Fractions strategy differences in those born extremely preterm

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Abstract

Introduction: For those with weak cognitive skills, certain mathematical problem-solving strategies may be more difficult than others. Tailored mathematical instruction that recognizes cognitive load and incorporates ways to reduce this may help to overcome mathematical difficulties. To investigate the effects of different strategies and cognitive load we explored brain

47   hemodynamic responses associated with the use of different strategies to solve subtraction of
48   fractions. We focused on those born extremely preterm (EPT; <28 weeks' gestation) as they are
49   known to have cognitive challenges and struggle with mathematics in particular. We also included
50   a group of full-term (FT) peers for comparison.
51
52   Methods: Functional MRI was acquired while the participants mentally solved fraction equations
53   using either an improper fractions strategy, where whole numbers are converted to improper
54   fractions before solving, or a mixed fractions strategy, where computations are carried out
55   separately for the whole numbers and fraction components. Different fraction item types were
56   given, which affected respective required cognitive loads per strategy. Diffusion and T1-weighted
57   structural images were also acquired. All imaging modalities were compared between the two
58   groups.
59
60   Results: The EPT and FT groups differed in terms of task-related hemodynamic responses,
61   regional volumes, and white matter connectivity. Functional group differences varied with strategy
62   and item type. These differences were greatest when the mixed fractions strategy was prompted
63   for an item type that required relatively greater cognitive load and involved borrowing. Other
64   findings showed reduced white and grey matter volume and reduced white matter connectivity in
65   widespread areas in the EPT group compared to the FT group.
66
67   Conclusion: Changes in the brain related to preterm birth are complex. The understanding of
68   function and structure presented here may help inform pedagogical practices by allowing for
69   tailoring of mathematical education through identifying suitable strategy adoption that depends on
70   problem type, to circumvent weaknesses in cognitive skills.
71
72   1.0 Introduction
73   Extremely preterm (EPT) birth is defined as birth before 28 completed weeks of gestation. The
74   incidence of preterm birth (gestational age (GA) < 37 weeks) in the US is about one in ten births
75   [1] and globally, 2-5 births in 1000 are EPT [2]. Survival rates among those born EPT are around
76   33% at 23 weeks' GA, 65% at 24 weeks, 81% at 25 weeks and 94% at 27 weeks [3]. Children born
77   EPT often have deficits in working memory, executive function, inhibition, and processing speed
78   when compared to full-term (FT) control subjects [4, 5]. Children born EPT are known to have
79   cognitive difficulties through adolescence and by early adulthood they are likely to have lower IQ
80   and impaired visuomotor, prospective memory, language and executive functioning skills [6].
81   Therefore, EPT individuals are vulnerable to experience impairments in a range of neurocognitive
82   skills that are crucial for learning, problem solving and effective communication, which are likely
83   to exert a negative impact on their overall academic achievement (with up to 50% needing extra
84   educational help at mainstream schools) [7]. In particular, EPT individuals experience
85   mathematics learning difficulties to a greater extent than other academic and cognitive deficits [7].
86   Mathematics difficulties have been associated with poor performance on working memory and
87   visuo-spatial processing tasks, rather than impairments in numerical representation [4], suggesting
88   that the nature of mathematics difficulties of preterm children is different from that of individuals
89   with developmental dyscalculia. In middle childhood, among those born EPT, 44% had serious
90   difficulty with mathematics compared to 1.3% of FT peers. In contrast, 30% of EPT children had
91   serious difficulty with reading compared to 2% of FT children [7].
92

93 In FT individuals, multiple brain regions have been implicated in the neurobiology of computation,
94 including in the frontal, parietal, and temporal cortices, as well as subcortically, in the thalamus,
95 basal ganglia, and hippocampus [8, 9]. There are much data supporting the intraparietal sulcus
96 (IPS) in the inferolateral parietal lobe as the primary locus of numerical processing, although IPS
97 lesions have been associated with a variety of other deficits of motor, sensory, and associative
98 function, suggesting that the information processing it supports is critical to mathematical
99 reasoning but not necessarily specific [10]. Nevertheless, the IPS is considered as part of a "core"
100 visual-spatial number system, along with the fusiform gyrus [10, 11]. Research studies have
101 investigated white matter associated with mathematics in typically developing children and adults.
102 Tract-specific white matter microstructural characteristics, such as fractional anisotropy (FA),
103 have been associated with mathematical skill. These tracks are the superior longitudinal fasciculus
104 (connecting fronto-parietal cortices) [12-14], inferior longitudinal fasciculus (fronto-occipito-
105 temporal areas) [12, 15] and arcurate fasciculus (inferior fronto-occipito-temporal, connecting
106 Wernicke's and Broca's areas) [16]. The processing and maintenance of both visual and verbal
107 information is also often central to mathematical performance [17-19].

109 Few functional imaging studies have investigated the neural correlates associated with performing
110 mathematics in preterm-born individuals. Functional magnetic resonance imaging (fMRI) studies,
111 involving tasks such as the Stroop and number estimation, have shown an association between
112 longer gestation and more pronounced hemodynamic responses in parietal brain regions. Shorter
113 GA has also been associated with more prefrontal cortex activity in young adults born < 37 weeks'
114 gestation when completing a magnitude comparison task [20], in 6- to 7-year-old children born
115 between 27-32 weeks with a numerical distance effect task [21, 22] and 11-year-old youth born <
116 28 weeks' gestation with a working memory/selective attention task [23]. As FT children mature,
117 areas of the brain associated with performing mathematics change from mostly frontal to less
118 frontal and more parietal areas, possibly due to procedural changes in how mathematics is
119 performed [24, 25]. Individuals born EPT may thus have a more 'immature' mathematical network
120 [20].

122 A study of functional connectivity and performance on mathematical tests showed patterns of
123 association unique to preterm individuals born between 25-36 weeks' gestation. Functional
124 connectivity derived from resting state fMRI in adulthood (26 years old) showed associations with
125 mathematical ability in childhood in bilateral fronto-parietal networks in preterm adults that were
126 different to FT adults [26]. Specifically, in the right fronto-parietal network, math abilities were
127 correlated with left lateral occipital/middle temporal cortex intrinsic functional connectivity in
128 preterm but not FT individuals. In the left fronto-parietal network a similar pattern was observed,
129 with math abilities being correlated with right angular gyrus/middle temporal cortex intrinsic
130 functional connectivity in preterm but not FT individuals. Also, mathematical abilities recorded in
131 childhood (8 years old) were more positively associated with adult IQ for preterm than for FT
132 individuals.

134 A study of mathematics and regional brain volumes found an association between reduced grey
135 matter volume in left parietal lobe and poor mathematics performance in EPT teenagers [27].
136 Diffusion weighted imaging studies assessing white matter characteristics have shown that EPT
137 infants scanned at 38 weeks' post-conceptual age have alterations in white matter microstructure
138 (reduced FA and increased radial diffusivity) in widespread areas associated with early

139   myelination (such as sensorimotor areas) [28] and frontal and occipital areas [29] compared with
140   FT babies. In older EPT children, 9-16 years of age, lower FA values in the corpus callosum,
141   forceps minor and major, cingulate gyrus, inferior fronto-occipital fasciculus, inferior and superior
142   longitudinal fasciculi and corticospinal tract have been associated with impaired executive
143   functioning [30]. In EPT infants scanned between birth and 4 years of age, changes in mean
144   diffusivity values in the internal and external capsules have been associated with intelligence and
145   language [31]. The long-range connections between frontal, temporal and parietal lobes serve to
146   integrate and control complex brain processes involved in cognition and skills. The authors are not
147   aware of any research investigating mathematics and white matter connectivity in individuals who
148   were born EPT. In summary, the EPT population has a multitude of structural and functional brain
149   changes that affect both their ability to do mathematics and domain-general functions such as
150   attention and working memory.
151
152   Here, we investigate functional and structural brain differences associated with mathematical
153   problem-solving in adolescents born EPT and FT control participants. We focus on fraction
154   problem-solving, as this mathematics domain poses demands on multiple computational abilities,
155   requires more advanced skills than arithmetic problem-solving, and is a key mathematical subject
156   area. Another benefit of focusing on fractions is that the same fraction problems can be solved
157   using either an improper fractions or mixed fractions strategy approach. Depending on the item,
158   the two strategies can impose different cognitive loads (e.g., more or fewer mental operations, or
159   interim steps requiring working memory for problem-solving). We illustrate this further below.
160
161   The present study represents an initial effort to identify individual differences in brain structure
162   and function as a means for developing more targeted approaches to mathematical instruction. We
163   focused on adolescents as they adapt well as an age group to fMRI experimentation and are
164   mathematically advanced enough to have already had instruction in solving fraction problems.
165   fMRI was used to examine hemodynamic response differences between adolescents born EPT and
166   FT control subjects during tasks that required different strategies of fraction problem-solving. The
167   goal was to investigate group differences in hemodynamic response patterns during processing of
168   same types of test items invoking different strategies that varied in cognitive load. We also aimed
169   to explore between group differences in brain structure. We hypothesized that there would be
170   differences between FT and EPT groups in hemodynamic response patterns, particularly for the
171   math problem and strategy combinations that require relatively higher cognitive loads. Discovery
172   of group differences could suggest the need for stronger emphasis on flexible strategy adoption for
173   adolescents born EPT that would allow for reductions in cognitive load.
174
175   2.0 Methods
176
177   2.1 Participants
178
179   The participants made two visits to University Hospitals Cleveland Medical Center (UHCMC) on
180   separate days. The first visit was to undertake neuropsychological testing and training in fractions,
181   (lasting 3 - 4 hours). The second visit was to the MRI department, lasting around 2 hours. Duration
182   between visits ranged from 7 to 364 days with the median duration being 22 days (SD 81.2 days).
183   In total 50 subjects attended for neuropsychological training and a subset was selected for MRI
184   based on: 1) the subject's willingness to participate in an MRI, 2) the lack of physical

