The impact of a lack of mathematical education on brain development and future attainment

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Formal education has a long-term impact on an individual's life. However, our knowledge of the effect of a specific lack of education, such as in mathematics, is currently poor but is highly relevant given the extant differences between countries in their educational curricula and the differences in opportunities to access education. Here we examined whether neurotransmitter concentrations in the adolescent brain could classify whether a student is lacking mathematical education. Decreased γ-aminobutyric acid (GABA) concentration within the middle frontal gyrus (MFG) successfully classified whether an adolescent studies math and was negatively associated with frontoparietal connectivity. In a second experiment, we uncovered that our findings were not due to pre-existing differences before a mathematical education ceased. Furthermore, we showed that MFG GABA not only classifies whether an adolescent is studying math or not, but it also predicts the changes in mathematical reasoning ~19 mo later. The present results extend previous work in animals that has emphasized the role of GABA neurotransmission in synaptic and network plasticity and highlight the effect of a specific lack of education on MFG GABA concentration and learning-dependent plasticity. Our findings reveal the reciprocal effect between brain development and education and demonstrate the negative consequences of a specific lack of education during adolescence on brain plasticity and cognitive functions.

mathematical education | GABA | plasticity | middle frontal gyrus

Educational decisions have a long-lasting impact on both the individual and wider society (1). Mathematical education and attainment has been associated with several quality-of-life indices, including educational progress, socioeconomic status, employment, mental and physical health, and financial stability (2–5). In several countries, such as the United Kingdom and India, 16-y-old adolescents as part of their advanced (i.e., A-level) subjects can choose to stop studying math. The consequences of not choosing math as an A-level subject can be significant. When controlling for potential confounding factors such as socioeconomic status it emerged that the decision to not study math as an A-level subject can lead to an 11% decrease in financial income compared to those who choose to study math as part of their A-level curriculum. No other A-level subject category is associated with such a wage premium (6). In addition, previous studies highlighted the cognitive, emotional, and societal factors that are associated with mathematical education (7, 8).

In recent years, there has been significant interest in the investigation of the neural substrates of mathematical cognition and education, and frontal and parietal regions have been repeatedly highlighted as key regions (9–13). Despite the advancement of our knowledge on the neurobiological underpinnings of math abilities, little is known about whether and how they are involved in a lack of mathematical education. At the neurobiological level, the lack of math education could impact neural changes in regions that are involved in skill acquisition of math, primarily in frontoparietal regions ("plasticity account"). This process can be subserved by neurotransmitter concentrations that preceded anatomic changes

(14). However, such differences may exist before the continuation of math education and represent baseline differences at the time of the educational decision not to study vs. to study further math ("biomarker account").

Using single H-magnetic resonance spectroscopy (MRS), we scanned two previously defined key regions involved in numeracy: the intraparietal sulcus (IPS) and the middle frontal gyrus (MFG) (Fig. 1). We also examined their functional connectivity using resting-state functional MRI (for reviews see refs. 15–19). Such an approach allowed us to examine the role of γ-aminobutyric acid (GABA) and glutamate, the brain major inhibitory and excitatory neurotransmitters, respectively. Brain inhibition and excitation levels are thought to be critical in triggering the onset and defining the duration of sensitive periods of a given function, during which the neural system is particularly plastic in its response to environmental stimulation (20). It is thought that this is achieved by a shift in the ratio of intrinsic and spontaneous activity and activity in response to the environmental stimulation, whereby the intrinsic and spontaneous activity is reduced and the activity in response to the environmental stimulation is increased (21). Although very early in development, GABA functions as an excitatory neurotransmitter (22), during adolescence GABA and glutamate function as the main inhibitory and excitatory neurotransmitters, respectively, and previous studies have shed some light on the actions of these two neurotransmitters during adolescence. For example, compared to early childhood where there is a peak synaptic density, but the synaptic density is significantly

