between sensor proximity and head circumference. Head circumference was estimated as follows: the whole head MRI was binarised (to delineate the surface of the head); the axial slice with the largest area was selected and circumference of the head within that slice measured. We then plotted sensor proximity versus head circumference, for both the real (adaptive) and simulated (non-adaptive) case (expecting a negative relationship – i.e. larger heads mean closer sensor proximity). The slope of the relationship was measured and we used a permutation test to determine whether the use of adaptable helmets significantly lowered the identified slope (i.e. do adaptable helmets significantly improve sensor proximity in those with smaller head circumference).

Results are shown in **Figure S4** [in the main manuscript](#). We found no measurable relationship between sensor proximity and age ($r = -0.19$; $p = 0.17$) in the case of the real helmets (panel A). When simulating a non-adaptable helmet, we did see a significant effect of age on scalp-to-sensor distance ($r = -0.46$; $p = 0.001$; panel B). This demonstrates the advantage of the adaptability of OPM-MEG; without the ability to flexibly locate sensors, we would have a significant confound of sensor proximity.

Plotting sensor proximity against head circumference we found a significant negative relationship in both cases ($R = -0.37$; $p = 0.007$ and $R = -0.78$; $p = 0.000001$); however, the difference between slopes was significant according to a two-tailed permutation test ($p < 0.025$) suggesting that adaptable helmets do indeed improve sensor proximity, in those with smaller head circumference. This again shows the benefits of adaptability to head size.

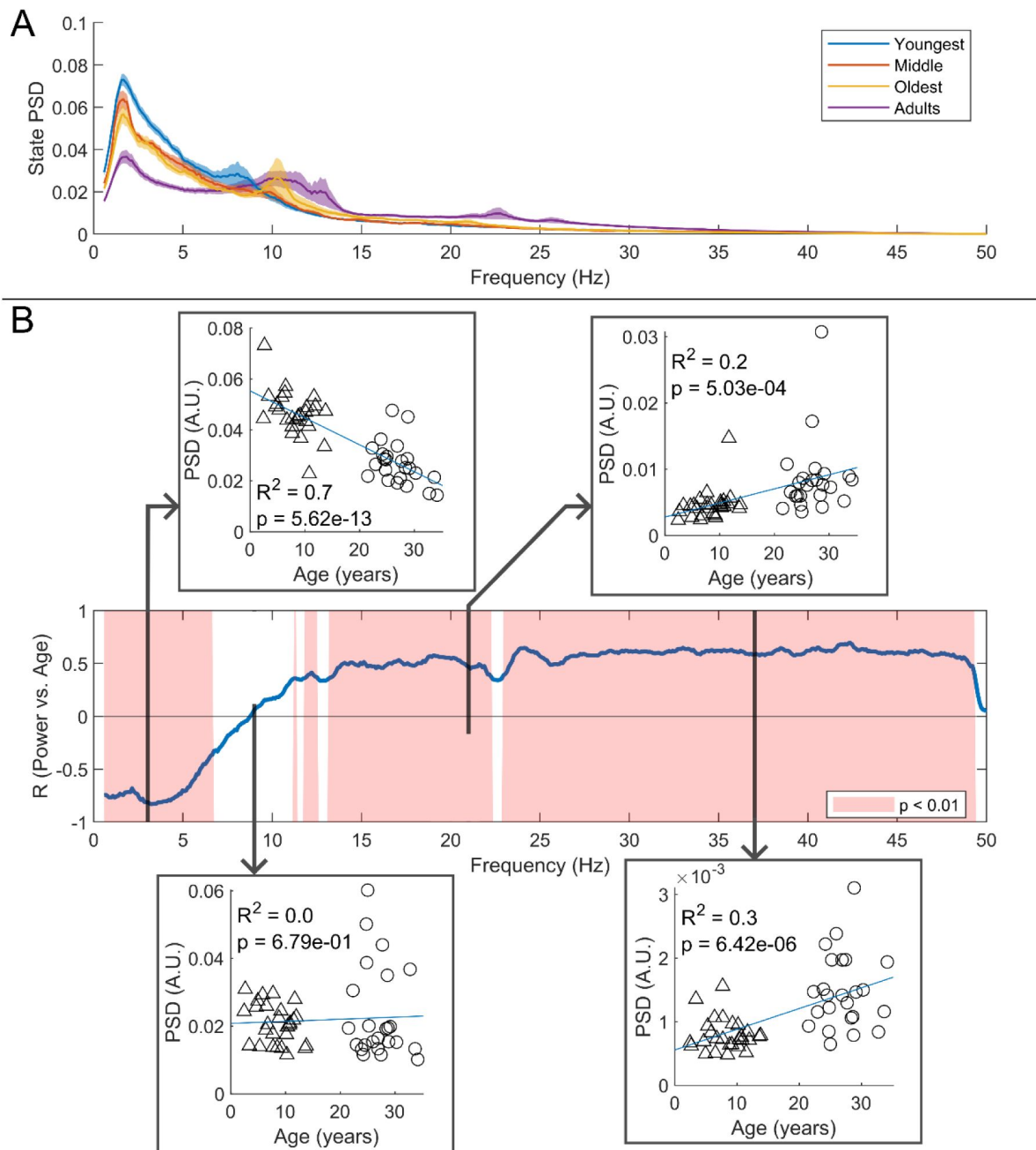


Figure S3

Spectral content of the non-burst states. (A) Average **non-burst-state** spectra across groups. Shaded areas indicate standard error on the group mean. (B) Pearson correlation coefficient for the PSD values in (A) against age across all frequency values. Red shaded areas indicate $p < 0.01$ (uncorrected). The four inset plots show example scatters of PSD values with age at select frequencies (3 Hz, 9 Hz, 21 Hz, and 37 Hz). Low-frequency spectral content decreases with age while high-frequency content increases. Results broadly mirror the frequency content and age relationships found in the burst state, however, features in the spectra corresponding to classical alpha and beta peaks are less prominent outside the burst state.

