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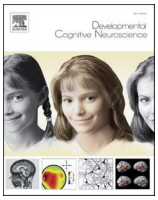

Testosterone levels mediate the dynamics of motor oscillatory coding and behavior in developing youth

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ABSTRACT

Recent investigations have studied the development of motor-related oscillatory responses to delineate maturational changes from childhood to young adulthood. While these studies included youth during the pubertal transition period, none have probed the impact of testosterone levels on motor cortical dynamics and performance. We collected salivary testosterone samples and recorded magnetoencephalography during a complex motor sequencing task in 58 youth aged 9–15 years old. The relationships between testosterone, age, task behavior, and beta (15–23 Hz) oscillatory dynamics were examined using multiple mediation modeling. We found that testosterone mediated the effect of age on movement-related beta activity. We also found that the effect of age on movement duration was mediated by testosterone and reaction time. Interestingly, the relationships between testosterone and motor performance were not mediated by beta activity in the left primary motor cortex, which may indicate the importance of higher-order motor regions. Overall, our results suggest that testosterone has unique associations with neural and behavioral indices of complex motor performance, beyond those already characterized in the literature. These findings are the first to link developmental changes in testosterone levels to maturation of beta oscillatory dynamics serving complex motor planning and execution, and specific measures of motor performance.

1. Introduction

Movement is paramount to daily life and is needed for tasks such as securing food for nutrients and escaping dangerous environments. Motor coordination occurs at the level of the motor cortex (Georgopoulos and Carpenter, 2015), where movement kinematics are converted into specific plans for carrying out voluntary movements (Spooner et al., 2021). Populations of neurons exhibit beta frequency (e.g., 15–30 Hz) oscillatory activity, which supports the planning and execution of these voluntary movements. Hundreds of milliseconds before a movement is initiated there is a strong decrease in beta power, which is generally sustained through the duration of the movement (Gehringer et al., 2019; Heinrichs-Graham et al., 2016, 2017, 2018, 2020; Trevarrow et al., 2019; Wilson et al., 2010). Studies show that this peri-movement beta event-related-desynchronization (beta ERD) is associated with movement complexity (Heinrichs-Graham and Wilson, 2015), the certainty of the movement to be made (Heinrichs-Graham et al., 2016; Tzagarakis et al., 2010), and chronological age (Heinrichs-Graham et al., 2018, 2020; Heinrichs-Graham and Wilson, 2016; Trevarrow et al., 2019; Wilson et al., 2010).

In studies regarding chronological age, older adults exhibit significantly stronger beta ERD responses than younger adults in the

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contralateral primary motor cortices during a motor sequencing task (Heinrichs-Graham and Wilson, 2016), with a later study suggesting that this effect follows a linear trajectory from around age nine years to over 70 years-old (Heinrichs-Graham et al., 2018). Using a developmental sample of youth between eight and 15 years of age, a study focusing on single flexion-extension movements found that age was positively correlated with peri-movement beta ERD in the right supplementary motor area, left cerebellum, and other regions of the motor network (Wilson et al., 2010). Lastly, results from a recent developmental investigation showed that chronological age significantly predicts the beta ERD associated with motor planning in parietal cortices, which was positively associated with execution-related beta ERD and negatively associated with movement duration (Heinrichs-Graham et al., 2020). Altogether these studies point to a multidimensional relationship between age and beta ERD activity across an extended motor network, with findings dependent on the age range being examined.

Although these studies have improved our understanding of motor oscillations during development, with clear associations between age, oscillatory activity, and behavior, many questions remain about the underlying developmental mechanisms and processes. For example, whether these maturational alterations are closely linked to the cascade of hormonal changes that occur during the pubertal transition is poorly understood, and such knowledge could provide greater insight about the nuanced developmental progression of motor behavior. Testosterone, in particular, surges in males and females during the pubertal transition years and studies have shown that this increase affects neural networks that impact behavior in addition to its effects on physical maturity (Bramen et al., 2012; Goddings et al., 2019). Work in animal models has shown that perinatal testosterone levels impact motor circuits within the adult cerebral cortex (Venkatesan and Kritzer, 1999), but most human studies of pubertal testosterone have mainly focused on its effect on higher-order cognitive processes like reward and emotional processing (Braams et al., 2015; Op De Macks et al., 2011). Two recent studies have shown testosterone and dehydroepiandrosterone (DHEA) exhibit sex and region-specific effects on oscillatory activity serving visuospatial processing (Fung et al., 2020, 2022a), while a third has shown that DHEA modulates resting-state spontaneous activity during this same developmental period (Penhale et al., 2022). Most recently, Fung and colleagues examined the relationship between endogenous testosterone levels and motor responses during a visual stimulus detection task (Fung et al., 2022b). Their modeling results indicated that testosterone was directly and indirectly related to both spontaneous beta levels during the pre-movement baseline and the strength of the beta ERD response during movement. Importantly, given the task design (i.e., stimulus detection), reaction time was the only behavioral metric of interest in the Fung et al. (2022b) study and was not included in their mediation models.

Despite mounting evidence that testosterone impacts neural oscillatory dynamics across distributed cognitive and sensory systems, the role of testosterone on the maturation of cortical dynamics serving motor control has not been widely examined. Thus, in the present study, we sought to characterize the specific effects of endogenous testosterone levels on the development of peri-movement beta ERD responses serving the planning and execution of motor sequences in typically developing youths. We chose to use a more complex motor sequencing paradigm compared to previous studies (e.g., Fung et al., 2022b) to have multiple behavioral output metrics, which could aid in understanding beta ERD development. Our main hypothesis was that testosterone would exert effects on the beta ERD in cortical regions supporting both motor planning and execution, as a mediator of the developmental effects of age.