Significance

Our knowledge of the effect of a specific lack of education on the brain and cognitive development is currently poor but is highly relevant given differences between countries in their educational curricula and the differences in opportunities to access education. We show that within the same society, adolescent students who specifically lack mathematical education exhibited reduced brain inhibition levels in a key brain area involved in reasoning and cognitive learning. Importantly, these brain inhibition levels predicted mathematical attainment ~19 mo later, suggesting they play a role in neuroplasticity. Our study provides biological understanding of the impact of the lack of mathematical education on the developing brain and the mutual play between biology and education.
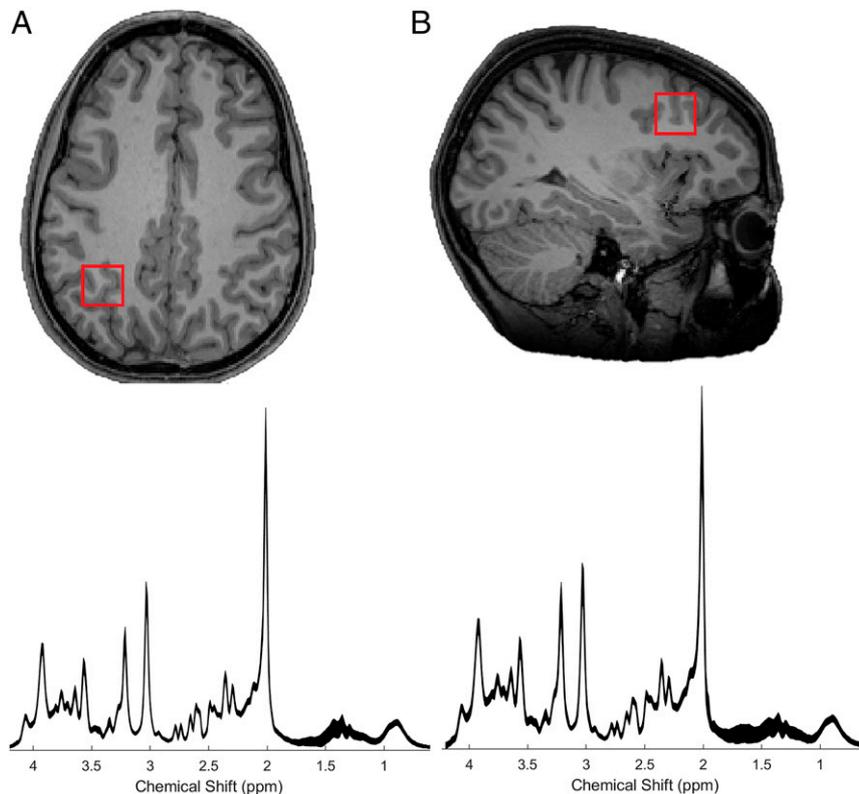
Fig. 1. Positions of the volumes of interest displayed in a representative T1-weighted image for the (*A*) IPS and (*B*) MFG, on axial and sagittal slices, respectively. Average spectra from each of these regions are shown below (thickness corresponds to ±1 SD from the mean) (chemical shift expressed in parts per million, ppm, on the *x* axis).

reduced during adolescence (even more so compared to adulthood) and such synaptic pruning is thought to be underpinned by glutamatergic-mediated synaptic mechanisms of long-term potentiation and depression (23). Moreover, previous studies have shown that GABA matures during adolescence, and frontal lobe GABA receptors reach adult levels late in adolescence with lower GABA levels being associated with poor cognitive functioning during adolescence (24, 25).

In the present study, rather than examining a general lack of academic education, which could stem from several confounding factors (e.g., socioeconomic status, lack of learning materials, insufficient educational infrastructure, cultural differences), we specifically examined the lack of math education. As mentioned earlier, in the United Kingdom, 16-y-old adolescents can choose to cease their mathematical education while still being enrolled in other nonmathematical academic education. This allowed us to better control for these confounds by recruiting participants from similar educational systems who differ specifically in their math education.

Based on the existing literature reviewed previously, we hypothesized that the lack of mathematical education would be associated with reduced GABA and/or increased glutamate. While both left and right frontoparietal regions were shown to underpin numerical processing (13, 26, 27) in the present study, we focused on the left frontoparietal regions due to their central role in mathematical learning (28–31). Our decision to a priori select the left IPS and MFG was based on the following reasons: First, the left IPS and MFG are frequently reported in neuroimaging studies that examined arithmetic, including a meta-analysis (10). Second, previous studies in the field of numerical cognition have shown the involvement of those brain regions in cognitive training (32–34). Third, brain stimulation studies have

suggested a causal role of the MFG in algorithmic learning and the IPS in learning concerning more low-level computation (numerosity, symbolic representation) (30, 35, 36). Using classification approaches, we discerned the differences in these neurotransmitters in adolescents who lack further math education (A-level nonmathematics) vs. those who underwent further math education (A-level mathematics). To dissociate the plasticity account from the biomarker account, we examined in a second experiment an independent cohort of students who made the same decision but who had not yet started their A level. Such a design allowed us to understand the exact role of frontoparietal GABA and glutamate, the main determinants of neuroplasticity and cognitive functions, during this critical developmental and educational stage.

Results

Contrasting Nonmath vs. Math Students. In line with previous studies (7, 8, 37), we identified that those who ceased to study A-level mathematics, compared to those who continued to study A-level mathematics, showed lower performance in tests involving numerical operations [Fig. 2*A*, $t(84) = -5.27$, $P < 0.001$, Cohen's d = −1.18] and mathematical reasoning [Fig. 2*B*, $t(83) = -4.61$, $P < 0.001$, Cohen's d = −0.99], but scored higher on a test that assessed math anxiety [Fig. 2*C*, $t(84) = 3.3$, $P = 0.001$, Cohen's d = 0.71]. For the descriptive statistics of these cognitive and emotional differences, see *SI Appendix* 1.