185 contraindications to MRI (e.g., claustrophobia, the presence of cardiac pacemakers or other
186 medical devices, metallic fragments such as shrapnel, etc.), and 3) competency in doing fractions
187 without pen and paper. A total of 30 subjects underwent MRI, including 14 EPT adolescents, all
188 with either GA <28 weeks and/or birth weight < 1000 g. EPT participants were 15-17 years of age
189 and included 12 females. The 16 FT adolescences were aged 15-17 years old and included 8 males.
190 The FT youth were recruited from the same regular classrooms as the children born extremely
191 preterm and were thus representative of children attending regular education classes. Eleven EPT
192 and 15 FT participants were right-handed, 2 EPT and 1 FT participants were left-handed and 1
193 EPT participant was ambidextrous. Participant characteristics are summarized in Table 1.
194
195 The Institutional Review Board office at UHCMC granted ethics approval prior to the study. The
196 ethical considerations complied with the Declaration of Helsinki for human subject research.
197 Subjects and their parents gave informed consent prior to taking part.
198
199 2.2 Neuropsychological testing
200
201 Neuropsychological testing was performed using the NIH toolbox -
202 https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox. It includes a range of
203 tests to assess cognition, emotion, sensory and motor function. The cognition tests assessed
204 executive function, working memory, verbal fluency, attention, processing speed and episodic
205 memory. In the interests of brevity, the reader is directed to [32] for full details of the tests. Test
206 score summaries of working memory as assessed by WRAML2 (Wide Range Assessment of
207 Memory and Learning, second edition), by birth group, are also reported in Table 1.
208
209 2.3 Fractions strategies
210
211 We have developed a set of problems assessing subtraction of mixed fractions for administration
212 in the scanner that are similar to a diagnostic subtraction of mixed fractions test developed by K.
213 Tatsuoka [33, 34]. This test and its item-skill specifications have been widely studied and
214 validated, with data available at the Royal Statistical Society website (https://rss.org.uk) [35]. The
215 problems are solved using mental arithmetic. Each item can be solved with one of two strategies,
216 with the required strategy prompted during the fMRI session. Item types are described as:
217

$$\text{Item Type I:} \quad X\left(\frac{x}{z}\right) - Y\left(\frac{y}{z}\right), \qquad \textit{where } x > y \textit{ and } X > Y \tag{Eq. 1}$$

$$\text{Item Type II:} \quad X\left(\frac{x}{z}\right) - \left(\frac{y}{z}\right), \qquad \textit{where } y > x \tag{Eq. 2}$$

218 Solving strategies include "mixed" and "improper" methods. Consider $1\frac{3}{4} - \frac{1}{4}$, an Item Type I
219 problem. The "mixed" method involves separate computations on whole number and fraction
220 components, e.g.,

$$1\frac{3}{4} - \frac{1}{4} = (1 - 0) + \left(\frac{3}{4} - \frac{1}{4}\right) = 1\frac{2}{4}$$

221

222 (Eq. 3)
223 while the "improper" strategy involves solving using improper fractions by converting a whole
224 number to fraction, e.g.,

5

225
$$1\frac{3}{4} - 1\frac{1}{4} = \left(\frac{4}{4} + \frac{3}{4}\right) - 1\frac{1}{4} = \frac{7}{4} - 1\frac{1}{4} = \frac{6}{4}$$

226 (Eq. 4)

227

228 Note that in solving an item of this type, the improper strategy requires higher cognitive load,
229 specifically in working memory. However, the relative cognitive demands or difficulty levels
230 imposed by the two strategies (easier vs. harder) vary by the type of problem. For an Item Type I
231 problem, the mixed method requires fewer steps, and thus a lower cognitive load, than does the
232 improper fraction method. However, for an Item Type II problem, the improper fraction approach
233 is more efficient than the mixed fraction method. A problem of this type would be: $2\frac{1}{4} - 1\frac{3}{4}$,
234 which is an Item Type II.

235

$$2\frac{1}{4} - 1\frac{3}{4} = (2 - 1) + \left(\frac{1}{4} + \frac{4}{4}\right) - 1\frac{3}{4} = 1\frac{5}{4} - 1\frac{3}{4} = (1 - 1) + \left(\frac{5}{4} - \frac{3}{4}\right) = \frac{2}{4} \qquad \text{(Eq. 5)}$$

$$2\frac{1}{4} - 1\frac{3}{4} = \left(\frac{1}{4} + \frac{8}{4}\right) - \left(\frac{3}{4} + \frac{4}{4}\right) = \frac{9}{4} - \frac{7}{4} = \frac{2}{4} \qquad \text{(Eq. 6)}$$

236

237 In this problem the mixed fractions strategy requires borrowing from a whole number, i.e. 1 or $\frac{4}{4}$
238 from the 2 on the left-hand side of the problem, yielding $1\frac{5}{4}$. In this case, and more generally for
239 items of Type II, converting both numbers to improper fractions before subtracting places similar
240 or even fewer demands on working memory. This can be made more explicit by listing out the
241 computations and steps and numbers that must be held in memory during the problem-solving
242 process. In general, cognitive load varies depending on strategy and item type. Depending on item
243 type, one strategy can impose a higher demand on working memory than the other. See Figure 1.

244

245 For the two item types that we considered for fMRI, there are thus harder and easier difficulty
246 levels for each of the two strategies. For the items considered, when one strategy is at the harder
247 level, the other strategy is at the easier level, as illustrated above. This suggests that more difficult
248 levels of specific strategies can be avoided through flexibility in adopting alternative strategies.
249 The present study examines associations of different problem-solving strategies that have been
250 taught and practiced to mastery by the participants with patterns of neural activation on fMRI.

251

252 2.4 Fraction Strategy Training

253

254 Training in subtraction of mixed fractions was carried out as part of the initial visit, through a
255 multi-step program that began with review of basic concepts followed by (1) instruction and
256 practice in converting whole and mixed numbers to proper and improper fractions, subtraction of
257 simple proper fractions, and written subtraction problems, using each of the two strategies in order
258 of increasing difficulty; 2) practice and review in mental problem solving, using two strategies (the
259 "improper fraction" and "mixed fraction" approach) for solving problems that are easier or harder
260 depending on whether the items are Type I or Type II ; and 3) computer administration of similar
261 sets of problems to prepare participants to solve fraction problems in the same format that was
262 used for subsequent in-scanner presentations. During training with written problems, the examiner
263 taught each of the two problem solving strategies explicitly and had the subject verbalize the
264 strategy after solving each problem. Practice in doing the problems mentally also included the

6

265 requirement that subjects verbalize the strategy used after giving their answers. For the computer
266 administrations, subjects were first presented with a problem on the screen and asked to provide
267 the answer verbally as soon as they could while pressing the space bar to indicate their time to
268 solve the problem. They were then asked to verbalize the strategy used to solve that problem.
269 Problems were limited to those with common denominators and subtraction of relatively simple
270 fractions to ensure that subjects could be taught the problem-solving strategies to a high level of
271 accuracy and that in-scanner mental calculations would be feasible. The majority of subjects from
272 both the EPT and FT groups were able to achieve a high level of accuracy on the computer
273 administration, median values for EPT - 32.5 out of 35 (IQR 4.5) and FT - 34 out of 35 (IQR 1.0).
274
275 2.5 fMRI Stimulus protocols
276
277 Respective blocks of items requiring the two fraction solving strategies were presented separately
278 in the scanner. An example sequence is shown in Figure 2. Which strategy to use was prompted
279 through instructions printed on a screen at the beginning of each scan and with the presentation of
280 each equation. Colored Xs were used to prompt the format of the expected solution, e.g.:
281

$$1\frac{3}{4} - \frac{1}{4} = \frac{X}{X} \qquad or \qquad 1\frac{3}{4} - \frac{1}{4} = X\frac{X}{X}$$