2. Materials and methods

2.1. Participants

A total of 68 participants between the ages of 9- and 16-years-old ($M = 13.08$ years, $SD = 1.66$; 33 males; 4 left-handed) were recruited from the community, as part of the Developmental Chronnecto-Genomics (Dev-CoG) study (Stephen et al., 2021). The MEG data used herein has not been previously reported and was collected at the Omaha site of the Dev-CoG study, although note that the sample of typically developing youth overlaps with those who completed the stimulus detection task reported in Fung et al. (2022b) by over 90 %. Further, note that this investigation only uses data from the subset of Dev-CoG youths who provided saliva samples for hormone quantification. Participants were all typically developing primary English speakers and did not have diagnosed psychiatric or neurological conditions, previous head trauma, learning disability, or non-removable ferromagnetic material. After a complete description of the study was given to participants, written informed assent/consent was obtained from the child/child's parent or legal guardian, respectively. All procedures were completed at the University of Nebraska Medical Center (UNMC) and approved by the UNMC Institutional Review Board (IRB).

2.2. Salivary testosterone collection and measurement

At least 2.0 mL of whole unstimulated saliva was collected from each participant. Specifically, children were asked to passively drool into an Oragene DISCOVER (OGR-500; www.dnagenotek.com) collection tube until liquid saliva (not bubble) exceeded the fill line indicated on the tube. A single-channel pipette was then used to extract 0.5 mL from the collection tube (prior to the release of the protease inhibitors for long-term storage), and this 0.5 mL was immediately transferred into a labeled micro-centrifuge tube and placed in a − 20 °C freezer for storage. Participants were instructed to refrain from consuming any food, liquids, or chewing gum for at least an hour before providing the saliva sample, and generally completed the study in the afternoon (15:45, SD = 3.23 h). All samples were assayed in duplicate using a commercially available assay kit for salivary testosterone (Salimetrics; www.salimetrics.com) at the University of Nebraska Lincoln Salivary Biosciences Lab. The assay kit had a sensitivity of 1 pg/mL, with a range of 6.1–600 pg/mL. The intra- and inter-assay coefficients of variation were 5.28 % and 8.93 %, respectively. The average of the duplicate tests was used for further analyses in the present study. Testosterone levels across our sample were not normally distributed, thus these data were log-transformed.

2.3. Task paradigm

Participants sat in a nonmagnetic chair within a magnetically shielded room during MEG recording. Participants rested their right hand on a custom five-finger button response pad while fixating on a centrally presented crosshair. The response pad was directly connected to the MEG system so that each button press sent a TTL pulse to the acquisition computer in real-time, enabling behavioral responses to be temporally synced with the MEG data. Accuracy, reaction time, and movement duration (in ms) were computed offline. Following an initial baseline period of 3.75 s, an array of three black numbers (1–4), each corresponding to a finger on the right hand, was presented for 0.5 s. After 0.5 s, the set of numbers changed color, signaling the participant to complete the motor sequence by pressing the corresponding buttons as quickly and accurately as possible. The participant was allowed 2.25 s to execute the motor plan and return to rest. An example of one trial is shown in Fig. 1. A total of 160 trials were completed, making the overall MEG recording time about 16 min for the task. Visual stimuli were presented using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and back-projected onto a semi-translucent

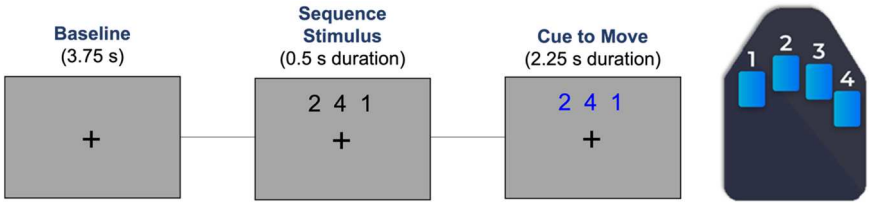

Fig. 1. Participants fixated on a crosshair for 3.75 s before trial onset. Following this baseline period, a series of three numbers appeared on the screen for 0.5 s, after which they turned blue. Participants responded with their right hand using the fingers corresponding to the numbers presented on the screen as quickly and accurately as possible.

nonmagnetic screen at an approximate distance of 1.07 m, using a Panasonic PT-D7700U-K model DLP projector with a refresh rate of 60 Hz and a contrast ratio of 4000:1 (see McCusker et al., 2021, for further description).

2.4. MEG data acquisition

All MEG recordings were conducted in a one-layer magnetically shielded room with active shielding engaged. Neuromagnetic responses were sampled continuously at 1 kHz with an acquisition bandwidth of 0.1–330 Hz using an MEG system with 306 magnetic sensors (MEGIN, Helsinki, Finland). MEG data from each subject were individually corrected for head motion (MaxFilter v2.2; MEGIN) and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu and Simola, 2006; Taulu et al., 2005). The individual's head position throughout the recording was aligned to their head position at the beginning of the recording.

2.5. Structural MRI data acquisition and MEG co-registration

A 3 T Siemens Prisma scanner equipped with a 32-channel head coil was used to collect high-resolution structural T1-weighted MRI data from each participant (TR: 24.0 ms; TE: 1.96 ms: field of view: 256 mm; slice thickness: 1 mm with no gap; in-plane resolution: 1.0 × 1.0 mm). Structural volumes were aligned parallel to the anterior and posterior commissures and transformed into standardized space. Each participant's MEG data were co-registered with their MRI data using BESA MRI (Version 2.0). After source imaging (beamformer), each subject's functional images were also transformed into standardized space using the transform previously applied to the structural MRI volume, and spatially resampled.