We then used GABA and glutamate concentrations in the MFG and IPS to classify students based on their present lack of math education (nonmath students vs. A-level math) using a binary logistic regression. Lower MFG GABA concentrations increased the likelihood that a student lacked math education rather than continued their math education [Fig. 2*D*, $n = 83$,
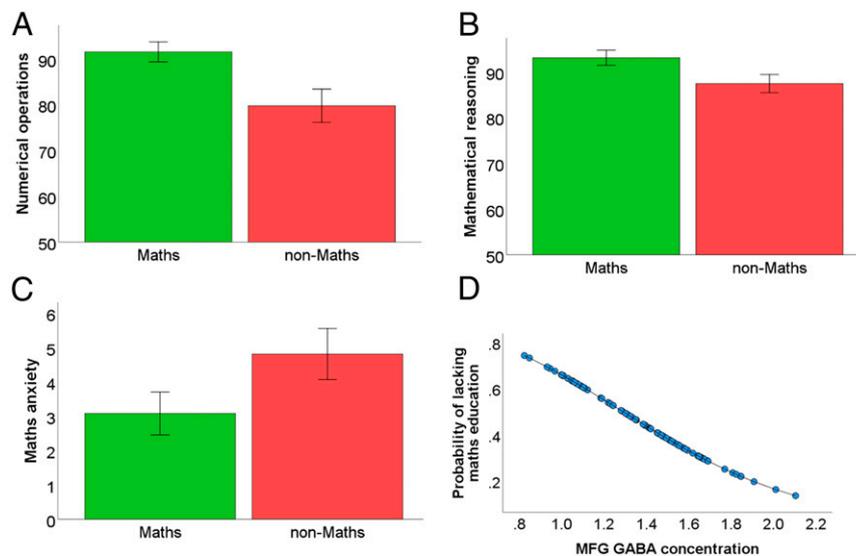
Fig. 2. Behavioral performance and GABA-based classification of whether a student is currently lacking math education. Behavioral results showing worse performance for adolescents who did not study math compared to those who did study math on (*A*) numerical operation attainment test and (*B*) mathematical reasoning attainment test. (*C*) Those who did not study math scored higher on a test that assessed math anxiety. Error bars represent 95% confidence intervals. (*D*) MFG GABA classified math education; predicted probabilities of those currently lacking math education (*y* axis) plotted against MFG GABA concentrations (*x* axis).

standardized beta(β) = −0.3, P = 0.009, Exp(pβ) = 0.524, Exp(β) = 0.742]. This finding survived multiple comparisons [Benjamini–Hochberg adjusted P = 0.037, based on the two regions of interest (IPS/MFG) × two neurochemicals (GABA/glutamate)].

To examine whether GABA's role is regionally and neurochemically specific in classifying the lack of a present math education, we ran a binary logistic regression with the predictors of MFG GABA [n = 82, β = −0.31, P = 0.007, Exp(pβ) = 0.49, Exp(β) = 0.74], MFG glutamate [n = 82, β = −0.01, P = 0.9, Exp(pβ) = 0.97, Exp(β) = 0.99], and IPS GABA [n = 82, β = 0.14, P = 0.19, Exp(pβ) = 1.39, Exp(β) = 1.15]. As the results indicate, only the MFG GABA predictor was significant. These results allowed us to conclude that our finding is regionally and neurochemically specific.

To examine whether the contribution of MFG GABA is confounded by math ability or math anxiety, we ran a binary logistic regression classifying whether a student lacks math education based on numerical operations [n = 80, β = −0.3, P = 0.023, Exp(pβ) = 0.38, Exp(β) = 0.74], mathematical reasoning [n = 80, β = −0.24, P = 0.074, Exp(pβ) = 0.47 Exp(β) = 0.79], and math anxiety [n = 80, β = 0.12, P = 0.26, Exp(pβ) = 1.46, Exp(β) = 1.13], and MFG GABA [n = 80, β = −0.23, P = 0.023, Exp(pβ) = 0.48, Exp(β) = 0.79]. These findings support the notion that math ability measures, but not math anxiety, successfully classify whether an adolescent lacks a math education program. More importantly, the findings highlight the contribution of MFG GABA in classifying whether an adolescent does not study math above and beyond the other aforementioned common determinants. Further analyses examined the effect of potential confounds. First, we excluded the role of gender in the observed results (*SI Appendix* 2). Second, we revealed that students who lack vs. those who did not lack math did not differ in their A-level education duration, age at scanning, and matrix reasoning (*SI Appendix* 3), and that MFG GABA successfully classified those students who lack math education even after controlling for the total number of enrolled A-level subjects (*SI Appendix* 3). Third, MFG GABA successfully classified students who lack math education at this age, even after controlling for the choice of biology, chemistry, and physics, while it failed to classify students who lack a physics, biology, or chemistry education at the same developmental stage.

Furthermore, we employed resting fMRI to investigate whether the lack of math education is associated with the functional connectivity between the left MFG, the region in which the main neurochemical finding was obtained, and the rest of the brain, using a seed-to-voxel method (*Materials and Methods*). However, no significant clusters were obtained, even after lowering the threshold to that of a liberal one (voxel-wise P value = 0.01).

We then employed resting fMRI to investigate whether MFG GABA concentration regulates functional connectivity between the left MFG and the rest of the brain (*Materials and Methods*). The identified associations with the MFG GABA and the functional connectivity with this region were restricted to the parietal cortex and included three clusters: the right supramarginal gyrus (Fig. 3*A*, x = 56, y = −22, z = 48, k = 300 voxels, positive false discovery rate [pFDR] = 0.016) and the bilateral superior parietal lobules (Fig. 3*A*, x = 30, y = −46, z = 60, k = 231 voxels, pFDR = 0.024; Fig. 3*B*, x = −26, y = −42, z = 68, k = 199 voxels, pFDR = 0.028). In all of these cases, higher MFG GABA concentrations were associated with negative connectivity, while low MFG GABA concentrations were associated with positive connectivity (Fig. 3 *C*–*E*).