283
284 Correct strategy adoption was validated by high correctness rates. See Figure 2 for further details.
285 For each strategy, Item Types I and II were presented within each scan in an interleaved fashion.
286 For the improper fractions strategy, the Item Type II involves 3 steps, while Item Type I involves
287 5 steps. For mixed fractions, Item Type I is only 2 steps, while Item Type II is 4 steps. A fraction
288 was displayed on the screen for 12-18 seconds, depending on difficulty level. Difficulty was
289 determined by the cognitive load/number of steps required to solve the equation. In the response
290 phase of solving an item, another screen was then displayed with two possible answers to choose
291 from. The answers were displayed in the format related to the strategy in use, and displayed for
292 only 6 seconds. There was thus insufficient time for subjects to convert their answer if they had
293 used the incorrect strategy, which encouraged correct adoption. Subjects indicated their answer
294 choice by pressing a button on a response box held in the right hand. Finally, the presentation of
295 each fraction item was separated by a 'rest' condition. A black dot was displayed in the center of
296 the screen and subjects were instructed before the scan to look at the dot for the duration.
297
298 The visual stimulus was presented using an in-house custom written program that was developed
299 using Python (Python Software Foundation, https://www.python.org/) and libraries from
300 PsychoPy - an open source visual presentation program [36-38]. The Cedrus Lumina controller
301 was used to integrate all the signals. The program connected to the controller box which received
302 the subject responses as well as a trigger pulse from the MRI scanner. The trigger pulse was
303 outputted every scan (every 3 seconds) and was used to synchronize the stimulus to the scan
304 acquisition. On the experimenter's computer screen was displayed a Supervisor Window that
305 tracked the current block number being presented, how many remaining blocks there were and
306 when the subject responded. The software has been made available from the Bitbucket repository:
307 https://bitbucket.org//tatsuoka-lab/fmri-presentation.
308
309 2.6 MR Imaging Parameters
310

311 Scans were acquired using a Philips Ingenuity 3T PET/MR scanner at UHCMC. Subjects were
312 positioned supine on the scanner bed. The head was fixed in position using inflatable pads and an
313 8-channel head coil was used for data acquisition. Echo planar imaging scans were acquired with
314 the following parameters: TR = 3.0 s, TE = 35 ms, voxel resolution = 1.797 x 1.797 x 4 mm (matrix
315 128 x 128), 36 slices in total provided full brain coverage, and flip angle was 90°. A SENSE P
316 reduction factor of 2 was implemented and scans were acquired in an ascending interleaved
317 fashion. Two fMRI scan sessions were run, one for each fraction solving strategy. They consisted
318 of 200 scans each. A high-resolution T1-weighted anatomical image was also acquired using a
319 magnetic preparation gradient-echo sequence (3D IR TFE) with the parameters: TR = 7.5 ms, TE
320 = 3.7 ms, voxel resolution = 1 x 1 x 1 mm, number of slices = 200 slices and flip angle = 8°. A 64-
321 direction diffusion weighted image with a FOV of 224 x 224 producing a final in-plane resolution
322 of 1.75 x 1.75 mm^2 and 2 mm slices. A TR of 7415 ms was used. Full-brain coverage was achieved
323 with 60 slices. One B_0 image was acquired, and the b factor was 1000.

324

325 2.7 fMRI Individual-level Analysis

326

327 FSL FEAT [39] was used to perform motion correction, spatial smoothing and apply a high pass
328 filter to preprocess the raw data. A rigid body transform with 6 degrees of freedom was used for
329 motion correction. Spatial smoothing was performed with a full-width-at-half-maximum Gaussian
330 kernel of 6 mm, a high pass temporal filter of 90 s was used. All scans were then co-registered to
331 a standard space template (MNI) and an individual level general linear model (GLM) analysis was
332 run. The fractions were presented in a block design and a hemodynamic response double gamma
333 function was convolved with a boxcar function to model the expected signal. We were most
334 interested in the neural correlates of calculation so only scans during the computation time were
335 modelled as active, not the scans during the response phase. The scans related to the response
336 phase recorded the process of reading the possible answers and indicating their choice via a button
337 press. The allowed response duration was kept short to ensure that calculations could not continue
338 into this phase. Recorded response times were related to the time taken by participants to indicate
339 their choice, not the time to do the mental calculation. Response times were not included as
340 regressors in the GLM.

341

342 Note, one EPT subject was unable to complete the fMRI tests and a technical issue prevented one
343 FT subject from taking the fMRI tests, hence the fMRI data reported at both individual and group
344 level contains 13 EPT and 15 FT subjects. However, structural data (DTI and T1 images) were
345 obtained for all 30 subjects. Also note, due to the anatomical heterogeneity reported in EPT
346 individuals, we considered the use of a custom structural brain template created from a group
347 average instead of using the MNI standard template. There were differences in the size of the brain
348 between the MNI and custom templates with the custom template being comparatively smaller
349 (228,453 and 177,110 voxels respectively, custom template was 22 % smaller). The fMRI results
350 were largely in the same anatomical locations. However, peak t-scores and total number of active
351 voxels differed with the fraction solving strategy. The MNI template was kept through all analyses
352 for ease of reporting and interpreting results, as well as minimizing the number of transformation
353 steps. Also note, in the Supplement section S2, activation status of specific regions are compared
354 by birth group.

355

356 2.8 fMRI Group Analysis

357
358   The statistical output from the individual analyses were used to perform the group level statistics
359   using fixed effects modelling in a factorial design involving group and strategy/item type
360   combination. Below, we focus on comparing birth group (EPT and FT) by strategy (mixed or
361   improper), birth group by item type (Type I or Item Type II), and 3-way interaction effects. The
362   latter consisted of within group comparisons of activations to Item Types I vs. II using the same
363   strategy (mixed or improper), and of activations associated with the same item types (Types I and
364   II) using different strategies. Note that strategy by item type interactions were purposely designed
365   so that differences in difficulty levels associated with the two item types would depend on the
366   strategy used to solve the problems. The inclusion of sex as a covariate was considered. However,
367   given that the EPT group consisted of predominantly females (11 out of 13), the sex results were
368   confounded with birth status and so are not reported. To reflect multiple hypotheses at least to
369   some degree, a result was considered significant if the resulting p-value was < 0.001 which equates
370   to a t-score > 3.1.
371
372   2.9 Linear SVM Classification
373
374   To further explore the activation differences between birth groups and strategy adoption, a linear
375   support vector machine (SVM) analysis was performed. The aim was to determine if it was
376   possible to systematically distinguish activation patterns in each of the item types in an automated
377   way. Preprocessing of BOLD signal were performed using FEAT, as described above. Additional
378   preprocessing steps via PyMVPA toolbox [40] included detrending, normalization, and ANOVA-
379   based feature selection (using top 5% of active voxels) as described in [40]. Rest volumes were
380   excluded from analysis. The linear SVM was implemented using a leave-one-out cross validation
381   approach. For the group level analyses, a single subject's mean activation for all conditions related
382   to a specific strategy type (or strategy-item type combination) was used in classification to perform
383   a leave-one-(subject)-out cross validation. As a result, the SVM would be trained on all strategy
384   conditions from n-1 subjects prior to testing on the subject left out. Overall classification
385   accuracies were determined using the PyMVPA toolbox built-in statistics.
386
387   2.10 Volumetrics and DWI analysis
388
389   MRI-based volumetrics and DWI analyses are described in the Supplement sections S3 and S4.
390   This includes group comparisons of regional volumes and white matter connectivity.
391
392   3.0   Results
393
394   3.1 Accuracy of responses by strategy/item type
395
396   We first establish the accuracy of the performance on the fraction subtraction problems. The
397   accuracy rates by strategy, item type (difficulty level), and strategy/item type combination are
398   given for both the FT and EPT groups in Table 2. Note that in general accuracy is quite high, which
399   supports the effectiveness of the training protocol, and the correct adoption of prompted strategy
400   per item. A Wilcoxon rank sum test was used to compare the differences in accuracy rate between
401   groups for each strategy/item type combination. Within birth groups, item types for same strategy
402   were compared, as well as strategies for a same item type. Most comparisons were not statistically

403 significant. Still, it was found that for both EPT and FT subjects, when using the mixed strategy,
404 Item Type II (harder) problems had significantly lower accuracy rates compared to Item Type I (p
405 = 0.007 and p = 0.002). Performance using different strategies on same item types were compared
406 as well. For Item Type II, both EPT and FT had lower correctness rates (p = 0.049 and p = 0.005)
407 for the mixed fractions strategy compared to improper fractions strategy. No significant difference
408 was found for other item type and strategy combinations. When using the mixed strategy to solve
409 Item Type II problems, EPT subjects had lower correctness rates compared to FT subjects (85.7
410 versus 71.4%, p = 0.050), though even the EPT had relatively high accuracy rates.

412 3.2 Main effects of strategy and their interaction with item type

414 The main effect of strategy was investigated. The data were modelled as task (Item Type I and II)
415 versus rest and both EPT and FT groups were included. The improper fraction strategy was
416 associated with hemodynamic response in the left superior and inferior frontal gyri, paracentral
417 lobule, precuneus and middle temporal gyrus; and right cingulate gyrus. Modelling the mixed
418 fractions strategy in a similar way revealed hemodynamic response in left medial frontal gyrus,
419 inferior parietal lobule and thalamus; right superior parietal lobule, superior frontal gyrus,
420 precuneus, precentral gyrus and caudate nucleus.