2.6. MEG time-frequency decomposition and statistical analysis

Cardiac and ocular artifacts were visually inspected and removed from the data using signal-space projection, which was accounted for during source reconstruction (Uusitalo and Ilmoniemi, 1997). The continuous magnetic time series was divided into 6.4 s epochs, with movement onset (i.e., first button press) defined as 0.0 s and the baseline defined as the − 2.25 to − 1.75 s time window (i.e., before movement onset; Fig. 1). Only correct trials were used for analysis. Epochs containing artifacts were rejected based on a fixed threshold method, which was supplemented with visual inspection. Briefly, the distributions of amplitude and gradient values per participant were computed using all trials, and the highest amplitude/gradient trials relative to the total distribution were excluded. Notably, individual thresholds were set for each participant for both signal amplitude ($M = 1656.51$ fT, $SD = 566.34$) and gradient ($M = 574.90$ fT/s, $SD = 320.38$) due to differences among individuals in head size and sensor proximity, which strongly affect MEG signal amplitude. Following artifact rejection, an average of 122.06 (SD: 11.66) trials per participant remained for further analysis. We tested whether the number of accepted trials was associated with age and testosterone and found that neither age ($r = 0.14$, $p = .31$) nor testosterone ($r = 0.16$, $p = .26$) were significantly correlated with the total number of trials retained. Additionally, the number of accepted trials did not differ between sexes ($t = -.32$, $p = .75$).

Artifact-free epochs were then transformed into the time-frequency domain using complex demodulation using a resolution of 1.0 Hz and 50 ms (Kovach and Gander, 2016; Papp and Ktonas, 1977). The single-trial data was subject to a discrete Fourier decomposition to determine the signal power in each 1 Hz frequency bin in overlapping 50 ms time windows for the length of each epoch. The resulting spectral power estimations per sensor were averaged over trials to generate time-frequency plots of mean spectral density. These sensor-level data were normalized per frequency bin using the mean power during the − 2.25 to − 1.75 s baseline period. The specific time-frequency windows used for imaging were determined by statistical analysis of the sensor-level spectrograms across the entire array of gradiometers. Each data point in the spectrogram was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false-positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired-samples t-tests against baseline were conducted on each data point and the output spectrogram of t-values was threshold at $p < .05$ to define time-frequency bins containing potentially significant oscillatory deviations across all participants. In stage two, time-frequency bins that survived the threshold were clustered with temporally and/or spectrally neighboring bins that were also below the ($p < .05$) threshold, and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values, and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Ernst, 2004; Maris and Oostenveld, 2007). For each comparison, 10,000 permutations were computed to build a distribution of cluster values. Based on these analyses, time-frequency windows that corresponded to events of a priori interest (i.e., the peri-movement beta ERD) and contained a significant oscillatory event based on permutation testing were subjected to the beamforming analysis.

2.7. MEG source imaging and statistics

Cortical oscillatory activity was imaged through an extension of the linearly constrained minimum variance vector beamformer (Gross et al., 2001; Hillebrand et al., 2005) using the Brain Electrical Source Analysis (BESA 7.0) software. This approach, commonly referred to as DICS or dynamic imaging of coherent sources, applies spatial filters to time-frequency sensor data to calculate voxel-wise source power for the entire brain volume. The single images are derived from the cross-spectral densities of all combinations of MEG gradiometers averaged over the time-frequency range of interest, and the solution of the forward problem for each location on a 4.0 × 4.0 × 4.0 mm grid specified by input voxel space. Following convention, we computed noise-normalized, source power per voxel in each participant using active (i.e., task) and passive (i.e., baseline) periods of equal duration and bandwidth. Such images are typically referred to as pseudo-*t* maps,

with units (pseudo-*t*) that reflect noise-normalized power differences (i.e., active vs. passive) per voxel. This generated participant-level pseudo-*t* maps for each time-frequency-specific response identified in the sensor-level permutation analysis, which was then transformed into standardized space using the transform previously applied to the structural MRI volume and spatially resampled. We computed grand-average maps across all participants for each time-frequency window of interest (motor planning, motor execution). These grand-average maps were used to discern the spatial origin of each response and to extract peak voxel values per time bin (i.e., planning and execution) and participant. These values were then used in further statistical analyses to examine their relationship to testosterone, age, and behavioral parameters (e.g., reaction time and movement duration).

Our primary hypothesis was that age would predict testosterone levels, and testosterone levels would predict neural dynamics and motor behavior during planning and execution. Specifically, we tested a multiple mediation model whereby age predicted testosterone, and testosterone and age predicted beta oscillatory activity in the left primary motor cortex during motor planning. Such beta oscillatory activity during motor planning, along with testosterone and age, then predicted both reaction time and beta oscillatory activity during motor execution. Age, testosterone, and all variables during planning and execution then predicted movement duration (i.e., time to completion). Given the known sex-based differences in testosterone and neural development, we also tested a more complex model for potential interactive sex effects but there were no significant differences between groups and the parameters for this more complex model suggested a less robust, more poorly fit model. Additionally, we tested a model controlling for the effects of sex, but model fit statistics did not significantly improve. Thus, the simplified model that collapses across sex was more parsimonious and explains the relationship between age, testosterone, and oscillatory motor dynamics equal to or better than the more complex models. Because traditional tests of indirect effects (e.g., the Sobel test) often violate the assumption of normality, we utilized asymmetrical confidence intervals which best represent the true distribution of the indirect effect (i.e., the product of coefficients from the "a" and "b" paths). Thus, we examined the 95 % confidence intervals of bias-corrected bootstrapped confidence intervals based on 1000 bootstrapped samples, which provide a robust estimate of mediation effects and are asymmetrical (Austin and Tu, 2004; Efron and Tibshirani, 1986; Fritz and Mackinnon, 2007).