Dissociating the Plasticity and Biomarker Accounts. At this stage, the relation between MFG GABA concentrations and math education might reflect baseline differences before studying A-level math. Such baseline differences, for example, might reflect differences in cortical maturation (20), which could prove to be advantageous when studying math, and thus impacting the likelihood of continuing their math education. To investigate this possibility, we examined a new cohort who had already decided whether they would stop studying math as part of their A-level curriculum but were at that time engaged in math education (pre-A level).

Pre-A-level students who had chosen to stop studying math compared to those who had decided to continue studying math show lower performance on tests that included numerical operations [t (40) = −5.03, P < 0.001, Cohen's d = −1.67] and mathematical reasoning [t (40) = −4.1, P = 0.001, Cohen's d = −1.37]. However, the difference between both groups in terms of math anxiety was not significant [t (40) = 0.91, P = 0.4, Cohen's d = 0.28].

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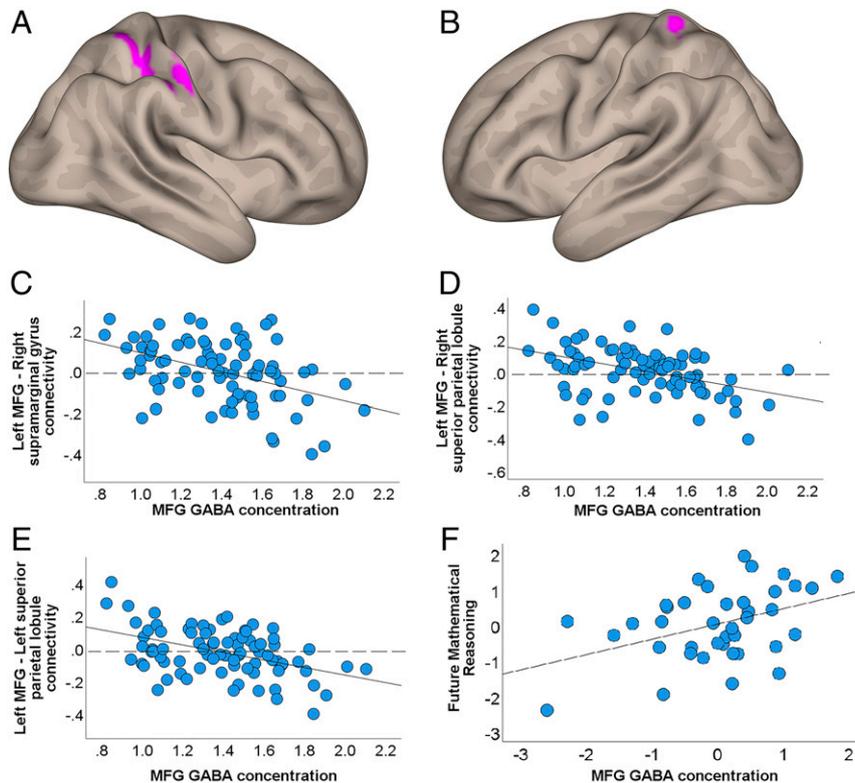https://doi.org/10.1073/pnas.2013155118

Fig. 3. MFG GABA is associated with frontoparietal functional connectivity and predicts future math performance. Regions negatively connected to left MFG as a function of MFG GABA concentration included (*A*) the right supramarginal gyrus and the right superior parietal lobule and (*B*) the left superior parietal lobule. Scatterplots depict the negative associations between MFG GABA concentration and MFG-based brain connectivity in three parietal clusters: (*C*) left MFG–right supramarginal gyrus, (*D*) left MFG–right superior parietal lobule, and (*E*) left MFG–left superior parietal lobule. Dotted vertical lines in *C–E* correspond to the zero-connectivity point. (*F*) MFG GABA concentration predicted future mathematical reasoning after controlling for mathematical reasoning scores when MFG GABA concentration was acquired ∼19 mo before. We plotted the residuals on the *y* axis and *x* axis after controlling the variance of the other predictors in the regression model described in the text.

For the descriptive statistics of these cognitive and emotional differences, see *SI Appendix* 1. The biomarker account did not receive support as the classification of the nonmath vs. math educational decision before starting to study math based on MFG GABA was not significant [$n = 36$, $\beta = 0.14$, $P = 0.42$, Exp(pβ) = 1.33, Exp(β) = 1.14]; for further analysis to exclude potential artifacts see *SI Appendix* 4.