422 The interaction of item type and strategy was also investigated. Improper fractions strategy for
423 Item Type II (easier to solve problems) was associated with hemodynamic response in left superior
424 and medial frontal gyri, paracentral lobule and middle temporal gyrus. Item Type I problems
425 solved by this strategy was associated with hemodynamic response in left superior frontal gyrus
426 and right posterior cingulate. For the mixed fractions strategy, Item Type I (easier to solve
427 problems) showed hemodynamic response in left medial frontal gyrus, insula and fusiform gyrus;
428 right cingulate, superior frontal gyrus, precuneus, precentral gyrus and caudate; and bilateral
429 lingual gyrus. Hemodynamic response associated with Item Type II of mixed fractions strategy
430 were widespread and included in left medial frontal gyrus, lingual gyrus, inferior parietal lobule,
431 cingulate, thalamus and caudate; right superior frontal gyrus, superior parietal lobule and
432 precuneus; bilateral precentral gyrus and posterior cingulate gyrus.

434 A conjunction analysis for each strategy and item types shows that much of the functional
435 activation that differs between item types appears around the edges of the overlapping clusters.
436 Statistical contrasts of improper strategy Item Type I versus II and Item Type II versus I were not
437 significant. The contrast of Item Type I versus II for mixed fractions strategy showed statistical
438 differences in left paracentral lobule, insula and precentral gyrus; right lingual and postcentral gyri.
439 The contrast of Item Type II versus I showed greater hemodynamic response mainly in left brain
440 areas including the precuneus, middle frontal gyrus, precentral gyrus and bilateral cingulate gyrus.

442 3.3 Between birth group differences by strategy and difficulty level

444 Table 3 shows between group differences in hemodynamic response for the easy and hard levels
445 for each fraction strategy.

447 3.3.1 Improper strategy. Comparison of the EPT vs FT groups on the less difficult items (Item
448 Type II) for the improper strategy vs rest revealed greater hemodynamic response in right

10

449   precuneus in the EPT group compared to the FT group (contrast EPT vs FT). The FT group showed
450   greater hemodynamic response in the left middle and superior frontal gyri, superior parietal lobule
451   and right paracentral lobule (contrast FT vs EPT). For Item Type I (hard) vs rest, we observed no
452   areas displaying greater hemodynamic response in the EPT group compared to the FT group. For
453   the more difficult Item Type I, the FT group showed greater hemodynamic response in left
454   cingulate gyrus, middle and superior frontal gyri, caudate and thalamus, and bilateral superior and
455   inferior parietal lobules compared to the EPT group. Locations for each contrast are shown in
456   Figure 3 and listed in Table 3. A conjunction analysis of EPT and FT group activity is shown in
457   Figure 4. These results are suggestive of the EPT group demonstrating either widespread under-
458   activation during the task compared to FT subjects or it may be due to more variability in brain
459   responses across subjects. Closer inspection of the variance between the groups showed that the
460   EPT group variance is almost twice as much as the FT group – for example FT improper Item
461   Type I: mean voxel level variance = 222.6 (SD 151.6) and EPT improper Item Type I: mean voxel
462   level variance = 428.2 (SD 327.2). Across all strategies and item types, the variance in the EPT
463   group remains consistently around twice the variance in the FT group.
464
465   3.3.2 Mixed strategy. In group comparisons of the less difficult items (Item Type I) versus rest for
466   the mixed strategy data, the EPT group compared to the FT group showed greater hemodynamic
467   response in left insula, middle and medial frontal gyri; right superior frontal gyrus, cingulate,
468   superior parietal lobule and precuneus. In contrast, the FT group compared to the EPT group
469   showed greater hemodynamic response in left cingulate, middle and superior frontal gyri; right
470   precentral gyrus, inferior parietal lobule, caudate nucleus; bilateral medial frontal and postcentral
471   gyri. For Item Type II (hard) versus rest, the EPT group compared to the FT group showed greater
472   hemodynamic response in left medial frontal gyrus and parahippocampal gyrus; right middle
473   frontal and precentral gyri; bilateral precuneus. For the easier Item Type II, the FT group had
474   greater hemodynamic response in left middle, medial and superior frontal gyri, pre- and post-
475   central gyri; right inferior parietal lobule, cingulate, paracentral lobule and thalamus compared to
476   the EPT group. The conjunction analysis for mixed fractions Item Types I and II in Figure 5 shows
477   that much of the activity that is different between the groups appears around the edges of the
478   overlapping clusters where statistical certainty is the lowest. These areas coincide with those listed
479   above.
480
481   3.4 SVM classification
482
483   The purposes of these analyses were to determine if 1) birth group membership can be
484   distinguished from hemodynamic response patterns from each strategy and item type, 2) difficulty
485   level within a birth group and for a given strategy, and 3) strategy adoption within each birth group
486   and for each of the item types. Discriminability with SVM corroborates findings of activation
487   differences with the GLM-based analyses.
488
489   Classification of difficulty level (i.e., distinguishing item types) for the mixed fractions strategy
490   demonstrated accuracies of 56.67% and 71.43% for FT and EPT groups, respectively (Figure 6a).
491   Difficulty level classification for the improper fractions strategy demonstrated accuracies of
492   63.33% and 61.54% for FT and EPT groups, respectively. A similar analysis was performed to
493   classify different strategies within the same item type. Classification of mixed versus improper
494   strategies for Item Type II (improper easy vs mixed fractions hard) demonstrated accuracies of

11

495   86.67% and 80.77% for FT and EPT groups, respectively (Figure 6b). Strategy classification for
496   Item Type I (improper hard vs mixed fractions easy) demonstrated accuracies of 70% and 69.23%
497   for FT and EPT groups, respectively.
498
499   A further goal was to determine if the task-related BOLD signal measured here could be used by
500   the SVM to identify specific traits about a subject, or more specifically, if the SVM could
501   distinguish between birth status. BOLD signal data from a specific strategy and an item type (e.g.,
502   harder level of mixed fractions) was used with the goal of classifying untested BOLD signal data
503   as belonging to an EPT versus FT subject. This was conducted over multiple cross validation
504   iterations. The resulting classification accuracies and confusion matrices for each strategy-
505   difficulty combination are detailed in Table 4. The strategy-difficulty combinations with the
506   hardest difficulty produced the highest classification accuracies (67.86% and 64.29% for mixed
507   and improper fractions, respectively).
508
509   4.0 Discussion
510
511   This study explored differences in hemodynamic response between extremely preterm and FT born
512   teens associated with using two strategies to solve fractions, where cognitive loads varied by item
513   type and strategy. A main hypothesis of the study was that among the specific strategy and item
514   type combinations, activation differences between birth groups would be particularly pronounced
515   for the harder versus easier difficulty levels of a given strategy.
516
517   Overall, the estimated main effects of strategy indicated hemodynamic responses across
518   widespread areas of the brain associated with mathematical processing. Mixed fractions strategy
519   was associated with the highest number of active voxels and with a pattern of functional activation
520   that was distinct from the improper fractions strategy. Mixed fractions related hemodynamic
521   responses were located in fronto-parietal areas, while improper fractions hemodynamic responses
522   were centered around the precuneus and temporal gyrus. The hemodynamic response of the mixed
523   fractions strategy is consistent with that reported in the literature for mathematics tasks [8, 9].
524
525   In terms of group differences, the interaction between strategy and item type showed areas of
526   greater hemodynamic response specific to each group for each condition, with the exception of
527   Item Type I improper fractions strategy, where the EPT did not show greater functional activation
528   compared to the FT group. The areas of increased hemodynamic response for all other conditions
529   were widespread in fronto-parietal areas and along the midline and temporal gyri and by birth
530   group, strategy and item type. Efforts to solve both item types (I and II) using the mixed fractions
531   produced similar patterns of activity for both groups (see Supplement section S1, within group
532   analyses). In comparison, functional activations for this strategy in the EPT group compared to the
533   FT group were greater in bilateral insulae and middle frontal gyri. The different networks for each
534   strategy may be due to the different processes involved with the calculations (see Figure 1). The
535   mixed fraction strategy can have a greater cognitive load attributable to a higher demand for
536   number memorization necessary to achieve the answer (i.e., the separate answers for the whole
537   number and fractions must both be remembered and one must be kept in memory while the other
538   is calculated), particularly for Type II items (harder level). This finding may also reflect a relatively
539   higher level of demand on executive function. In contrast, when using the improper fractions
540   strategy, each calculation at a given step is used in the next step until the final result is obtained.