We examined the goodness of fit for each model using standard criteria (Hu and Bentler, 1999). Specifically, we evaluated models for the root mean square error of approximation (RMSEA) $< .06$, and comparative fit index (CFI) $> .95$. We also examined the χ^2 test of model fit, where a nonsignificant result indicates good model fit. In addition, model fit comparisons were inspected, including absolute fit indices such as Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). To determine model fit improvement, we primarily relied on an AIC or BIC difference of 10 points or more, between the old and new models. Mediation analyses were conducted in Mplus version 8.1.

3. Results

3.1. Demographic and behavioral results

Of the 68 participants who completed the task, we excluded one for testosterone levels higher than 3 SD above the overall mean, seven for low accuracy (< 50 %), and two for MEG artifacts. Therefore, the final sample used for analysis consisted of 58 participants ($M = 13.20$ years, $SD = 1.57$; 29 males; 4 left-handed; Table 1). There were no differences in chronological age by sex ($p = .48$). As expected, chronological age was positively correlated with log-transformed testosterone levels across the whole sample ($r = .52$, $p < .001$), such that older youth tended to have higher levels of testosterone. Testosterone levels did not differ by sex in either transformed ($p = .19$) or untransformed testosterone ($p = .23$; Table 1; Fig. 2). Average accuracy on the motor sequencing tasks was 74.5 % ($SD = 8.6$ %), average reaction time was 605.01 ms ($SD = 161.90$ ms), and the average movement duration was 846.40 ms ($SD = 165.98$ ms). An independent samples t-test showed males and females differed significantly in reaction time ($t = -2.36$, $p < .05$) and movement duration ($t = -4.08$, $p < .001$), but not on accuracy ($p = .75$; Fig. 2).

3.2. MEG sensor-level oscillatory responses

We statistically examined sensor-level time-frequency spectrograms to determine the time-frequency bins for imaging. Significant beta ERD (17–23 Hz) responses were found before and after the initial button response across gradiometers near the sensorimotor cortex, extending from 0.5 s before movement onset until 0.75 s after movement (Fig. 3; $p < 0.0001$, permutation corrected). To distinguish between motor planning and motor execution-related beta activity, the significant beta ERD response period was divided into two temporally distinct 17–23 Hz windows. Motor planning (− 0.4 to 0.0 s) and motor execution (0.0–0.4 s) were independently imaged in each participant using a baseline period of − 2.15 s to − 1.75 s. The resulting images were first averaged in each participant across both planning and execution periods and then grand-averaged across all participants to determine the peak motor-related beta ERD responses induced by the task. This yielded two distinct peaks within the left and right primary motor cortices, and follow-up analyses showed that these peak voxels were the same in the grand-averaged planning and execution maps (Fig. 3). The peak voxel values (pseudo-*t*) were then extracted from the left primary motor cortex per time bin (i.e., planning and execution) and utilized for further statistical analysis.

3.3. Full model results of the effects of age and testosterone on motor network dynamics

Next, we tested a multiple mediation model (Fig. 4) in which age

Table 1
Demographic and behavioral data for the sample.

	Full sample		Females		Males			
Variable	Mean (SD)	Range	Mean (SD)	Range	Mean	Range	t	p
Age	13.20 (1.57)	9–16	13.05 (1.43)	10–16	13.34 (1.70)	9–16	0.71	.48
Testosterone	39.02 (27.99)	4–118	34.60 (27.52)	4–118	43.45 (28.23)	5–109	1.21	.23
Testosterone (log)	1.47 (0.36)	0.63–2.07	1.40 (0.37)	0.63–2.07	1.53 (0.35)	0.69–2.04	1.32	.19
Accuracy (%)	74.50 (8.64)	51–88	74.90 (9.40)	51–88	74.14 (8.00)	53–74	− 0.32	.75
Reaction Time	605.01 (161.90)	269–988	653.36 (170.26)	362–988	556.66 (139.74)	269–810	− 2.36[a]	.02
Movement Duration	846.40 (165.98)	557–1264	925.18 (172.03)	655–1264	767.63 (116.77)	557–1044	− 4.08[b]	< .001

Age is measured in years, testosterone and log-transformed testosterone measured in (pg/mL), reaction time and movement duration measured in ms.
[a] $p < .05$.
[b] $p < .001$.

