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Brain activity during a visuospatial working memory task predicts arithmetical performance two years later

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Running title: IPS working memory activity and arithmetic

Abstract

Visuospatial working memory (WM) capacity is highly correlated with mathematical reasoning abilities and can predict future development of arithmetical performance. Activity in the intraparietal sulcus (IPS) during visuospatial WM tasks correlates with interindividual differences in WM capacity. This region has also been implicated in numerical representation and its structure and activity reflect arithmetical performance impairments (e.g. dyscalculia). We collected behavioural (N=246) and neuroimaging data (N=46) in a longitudinal sample to test whether IPS activity during a visuospatial WM task could provide more information than psychological testing alone and predict arithmetical performance two years later in healthy participants aged 6 to 16 years. Non-verbal reasoning and verbal and visuospatial WM measures were found to be independent predictors of arithmetical outcome. In addition, WM activation in the left IPS predicted arithmetical outcome independently of behavioural measures. A logistic model including both behavioural and imaging data showed improved sensitivity by correctly classifying more than twice as many children as poor arithmetical performers after two years than a model with behavioural measures only. These results demonstrate that neuroimaging data can provide useful information in addition to behavioural assessments and be used to improve the identification of individuals at risk of future low academic performance.

Key Words: child development; fMRI; mathematics; numerical abilities; working memory

Of the various mathematical domains taught at school, number, counting and arithmetic are those in which cognitive theory and experimental methods are the most developed (Butterworth 2005). Arithmetic is an academic skill which relies on a range of cognitive processes (Dehaene et al. 2004). Poor arithmetical abilities are a serious handicap for individuals and for society in general, increasing the risk of unemployment and depression, and significantly reducing lifetime earnings (Gross 2009). Children who have difficulties in arithmetic early on tend to remain low achievers (Andersson 2010). For this reason, finding early cognitive markers of individual differences in arithmetical abilities and their future development is a critical step for the implementation of successful intervention (Ramani and Siegler 2008; Räsänen et al. 2009; Holmes et al. 2009).

Behavioural studies have suggested that working memory (WM) could be one of the cognitive markers associated with arithmetical achievement (see Raghubar et al. 2010 for review). WM refers to a set of mental processes that enable us to hold and manipulate relevant information for brief periods of time. WM capacity is correlated with arithmetical performance both in children with and without known learning difficulties (Henry and MacLean 2003; Maybery and Do 2003; Kyttälä et al. 2003; Alloway et al. 2005; Alloway et al. 2009; Geary et al. 2009; Meyer et al. 2010). WM measures can also predict future development of arithmetical ability (Jarvis and Gathercole 2003; Gersten et al. 2005; Bull et al. 2008; Alloway and Alloway 2010, but see Gathercole et al. 2003; Geary et al. 2009) above and beyond measures of general intelligence or reasoning abilities (Alloway and Alloway 2010).

A number of theoretical models of WM have been proposed and these may differ in their potential use for the study of differences in arithmetical development (Berch 2008). Experimental studies typically make a distinction based of the type of information held in WM, whether it is verbal or visuospatial. The evidence is mixed regarding whether visuospatial or verbal WM has the most predictive value regarding the development of arithmetical abilities (Gathercole et al. 2003;

Rasmussen and Bisanz 2005; Bull et al. 2008; Meyer et al. 2010), and whether WM and non-verbal reasoning have independent predictive values (Passolunghi et al. 2007; Alloway and Alloway 2010; Primi et al. 2010).

Arithmetical impairments, for example in the case of developmental dyscalculia, may arise from deficits in elementary numerical processing such as impaired representation and processing of basic numerical magnitude, impaired numerosity coding or impaired “number sense” (see Butterworth 2005; 2010 for review). Meta-analyses have identified the intraparietal sulcus (IPS) as the locus of numerical representation (Dehaene et al. 2003; Cohen Kadosh et al. 2008). Both structure (Isaacs et al. 2001; Rotzer et al. 2008; Rykhlevskaia et al. 2009) and brain activity (Kaufmann et al. 2009; Kucian et al. 2006; Mussolin et al. 2010; Price et al. 2007; Rotzer et al. 2009) in this region reflect group differences in mathematical difficulties and current research points to IPS abnormalities as the single biological marker of developmental dyscalculia (Rubinsten and Henik 2009; Butterworth 2010). Brain imaging data indicate that numerical and WM functions converge in the IPS (Zago and Tzourio-Mazoyer 2002; Zago et al. 2008), which shows WM activation across several stimulus presentation modalities (Linden 2007). Moreover, individual differences in activity in the IPS are correlated with WM capacity differences among adults (Todd and Marois 2005), as well as when comparing children and adults (Klingberg et al. 2002a; Crone et al. 2006).