MFG GABA Predicts Future Mathematical Ability. The plasticity account posits that the decreased MFG GABA concentration may reflect a lack of an advanced math education, which would otherwise benefit better math acquisition. Taking the results of the two preceding sections together, a corollary from the plasticity account is that the MFG GABA concentration will predict future math attainment. To test this hypothesis, we asked the students to complete the standardized numerical operations and mathematical reasoning tests 19.37 mo (SD = 3.94) after we acquired their MFG GABA concentration. Using regression analysis, we assessed whether MFG GABA in the A-level students could predict future math attainment while controlling for math attainment when the MFG GABA was acquired. We also controlled for other confounding factors (age during neuroimaging and behavioral data acquisition [T1], age during the second testing [T2], and group [lacking vs. not lacking math education]). The numerical operations score at T2 was predicted by numerical operations at T1 [$\beta = 0.51$, $t (33) = 4.1$, $P < 0.001$] and by math group [$\beta = -0.43$, $t (33) = -3.63$, $P = 0.0005$, a directional hypothesis based on our results at T1], but not by MFG GABA concentration [$\beta = 0.06$, $t (33) = 0.59$, $P = 0.56$]. The mathematical reasoning

score at T2 was predicted by mathematical reasoning at T1 [$\beta = 0.61$, $t (33) = 5.85$, $P < 0.001$], and there was a trend with the factor group [$\beta = -0.16$, $t (33) = -1.52$, $P = 0.068$, a directional hypothesis based on our results from T1]. Most notably, the MFG GABA concentration at T1 was a significant predictor of the mathematical reasoning 19 mo later [Fig. 3*F*, $\beta = 0.25$, $t (33) = 2.59$, $P = 0.014$, Benjamini–Hochberg adjusted $P = 0.028$, based on two comparisons, i.e., numerical operations and mathematical reasoning]. See *SI Appendix* 5 for further analysis.

Discussion

In the present study, we examined the impact of the lack of math education on brain development and future attainment. Using MRS, we scanned the left MFG and IPS, two previously defined key regions involved in numeracy, and observed three main findings: 1) adolescents who lack math education exhibited a decrease in GABA levels within the MFG compared to those who receive math education; 2) these differences were not present when deciding to cease math education, but before this action took place; and 3) MFG GABA levels predicted future mathematical reasoning when our sample was reassessed ∼19 mo apart.

We found that MFG GABA concentration could classify whether A-level students are presently lacking math education. Low MFG GABA concentrations increase the likelihood of not undergoing math education as a result of not choosing math as one of one's A-level subjects. Notably, this finding was specific to math education and was not explained by other A-level subjects that are usually taken by those who are enrolled in math education such as biology, chemistry, and physics, or by the number of

A-level subjects studied by the individuals (*SI Appendix* 3). GABA and glutamate within the IPS and glutamate within the MFG were not successful classifiers, and in further analyses, we showed that our results are specific to GABA and the MFG. Moreover, while we demonstrated that relevant cognitive and emotional factors, namely, math ability and math anxiety, differ between A-level students who lack vs. A-level students who do not lack math education, similar to previous studies (7, 8, 37), MFG GABA could still successfully classify whether A-level students lack math education even when we took into account the variance explained by these behavioral measures.

The neurochemical concentration within the MFG, but not within the IPS (a key region in numerical cognition), successfully classifies whether A-level students lack math education. The parietal cortex plays a crucial role in low-level computation, symbolic and nonsymbolic representation, and automatic execution after extensive practice (e.g., fact retrieval), whereas the prefrontal cortex is involved in more complex computations and algorithmic processing (36, 38–40), and it supports the allocation of mental resources during cognitive learning before automatic execution is reached (41). Such a distinction could explain our results, as A-level math students were involved in further mathematical education, which requires ongoing complex computation and algorithmic processing rather than low-level computation or automatization. While we acknowledge that the IPS is also found in some studies that examined the neural correlates of complex computation and algorithmic processing (26, 28, 42, 43), these findings do not provide causal evidence for the role of the IPS in the learning of these processes. A support for our suggestion is coming from brain stimulation studies over the MFG or IPS during a 5-d arithmetic learning, which found improved arithmetic learning and hemodynamic changes in the left MFG, but not the IPS (30). Furthermore, other brain stimulation studies have highlighted the role of the IPS in numerosity training and automatization, which requires low-level computation (35, 36, 40, 44). However, our current explanation for the lack of IPS involvement in A-level mathematical learning is based on a null result, and could have originated as a result of other factors. For example, the involvement of different brain regions, such as the MFG and IPS, in mathematical learning might depend on the exact stage of development (29, 45–47).

By further examining whether MFG GABA concentration could classify the decision to choose advanced math education before being enrolled in the A-level program, we inferred that MFG GABA concentrations reflect a lack of further math education during adolescence, rather than the likelihood of the student choosing A-level math. Our conclusions are in line with previous studies that linked GABA to cognitive performance (48) and plasticity (49–51) and the role of the frontal cortex functions in high-level cognition (52–56), including cognitive learning (41). An additional support to our proposal that GABA concentration in the MFG reflects neural priming for better skill acquisition of math is our ability to predict future mathematical reasoning in a standardized mathematical attainment test using MFG GABA concentration values that we obtained ~19 mo earlier. This result is supported by previous neuropsychological and functional MRI studies that have highlighted the role of the left MFG in reasoning and problem solving (57–59) (for the overlapped Montreal Neurological Institute [MNI] coordinates between the left MFG in our study and previous fMRI studies, see *SI Appendix* 5).