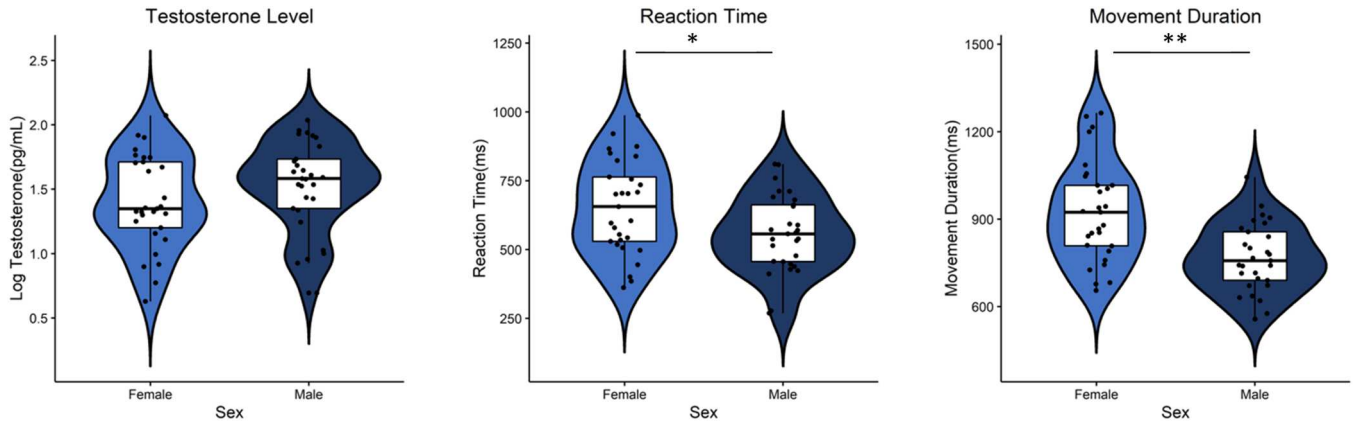

Fig. 2. (Left) Average log-transformed testosterone levels (pg/mL) did not significantly differ between males and females. (Middle) Reaction time significantly differed between males and females, such that males responded more quickly than females. (Right) Movement duration significantly differed between males and females, with females having a longer average movement duration than males. *$p < .05$, **$p < .001$.

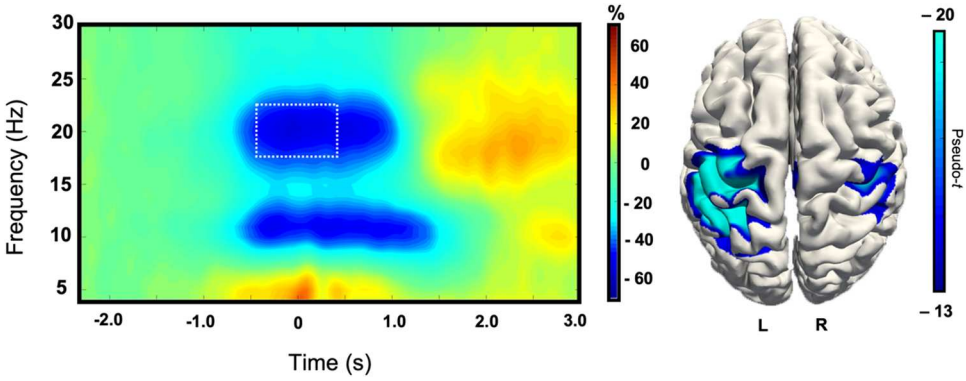

Fig. 3. (Left) Grand-averaged time-frequency spectrogram taken from a representative sensor near the left motor cortex. Time is denoted on the x-axis (0.0 s = movement onset) and frequency (Hz) is shown on the y-axis. The time-frequency windows used for subsequent beamforming are denoted by the dashed white box. The spectrogram is shown in percent power change from baseline, with the color scale shown to the right of the spectrogram. (Right) Grand-averaged beamformer image of beta ERD activity (17–23 Hz, − 0.40 to 0.40 s), with the scale bar (pseudo-*t* units) shown to the right.

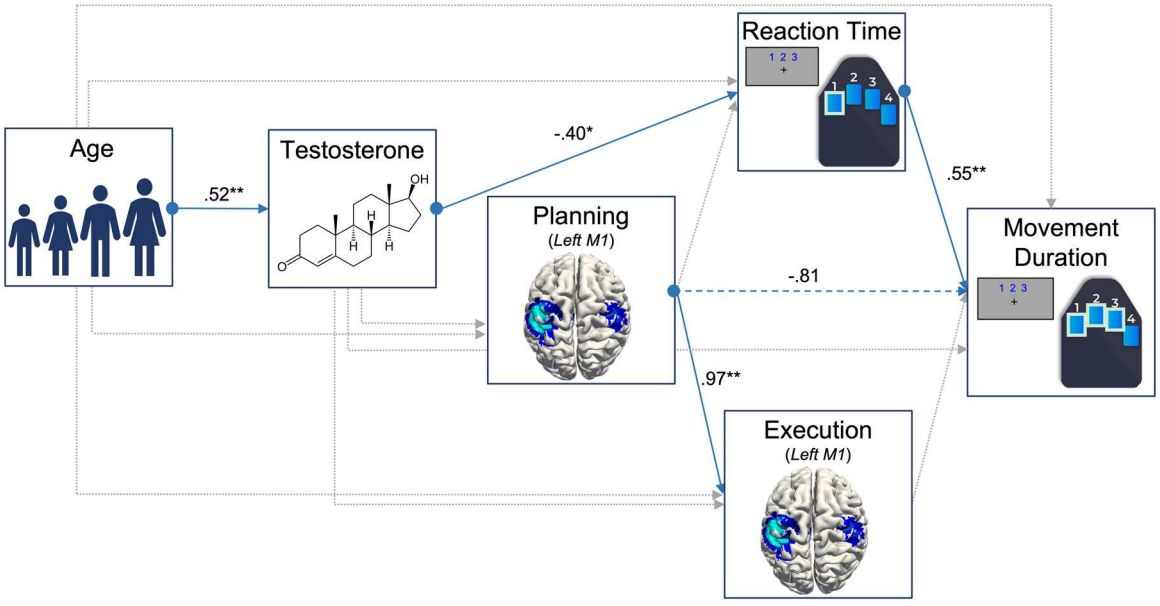

Fig. 4. Full mediation model tested. Age measured in years (to two decimal places) and log-transformed testosterone measured in pg/mL were included in the model. Motor planning (− 0.4 to 0.0 s) and execution (0.0–0.4 s) variables were in pseudo-*t* units extracted from the peak response, which was within the left primary motor cortex. Reaction time and movement duration were measured in ms. Solid blue lines indicate significant effects, dashed blue lines indicate effects trending towards significance. Dashed grey lines indicate non-statistically significant effects. *$p < .05$; **$p < .001$.

predicted testosterone levels, and both age and testosterone levels were used to predict the strength of the beta ERD response in the left primary motor cortex during the planning period (− 0.4 to 0.0). The planning period beta ERD, testosterone, and age were used to predict beta oscillatory activity in the left primary motor cortex during the execution period (0.0–0.4 s), as well as reaction time. Finally, all previous variables were used to predict movement duration (i.e., time that it took to complete the sequence of button presses). Of note, the beta ERD power values (pseudo-*t* units) were extracted from the left primary motor cortex for the planning (− 0.4 to 0.0 s) and execution (0.0–0.4 s) periods.