In the present study we first attempted to replicate previous findings regarding the predictive power of WM and reasoning measures for future arithmetical performance (Raghubar et al. 2010) using longitudinal data collected in a large sample of participants ranging in age from 6 to 16 years (N = 246). This focus on a wide age range is novel compared to previous studies, which tested single age groups (Gathercole et al. 2003; Bull et al. 2008; Alloway and Alloway 2010), or used age-corrected measures (Bull et al. 2008). Moreover, the inclusion of different age groups allowed us to investigate whether the relationship between predictive measures and arithmetical outcome changes with age.

Because of the mixed evidence regarding whether visuospatial or verbal WM is most relevant to arithmetical abilities, and of the value of recording multiple and varied measures, we assessed three behavioural measures of WM, which differed in terms of stimulus-type: a verbal WM task with word stimuli, a verbal WM task with number stimuli, and a visuospatial WM task.

We first tested whether the different types of WM measures and non-verbal matrix reasoning contributed to prediction of arithmetical performance two years later. Arithmetical performance was assessed with grade-dependent tests of elementary arithmetic. Our second and main goal was to assess whether brain activity, measured as change in the blood-oxygenation level dependent (BOLD) contrast, could improve prediction of arithmetical outcome. The hypothesis behind this analysis was that physiological measures would provide a more direct evaluation of the key neural substrates necessary for arithmetical performance. Whole-brain and local IPS activation during a visuospatial WM task was measured in a subset of 46 participants. Bilateral IPS regions of interests (ROI) were defined using the results of a meta-analysis of numerical representation (Cohen Kadosh et al. 2008) and we separately assessed the predictive use of the left and right IPS ROIs.

Materials and Methods

Participants

Participants were healthy volunteers recruited using random sampling from the population registry in Nynäshamn in Sweden, and part of a longitudinal study of typical development ('Brainchild' study, Söderqvist et al. 2010). Included here were participants aged between 6 and 16 years at the first time of testing (T1) who participated in the second round of testing (T2) two years later. The upper limit of the age range was chosen to only include participants in the educational system at T1 and T2. Exclusion criteria were a diagnosed neuropsychological disorder other than attention deficit and hyperactivity disorder (ADHD) and dyslexia, a mother tongue other than Swedish and severe hearing or vision impairment. We expected normal rates of these disorders in the population. ADHD symptoms corresponding to the DSM-IV criteria (American Psychiatric Association [*DSM-IV-TR*], 2000) were rated by parents for 223 out of the 246 participants at T1. One child was rated as having more than 6 symptoms of hyperactivity, none was rated as having more than 6 symptoms of inattention. Informed consent was obtained from the participants and from the parents of children under 18. The study was approved by the local ethics committee of the Karolinska University Hospital, Stockholm.

Behavioural assessment

A total of 246 participants (125 males) participated in the behavioural assessment. The sample included participants aged 6 (N=42), 8 (N=37), 10 (N=46), 12 (N=45), 14 (N=40) and 16 years old (N=36) at T1 (mean age: T1 10.83 years (SD 3.33); T2 12.86 (3.36)). Participants completed a large neuropsychological battery administered individually in a quiet room. In a separate session arithmetical achievement was measured by a written test performed individually in isolation or in a group.