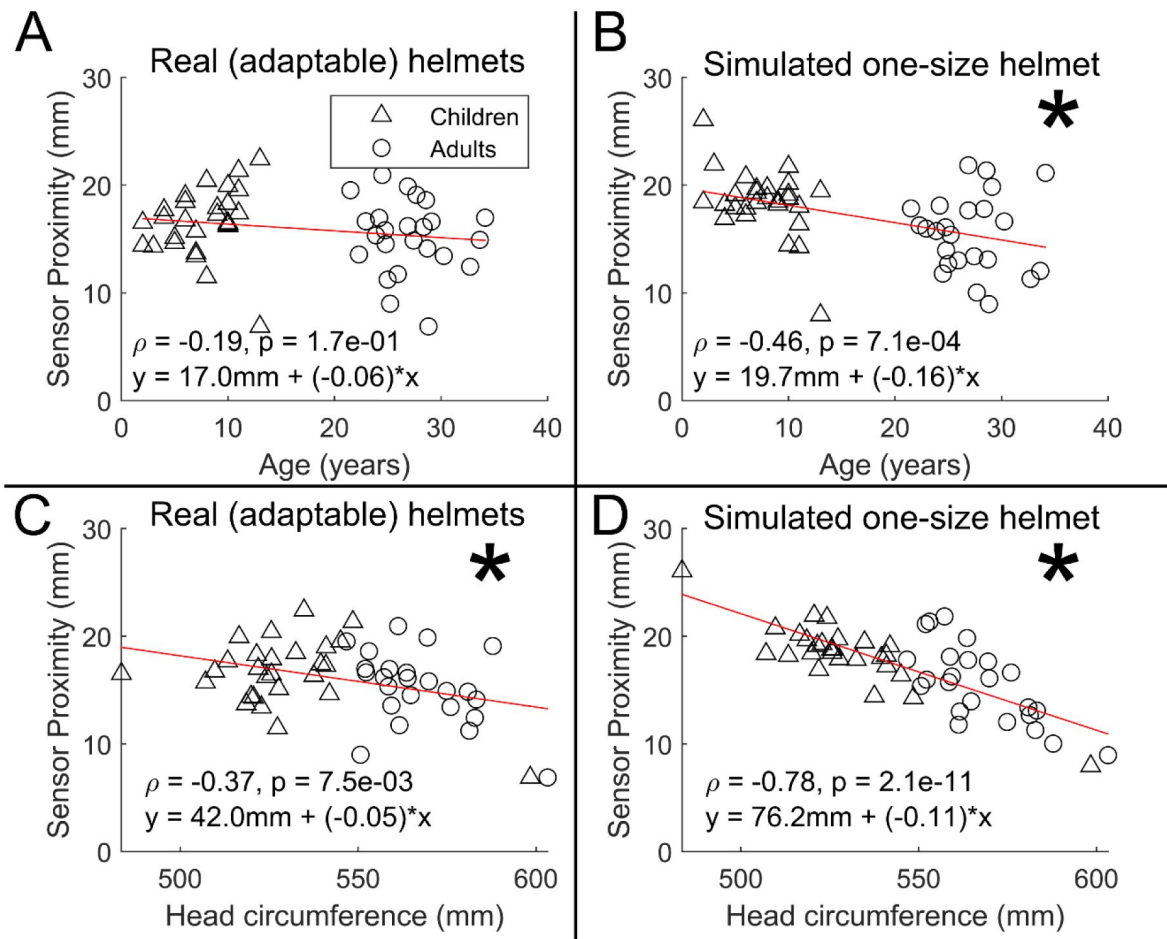


Figure S4

Scalp-to-sensor distance as a function of age (A/B) and head circumference (C/D). A and C show the case for the real helmets; B and D show the simulated non-adaptable case.

In sum, the ideal wearable system would see sensors located on the scalp surface, to get as close as possible to the brain in all subjects. Our system of multiple helmet sizes is not perfect in this regard (there is still a significant relationship between proximity and head circumference). However, our solution has offered a significant improvement over a (simulated) non-adaptable system. Future systems should aim to improve even further on this, either by using additively manufactured bespoke helmets for every subject (this is a gold standard, but also potentially costly for large studies), or adaptable flexible helmets.

Section 5: Reduced trial analyses

In our study we had to discard more trials in children than adults. This potentially means a confound with a larger signal to noise ratio in adults than children, which could affect the results. For this reason we reanalysed our data, discarding trials from the adults to ensure equal numbers (on average) in our adult and child cohorts. Results are shown in **Figure S5** [↗](#). Panel A shows beta modulation with age (equivalent to **Figure 3B** [↗](#)); Panel B shows evoked response (M50) modulation with age (equivalent to **Figure 3C** [↗](#)); Panel C shows functional connectivity with age (equivalent to **Figure 4B** [↗](#)) and Panel D shows burst probability modulation with age (equivalent to **Figure 5C** [↗](#)). In all cases, the significant modulations with age captured in the main manuscript remain.

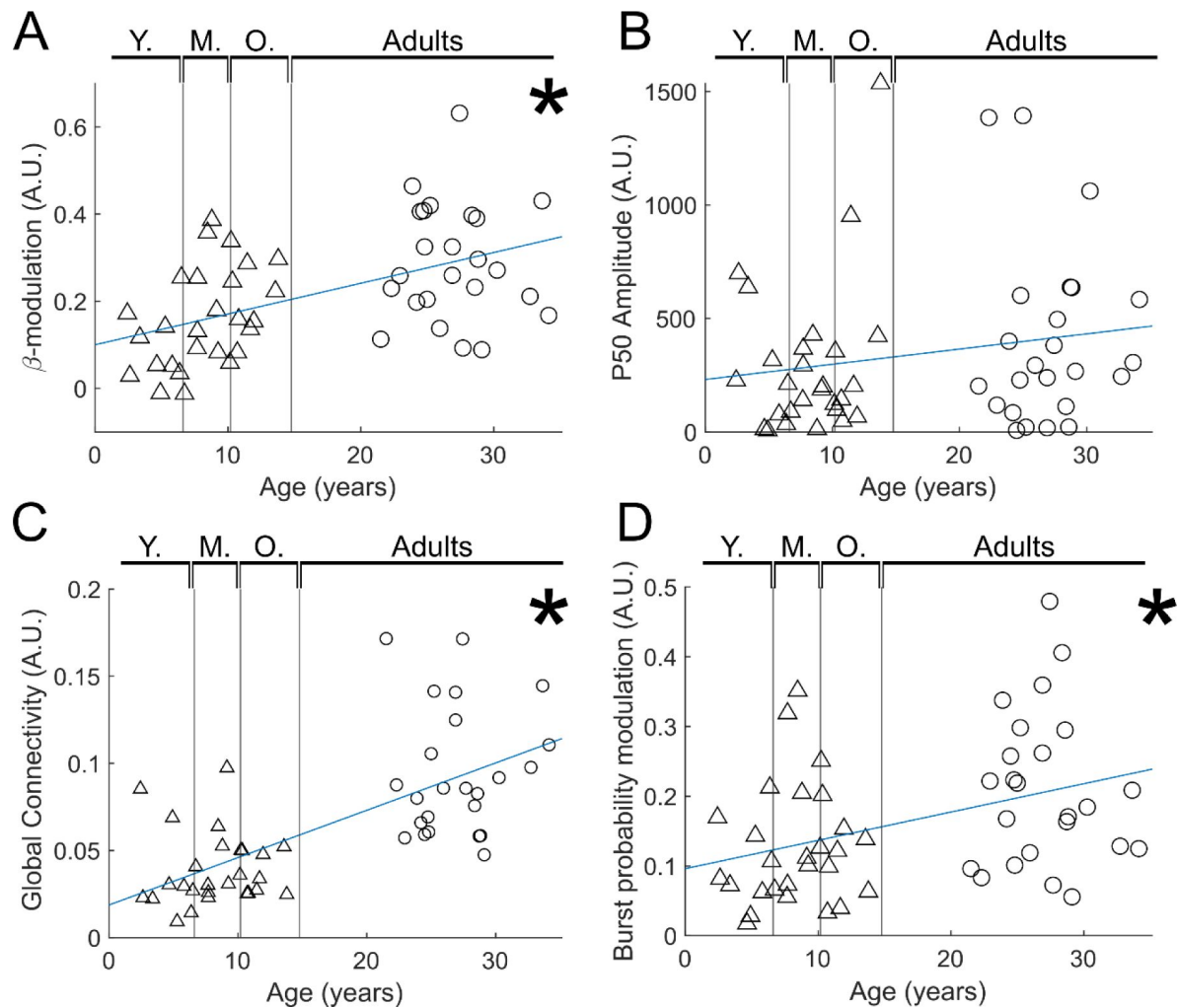


Figure S5

Reduced trial analysis for index finger stimuli: A) Beta modulation with age. ($R^2 = 0.26$, $p = 0.00014$) B) Evoked response (P50) modulation with age. ($R^2 = 0.03$, $p = 0.199$) C) Functional connectivity with age. ($R^2 = 0.45$, $p = 7 \times 10^{-8}$) D) Burst probability modulation with age ($R^2 = 0.15$, $p = 5.4 \times 10^{-3}$)