MFG GABA predicted future mathematical reasoning but not numerical operations. The numerical operations used in standardized tests, as in our testing battery, mainly emphasize the implementation of arithmetical procedure and the retrieval of arithmetic facts; the latter is mastered by students and is acquired in earlier years (60, 61) therefore leading to less room for future improvement. In contrast, mathematical reasoning emphasizes

problem-solving abilities, which is a more malleable set of skills. Indeed, in our sample mathematical reasoning, but not numerical operations, significantly improved at T2 compared to T1 [mathematical reasoning: $t (42) = 4.3$, $P < 0.001$; numerical operations: $t (42) = 0.52$, $P = 0.6$]. Consequently, we tentatively suggest that the predictive capacity of MFG GABA becomes more relevant for skills that are more susceptible to change and plasticity rather than numerical operations, a more basic skill, which reached the level of proficiency in both groups.

What do these education-related GABA level differences reflect at the cellular level, and how may these differences affect plasticity? The learning of math is an evolving skill that is accumulated and refined over years, suggesting that its underlying sensitive period or plasticity extends beyond childhood and adolescence. Critically, however, sensitive periods for developing a skill are not an on/off process but are rather known to be plastic in terms of their onset, closure, duration, and intensity (20). Such plasticity mechanisms are thought to involve the maturation of parvalbumin cells, a positive subtype of GABA neurons (62), leading to an optimal excitation/inhibition ratio underlying plasticity and corresponding learning (20, 63–65). Notably, the parvalbumin cells account for 25% of GABAergic cells in the primate dorsolateral prefrontal cortex (66, 67). Therefore, a potential mechanistic explanation for our results is that the elevated GABA observed in the group that received math education vs. those who lack it reflect the maturation of parvalbumin cells. Moreover, individual variation in these prefrontal GABA levels predicted future mathematical reasoning, thus suggesting that the elevated GABA levels observed in the group that received an enhanced math education likely shifted the GABA prefrontal circuits from static to more plastic ones perhaps by increasing the amplitude or duration of plasticity (20). Subsequently, our findings propose testable hypotheses linking learning mechanisms from animal models described at the microcircuits profile to the lack of math education and corresponding math learning and underlie the macroscopic learning-dependent plasticity.

Work in animals has highlighted the role of GABA neurotransmission in neuronal coding and processing as it influences membrane potential, neuronal activity, and synaptic and network plasticity (49–51, 68, 69). Given this effect of GABA on neural networks, our study additionally examined whether individual variation in MFG GABA concentration is associated with the functional connectivity between the MFG and the rest of the brain. Our analyses revealed three parietal regions whose connectivity to the MFG was negatively associated with the amount of GABA concentration: the right supramarginal gyrus and the right and left superior parietal lobules. In all of these cases, high MFG GABA concentrations were associated with negative connectivity. These frontal and parietal regions have been repeatedly highlighted as structures involved in numerical cognition in both children and adults (9, 13), and we demonstrate here that such functional connectivities are linked to MFG GABA concentration during adolescence. Previous work discovered a negative association between regional GABA levels and resting-state brain connectivity (70, 71); for example, work in adults focused on the motor system found a negative association between GABA within the M1 and the connectivity strength of the motor network (72). Here, we found that higher frontal GABA concentration is related to negative frontoparietal connectivity. These results suggest that in adolescence, individuals with high MFG GABA levels exhibit increased negative associations between frontoparietal regions compared to individuals with low MFG GABA levels who exhibit increased positive associations. Since GABAergic interneurons are thought to coordinate the synchrony of neural circuits (71, 73, 74), a likely explanation at the neurobiological level is that regional GABA concentrations may determine the synchronicity valance of that region with other functionally connected regions, in this case, the frontoparietal

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network during adolescence. However, how GABA concentrations might impact the organization of neural networks during development remains unclear. One possibility is that the negative connectivity facilitates the allocation of more resources to the prefrontal regions due to their primary role in cognitive learning (41). Nonetheless, our data provide strong motivation to clarify the exact role of GABA in shaping the development of neural networks and to examine its potential causal effect, which could have implications for future brain-based interventions (75).

MRS-based neurochemicals like GABA or glutamate have been extensively examined in relation to their associations with laboratory-based tasks (47, 56, 63, 76–82). Moreover, MRS has been highlighted as a promising tool in the classification and prediction of brain-related diseases by focusing on neurochemical concentrations that preceded anatomic changes (14). Our findings extend the unique contribution of MRS from basic research and clinical applications to educational settings to gain insight into the effect of a specific lack of math education. From a societal perspective, this is highly relevant given differences between countries in their educational curricula. For example, in some countries, adolescents can stop their math education at the age of 16, while in other countries math is mandatory. We show that within a society such decisions can alter neural and cognitive development. This, in turn, can introduce an advantage to individuals and societies who introduced math education as mandatory until school graduation. In addition, one might further consider how the differences in opportunities to access education, as reflected especially during the Covid-19 pandemic, might impact neural and cognitive development.

In summary, our work highlights the role of a specific neurochemical, GABA, in education during adolescence, its association with brain connectivity, and its capacity to predict future math ability. These results raise further questions, such as the impact of MFG GABA differences on other cognitive abilities associated with math education, such as working memory and logic (43, 83, 84), whether mathematical education should be mandatory during adolescence, and whether ceasing to pursue mathematical education should be replaced with nonmath materials, such as reasoning and logic, to allow ongoing engagement of the MFG that has been implicated in such cognitive processes (59). A more integrative understanding of the role of neurochemicals in behavior and their potential impact on brain structures and neural activity could lead to better tools for improving education and understanding brain development and cognition.