Working memory measures

Visuospatial WM was assessed using the Dot Matrix task from the Automated Working Memory Assessment (AWMA) battery (Alloway 2007). This task involves remembering the location and order of dots displayed sequentially in a grid on a computer screen. Verbal WM was assessed with a Backwards Digit recall task. Numbers were read aloud to the participants, who verbally repeated them in the reverse order. In both these tests, difficulty was increased after four trials were correctly answered by adding one item to be remembered. The tests terminated when three errors were committed on one level. The scores used were the total number of correct trials. The third WM task was a 3-back task. Participants were read a total of twenty Swedish words and were asked to indicate, by responding yes or no on each trial, whether the word was the same as the word read three trials before. A score was calculated by subtracting the number of false alarms (wrong yes responses) from the number of correct responses. Although this task has not been validated and the data suggest poorer reliability than the other WM measures, it was included to obtain a measure of non-numerical verbal WM.

Reasoning ability

Raven's Progressive Matrices were used as a measure of reasoning ability (Raven 1998). Participants in the youngest age group (6 year-olds) performed sub-tests A-D, whilst all other participants performed all subtests (A-E), each comprising 12 items. The test did not have a time limit, although if the participant did not give an answer within one minute the administrator asked for an answer.

Arithmetical abilities

The arithmetical assessment was based on the Trends in Mathematics and Science Study (TIMSS; Martin et al. 2004) and Basic Number Screening Test (BNST; Gillham and Hesse 2001) and was designed in four school-grade dependent versions (grades 2, 4, 6 and grade 8, suitable for 14-27 year olds). Grades 2 and 4 problems included magnitude judgements, questions about the number sequence, as well as elementary arithmetic (addition, subtraction, division, multiplication and fractions). Grades 6 and 8 problems included elementary arithmetic and elementary algebra (simple equations with variables). Items were piloted in second and sixth graders (N = 400) at three schools in a suburb of Stockholm. Testing time was 30 minutes.

Preprocessing analyses

The raw results of the arithmetical and reasoning tests were initially transformed into ability scores. This transformation was carried out by item response theory (IRT) analyses using a partial credit model. The ability score of the IRT analyses is a measure of the probability of a participant passing the test, a function of the difficulty level of the item and the ability of the participant (see Berman Nutley et al. 2010, for details). These measures were then transformed into Z-scores. This preprocessing permitted combined analyses of different age groups, even though the groups did not perform the exact same tasks since the tests were age dependent.

Brain imaging

Data collection

A subset of 46 participants (23 males) were randomly selected to participate in the imaging part of the study (Söderqvist et al. 2010). This sample included participants aged 6 (N=6), 8 (N=9), 10 (N=9), 12 (N=6), 14 (N=9) and 16 years old (N=7) at T1 (overall mean age: T1 10.96 (3.35); T2 13.02 (3.35)). MRI data was collected on a 1.5 T Siemens scanner. T2*-weighted functional images were acquired with a gradient echo EPI (Echo Planar Imaging) pulse sequence with TR = 3000 ms, TE = 50 ms, flip angle = 90º, 30 oblique slices, 4.5 mm slice thickness, 0.5 mm interslice distance, 220 x 220 mm FOV, 64 x 64 grid, resulting in a voxel size of 3.44 x 3.44 x 4.5 mm. Structural T1-weighted spin echo images were acquired with a 3D MPRAGE sequence (FOV = 256 x 256 mm, 256 x 256 grid, 1 mm^3 voxel size).

fMRI paradigm

Participants performed a visuo-spatial WM grid task in two 5 min sessions including 16 WM and 16 Control trials. Trial order was pseudo-randomized. Stimuli were presented with E-Prime software using an MR compatible visual system (NordicNeuroLab). Dots were presented sequentially in a four-by-four grid for 500 ms, with 500 ms interval between dots. Two loads (2 dots or 4 dots) were implemented in the paradigm. 1500 ms after the last dot and the grid disappeared a cue was presented in the grid for 3000 ms. The cue was a number referring to a serial position in the previous stimulus sequence. Participants indicated with a yes/no response (right index and middle finger responses respectively) whether the number and its position in the grid matched, e.g. “2?” would prompt the participant to indicate whether the second circle had appeared in the grid position filled by the number. In the Control condition, the cue (number 8) always required a “no” response. A new sequence began 2000 ms after the response cue disappeared.