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Reviewer #3 (Public Review):

This study demonstrated the application of OPM-MEG in neurodevelopment studies of somatosensory beta oscillations and connections with children as young as 2 years old. It provides a new functional neuroimaging method which has high spatial-temporal resolution as well as a wearable which makes it a new useful tool for studies in young children. They have constructed a 192-channel wearable OPM-MEG system which includes field compensation coils which allows free head movement scanning with a relatively high ratio of usable trials. Beta band oscillations during somatosensory tasks are well localized and the modulation with age are found in the amplitude, connectivity, and pan-spectral burst probability. It is

demonstrated that the wearable OPM-MEG could be used in children as a quite practical and easy to deploy neuroimaging method with performance as good as conventional MEG. With both good spatial (several millimeter) and temporal (milliseconds) resolution, it provides a novel and powerful technology to neurodevelopment research and clinical application not limited to somatosensory areas.

The conclusions of this paper are mostly well supported by data acquired under proper method.

<https://doi.org/10.7554/eLife.94561.2.sa0>

Author response:

The following is the authors' response to the original reviews.

eLife assessment

This study provides important evidence supporting the ability of a new type of neuroimaging, OPM-MEG system, to measure beta-band oscillation in sensorimotor tasks on 2-14 years old children and to demonstrate the corresponding development changes, since neuroimaging methods with high spatiotemporal resolution that could be used on small children are quite limited. The evidence supporting the conclusion is solid but lacks clarifications about the much-discussed advantages of OPM-MEG system (e.g., motion tolerance), control analyses (e.g., trial number), and rationale for using sensorimotor tasks. This work will be of interest to the neuroimaging and developmental science communities.

We thank the editors and reviewers for their time and comments on our manuscript. We have responded in detail to the comments, on a point-by-point basis, below. Included in our responses (and our revised manuscript) are additional analyses to control for trial count, clarification of the advantages of OPM-MEG, and justification of our use of sensory (as distinct from motor) stimulation. In what follows, our responses are in bold typeface; additions to our manuscript are in bold italic typeface.

Reviewer #1 (Public Review):

Summary:

Compared with conventional SQUID-MEG, OPM-MEG offers theoretical advantages of sensor configurability (that is, sizing to suit the head size) and motion tolerance (the sensors are intrinsically in the head reference frame). This study purports to be the first to experimentally demonstrate these advantages in a developmental study from age 2 to age 34. In short, while the theoretical advantages of OPM-MEG are attractive - both in terms of young child sensitivity and in terms of motion tolerance - neither was in fact demonstrated in this manuscript. We are left with a replication of SQUID-MEG observations, which certainly establishes OPM-MEG as "substantially equivalent" to conventional technology but misses the opportunity to empirically demonstrate the much-discussed theoretical advantages/opportunities.

Thank you for reviewing our manuscript. We agree that our results demonstrate substantial equivalence with conventional MEG. However, as mentioned by Reviewer 3, most past studies have "focused on older children and adolescents (e.g., 9-15 years old)" whereas our youngest group is 25 years. We believe that by obtaining data of sufficient quality in these age groups, without the need for any restriction of head movement, we have demonstrated the advantage of OPM-MEG. We now have made this clear in our discussion:

“...our primary aim was to test the feasibility of OPM-MEG for neurodevelopmental studies. Our results demonstrate we were able to scan children down to age 2 years, measuring high-fidelity electrophysiological signals and characterising the neurodevelopmental trajectory of beta oscillations. The fact that we were able to complete this study demonstrates the advantages of OPM-MEG over conventional-MEG, the latter being challenging to deploy across such a large age range...”

Strengths:

A replication of SQUID-MEG observations, which certainly establishes OPM-MEG as "substantially equivalent" to conventional technology but misses the opportunity to empirically demonstrate the much-discussed theoretical advantages/opportunities.

As noted above the demonstration of equivalence was one of our primary aims. We have elaborated further on the advantages below.

Weaknesses:

The authors describe 64 tri-axial detectors, which they refer to as 192 channels. This is in keeping with some of the SQUID-MEG description, but possibly somewhat disingenuous. For the scientific literature, perhaps "64 tri-axial detectors" is a more parsimonious description.

The number of channels in a MEG system refers to the number of independent measurements of magnetic field. This, in turn, tells us the number of degrees of freedom in the data that can be exploited by algorithms like signal space separation or beamforming. E.g. the MEGIN (cryogenic) MEG system has 306 channels, 102 magnetometers and 204 planar gradiometers. Sensors are constructed as “triple sensor elements” with one magnetometer and 2 gradiometers (in orthogonal orientations) centred on a single location. In our system, each sensor has three orthogonal metrics of magnetic field which are (by definition) independent. We have 64 such sensors, and therefore 192 independent channels – indeed when implementing algorithms like SSS we have shown we can exploit this number of degrees of freedom.¹ 192 channels is therefore an accurate description of the system.

A small fraction (<20%) of trials were eliminated for analysis because of "excess interference" - this warrants further elaboration.

We agree that this is an important point. We now state in our methods section:

“...Automatic trial rejection was implemented with trials containing abnormally high variance (exceeding 3 standard deviations from the mean) removed. All experimental trials were also inspected visually by an experienced MEG scientist, to exclude trials with large spikes/drifts that were missed by the automatic approach. In the adult group, there was a significant overlap between automatically and manually detected bad trials (0.7+-1.6 trials were only detected manually). In the children 10.0 +-9.4 trials were only detected manually)...”

We also note that the other reviewers and editor questioned whether the higher rejection rate in children had any bearing on results. This is an extremely important question. In revising the manuscript this has also been taken into account with all data reanalysed with equal trial counts in children and adults. Results are presented in Supplementary Information Section 5.

Figure 3 shows a reduced beta ERD in the youngest children. Although the authors claim that OPMMEG would be similarly sensitive for all ages and that SQUID-MEG would be

relatively insensitive to young children, one trivial counterargument that needs to be addressed is that OPM has NOT in fact increased the sensitivity to young child ERD. This can possibly be addressed by analogous experiments using a SQUID-based system. An alternative would be to demonstrate similar sensitivity across ages using OPM to a brain measure such as evoked response amplitude. In short, how does Figure 3 demonstrate the (theoretical) sensitivity advantage of OPM MEG in small heads ?