Materials and Methods

Participants. In experiment 1, we tested 87 A-level students {56 females, mean age in months = 202.7, SD = 4.7, range = [193 (16.1 y), 216 (18 y)]}. In the United Kingdom, A level is an advanced level subject-based qualification that can lead to university, further study, training, or work. In experiment 2, we tested 42 pre-A-level students {21 females, mean age in months = 172.31, SD = 3.71, range = [164 (13.7), 182 (14.92)]}. This group comprised prospective A-level students who indicated their decision of whether they would study math as part of their A-level curriculum. All participants completed two separate sessions; an imaging session that lasted ~60 min and a mathematical assessment session that lasted ~60 min. During the structural imaging and the MRS acquisition, participants merely watched the LEGO movie (85), and during the resting fMRI participants were asked to fixate on a white cross on a black background. All participants were predominantly right-handed, as measured by the Edinburgh Handedness Inventory (86). Exclusion criteria were any current or past neurological, psychiatric, or learning disability or condition that might affect cognitive or brain functioning; these were confirmed via self-report. As compensation, participants received a £35 Amazon or iTunes voucher.

The study was approved by the University of Oxford Medical Sciences Interdivisional Research Ethics Committee. Upon arrival on the scanning or behavioral site, and after being informed about the study's aims and procedures, all participants above 16 y of age or the participants' parents/guardians if the children were below 16 y of age, were asked to complete the relevant consent form. In addition to the consent form completed by the parent/guardian, children below 16 y of age were given an age-appropriate

assent form. This form included several statements such as "I have read the study information sheet and I had the opportunity to consider the information, ask questions and have had these answered satisfactorily." The children were asked to put their initials next to each statement if they agreed and signed the form.

Outliers were defined as cases with a score of three SDs beyond the mean (in the brain or behavioral measures, and in the residuals in the regression model), and were excluded from the analysis. Cases with missing scores were excluded from a given analysis only if the variables involved featured missing scores/excluded cases (SI Appendix 6).

The behavioral test at T2 after the neuroimaging data acquisition and behavioral testing was run on 39 participants. This attrition rate was due to the inability of the participants to return for testing as most of them had graduated and moved away from the testing location to pursue a university degree.

Math Group. The math group, the single dependent variable of this work, was coded as a dichotomous variable (1: math group vs. 0: nonmath group). In the A-level cohort, the math group consisted of students engaged in A-level math (n = 49), while the nonmath group consisted of students who were not engaged in A-level math (n = 38). In the pre-A-level cohort, the math group was composed of students who indicated their willingness to study math as one of their A-level subjects (n = 21) or to avoid such a subject (n = 21). The participants confirmed at a later date that they had taken such a decision.

MRI Data Acquisition and Preprocessing. All MRI data were acquired at the Oxford Centre for Functional MRI of the Brain (FMRIB) on a 3T Siemens MAGNETOM Prisma MRI System equipped with a 32-channel receive-only head coil.

Structural MRI. Anatomical high-resolution T1-weighted scans were acquired using an MPRAGE sequence consisting of 192 slices (repetition time [TR] = 1,900 ms; echo time [TE] = 3.97 ms; voxel size = 1 × 1 × 1 mm).

Magnetic Resonance Spectroscopy. Spectra were measured by semiadiabatic localization using an adiabatic selective refocusing (semi-LASER) sequence (TE = 32 ms; TR = 3.5 s; 32 averages) (87, 88) and variable power radio frequency (RF) pulses with optimized relaxation delays (VAPOR), water suppression, and outer volume saturation. Unsuppressed water spectra acquired from the same volume of interest were used to remove residual eddy current effects and to reconstruct the phased array spectra with MRspa (https://www.cmrr.umn.edu/downloads/mrspa/). Two 20 × 20 × 20 mm³ voxels of interest were manually centered in the left IPS and the MFG based on the individual's T1-weighted image while the participant was lying down in the MR scanner. Acquisition time per voxel was 10 to 15 min, including sequence planning and shimming.

MRS neurotransmitters were quantified with an LCModel (89) using a basis set of simulated spectra generated based on previously reported chemical shifts and coupling constants based on a VeSPA (versatile simulation, pulses, and analysis) simulation library (90). Simulations were performed using the same RF pulses and sequence timings as in the aforementioned 3T system. Eight LCModel-simulated macromolecule resonances were included in the analysis at the following positions: 0.91, 1.21, 1.43, 1.67, 1.95, 2.08, 2.25, and 3 ppm (91). Absolute neurochemical concentrations were extracted from the spectra using a water signal as an internal concentration reference.

The exclusion criteria for the data were 1) Cramér–Rao bounds and 2) the signal-to-noise ratio (SNR) (92). Neurochemicals quantified with Cramér–Rao lower bounds (CRLB, the estimated error of the neurochemical quantification) >50% were classified as undetected. Additionally, we excluded cases with an SNR ranging beyond 3 SDs (per region, per neurochemical, per age group), and cases with a neurochemical score beyond 3 SDs, as mentioned previously.