Data analysis

Preprocessing and statistical analyses (see Söderqvist et al. 2010) were carried out with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). Separate boxcar regressors modeled correct trials of the WM and Control load 2 and 4 conditions, with durations of 8 s (load 2) or 10 s (load 4). These regressors were convolved with a canonical hemodynamic response function, its temporal and dispersion derivatives, and, together with regressors representing residual movement-related artifacts and the mean over scans, comprised the full model for each session. Parameter estimates calculated from the least mean squares fit of the model to the data were used in a pair-wise contrast at the individual subject level to compare WM and Control conditions, irrespective of load. Contrast images for each participant were then entered in a one-sample test group analysis. Three regions of interest (ROIs) were defined and mean WM – Control parameter estimates were calculated for each ROI using MarsBar (Brett et al 2002). The first ROI corresponded to the whole-brain contrast WM – Control corrected for false discovery rate ($P < 0.05$). The other two ROIs were 8 mm-radius spheres centered in the left (-31 -54 46) and right (37 -50 43) IPS (coordinates from Cohen Kadosh et al. 2008)

(Figure 2). ROIs were plotted on a surface based human atlas (PALS)(Van Essen 2005) using the Caret software (Van Essen et al. 2001; http://www.nitrc.org/projects/caret/).

Results

Prediction of arithmetical performance: Behavioural measures

A total of 246 participants were included in the behavioural analyses. T1 behavioural measures were scores on the Dot Matrix, Backwards Digit and 3-back WM tasks, and on the Raven's matrices reasoning task. Arithmetical performance was the dependent variable assessed at T2. Reasoning and arithmetical scores were preprocessed using IRT to take into account age group differences in items tested, obtaining individual ability scores subsequently transformed into Z scores (see Berman Nutley et al. 2010, for details).

In a first step, a curve fitting analysis was performed to assess how best to model changes in arithmetical performance at T2 as a function of age at T1 (Figure 1). Linear, logarithmic and inverse fits were tested and the results indicated that an inverse function of age at T1 was the best fit for Arithmetic_Z at T2 (R^2 = .580, .622 and .642 respectively). Age^{-1} at T1 was thus the variable entered in all subsequent regression analyses.

Insert Figure 1 here

Multiple regression analyses were performed comparing a model with T1 Age^{-1} only and a model including reasoning and all three WM measures at T1. T2 Arithmetic_Z was the dependent variable. Including the behavioural measures significantly improved the fit of the model. All four behavioural measures were found to be significant independent predictors of arithmetical outcome (Table 1). High reasoning and high WM scores at T1 predicted high arithmetical scores at T2.

Insert Table 1 here

A second set of multiple regression analyses was performed to test for possible changes with age in the relationship between the behavioural measures and arithmetical outcome. T1 Age^{-1} was transformed into *Z*-scores to reduce collinearity between main effects and interactions (Aiken and West, 1991). T1 Age^{-1}_{Z}, reasoning and all three WM measures at T1 were first entered in the model predicting arithmetical score at T2. In a second stage, interaction terms between T1 Age^{-1}_{Z} and the four behavioural measures at T1 were entered in the model. The R^2 change following inclusion of the interaction predictors was not significant ($\Delta R^2 = .006$, $P = 0.213$). Individually, the only significant interaction predictor was the interaction between Backwards Digit score and T1 Age^{-1}_{Z} ($\beta = .21$, $P = 0.044$, all other *P*s > 0.24). Thus the predictive relationship between reasoning and WM measures and arithmetical outcome was mostly stable across the age range (6-16 years old) of our participants.

Prediction of arithmetical performance: Neuroimaging

A subset of 46 participants were scanned at T1 while performing a visuospatial WM task. The contrast of interest compared WM conditions (loads 2 or 4) to Control conditions matched for stimulus presentation and response production. WM – Control mean activation was calculated in the whole-brain WM – Control activation ROI, and in two 8 mm-radius sphere ROIs centered in the left (-31 -54 46) and right (37 -50 43) IPS (coordinates from Cohen Kadosh et al. 2008) (Figure 2).