541 Some degree of working memory is thus needed to apply the improper fractions strategy,
542 particularly for Type I items (harder level). However, this approach may not require the same
543 magnitude of retention and manipulation as the mixed fractions strategy. The difference between
544 the strategies may also be due to more familiarity with the improper fractions strategy which is
545 often taught in schools. In support of this possibility, Tenison and colleagues found that unfamiliar
546 mathematics problems, compared to more familiar ones, took longer to solve and were
547 accompanied by increased brain activity in the intraparietal sulcus [41].

549 Group differences in patterns of functional activation may be associated with several factors. The
550 EPT subjects generally had lower working memory function (see WRAML2 scores in Table 1)
551 and they may have adopted different cognitive strategies to compensate for this weakness,
552 resulting in different areas of neural recruitment. An alternative explanation is that there may be
553 alterations in brain structure. Consistent with the group differences in brain structure observed in
554 this study (discussed below), past research has revealed alterations in grey and white matter
555 volumes and altered folding patterns of the cortical gyri in individuals born EPT [42, 43]. The
556 pattern of functional activity observed here may also be reflective of compensation for reduced
557 capacity or neural efficiency in the areas typically used by FT control subjects. A previous study
558 found evidence for neural compensation in adults with preterm birth on a visual learning task [44].
559 Further evidence in support of compensatory processes, as manifest in "cognitive reserve," is
560 provided by findings indicating age differences between younger and older adults in the level of
561 task difficulty at which patterns of neural activation change from those observed while doing less
562 difficult problems [45]. Greater variability in brain response at the individual level may also have
563 contributed to activation differences between the EPT and FT groups. Greater variability in
564 functional brain activity has been found among those with developmental dyscalculia [46] and
565 those born EPT [47]. The source of the greater variability may arise from differences in the brain
566 structure associated with preterm birth [42, 43], but may also reflect different developmental
567 trajectories related to atypical patterns of maturation and neuronal pruning [48, 49]. One study
568 found evidence of accelerated brain maturation and earlier neuronal pruning in individuals with
569 EPT compared to those born FT [50].

571 The SVM-based classifications with the highest accuracies were observed for strategy
572 classification based on item type (i.e., difficulty level). This higher classification accuracy (> 80%)
573 is seen for both groups. These findings suggest BOLD signals that differentiate strategy may be
574 shared across groups and are consistent with the group-level GLM activation pattern results, which
575 indicate different neural activation patterns by strategy. Classification rates for distinguishing
576 difficulty levels were higher for the EPT group than for the FT participants, particularly for the
577 mixed fractions strategy (71.43% versus 56.67%). This finding provides further evidence that the
578 EPT participants may be straining to solve the more difficult Type II items with this strategy. These
579 results are consistent with other findings from this study, including group differences in accuracy,
580 GLM-based activation patterns, and DWI-based connectivity, indicating that group differences
581 were most pronounced when participants were solving more difficult problems.

583 The above-noted group differences in patterns of brain functional activations and structure suggest
584 that some youth with EPT birth may engage different brain networks than FT youth in solving
585 fraction problems. These findings suggest a need to tailor instructions in fraction problem-solving,
586 and perhaps other aspects of mathematics, to individual differences. In solving problems relying

587   on brain networks similar to those engaged by FT youth, similar approaches may be justified.
588   However, the present findings indicate that at least some EPT adolescents may engage different
589   brain networks, depending on the strategy employed in solving a problem, the type of item, and
590   the cognitive competencies of the learner. One implication of these findings for mathematics
591   instruction is the support they provide for adapting problem-solving strategies in ways that are
592   biologically informed. Although procedures for making these modifications are to be determined,
593   the present results suggest the need for the student to recognize both their individual cognitive
594   competencies and the characteristics of the mathematics problems, such as their cognitive load and
595   the corresponding respective efficiencies of problem-solving strategies. Alternatively, efforts
596   could be made to strengthen some of the processes that contribute to problem-solving. An example
597   of these efforts as applies to fraction problem-solving would be to increase the automaticity of
598   retrieval of arithmetic facts as a means for compensating for weaknesses in working memory. In
599   the Supplement section S2, it was found that several areas were more likely to be functionally
600   active in the EPT group than the FT group, including the left parahippocampal and bilateral medial
601   frontal gyri, as well as a lack of functional activation in the precuneus. The precuneus has been
602   studied as a functional hub between multiple interacting brain networks and supports visuospatial
603   imagery and attention activation [51], skills necessary for mathematical calculations.
604
605   We also compared the EPT and FT groups on measures of brain structure using volumetrics and
606   DTI analysis (see Supplement sections S3 and S4). Volumetric analysis revealed reduced volume
607   in the left lingual and parahippocampal gyri in the EPT compared to the FT group. DTI analysis
608   revealed several altered connections for these youth, particularly involving the left
609   parahippocampal gyrus, left visual area and right superior parietal lobule. The findings indicating
610   alterations in the EPT group in brain volumes and connectivity are in line with other studies in
611   very preterm individuals (GA < 33 weeks) [42, 43, 52, 53]. Increased volumes and abnormal
612   patterns of structural connectivity may reflect alterations in brain growth that occur in response to,
613   or in compensation for, the above-noted decreases in brain volumes. For example, stronger
614   connectivity between some brain regions may compensate for weaker connectivity between other
615   regions. The overlap we found between the volumetric and DTI analyses suggests structural
616   changes in the left parahippocampal gyrus and right superior parietal lobule. Both regions had
617   reduced white matter volume and structural connectivity. The superior parietal lobule is involved
618   with action processes and visuomotor functions, attention, reasoning, spatial perception, visual
619   perception and working memory [54]. The function of the parahippocampal gyrus has been linked
620   to retrieval fluency in 7- to 9-year-old children [55]. Reduced grey and white matter volume in this
621   area may impact fluency in retrieval of math facts and suggests that EPT individuals may need to
622   invest more effort in making mental computations. The volumetric analysis also suggested that the
623   EPT group had reduced grey and white matter volume in the left lingual gyrus. The left lingual
624   gyrus has been linked to abilities in visual memory [56], a component of the working memory
625   system [57]. Reduced volume in both the grey and white matter of the lingual gyrus areas raises
626   the possibility of deficits in aspects of the working memory system supported by that region.
627
628   Major study limitations are the small sample size and questions regarding sample
629   representativeness. Participants were recruited from a larger sample of youth assessed several
630   years prior to this study. Many of the families could not be located. Although the EPT and FT
631   groups did not differ in age, most youth in the EPT group were female; thus, the sample was not
632   representative of the broader regional or national population of EPT youth. Further MRI studies

14

633   with larger and more representative samples are needed to confirm our results, and to continue to
634   explore how heterogeneity in cognitive outcomes of EPT birth may be associated with variability
635   in neural activations that we observed at the group level.

636
637   5.0 Conclusion
638

639   The effects of being born EPT on the brain are multifactorial and complex. The present study
640   explored brain function and structure in those born EPT through the lens of mathematical strategies
641   used in performing mental computation of fraction problems. We found both group and strategy-
642   dependent differences in neural activations to fraction problem-solving. The findings offer support
643   for considering individual differences among EPT in neural structure and function, along with the
644   specific demand characteristics or mathematics problems, in developing more targeted approaches
645   to mathematics instruction. This information may inform pedagogical practices and allow
646   educators to tailor mathematical approaches adapted to the cognitive and neural profiles of EPT
647   individuals. Particularly, hemodynamic response patterns associated with different problem-
648   solving strategies in youth born EPT compared to FT youth could serve as potential biomarkers of
649   approaches to mathematics instruction that may be most appropriate for youth born EPT. The
650   present findings suggest consideration of instructional approaches that focus on strategies with
651   relatively lower cognitive loads and on emphasizing flexibility in strategy adoption.

652
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654
655   SC – Study design, analysis and interpretation of data, drafting of manuscript
656   MB – Study design, analysis and interpretation of data, review of manuscript
657   AI – Study design, analysis and interpretation of data, review of manuscript
658   BM-D – Study design, analysis and interpretation of data, review of manuscript
659   GW – analysis and interpretation of data, review of manuscript
660   WC – Study design, analysis and interpretation of data, software development, review of
661   manuscript
662   JF – Study design and software development, review of manuscript
663   JZ – Study design, analysis and interpretation of data, review of manuscript
664   MW – analysis and interpretation of data, review of manuscript
665   SYY – analysis and interpretation of data, review of manuscript
666   AB – Study design, data collection, review of manuscript
667   ER – Study design, analysis and interpretation of data, review of manuscript
668   CG – Study design, analysis and interpretation of data, review of manuscript
669   NM – Study design, analysis and interpretation of data, review of manuscript
670   LT – Study design, analysis and interpretation of data, review of manuscript
671   WHK - Study design, analysis and interpretation of data, review of manuscript
672   YS – study design, interpretation of data, review of manuscript
673   CN – interpretation of data, review of manuscript
674   HGT – Study design, analysis and interpretation of data, drafting of manuscript
675   CT – Study design, analysis and interpretation of data, drafting of manuscript

676

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684
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687
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689