We completely understand the referees' point – indeed the question of whether a neuromagnetic effect really changes with age, or apparently changes due to a drop in sensitivity (caused by reduced head size or - in conventional MEG and fMRI - increased subject movement) is a question that can be raised in all neurodevelopmental studies.

Our authors have many years' experience conducting studies using conventional MEG (including in neurodevelopment) and agreed that the idea of scanning subjects down to age two in conventional MEG would not be practical; their heads are too small and they typically fail to tolerate an environment where they are forced to remain still for long periods. Even if we tried a comparative study using conventional MEG, the likely data exclusion rate would be so high that the study would be confounded. This is why most conventional MEG studies only scan older children and adolescents. For this reason, we cannot undertake the comparative study the reviewer suggests. There are however two reasons why we believe sensitivity is not driving the neurodevelopmental effects that we observe:

Proximity of sensors to the head:

For an ideal wearable MEG system, the distance between the sensors and the scalp surface (sensor proximity) would be the same regardless of age (and size), ensuring maximum sensitivity in all subjects. To test how our system performed in this regard, we undertook analyses to compute scalp-to-sensor distances. This was done in two ways:

(1) Real distances in our adaptable system: We took the co-registered OPM sensor locations and computed the Euclidean distance from the centre of the sensitive volume (i.e. the centre of the vapour cell) to the closest point on the scalp surface. This was measured independently for all sensors, and an average across sensors calculated. We repeated this for all participants (recall participants wore helmets of varying size and this adaptability should help minimise any relationship between sensor proximity and age).

(2) Simulated distances for a non-adaptable system: Here, the aim was to see how proximity might have changed with age, had only a single helmet size been used. We first identified the single example subject with the largest head (scanned wearing the largest helmet) and extracted the scalp-to-sensor distances as above. For all other subjects, we used a rigid body transform to co-register their brain to that of the example subject (placing their head (virtually) inside the largest helmet). Proximity was then calculated as above and an average across sensors calculated. This was repeated for all participants.

In both analyses, sensor proximity was plotted against age and significant relationships probed using Pearson correlation.

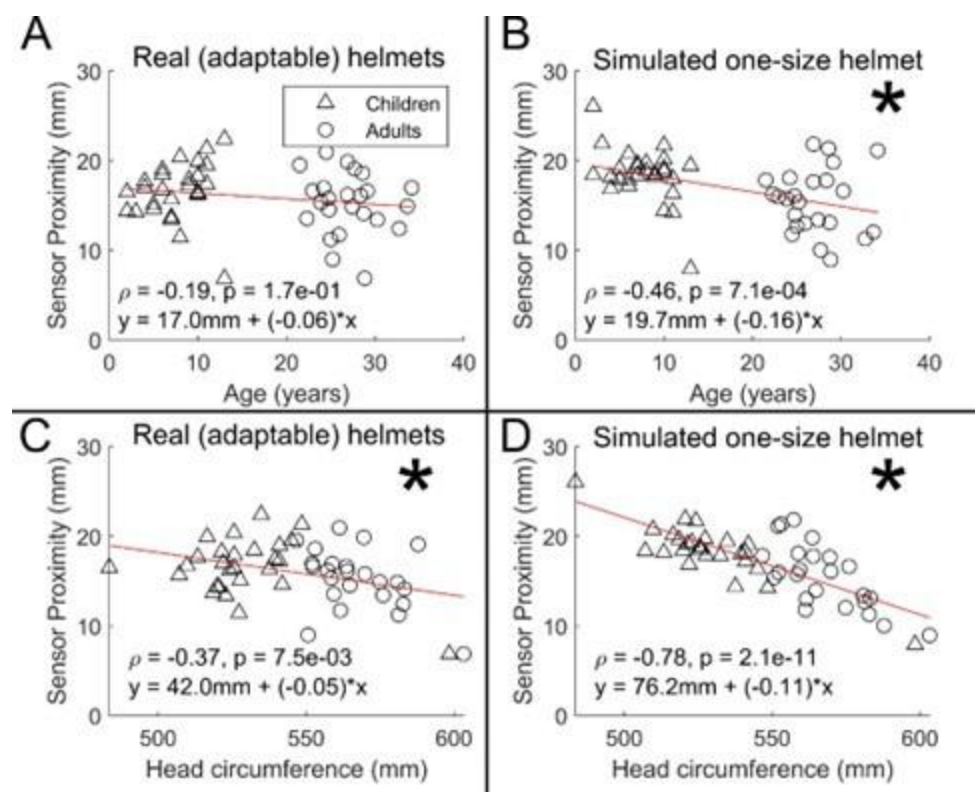
In addition, we also wanted to probe the relation between sensor proximity and head circumference. Head circumference was estimated by binarising the whole head MRI (to delineate volume of the head), and the axial slice with the largest circumference around was selected. We then plotted sensor proximity versus head circumference, for both the real (adaptive) and simulated (nonadaptive) case (expecting a negative relationship – i.e. larger heads mean closer sensor proximity). The slope of the relationship was measured and we used a permutation test to determine whether the use of adaptable helmets significantly lowered the identified slope (i.e. do adaptable helmets significantly improve sensor proximity in those with smaller head circumference).

Results are shown in Figure R1. We found no measurable relationship between sensor proximity and age ($r = -0.195$; $p = 0.171$) in the case of the real helmets (panel A). When simulating a non-adaptable helmet, we did see a significant effect of age on scalp-to-sensor distance ($r = -0.46$; $p = 0.001$; panel B). This demonstrates the advantage of the adaptability of OPM-MEG; without the ability to flexibly locate sensors, we would have a significant confound of sensor proximity.

Plotting sensor proximity against head circumference we found a significant negative relationship in both cases ($r = -0.37$; $p = 0.007$ and $r = -0.78$; $p = 0.000001$); however, the difference between slopes was significant according to a permutation test ($p < 0.025$) suggesting that adaptable has indeed improved sensor proximity in those with smaller head circumference. This again shows the benefits of adaptability to head size.

Author response image 1.

Scalp-to-sensor distance as a function of age (A/B) and head circumference (C/D). A and C show the case for the real helmets; B and D show the simulated non-adaptable case.



In sum, the ideal wearable system would see sensors located on the scalp surface, to get as close as possible to the brain in all subjects. Our system of multiple helmet sizes is not perfect in this regard (there is still a significant relationship between proximity and head circumference). However, our solution has offered a significant improvement over a (simulated) non-adaptable system. Future systems should aim to improve even further on this, either by using additively manufactured bespoke helmets for every subject (this is a gold standard, but also costly for large studies), or potentially adaptable flexible helmets.