Insert Figure 2 here

A first set of regression analyses were performed to test whether WM – Control activations were significant predictors of arithmetical outcome irrespective of participants' age. Individually, both whole-brain ROI BOLD and left IPS BOLD at T1 significantly positively predicted arithmetic performance at T2 (respectively $F(1,44) = 7.07$, $P = 0.011$, $\beta = .372$, $R^2 = .138$; $F(1,44) = 5.40$, $P = 0.025$, $\beta = .331$, $R^2 = .109$). There was a trend for a similar effect for the right IPS BOLD at T1 ($F(1,44) = 2.84$, $P = 0.099$, $\beta = .372$, $R^2 = .061$).

We then performed a set of multiple regressions where T1 Age^{-1} was entered first in the model, the whole-brain ROI activation second, and then either the right or left IPS ROI activations. This approach enabled us to assess specific IPS effects once overall brain activation and age were taken into account. The left IPS independently explained a significant amount (5.1%) of additional variance in T2 $Arithmetic_Z$ (Table 2). Greater left IPS residual activation once the effect of age was taken into account was associated with poorer arithmetical performance 2 years later. In this case, the right IPS was not a significant predictor of arithmetical outcome (ΔR^2 = .003, P > 0.5).

Similarly to the behavioural analyses, additional multiple regression analyses of the fMRI data were performed to test for possible changes with age in the relationship between the left IPS and whole-brain BOLD measures and arithmetical outcome. T1 $Age^{-1}{}_Z$, and whole-brain and left IPS WM-Control BOLD at T1 were first entered in the model. In a second stage, interaction terms between T1 $Age^{-1}{}_Z$ and the two BOLD measures at T1 were entered in the model. The R^2 change following inclusion of the interaction predictors was not significant (ΔR^2 = .007, P= 0.592, individual interaction predictors Ps >0.3). Thus the predictive relationship between whole-brain and left IPS BOLD measures and arithmetical outcome appeared stable across the age range (6-16 years old) of our participants.

Insert Table 2 here

A second set of multiple regression analyses assessed the significance of the WM and reasoning behavioural measures in the smaller neuroimaging sample of participants and tested whether the left IPS effect remained significant when behavioural measures were first included in the model. Results showed that in this smaller sample behavioural measures explained 10.1% more variance than age only. Only the reasoning and visuospatial WM measures significantly contributed to the model (Table 3). Importantly, adding activation in the left IPS to the model after whole-brain activation was included led to a further significant improvement of the full regression model of 2.5 % (Table 3).

Insert Table 3 here

Identification of the 20% lower performers

As an illustration of the added benefit of using neuroimaging data as a predictor of arithmetical outcome, we classified the fMRI sample into the 20% lower T2 Arithmetic_Z performers and 80% better performers per age group (6, 8, 10, 12, 14 or 16 years old at T1). The 20% threshold was chosen as an intermediary value between the 25% poor functional numeracy observed in adults (Parsons and Bynner 2005) and the 15% cutoff used for mathematics learning disability (MLD) in elementary school children (Geary et al. 2009). Binary logistic regression analyses were performed on these data to assess how well our models could classify the participants in these two categories. Sensitivity represents the proportion of lower 20% performers correctly identified as low performers, specificity the proportion of higher 80% performers correctly identified as high performers.

A model including age and all behavioural measures did not classify the participants better (trend only: X^2_4 = 8.6, *P* = 0.073, sensitivity 22.2%, specificity 97.3%, accuracy 82.6%) than a model with age alone (sensitivity 0%, specificity 100%, accuracy 80.4%). However, including whole-brain and left IPS WM – Control activity made a significant improvement to the model (X^2_2 = 6.5, *P* = 0.039), with the final full model (including behavioural and BOLD measures) classifying the participants in this smaller group significantly better than the model with age alone (X^2_6 = 15.1, *P* = 0.020, sensitivity 55.6%, specificity 94.6%, accuracy 87.0%). Adding fMRI measures to the model led to the correct classification of 5 out of 9 low performers instead of 2/9 when using the behavioural measures only.

Discussion

This longitudinal study combined behavioural and brain imaging measures to test whether functional imaging data could improve prediction of arithmetical outcome in 6 to 16 years-old participants. Our results show that greater activation in the left, but not right, IPS during a visuospatial WM task relative to the rest of the brain is associated with poorer arithmetical performance two years later. Left IPS activity is still a significant, although small, predictor when WM and reasoning abilities are first entered as predictors of arithmetical outcome. Although the participant samples were small, the use of brain imaging data improved more than two-fold the accurate classification of participants as poor arithmetical performers two years later. These results provide initial evidence that brain imaging is a sensitive tool for the identification of children at risk of poor academic outcome.