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822
823   **Figure 1:** Strategy/Item Type calculation steps demonstrating the cognitive load for each
824   combination.
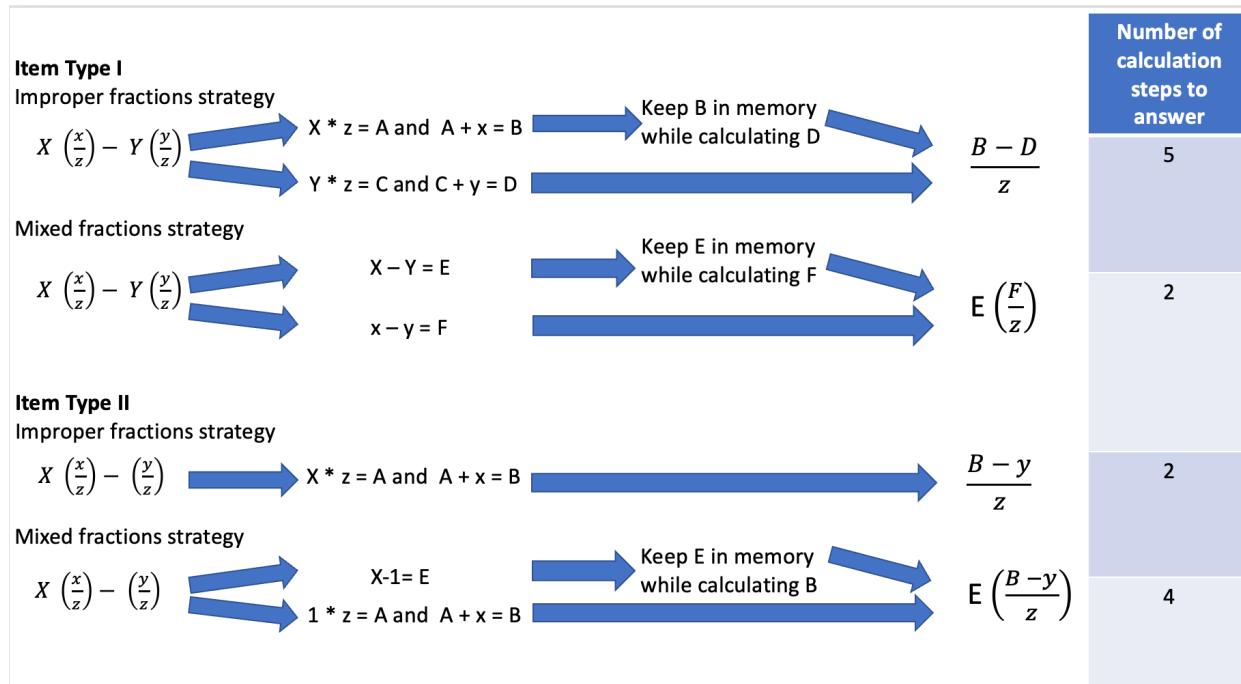
825
826
827   **Figure 2:** Sample fraction protocol demonstrating the two strategies.

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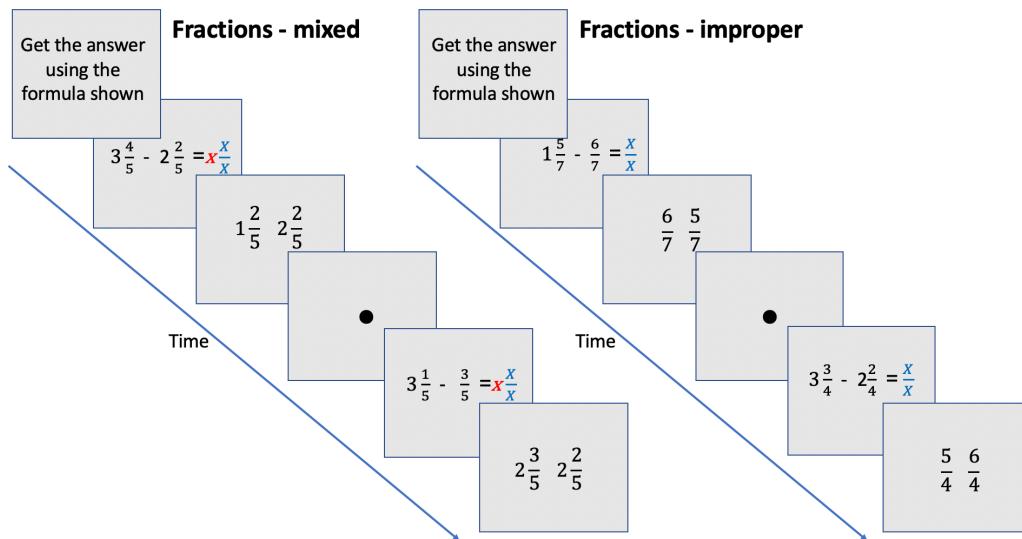
Figure 3: Hemodynamic responses associated with improper and mixed fractions for both groups. Contrasts are easy EPT vs FT, easy FT vs EPT, hard EPT vs FT, and hard FT vs EPT. Improper fractions (A) and mixed fractions (B) locations are shown separately. L = Left, R = Right, A = Anterior, P = Posterior. Regions include - left side: precuneus, superior, medial and middle frontal gyri, superior and inferior parietal lobule, pre- and post-central gyri, insula, cingulate gyrus, parahippocampal gyrus, caudate nucleus and thalamus. Right side: paracentral lobule, precuneus, pre- and post-central gyri, inferior and superior parietal lobule, superior, medial and middle frontal gyri, cingulate, caudate nucleus and thalamus.

A)

B)