Burst amplitudes:

The reviewer suggested to “demonstrate similar sensitivity across ages using OPM to a brain measure”. We decided not to use the evoked response amplitude (as suggested), since this

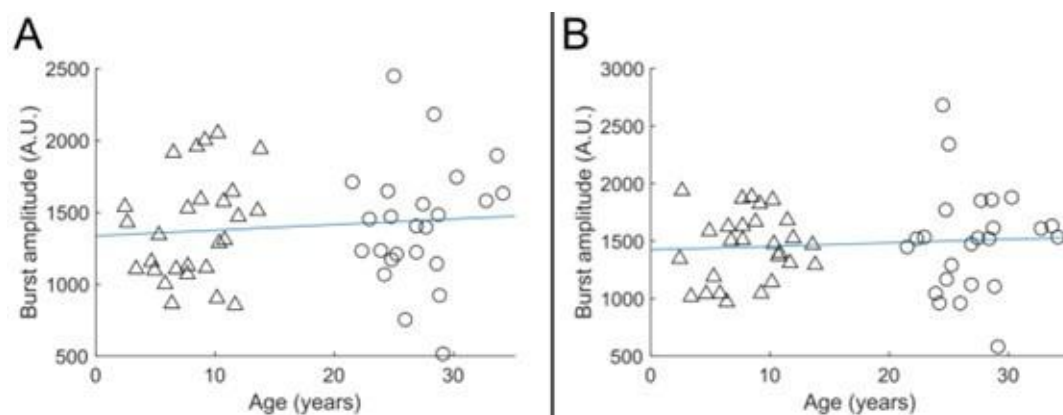
would be expected to change with age. Instead, we used the amplitude of the bursts.

Our manuscript shows a significant correlation between beta modulation and burst probability – implying that the stimulus-related drop in beta amplitude occurs because bursts are less likely to occur. Further, we showed significant age-related changes in both beta amplitude and burst probability leading to a conclusion that the age dependence of beta modulation was caused by changes in the likelihood of bursts (i.e. bursts are less likely to ‘switch off’ during sensory stimulation in children). We have now extended these analyses to test whether burst amplitude also changes significantly with age – we reasoned that if burst amplitude remained the same in children and adults, this would not only suggest that beta modulation is driven by burst probability (distinct from burst amplitude), but also show directly that the beta effects we see are not attributable to a lack of sensitivity in younger people.

We took the (unnormalized) beamformer projected electrophysiological time series from sensorimotor cortex and filtered it 5-48 Hz (the motivation for the large band was because bursts are known to be pan-spectral and have lower frequency content in children; this band captures most of the range of burst frequencies highlighted in our spectra). We then extracted the timings of the bursts, and for each burst took the maximum projected signal amplitude. These values were averaged across all bursts in an individual subject, and plotted for all subjects against age.

Author response image 2.

Beta burst amplitude as a function of age; A) shows index finger stimulation trials; B shows little finger stimulation trials. In both case there was no significant modulation of burst amplitude with age.



Results (see Figure R2) showed that the amplitude of the beta burst showed no significant age-related modulation ($R^2 = 0.01$, $p = 0.48$ for index finger and $R^2 = 0.01$, $p = 0.57$ for the little finger). This is distinct from both burst probability and task induced beta modulation. This adds weight to the argument that the diminished beta modulation in children is not caused by a lack of sensitivity to the MEG signal and supports our conclusion that burst probability is the primary driver of the age-related changes in beta oscillations.

Both of the above analyses have been added to our supplementary information and mentioned in the main manuscript. The first shows no confound of sensor proximity to the scalp with age in our study. The second shows that the bursts underlying the beta signal are not significantly lower amplitude in children – which we reasoned they would be if sensitivity was diminished at younger ages. We believe that the two together suggest that we have mitigated a sensitivity confound in our study.

The data do not make a compelling case for the motion tolerance of OPM-MEG. Although an apparent advantage of a wearable system, an empirical demonstration is still lacking. How was motion tracked in these participants?

We agree that this was a limitation of our experiment.

We have the equipment to track motion of the head during an experiment, using IR retroreflective markers placed on the helmet and a set of IR cameras located inside the MSR. However, the process takes a long time to set up, it lacks robustness, and would have required an additional computer (the one we typically use was already running the somatosensory stimulus and video). When the study was designed, we were concerned that the increased set up time for motion tracking would cause children to get bored, and result in increased participant drop out. For this reason we decided not to capture motion of the head during this study.

With hindsight this was a limitation which – as the reviewer states – makes us unable to prove that motion robustness was a significant advantage for this study. That said, during scanning there was both a parent and an experimenter in the room for all of the children scanned, and anecdotally we can say that children tended to move their head during scans – usually to talk to the parent. Whilst this cannot be quantified (and is therefore unsatisfactory) we thought it worth mentioning in our discussion, which reads:

“...One limitation of the current study is that practical limitations prevented us from quantitatively tracking the extent to which children (and adults) moved their head during a scan. Anecdotally however, experimenters present in the room during scans reported several instances where children moved, for example to speak to their parents who were also in the room. Such levels of movement could not be tolerated in conventional MEG or MRI and so this again demonstrates the advantages afforded by OPM-MEG...”

As a note, empirical demonstrations of the motion tolerance of OPM-MEG have been published previously: Early demonstrations included Boto et al. 2 who captured beta oscillations in adults playing a ball game and Holmes et al. who measured visual responses as participants moved their head to change viewing angle³. In more recent demonstrations, Seymour et al. measured the auditory evoked field in standing mobile participants⁴; Rea et al. measured beta modulation as subjects carried out a naturalistic handwriting task⁵ and Holmes et al measured beta modulation as a subject walked around a room.⁶

Furthermore, while the introduction discusses at some length the phenomenon of PMBR, there is no demonstration of the recording of PMBR (or post-sensory beta rebound). This is a shame because there is literature suggesting an age-sensitivity to this, that the optimal sensitivity of OPM-MEG might confirm/refute. There is little evidence in Figure 3 for adult beta rebound. Is there an explanation for the lack of sensitivity to this phenomenon in children/adolescents? Could a more robust paradigm (button-press) have shed light on this?

We understand the question. There are two limitations to the current study in respect to measuring the PMBR:

Firstly, sensory tasks generally do not induce as strong a PMBR as motor tasks and with this in mind a stronger rebound response could have been elicited using a button press. However, it was our intention to scan children down to age 2 and we were sceptical that the youngest children would carry out a button press as instructed. For this reason we opted for entirely passive stimulation, requiring no active engagement from our participants. The advantages of this was a stimulus that all subjects could engage with. However, this was at the cost of a diminished rebound.

The second limitation relates to trial length. Multiple studies have shown that the PMBR can last over ~10 s^{7,8}. Indeed, Pfurtscheller et al. argued in 1999 that it was necessary to leave 10 s between movements to allow the PMBR to return to a true baseline⁹, though this has rarely been adhered to in the literature. Here, we wanted to keep recordings short for the comfort of the younger participants, so we adopted a short trial duration. However, a consequence of this short trial length is that it becomes impossible to access the PMBR directly; one can only measure beta modulation with the task. This limitation has now been addressed explicitly in our discussion:

“...this was the first study of its kind using OPM-MEG, and consequently aspects of the study design could have been improved. Firstly, the task was designed for children; it was kept short while maximising the number of trials (to maximise signal to noise ratio). However, the classical view of beta modulation includes a PMBR which takes ~10 s to reach baseline following task cessation^{7–9}. Our short trial duration therefore doesn’t allow the rebound to return to baseline between trials, and so conflates PMBR with rest. Consequently, we cannot differentiate the neural generators of the task induced beta power decrease and the PMBR; whilst this helped ensure a short, child friendly task, future studies should aim to use longer rest windows to independently assess which of the two processes is driving age related changes...”