Developmental changes in arithmetical performance could be fitted by an inverse function of age, with the steepest improvements in performance observed between participants aged 6 and 8 at T1. A large part of the variance in arithmetical performance in our sample (64.2%) was predicted by age^{-1}. In this aspect the present study differs from previous longitudinal research in that a wide age range was included in the analyses instead of focusing on a single age group (Gathercole et al. 2003; Bull et al. 2008; Alloway and Alloway 2010) or using age-corrected measures (Bull et al. 2008). In line with previous longitudinal data (see Raghubar et al. 2010 for review), WM and reasoning abilities were found to be significant predictors of arithmetical outcome. Here, reasoning and all three WM measures were unique predictors of arithmetical performance two years later, accounting together for an additional 13% of variance when age was first entered in the model. These results fit with previous findings of unique contributing effects of WM and non-verbal IQ (Alloway and Alloway 2010) and verbal and visuospatial WM (Bull et al. 2008) for the prediction of mathematical outcome and extend the findings to a wide developmental age range. Overall there was little evidence for a change with age in the relationship between the behavioural predictors and arithmetical outcome.

Our findings thus suggest a consistent association between WM and reasoning measures and arithmetical abilities throughout childhood and adolescence.

In the smaller fMRI sample, only reasoning and visuospatial WM were significant predictors of arithmetical score at T2, which suggests verbal WM may be less strongly associated with arithmetical performance. In line with these results, verbal WM measures at age 4 have been found to predict reading comprehension, writing and spelling, but not mathematics, 2.5 years later (Gathercole et al. 2003), and to predict mathematical performance at the entrance but not at the end of the 1st or 3rd years of primary school (Bull et al. 2008) (see also Meyer et al. 2010). Note that, possibly counterintuitively, those verbal WM measures that were less strongly associated with arithmetical performance two years later in our sample, the Backwards Digit and 3-back tasks, were those that involved some aspect of numerical representation. Indeed it could be argued that although the 3-back task required maintaining and updating non-numerical Swedish words in WM, participants needed to count until 3 to perform the task accurately.

These results overall support the use of WM measures, in particular visuospatial WM, for the early identification of children at risk of poor academic outcome in arithmetic. WM training programmes (Klingberg 2010) have been shown to improve clinical symptoms of psychiatric disorders such as ADHD (Klingberg et al. 2002b; Klingberg et al. 2005), as well as performance on tests of mathematics, with mathematical reasoning improvements observed six months after WM training (Holmes et al. 2009). Previous mathematics training studies have focused on specific number-related training and obtained mixed results: training using number vs. colour-based board games led to improvements in performance of a range of numerical tasks at the end of training and nine weeks later (Ramani and Siegler 2008), while training on computerised tasks emphasising either numerical comparison or small exact numerosities showed improvement in number comparison but not counting or arithmetic after the training and three weeks later (Räsänen et al. 2009).

The main aim of the current study was to investigate whether brain imaging measures of WM would complement typical behavioural assessments and contribute uniquely to the prediction of arithmetical outcome. The analyses focused on the IPS, a brain region which has been specifically implicated in both numerical processing (Dehaene et al. 2003; Cohen Kadosh et al. 2008) and visuospatial WM (Linden 2007), and where visuospatial WM and arithmetical tasks show overlapping activity (Zago and Tzourio-Mazoyer 2002; Zago et al. 2008). IPS activation during number processing tasks correlates with arithmetical or mathematical abilities (Rubinsten and Henik 2009; Butterworth 2010), and IPS activation during visuospatial WM tasks correlates with WM capacity (Klingberg et al. 2002a; Todd and Marois 2005; Crone et al. 2006). However, there is no previous evidence that WM activation in the IPS may be directly linked to arithmetical performance. Instead, different neural populations may underlie the activations observed in visuopatial WM and number processing tasks. The present study argues against this by showing that neural activity during visuospatial WM tasks in the IPS has predictive value for the development of arithmetical abilities.