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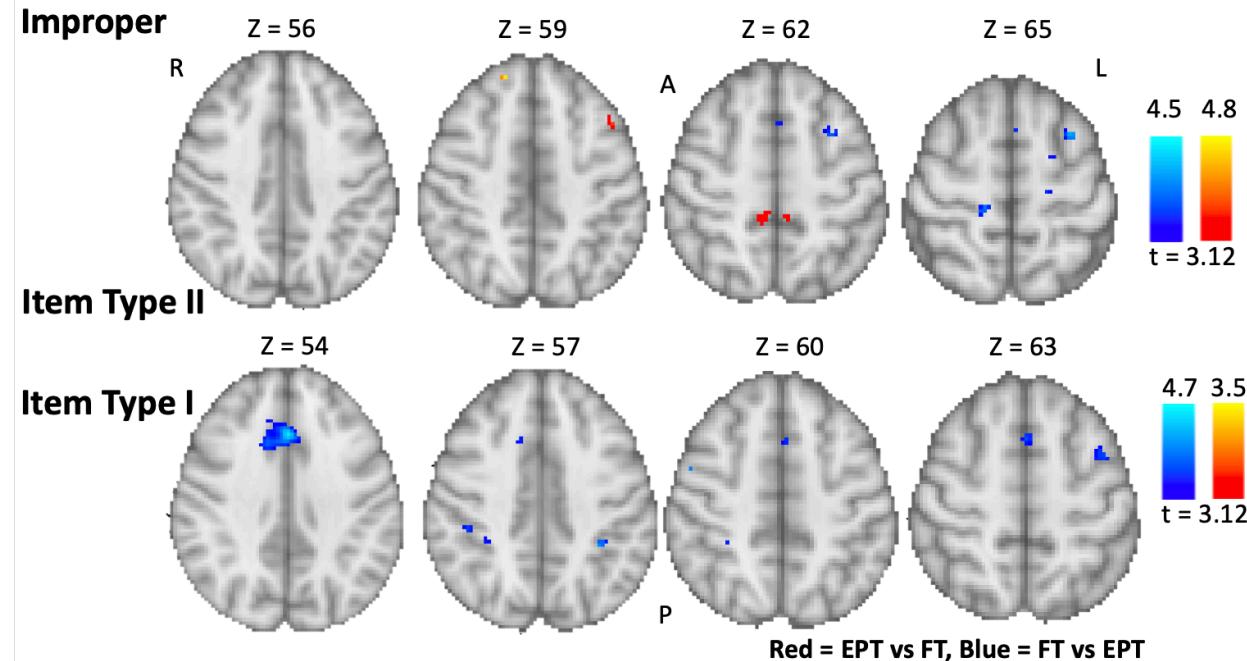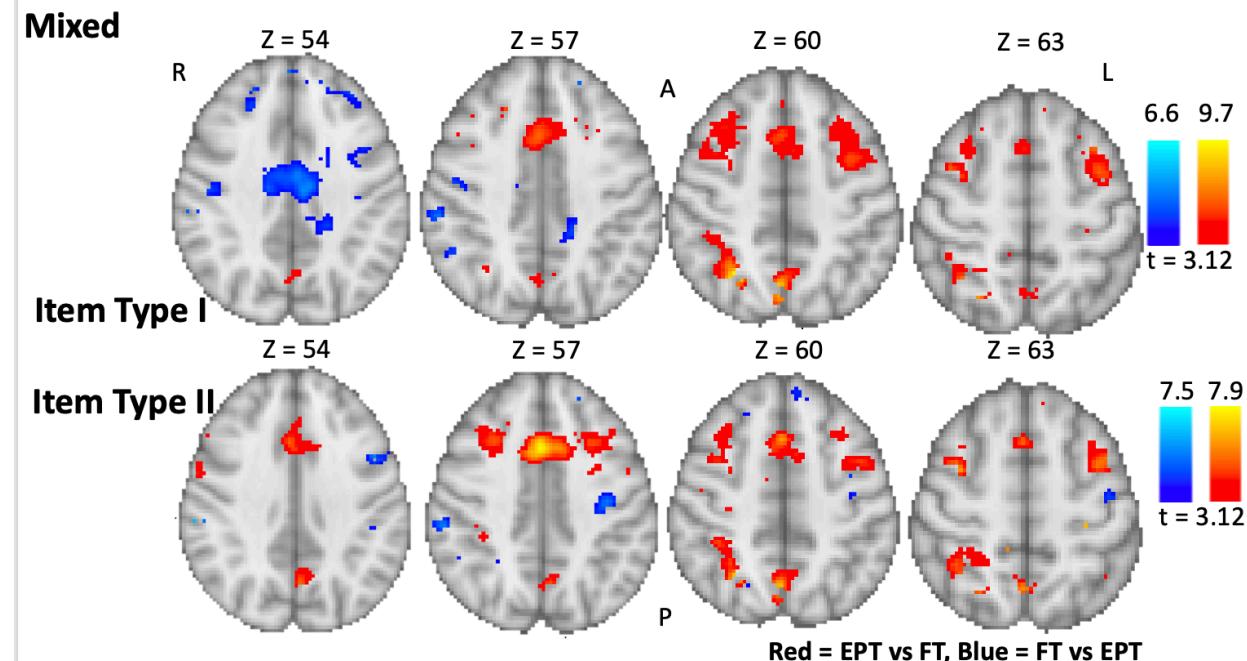
843 **Figure 4:** Conjunction analysis of EPT and FT group results for improper and mixed fractions.
844 The EPT (red) and FT (blue) results have been overlaid. Shared voxels between EPT and FT are
845 shown in yellow. Improper fractions and mixed fractions include both Item types I and II. The
846 brain activity is overlaid on the MNI template brain. L = left, R = right, A = anterior.
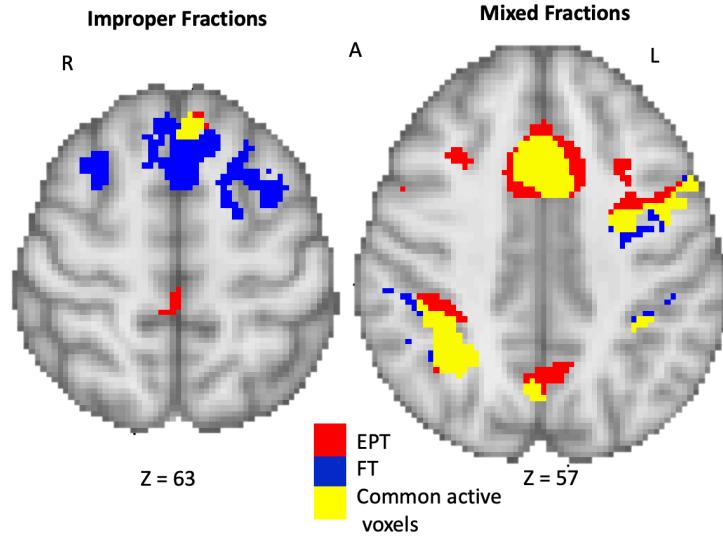
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849 **Figure 5:** Conjunction analysis of Item Types I and II for FT and EPT for mixed fractions. The
850 EPT (red) and FT (blue) results have been overlaid for each Item Type. Shared voxels are shown
851 in yellow. The brain activity is overlaid on the MNI template brain. L = left, R = right, A = anterior.
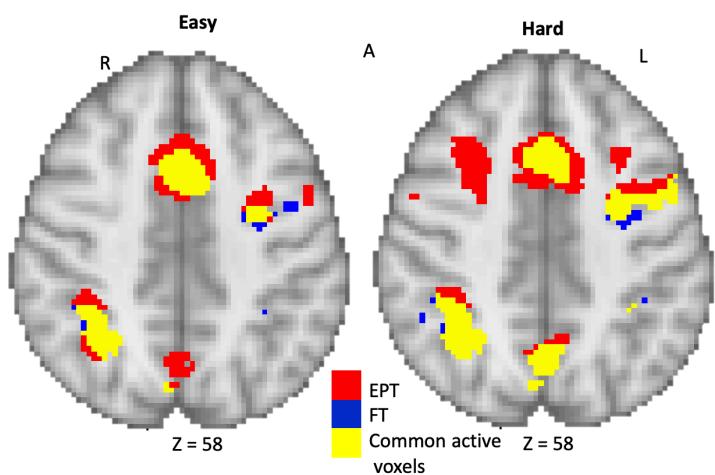
852
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854 **Figure 6:** Accuracies of group-level SVM classification of difficulty level (A) and strategy (B)
855 from both FT and EPT groups. A leave-one-out cross validation approach was used for all SVM
856 analyses.
857 A)

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859 **B)**
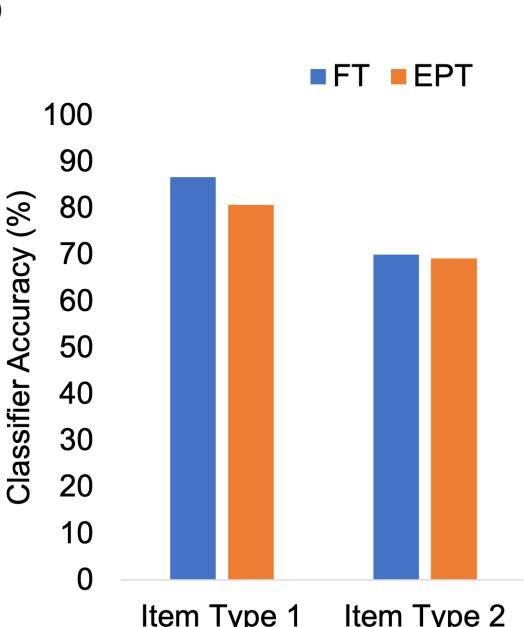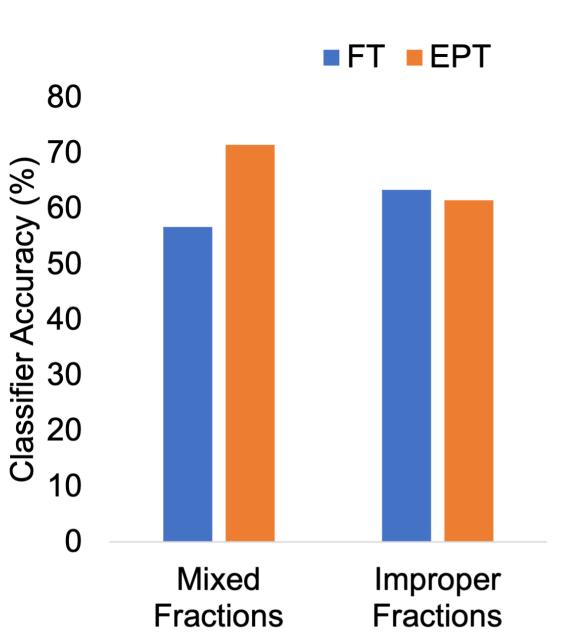
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863 **Table 1:** Summary of all subjects recruited for neuropsychological assessment. A subset of 30
864 subjects received MRI. Normally distributed continuous variables are described using mean (SD)
865 and tested using a t-test. Not normally distributed continuous variables are described using median
866 [IQR, interquartile range] and tested using a Wilcoxon test. Categorical variables are described
867 using percentages and tested using the Chi-squared test or Fisher's exact test (for variables with
868 small values). SD = Standard deviation, ZSES = a composite (mean of sample z scores) of maternal
869 education level, a measure of social advantage based on parent occupation, and medium income
870 of the family. HS = high school, GED = general education degree certificate, NDI =
871 neurodevelopment impairment (CP, Hearing, Vision and/or MDI<70), NeoRisk = number of

22

872 neonatal risk factors, SepsisNecMeningitis = sepsis, necrotising enterocolitis or menigitis present,
873 HUS = Head UltraSound, ROP = Retinopathy of prematurity, KTEA3 = Kaufman Test of
874 Educations Achievement third edition, WIAT3 = Wechsler Individual Achievement Test third
875 edition.WRAML2 = Wide Range Assessment of Memory and Learning, second edition.