Testing the full model, which was a good fit to the data, $\chi^2(1) = 0.82$, $p = .36$; RMSEA = 0.0, 95 % CI [.00,.34]; CFI = 1.00; SRMR = .01, we found several statistically significant direct effects (Fig. 4). Age significantly predicted testosterone levels, such that older participants had higher levels of testosterone ($\beta = .52$, $p < .001$). Testosterone significantly predicted reaction time ($\beta = -.40$, $p < .05$), such that youth with higher testosterone levels were quicker to respond to the stimulus. Planning-related beta ERD responses in the left primary motor cortex significantly predicted execution-related beta ERD activity in the same tissue ($\beta = .97$, $p < .001$), such that stronger beta oscillations during the planning period were associated with stronger beta oscillations during the execution period. Lastly, there was a significantly positive relationship between reaction time and movement duration ($\beta = .55$, $p < .001$), such that faster reaction times were associated with shorter movement durations. A complete summary of all model effects can be found in Table 2.

3.4. Mediating effects of testosterone on motor network dynamics and behavior

While testosterone did not significantly predict motor execution directly ($\beta = -.06$, $p = .10$), it did significantly mediate the relationship between age and execution-related beta ERD in the left primary motor cortex ($\beta = -.03$, b = − 0.47, 95 % CI [− 1.08, − 0.16]), such that older participants had higher levels of testosterone, which was associated with stronger execution-related beta ERD (Fig. 5). In addition, there was a significant multiple mediation ($\beta = -.12$, b = − 12.05, 95 % CI [− 26.92, − 3.63]), whereby the relationship between age and movement duration was mediated by testosterone and reaction time. Older participants had higher levels of endogenous testosterone, and this was associated with a faster reaction time and a shorter overall movement duration for completing the motor sequence. There were no other significant indirect effects.

Table 2
Full model results.

Effect tested	β	b	SE	*p*
Testosterone on				
Age	.520	.119	.096	< .001
Planning on				
Testosterone	− .028	− 1.551	.154	.858
Age	− .026	− .331	.154	.867
Execution on				
Planning	0.967	1.077	.011	< .001
Testosterone	− .062	− 3.904	.038	.100
Age	.021	.297	.037	.577
Reaction time on				
Planning	− .045	− .359	.110	.685
Testosterone	− .402	− 181.386	.122	.001
Age	− .210	− 21.695	.128	.100
Movement duration on				
Execution	.704	5.152	.419	.093
Reaction time	.549	.558	.108	< .001
Planning	− .805	− 6.560	.418	.054
Testosterone	.024	11.124	.128	.850
Age	− .123	− 12.937	.120	.303

4. Discussion

In the current study, we used endocrine and advanced neurophysiological approaches to characterize the role of age and endogenous testosterone levels in the developmental patterns of motor cortical function and behavioral performance. We observed strong direct effects of endogenous testosterone levels, such that increases in testosterone significantly predicted motor behavior. Additionally, testosterone strongly mediated the effects of age on motor-related neural oscillatory activity and resultant behavior. Regarding beta ERD strength, increased age strongly predicted increased testosterone, which predicted stronger beta ERD in the contralateral precentral gyrus (i.e., the left primary motor cortex). For motor behavior, increased age predicted increased testosterone, which subsequently predicted faster reaction times, and this significantly predicted shorter movement durations. Notably, oscillatory activity within the left primary motor cortex did not mediate the relationship between testosterone and motor-related behavior, which may indicate the involvement of critical regions outside of the precentral gyrus. Below, we discuss the implications of these findings for understanding the unique contribution of testosterone to the development of human neurophysiology and higher order motor control with increasing age.

Our findings coincide with well-established developmental patterns of stronger movement-related beta ERD in the precentral gyrus with increased age (Gaetz et al., 2010; Heinrichs-Graham et al., 2020; Heinrichs-Graham and Wilson, 2016; Rossiter et al., 2014). This is theorized to be the result of neurophysiological changes whereby increased γ-aminobutyric acid (GABA) transmission is associated with increased spontaneous beta activity within sensorimotor cortices, and a subsequent increase in beta suppression during movement (Heinrichs--Graham et al., 2018; Heinrichs-Graham and Wilson, 2016; Muthukumaraswamy et al., 2013; Spooner et al., 2018, 2019). Notably, a prior study using a simple motor task (i.e., single finger tap) in youth did not find a significant relationship between age and beta ERD strength in the contralateral precentral gyrus (Trevarrow et al., 2019). Our findings support this and extend the observation to a more complex motor sequencing task. However, when we applied a more sophisticated multiple mediation approach to this question, we found that testosterone fully mediated the effects of age on movement-related oscillatory beta power and behavior. Testosterone also had significant direct effects on behavioral outcomes, showing its unique predictive power above and beyond age. Interestingly, although males had significantly faster reaction times than females, testosterone's effect on reaction time did not differ by sex. Previous research suggests that males display advantages in motor learning, and this may be supported by puberty-related CNS changes during late adolescence. However, other studies have suggested that this may be indicative of peripheral motor performance advantages in post-adolescence (Dorfberger et al., 2009) and thus further work in this area is clearly needed. Taken together with previous research, our findings suggest that the use of neuroendocrine measures of maturation may provide improved sensitivity to detect developmental changes in beta oscillations within the primary motor cortices and behavioral performance, especially within the pubertal transition period that emerges during later childhood and often extends to mid-adolescence. Future work should examine the extended motor network, including the supplemental motor cortices, premotor, and prefrontal cortex to understand how sex differences in motor behavior emerge during puberty and whether oscillatory activity within these regions mediates the effects of testosterone on motor performance.