Data on functional connectivity are valuable but do not rely on OPM recording. They further do not add strength to the argument that OPM MEG is more sensitive to brain activity in smaller heads - in fact, the OPM recordings seem plagued by the same insensitivity observed using conventional systems.

Given the demonstration above that bursts are not significantly diminished in amplitude in children relative to adults; and further given the demonstrations in the literature (e.g. Seedat et al.¹⁰) that functional connectivity is driven by bursts, we would argue that the effects of connectivity changing with age are not related to sensitivity but rather genuinely reflect a lack of coordination of brain activity.

The discussion of burst vs oscillations, while highly relevant in the field, is somewhat independent of the OPM recording approach and does not add weight to the OPM claims.

We agree that the burst vs. oscillations discussion does not add weight to the OPM claims per se. However, we had two aims of our paper, the second being to “investigate how task-induced beta modulation in the sensorimotor cortices is related to the occurrence of pan-spectral bursts, and how the characteristics of those bursts change with age.” As the reviewer states, this is highly relevant to the field, and therefore we believe adds impact, not only to the paper, but also by extension to the technology.

In short, while the theoretical advantages of OPM-MEG are attractive - both in terms of young child sensitivity and in terms of motion tolerance, neither was in fact demonstrated in this manuscript. We are left with a replication of SQUID-MEG observations, which certainly establishes OPM-MEG as "substantially equivalent" to conventional technology but misses the opportunity to empirically demonstrate the much-discussed theoretical advantages/opportunities.

We thank the referee for the time and important contributions to this paper. We believe the fact that we were able to record good data in children as young as two years old was, in itself, an experimental realisation of the ‘theoretical advantages’ of OPM-MEG. Our additional analyses, inspired by the reviewers comments, help to clarify the advantages of OPM-MEG

over conventional technology. The reviewers' insights have without doubt improved the paper.

Reviewer #2 (Public Review):

Summary:

The authors introduce a new 192-channel OPM system that can be configured using different helmets to fit individuals from 2 to 34 years old. To demonstrate the veracity of the system, they conduct a sensorimotor task aimed at mapping developmental changes in beta oscillations across this age range. Many past studies have mapped the trajectory of beta (and gamma) oscillations in the sensorimotor cortices, but these studies have focused on older children and adolescents (e.g., 9-15 years old) and used motor tasks. Thus, given the study goals, the choice of a somatosensory task was surprising and not justified. The authors recorded a final sample of 27 children (2-13 years old) and 24 adults (21-34 years) and performed a time-frequency analysis to identify oscillatory activity. This revealed strong beta oscillations (decreases from baseline) following the somatosensory stimulation, which the authors imaged to discern generators in the sensorimotor cortices. They then computed the power difference between 0.3-0.8 period and 1.0-1.5 s post-stimulation period and showed that the beta response became stronger with age (more negative relative to the stimulation period). Using these same time windows, they computed the beta burst probability and showed that this probability increased as a function of age. They also showed that the spectral composition of the bursts varied with age. Finally, they conducted a whole-brain connectivity analysis. The goals of the connectivity analysis were not as clear as prior studies of sensorimotor development have not conducted such analyses and typically such whole-brain connectivity analyses are performed on resting-state data, whereas here the authors performed the analysis on task-based data. In sum, the authors demonstrate that they can image beta oscillations in young children using OPM and discern developmental effects.

Thank you for this summary and for taking the time to review our manuscript.

Strengths:

Major strengths of the study include the novel OPM system and the unique participant population going down to 2-year-olds. The analyses are also innovative in many respects.

Thank you – we also agree that the major strength is in the unique cohort.

Weaknesses:

Several weaknesses currently limit the impact of the study.

First, the choice of a somatosensory stimulation task over a motor task was not justified. The authors discuss the developmental motor literature throughout the introduction, but then present data from a somatosensory task, which is confusing. Of note, there is considerable literature on the development of somatosensory responses so the study could be framed with that.

We completely understand the referee's point, and we agree that the motivation for the somatosensory task was not made clear in our original manuscript.

Our choice of task was motivated completely by our targeted cohort; whilst a motor task would have been our preference, it was generally felt that making two-year-olds comply with instructions to press a button would have been a significant challenge. In addition, there

would likely have been differences in reaction times. By opting for a passive sensory stimulation we ensured compliance, and the same stimulus for all subjects. We have added text on this to our introduction as follows:

“...Here, we combine OPM-MEG with a burst analysis based on a Hidden Markov Model (HMM) 10–12 to investigate beta dynamics. We scanned a cohort of children and adults across a wide age range (upwards from 2 years old). Because of this, we implemented a passive somatosensory task which can be completed by anyone, regardless of age...”

We also state in our discussion:

“...here we chose to use passive (sensory) stimulation. This helped ensure compliance with the task in subjects of all ages and prevented confounds of e.g. reaction time, force, speed and duration of movement which would be more likely in a motor task.^{7,8} However, there are many other systems to choose and whether the findings here regarding beta bursts and the changes with age also extend to other brain networks remains an open question....”

Regarding the neurodevelopmental literature – we are aware of the literature on somatosensory evoked responses – particularly median nerve stimulation – but we can find little on the neurodevelopmental trajectory of somatosensory induced beta oscillations (the topic of our paper). We have edited our introduction as follows:

“...All these studies probed beta responses to movement execution; in the case of tactile stimulation (i.e. sensory stimulation without movement) both task induced beta power loss, and the post stimulus rebound have been consistently observed in adults^{9,13–18}. Further, beta amplitude in sensory cortex has been related to attentional processes¹⁹ and is broadly thought to carry top down influence on primary areas²⁰. However, there is less literature on how beta modulation changes with age during purely sensory tasks....”

We would be keen for the reviewer to point to any specific papers in the literature that we may have missed.

Second, the primary somatosensory response actually occurs well before the time window of interest in all of the key analyses. There is an established literature showing mechanical stimulation activates the somatosensory cortex within the first 100 ms following stimulation, with the M50 being the most robust response. The authors focus on a beta decrease (desynchronization) from 0.3-0.8 s which is obviously much later, despite the primary somatosensory response being clear in some of their spectrograms (e.g., Figure 3 in older children and adults). This response appears to exhibit a robust developmental effect in these spectrograms so it is unclear why the authors did not examine it. This raises a second point; to my knowledge, the beta decrease following stimulation has not been widely studied and its function is unknown. The maps in Figure 3 suggest that the response is anterior to the somatosensory cortex and perhaps even anterior to the motor cortex. Since the goal of the study is to demonstrate the developmental trajectory of well-known neural responses using an OPM system, should the authors not focus on the best-understood responses (i.e., the primary somatosensory response that occurs from 0.0-0.3 s)?