	Level	EPT	FT	P-value	Stat test
Total		**14**	**16**		
SEX (%)	**Female**	**12 (85.7)**	**8 (50.0)**	**0.058**	**Fisher's exact**
	Male	**2 (14.3)**	**8 (50.0)**		
Age (mean (SD))		**16.60 (0.61)**	**16.00 (0.56)**	**0.009**	**T-test**
Age by year (%)	**14**	**0 (0.0)**	**2 (12.5)**	**0.304**	**Fisher's exact**
	15	**2 (14.3)**	**4 (25.0)**		
	16	**10 (71.4)**	**10 (62.5)**		
	17	**2 (14.3)**	**0 (0.0)**		
Ethnicity (%)	**Black or African American**	**7 (50.0)**	**7 (43.8)**	**1.000**	**Fisher's exact**
	Mixed	**0 (0.0)**	**1 (6.2)**		
	White	**7 (50.0)**	**8 (50.0)**		
Handedness (%)	**Left**	**3 (21.4)**	**0 (0.0)**	**0.090**	**Fisher's exact**
	Right	**11 (78.6)**	**16 (100.0)**		
Grade completed (%)	**8th**	**1 (7.1)**	**2 (12.5)**	**0.046**	**Fisher's exact**
	9th	**1 (7.1)**	**7 (43.8)**		
	10th	**11 (78.6)**	**7 (43.8)**		
	11th	**1 (7.1)**	**0 (0.0)**		
ZSES (median [IQR])		**0.07 [-0.32, 1.01]**	**0.50 [-0.16, 1.39]**	**0.467**	**Wilcoxon**
Maternal type of education (%)	**<HS**	**2 (14.3)**	**1 (6.2)**	**0.785**	**Fisher's exact**
	>HS	**11 (78.6)**	**14 (87.5)**		
	HS/GED	**1 (7.1)**	**1 (6.2)**		
Duration in years of Mothers Education (median [IQR])		**14.00 [12.00, 16.00]**	**15.00 [13.75, 18.00]**	**0.187**	**Wilcoxon**
Multiple Birth (%)	**Multiple Birth**	**2 (14.3)**	**0 (0.0)**	**0.209**	**Fisher's exact**
	Single Birth	**12 (85.7)**	**16 (100.0)**		

Birthweight in grams (mean (SD))		**780.00 (191.65)**	**3348.79 (537.28)**	**<0.001**	**T-test**
Gestational age (mean (SD))		**25.21 (1.42)**			
NDI (%)	**Impaired**	**5 (35.7)**			
	Not Impaired	**9 (64.3)**			
NeoRisk (%)	**0**	**6 (46.2)**			
	1	**3 (23.1)**			
	2	**2 (15.4)**			
	3	**1 (7.7)**			
	4	**1 (7.7)**			
Oxygen At 36wks (%)	**Not on O2@36wksCA**	**9 (69.2)**			
	On O2@36wksCA	**4 (30.8)**			
SepsisNecMeningitis (%)	**No**	**9 (64.3)**			
	Yes	**5 (35.7)**			
Severe HUS Abnormality (%)	**No**	**12 (85.7)**			
	Yes	**2 (14.3)**			
ROP (%)	**No**	**10 (76.9)**			
	Yes	**3 (23.1)**			
KTEA3					
Math Computation (mean (SD))		**92.21 (19.53)**	**101.94 (17.99)**	**0.167**	**T-test**
Math Concepts and Applications (mean (SD))		**92.57 (15.28)**	**103.25 (18.99)**	**0.104**	**T-test**
WIAT3					
Addition (mean (SD))		**87.50 (11.63)**	**96.88 (17.95)**	**0.106**	**T-test**
Subtraction (mean (SD))		**92.71 (11.47)**	**98.81 (16.60)**	**0.258**	**T-test**
Multiplication (mean (SD))		**86.93 (13.82)**	**92.81 (11.93)**	**0.221**	**T-test**

WRAML2				
Number Letter Scaled Score (mean (SD))	**10.21 (3.31)**	**11.00 (3.06)**	**0.505**	**T-test**
Finger Windows Scaled Score (mean (SD))	**8.29 (3.45)**	**11.81 (2.43)**	**0.003**	**T-test**

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877 **Table 2**: Median accuracy rates for the mixed and improper fractions tasks performed during
878 fMRI. Easy and Hard is the overall rates for the improper or mixed fractions. SD = standard
879 deviation.

	Improper Median accuracy rate (%)(IQR)	**Mixed Median accuracy rate (%)(IQR)**
FT		
Easy	100 (17.6)	100 (14.3)
Hard	100 (17.6)	85.7 (17.9)
EPT		
Easy	100 (28.6)	85.7 (0.0)
Hard	100 (14.3)	71.4 (25.0)

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881 **Table 3:** Between group differences in hemodynamic responses for Item Types for each fraction
882 strategy. P = 0.001, minimum cluster extent = 10 voxels.

Group	**Strategy/ Level**	**Cluster No.**	**Coordinates (MNI)**	**No. of Voxels**	**Peak t-score**	**Side**	**Location**
EPT >FT	Improper/ Item Type II	1	8 -38 52	21	3.50	Right	Precuneus
FT > EPT	Improper/ Item Type II	1	-30 8 54	43	4.36	Left	Middle Frontal Gyrus
		2	14 -28 58	36	3.74	Right	Paracentral Lobule
		3	-2 14 54	25	4.01	Left	Superior Frontal Gyrus
		4	-28 -48 64	12	3.95	Left	Superior Parietal Lobule
	Improper/ Item Type I	1	0 22 36	313	4.56	Left	Cingulate Gyrus
		2	-10 -64 64	33	4.66	Left	Superior Parietal Lobule
		3	-28 44 26	25	3.81	Left	Middle Frontal Gyrus
		4	0 12 54	25	3.62	Left	Superior Frontal Gyrus
		5	-32 -42 42	22	4.00	Left	Inferior Parietal Lobule
		6	-12 6 20	21	3.50	Left	Caudate
		7	-40 4 54	16	3.56	Left	Middle Frontal Gyrus
		8	16 -58 64	15	3.67	Right	Superior Parietal Lobule
		9	42 -34 40	13	3.48	Right	Inferior Parietal Lobule
		10	-34 56 16	11	3.76	Left	Superior Frontal Gyrus
		11	-8 -26 16	10	3.28	Left	Thalamus

EPT >FT	Mixed/ Item Type II	1	2 14 42	1258	7.74	Left	Medial Frontal Gyrus
		2	2 -60 52	817	7.02	Left	Precuneus
		3	34 0 54	315	6.03	Right	Middle Frontal Gyrus
		4	58 0 36	15	4.34	Right	Precentral Gyrus
		5	4 -70 48	13	5,15	Right	Precuneus
		6	-30 -30 -22	12	3.34	Left	Parahippocampal Gyrus
FT > EPT	Mixed/ Item Type I	1	-8 -14 38	653	5.17	Left	Cingulate Gyrus
		2	-46 6 38	221	4.44	Left	Middle Frontal Gyrus
		3	-20 48 38	159	5.81	Left	Superior Frontal Gyrus
		4	-16 -38 40	113	4.33	Left	Cingulate Gyrus
		5	0 50 20	69	5.26	Left	Medial Frontal Gyrus
		6	50 -14 40	60	4.17	Right	Precentral Gyrus
		7	56 -30 38	45	6.42	Right	Inferior Parietal Lobule
		8	30 -26 66	39	3.99	Right	Postcentral Gyrus
		9	-20 -32 70	35	3.93	Left	Postcentral Gyrus
		10	48 -50 42	21	3.92	Right	Inferior Parietal Lobule
		11	18 -8 28	21	3.59	Right	Caudate
		12	2 46 34	12	4.87	Left	Medial Frontal Gyrus
		13	4 -14 60	11	3.34	Right	Medial Frontal Gyrus
	Mixed/ Item Type II	1	-46 6 38	187	6.86	Left	Middle Frontal Gyrus
		2	-32 -26 66	115	6.14	Left	Postcentral Gyrus
		3	-36 -16 42	106	5.1	Left	Precentral Gyrus
		4	58 -30 38	56	7.35	Right	Inferior Parietal Lobule
		5	22 -34 12	40	3.88	Right	Thalamus
		6	14 -40 68	27	4.06	Right	Paracentral Lobule
		7	4 4 26	25	3.71	Right	Cingulate Gyrus
		8	-4 -10 66	23	3.65	Left	Medial Frontal Gyrus
		9	-6 42 48	16	3.68	Left	Superior Frontal Gyrus
		10	-42 -14 54	15	4.09	Left	Postcentral Gyrus
		11	-32 44 14	10	4.11	Left	Middle Frontal Gyrus

883

884 **Table 4.** Accuracies and confusion matrices from SVM classification of birth status.

	Classifier Accuracy (%)	Confusion Matrix (Prediction – Target)			
		EPT-EPT	EPT-FT	FT-EPT	FT-FT
Mixed, Item Type I (Easy)	60.71	7	5	6	10
Mixed, , Item Type II (Hard)	67.86	6	2	7	13
Improper, , Item Type II (Easy)	28.57	1	8	12	7
Improper, Item Type I (Hard)	64.29	7	4	6	11
Item Type I (Mixed Easy, Improper Hard)	53.57	6	6	7	9
Item Type II (Mixed Hard, Improper Easy)	50.00	3	4	10	11

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