Only a limited number of studies have examined how testosterone levels may modulate motor processing in developmental samples. Studies of cortical thickness have shown relatively early maturation of the primary motor cortex, with cortical thinning starting to asymptote within this region around the age of nine (Giedd et al., 1999, 2006; Goddings et al., 2014; Gogtay et al., 2004). However, maturational changes in neurotransmitter levels and local circuitry within the motor

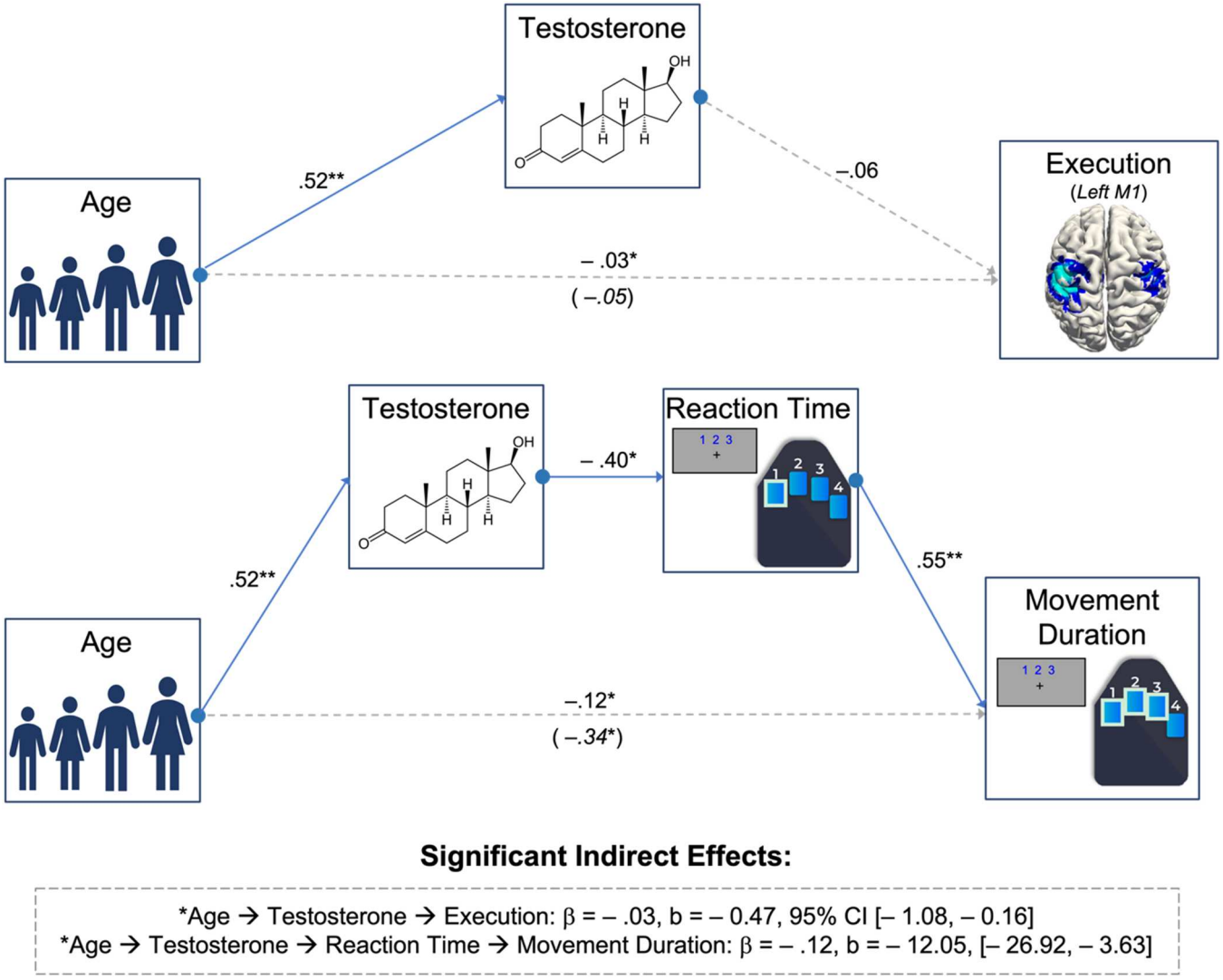

Fig. 5. Statistically significant mediating effects. Values in parentheses indicate the total effect of age on execution-related beta ERD (top), and the total effect of age on movement duration (bottom). Solid blue lines indicate significant main effects. Dashed grey lines indicate main effects. All listed parameters are standardized coefficients. $p^* < .05$; $^{**}p < .001$.