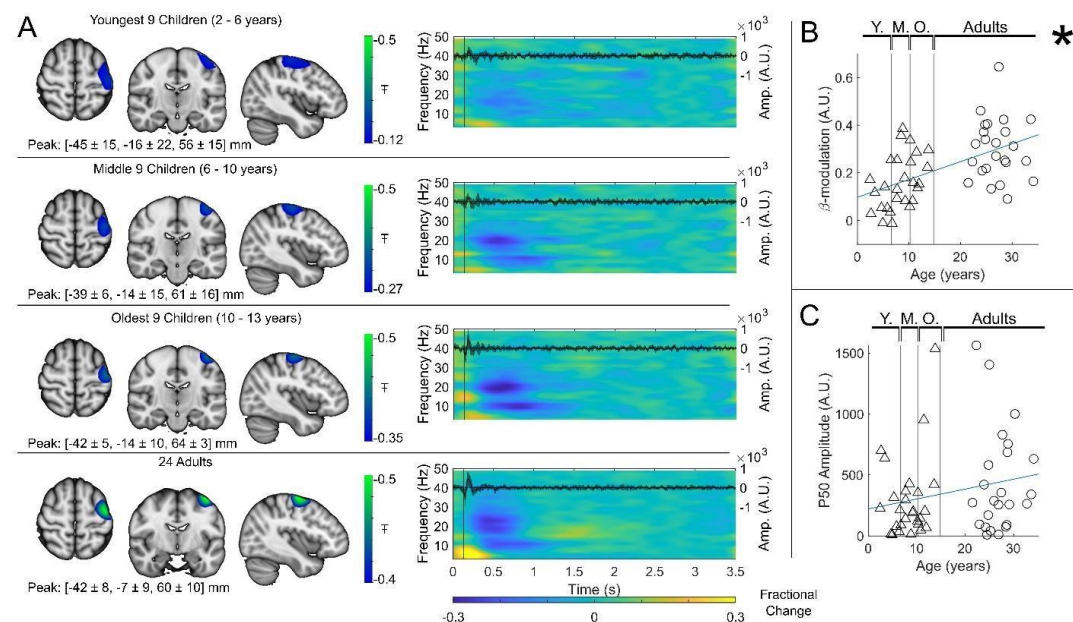
We understand the reviewer’s point. The original aim of our manuscript was to investigate the neurodevelopmental trajectory of beta oscillations, not the evoked response. In fact, the evoked response in this paradigm is complicated by the fact that there are three stimuli in a very short (<500 ms) time window. For this reason, we prefer the focus of our paper to remain on oscillations.

Nevertheless, we agree that not including the evoked responses was a missed opportunity. We have now added evoked responses to our analysis pipeline and manuscript. As surmised by

the reviewer, the M50 shows neurodevelopmental changes (an increase with age). Our methods section has been updated accordingly and Figure 3 has been modified. The figure and caption are copied below for the convenience of the reviewer.

Author response image 3.

Beta band modulation with age: (A) Brain plots show slices through the left motor cortex, with a pseudo-T-statistical map of beta modulation (blue/green) overlaid on the standard brain. Peak MNI coordinates are indicated for each subgroup. Time frequency spectrograms show modulation of the amplitude of neural oscillations (fractional change in spectral amplitude relative to the baseline measured in the 2.5-3 s window). Vertical lines indicate the time of the first braille stimulus. In all cases results were extracted from the location of peak beta desynchronisation (in the left sensorimotor cortex). Note the clear beta amplitude reduction during stimulation. The inset line plots show the 4-40 Hz trial averaged phase-locked evoked response, with the expected prominent deflections around 20 and 50 ms. (B) Maximum difference in beta-band amplitude (0.3-0.8 s window vs 1-1.5 s window) plotted as a function of age (i.e., each data point shows a different participant; triangles represent children, circles represent adults). Note significant correlation ($R^2 = 0.29$, $p = 0.00004$ *). (C) Amplitude of the P50 component of the evoked response plotted against age. There was no significant correlation ($R^2 = 0.04$, $p = 0.14$). All data here relate to the index finger stimulation; similar results are available for the little finger stimulation in Supplementary Information Section 1.



Regarding the developmental effects, the authors appear to compute a modulation index that contrasts the peak beta window (.3 to .8) to a later 1.0-1.5 s window where a rebound is present in older adults. This is problematic for several reasons. First, it prevents the origin of the developmental effect from being discerned, as a difference in the beta decrease following stimulation is confounded with the beta rebound that occurs later. A developmental effect in either of these responses could be driving the effect. From Figure 3, it visually appears that the much later rebound response is driving the developmental effect and not the beta decrease that is the primary focus of the study. Second, these time windows are a concern because a different time window was used to derive the peak voxel used in these analyses. From the methods, it appears the image was derived using the .3-.8 window versus a baseline of 2.5-3.0 s. How do the authors

know that the peak would be the same in this other time window (0.3-0.8 vs. 1.0-1.5)? Given the confound mentioned above, I would recommend that the authors contrast each of their windows (0.3-0.8 and 1.0-1.5) with the 2.5-3.0 window to compute independent modulation indices. This would enable them to identify which of the two windows (beta decrease from 0.3-0.8 s or the increase from 1.0-1.5 s) exhibited a developmental effect. Also, for clarity, the authors should write out the equation that they used to compute the modulation index. The direction of the difference (positive vs. negative) is not always clear.

We completely understand the referee's point; referee 1 made a similar point. In fact, there are two limitations of our paradigm regarding the measurement of PMBR versus the task-induced beta decrease:

Firstly, sensory tasks generally do not induce as strong a PMBR as motor tasks and with this in mind a stronger rebound response could have been elicited using a button press. However, as described above it was our intention to scan children down to age 2 and we were sceptical that the youngest children would carry out a button press as instructed.

The second limitation relates to trial length. Multiple studies have shown that the PMBR can last over ~10 s^{7,8}. Indeed, Pfurtscheller et al. argued in 1999 that it was necessary to leave 10 s between movements to allow the PMBR to return to a true baseline⁹ Here, we wanted to keep recordings relatively short for the younger participants, and so we adopted a short trial duration. However, a consequence of this short trial length is that it becomes impossible to access the PMBR directly because the PMBR of the *n*th trial is still ongoing when the (*n*+1)th trial begins. Because of this, there is no genuine rest period, and so the stimulus induced beta decrease and subsequent rebound cannot be disentangled. This limitation has now been made clear in our discussion as follows:

"...this was the first study of its kind using OPM-MEG, and consequently aspects of the study design could have been improved. Firstly, the task was designed for children; it was kept short while maximising the number of trials (to maximise signal to noise ratio). However, the classical view of beta modulation includes a PMBR which takes ~10 s to reach baseline following task cessation⁷⁻⁹. Our short trial duration therefore doesn't allow the rebound to return to baseline between trials, and so conflates PMBR with rest. Consequently, we cannot differentiate the neural generators of the task induced beta power decrease and the PMBR; whilst this helped ensure a short, child friendly task, future studies should aim to use longer rest windows to independently assess which of the two processes is driving age related changes..."