Absolute neurochemical concentrations were then scaled based on the structural properties of the selected regions and on the predefined values shown in Eq. 1 (89); these predefined scaling values were therefore determined prior to data collection. To quantify the structural properties, we segmented the images into different tissue classes including gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using the SPM12 segmentation facility. Next, we calculated the number of GM, WM, and CSF voxels within the two masks of interest separately around the left IPS and MFG in their native space. Subsequently, we divided these six numbers (GM, WM, and CSF for IPS and MFG) by the total number of GM, WM, and CSF voxels to obtain the corresponding GM, WM, and CSF fraction values per participant and region. As a final computation step, we scaled the absolute neurotransmitter values to these structural fractions using the following LCModel (89) computation:

$$\text{Tissue corrected concentration} = [(43{,}300/55{,}556 \times \text{GM fraction} \\ + 35{,}880/55{,}556 \times \text{WM fraction} + 1 \\ \times \text{CSF fraction})/(1 - \text{CSF fraction})] \\ \times \text{absolute neurochemical concentration.}$$

[1]

We additionally calculated the relative neurotransmitter concentration, which was calculated as the absolute neurotransmitter concentration divided by the concentration of total creatine, where tCr = creatine and phospho-creatine concentration. The neurotransmitter concentrations were referenced to total creatine since 1) creatine is commonly used as a reference and widely accepted as an internal reference standard; and 2) its signal shares the same imperfections (e.g., frequency drift, phase drift, and subject motion) as the signal of GABA and glutamate, as all concentrations are acquired simultaneously (47). We obtained similar results when we scaled GABA and glutamate to creatine and phosphocreatine (tCr, a relative concentration measure).

Resting fMRI. Functional images were acquired with a multiband acquisition sequence (multiband acceleration factor = 6; TR = 933 ms; TE = 33.40 ms; flip angle 64°; number of slices = 72; voxel dimension = $2 \times 2 \times 2$; number of volumes = 380). Resting fMRI data were preprocessed and analyzed using the CONN toolbox (http://www.nitrc.org/projects/conn, RRID:SCR_009550) (93) in SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK) and the default MNI-space direct normalization preprocessing pipeline. Functional volumes were motion corrected, slice-time corrected, segmented, normalized to a standardized (MNI) template, and spatially smoothed with a Gaussian kernel (8 mm full width at half maximum [FWHM]) and bandpass filter (0.01 Hz to infinity). Moreover, our preprocessing also involved outlier identification (>2 mm) and denoising where the default options were used. We excluded cases where 1) the outlier-identification step excluded more than 5% of the scans, and/or 2) the voxel-to-voxel correlation histogram was significantly nonzero ($r > 0.15$). To examine the effect of the math group, or the effect of neurochemical concentrations, on the brain network level, we employed seed-to-voxel analyses. Due to the findings (see *Results*), our seed was the left MFG. For testing significance, we utilized an initial voxel-wise uncorrected threshold $P < 0.001$ and a cluster-level FDR corrected to $P < 0.05$, which are also the default values of the CONN toolbox.

Behavioral Tests. We additionally assessed math ability and anxiety because these are common determinants of the decision to study A-level math (7, 37). The inclusion of these behavioral measures allowed us to examine whether our neural markers could explain the A-level math decision and advanced math learning over and above these common determinants (7, 8).

Math Ability Assessment. Math ability was assessed from the mathematical reasoning and the numerical operations tests in a standardized battery (the Wechsler Individual Achievement Test-II UK) (94). The mathematical reasoning test is composed of math problems requiring participants to create a mental model of the problem, extract relevant information, and then select and execute the appropriate operation (95). However, the numerical operation test is composed of written arithmetic problems, which require the implementation of arithmetic procedures. We calculated the proportion of correct responses in each math test for each participant. Note that the same results are obtained for the raw scores, as the proportion of correct responses is based on dividing the raw scores by the number of an overall fixed number of items in each test.

Math Anxiety Assessment. Math anxiety was assessed with the single-item math anxiety (SIMA) scale (96), in which higher scores indicate higher levels of math-related anxiety.

General Cognitive Ability. We measured general cognitive abilities using the raw scores matrix reasoning subtest of the Wechsler Abbreviated Intelligence Scale (97).

Statistical Analyses. To calculate the differences in math ability and math anxiety between the math and nonmath groups, we performed an independent sample t test. For effect size, we used Cohen's d based on the formula $(\text{Mean}_1 - \text{Mean}_2)/\text{sqrt}((SD_1{}^2 + SD_2{}^2)/2)$. To classify the math vs. nonmath groups, we also executed a binary logistic regression. For an effect size in this statistical analysis, we used standardized regression (β) coefficients. We also report the corresponding exponentiation of the partially standardized (pβ) coefficient, which is an odds ratio and is easier to interpret than the standardized regression (β) coefficient, which is in log-odds units. We also examined the equality of variances between the math and nonmath groups using the Levene's test for equality of variances; the variance did not differ between the math and nonmath groups in A levels [MFG GABA $F(81) = 0.005$, $P = 0.94$; MFG glutamate $F(83) = 0.0001$, $P = 0.99$; IPS GABA $F(83) = 0.298$, $P = 0.59$; IPS glutamate $F(82) = 1.051$, $P = 0.31$].

Data Availability. Anonymized RAW imaging files, behavioral scores data have been deposited in XNAT Central (https://central.xnat.org/data/projects/PN21).

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