cortex likely continue, which is supported by animal work. For example, higher testosterone levels in rats is linked to greater dendritic spine density and arborization of pyramidal cells in the hippocampus, sensory and motor cortices, which are abundant with intracellular androgen receptors (Chen et al., 2013; Li et al., 2012; Stewart and Kolb, 1994), and support increased communication between neurons and coordination of information processing. Additionally, testosterone and its metabolite androstenedione have been shown to exert positive allosteric effects on GABA receptors (Aikey et al., 2002; McHenry et al., 2014; Nyby, 2008; Reddy and Jian, 2010). While a direct comparison cannot be made between animals and humans, our results suggest that increased testosterone levels affect population-level neurophysiological responses within the primary motor cortex, and that testosterone levels are tightly coupled to improvements in multiple metrics of behavioral motor performance (i.e., faster reaction time and shorter movement). Such conclusions are also consistent with a recent study that examined the relationship between motor-related oscillations and testosterone levels (Fung et al., 2022b). The sample in this study overlapped with that of the current study, but the MEG tasks used in the two studies were very different, with Fung et al. using a stimulus detection task and the current work using a motor sequencing paradigm. The more sophisticated motor sequencing task resulted in a richer group of behavioral performance metrics, which were a key part of our modeling approach. Further, this task difference enabled beta dynamics during motor planning and execution to be probed separately in the current study, whereas given the limited behavioral data Fung et al. (2022b) focused more on how testosterone modulates spontaneous activity prior to movement and whether that impacts oscillations during movement. Key conclusions of Fung et al. (2022b) were that testosterone mediated the relationship between age and both spontaneous beta levels during the baseline and beta oscillations during movement in the primary motor cortex, whereas testosterone levels did not affect movement-related theta or gamma oscillations. While the current study did not examine spontaneous beta levels or theta and gamma oscillations, we replicated the finding of testosterone mediating the effect of age on beta oscillations in the motor cortex, and importantly extended this finding to show that this effect was only present for oscillatory activity serving motor execution and not motor planning. In addition, our more sophisticated behavioral measures enabled us to determine that testosterone levels strongly mediate the impact of age on reaction time and movement duration, which had not been previously shown. Note that we did not examine theta or gamma oscillations because motor sequencing tasks are not typically associated with such responses (Heinrichs-Graham et al., 2018; Heinrichs-Graham and Wilson, 2015, 2016) and that was the case in the

current data set as well. In sum, the current work replicates key findings of Fung et al. (2022b), while also extending this work in important new ways to show the impact of testosterone on motor performance and neural dynamics.

Probably our most important finding is that while testosterone mediates the effect of age on both motor behavior and neural processing within the contralateral primary motor cortex, testosterone's effect on behavior is not mediated by neural activity within the primary motor cortex. Increased levels of testosterone mediate an inverse relationship between age and behavior, such that older participants had higher testosterone levels, which was associated with decreased reaction time and decreased movement duration. Additionally, older participants had higher testosterone levels, which was associated with stronger beta ERD within the left primary motor cortex (i.e., precentral gyrus). However, this oscillatory activity did not mediate testosterone's effect on motor behavior. One possible explanation for the lack of an oscillatory beta ERD effect on the testosterone-behavior relationship is that oscillatory activity in regions outside of the contralateral primary motor cortex may mediate testosterone's effect on motor behavior. For example, Wilson and colleagues (2010) showed that beta ERD responses during flexion-extension index finger movements were strongly correlated with age in the supplementary motor area (SMA) and cerebellar cortices, but not the primary motor cortex. They suggested that maturation in these other regions of the motor network may follow a protracted trajectory well into adolescence, and that this may underlie the effect they observed in 8- to 15-year-olds (Wilson et al., 2010). In a more recent study using a complex motor sequencing task, Heinrichs-Graham et al. (2020) showed that the motor network is quite extended, with execution-related oscillatory activity within the right parietal cortices mediating the relationship between age and motor behavior in multiple ways. Specifically, they found that age was positively associated with planning-related beta responses within the right parietal cortex, and that such activity predicted longer movement durations in typically developing youth. On the other hand, planning-related beta ERD was associated with stronger execution-related beta within the right parietal cortex, and this execution-related activity subsequently predicted shorter movement durations (Heinrichs-Graham et al., 2020). These findings, alongside our results, exemplify the sophisticated nature of the relationship between motor performance and the neural activity supporting it during this developmental period.

Regarding study limitations, future studies with larger sample sizes should be conducted to probe testosterone's role in modulating both planning and execution-related beta ERD activity within extended motor areas such as the parietal cortices, SMA, and cerebellar cortices, particularly regarding the net impact of such oscillatory activity on motor control and performance. Additionally, future work would benefit from the use of multiple, more precise measures of endogenous testosterone such as blood or hair collection. The utilization of multiple hormone measurements would provide more precision in estimating the effects of testosterone, above and beyond the effects of age. Lastly, longitudinal study designs may offer even greater precision for deriving the impact of developmental shifts in testosterone levels and the temporal link between these shifts and changes in beta ERD activity and any concomitant improvements in motor performance.

In sum, we studied the relationship between age, testosterone, and the neural oscillatory dynamics supporting motor coding and movement performance. Our study shows that higher levels of testosterone mediate a direct relationship between age and movement-related beta ERD within the contralateral primary motor cortex. Additionally, we found that higher levels of testosterone also mediate an inverse relationship between age and reaction time, with shorter reaction times having an inverse relationship between testosterone levels and movement duration. Although we were primarily interested in the effect of testosterone above and beyond age on the development of the motor network, this work strongly supports the multi-factorial nature of development in which age, biological processes, and individual experiences interact with pubertal hormones to bring about functional changes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data will be made available on request.

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Data Statement

The data used in this article will be made publicly available through the COINS framework at the completion of the study (https://coins.trendcenter.org/).

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