To clarify our method of calculating the modulation index, we have added the following statement to the methods:

"The beta modulation index (β_{mod}) was calculated using the equation

$\beta_{mod} = (\beta_{Post} - \beta_{Stim}) / \beta_{Baseline}$, where β_{Stim} , β_{Post} , and $\beta_{Baseline}$ are the average

Hilbert-envelope-derived amplitudes in the stimulus (0.3-0.8s), post-stimulus (1-1.5s) and baseline (2.5-3s) windows, respectively."

Another complication of using a somatosensory task is that the literature on bursting is much more limited and it is unclear what the expectations would be. Overall, the burst probability appears to be relatively flat across the trial, except that there is a sharp decrease during the beta decrease (.3-.8 s). This matches the conventional trial-averaging

analysis, which is good to see. However, how the bursting observed here relates to the motor literature and the PMBR versus beta ERD is unclear.

Again, we agree completely; a motor task would have better framed the study in the context of existing burst literature – but as mentioned above, making 2-year-olds comply with the instructions for a motor task would have been difficult. Interestingly in a recent paper, Rayson et al. used EEG to investigate burst activity in infants (9 and 12 months) and adults during observed movement execution, with results showing stimulus induced decrease in beta burst rate at all ages, with the largest effects in adults²¹. This paper was not yet published when we submitted our article but does help us to frame our burst results since there is strong agreement between their study and ours. We now mention this study in both our introduction and discussion.

Another weakness is that all participants completed 42 trials, but 19% of the trials were excluded in children and 9% were excluded in adults. The number of trials is proportional to the signal-to-noise ratio. Thus, the developmental differences observed in response amplitude could reflect differences in the number of trials that went into the final analyses.

This is an important observation and we thank the reviewer for raising the issue. We have now re-analysed all of our data, removing trials in the adults such that the overall number of trials was the same as for the children. All effects with age remained significant. We chose to keep the Figures in the main manuscript with all good trials (as previously) and present the additional analyses (with matched trial numbers) in supplementary information. However, if the reviewer feels strongly, we could do it the other way around (there is very little difference between the results).

Reviewer #3 (Public Review):

This study demonstrated the application of OPM-MEG in neurodevelopment studies of somatosensory beta oscillations and connections with children as young as 2 years old. It provides a new functional neuroimaging method that has a high spatial-temporal resolution as well as being wearable which makes it a new useful tool for studies in young children. They have constructed a 192-channel wearable OPM-MEG system that includes field compensation coils which allow free head movement scanning with a relatively high ratio of usable trials. Beta band oscillations during somatosensory tasks are well localized and the modulation with age is found in the amplitude, connectivity, and panspectral burst probability. It is demonstrated that the wearable OPM-MEG could be used in children as a quite practical and easy-to-deploy neuroimaging method with performance as good as conventional MEG. With both good spatial (several millimeters) and temporal (milliseconds) resolution, it provides a novel and powerful technology for neurodevelopment research and clinical applications not limited to somatosensory areas.

We thank the reviewer for their summary, and their time in reviewing our manuscript.

The conclusions of this paper are mostly well supported by data acquired under the proper method. However, some aspects of data analysis need to be improved and extended.

(1) The colour bars selected for the pseudo-T-static pictures of beta modulation in Figures 2 and 3, which are blue/black and red/black, are not easily distinguished from the anatomical images which are grey-scale. A colour bar without black/white would make these figures better. The peak point locations are also suggested to be marked in Figure 2 and averaged locations in Figure 3 with an error bar.

Thank you for this comment which we certainly agree with. The colour scheme used has now been changed to avoid black. We have also added peak locations.

(2) The data points in plots are not constant across figures. In Figures 3 and 5, they are classified into triangles and circles for children and adults, but all are circles in Figures 4 and 6.

Thank you! We apologise for the confusion. Data points are now consistent across plots.

(3) Although MEG is much less susceptible to conductivity inhomogeneity of the head than EEG, the forward modelling may still be impacted by the small head profile. Add more information about source localization accuracy and stability across ages or head size.

This is an excellent point. We have added to our discussion relating to the accuracy of the forward model.

“...We failed to see a significant difference in the spatial location of the cortical representations of the index and little finger; there are three potential reasons for this. First, the system was not designed to look for such a difference – sensors were sparsely distributed to achieve whole head coverage (rather than packed over sensory cortex to achieve the best spatial resolution in one area²²). Second, our “pseudo-MRI” approach to head modelling (see Methods) is less accurate than acquisition of participantspecific MRIs, and so may mask subtle spatial differences. Third, we used a relatively straightforward technique for modelling magnetic fields generated by the brain (a single shell forward model). Although MEG is much less susceptible to conductivity inhomogeneity of the head than EEG, the forward model may still be impacted by the small head profile. This may diminish spatial resolution and future studies might look to implement more complex models based on e.g. finite element modelling²³. Finally, previous work ²⁴ suggested that, for a motor paradigm in adults, only the beta rebound, and not the power reduction during stimulation, mapped motortopically. This may also be the case for purely sensory stimulation. Nevertheless, it remains the case that by placing sensors closer to the scalp, OPM-MEG should offer improved spatial resolution in children and adults; this should be the topic of future work...”

Recommendations for the authors:

Reviewer #2 (Recommendations For The Authors):

Major items to further test include the differing number of trials, the windowing issue, and the focus on motor findings in the intro and discussion. First, I would recommend the authors adjust the number of trials in adults to equate them between groups; this will make their developmental effects easier to interpret.

Thank you for raising this important point. This has now been done and appears in our supplementary information as discussed above.

Second, to discern which responses are exhibiting developmental effects, the authors need to contrast the 0.3-0.8 window with the later window (2.5-3.0), not the window that appears to have the PMBR-like response. This artificially accentuates the response. I also think they should image the 1.0-1.5 vs 2.5-3.0s window to determine whether the response in this time window is in the same location as the decrease and then contrast this for beta differences.

We completely understand this point, which relates to separating the reduction in beta amplitude during stimulation and the rebound post stimulation. However, as explained above, doing so unambiguously would require the use of much longer trials. Here we were only able to measure stimulus induced beta modulation (distinct from the separate contributions of the task induced beta power reduction and rebound). It may be that future studies, with >10 s trial length, could probe the role of the PMBR, but such studies require long paradigms which are challenging to implement with children.

Third, changing the framing of the study to highlight the somatosensory developmental literature would also be an improvement.

We have added to our introduction a stated in the responses above.

Finally, the connectivity analysis on data from a somatosensory task did not make sense given the focus of the study and should be removed in my opinion. It is very difficult to interpret given past studies used resting state data and one would expect the networks to dynamically change during different parts of the current task (i.e., stimulation versus baseline).

We appreciate the point regarding connectivity. However, it was our intention to examine the developmental trajectory of beta oscillations, and a major role of beta oscillations is in mediating connectivity. It is true that most studies are conducted in the resting state (or more recently – particularly in children – during movie watching). The fact that we had a sensory task running is a confound; nevertheless, the connectivity we derived in adults bears a marked similarity to that from previous papers (e.g. 25) and we do see significant changes with age. We therefore believe this to be an important addition to the paper and we would prefer to keep it.

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