Our results first indicated that greater activation in the whole-brain WM-Control network, in the left IPS or in the right IPS (although at trend level only), predicted better arithmetical performance two years later. These results are broadly consistent with those of Rotzer et al. (2009), which showed that poor arithmetical abilities were associated with weaker right IPS activation during a spatial WM task in 8-10 years-old children. When the age of the participants was included in our analyses, the results showed that in combination with whole brain activity, left IPS activity during a visuospatial WM task predicted 5% more variance in arithmetical performance two years later than age alone. There was no significant interaction between the BOLD predictors and age, suggesting the observed effects were consistent across the age range of the participants. Further, whole brain activity and left IPS activity predicted 2.5% more variance than age and the behavioural reasoning and WM measures. Interestingly, in the full regression models the only significant predictors were age^{-1}, visuospatial WM and left IPS activity during the visuospatial WM task, highlighting the specifically high association between visuospatial WM and arithmetical performance.

When age was taken into account as a predictor, greater activation in the left IPS was thus associated with poorer arithmetical performance two years later, while there was a trend for greater activation in the whole-brain ROI to be associated with better arithmetical outcome. This direction of the IPS association, and its hemispheric localisation, differ from Rotzer et al. (2009)'s findings. However, in their study age was not taken into account. It is possible that age effects on the WM activation in the right IPS might have affected the observed positive correlation between right IPS WM activation and arithmetical performance observed by Rozter et al. (2009). The direction of the left IPS residual effect observed in the current study is novel and will need to be investigated further. It is possible that a complex pattern of relative activation levels in the different brain regions of the WM network is what is relevant for predicting arithmetical outcome. Such a pattern may be behind the present finding that, when age is covaried, weaker left IPS activation, in the context of a greater whole-brain network WM activation, is associated with better arithmetical outcome.

A potential limitation of these results lies in the fact that the visuospatial WM task in the scanner included the presentation of a single digit number in the response phase of the task. It is thus possible that the association between IPS activation during the task and arithmetical performance two years later partly reflects the processing of numerical representation in the response phase. Indeed both spoken and written numerals have been shown to specifically activate the IPS (Eger et al. 2003; Naccache and Dehaene 2001). However, the Control condition of the visuospatial WM task also included the presentation of a single digit number, which should have reduce this potential confound and suggests that the findings observed here may be specific to visuospatial WM activation.

To test a potential application of these results, we performed additional analyses which showed that age and behavioural measures could correctly classify only 2/9 of the 20% lower arithmetical performers, while adding fMRI WM data to the model improved this classification more than two-fold to 5/9. Although the sample sizes were small, these results suggest than fMRI data can be used to improve the identification of individuals at risk of future low academic performance in the domain of mathematics. This study thus extends previous research showing that brain measures (event-related potentials), could identify infants and young children at risk for dyslexia (Maurer et al. 2009; Guttorm et al. 2010, see Gabrieli 2009 for review) and provides further support for the usefulness of neuroimaging data. It remains to be seen which fMRI cognitive task would best predict arithmetical outcome. A combination of brain activation during a numerical processing task and numerical performance measures outside the scanner may have the best predictive power. However, an advantage of WM tasks is that they do not require number knowledge and could thus be performed, and trained, at an earlier age.

Underlying the link between visuospatial WM and arithmetical abilities may be their reliance on a common spatial “memory map”. In non-human primates, visuospatial information is assumed to be kept in WM by sustained activity in neurons coding specifically for stimuli at different visual angles (Funahashi et al. 1989). In humans, neural specificity for the visuospatial location of stimuli can be demonstrated by showing retinotopic organisation in a cortical region. Retinotopy has been found both in the IPS and the frontal eye field during the delay period of a visuospatial WM task (Konen and Kastner 2008; Silver and Kastner 2009). Such a spatial memory map could also be used for an analogue, spatial representation of numbers, and there is indeed evidence of spatial aspects of the representation of numbers. Behavioural data suggest that number comparison is performed using a mental number line, an analogue spatial representation in which numerical magnitude is represented along an axis oriented according to the direction of writing (Dehaene et al. 1993). This representation enhances responses to number stimuli whose values accord with the spatial position of the response

(SNARC task, Dehaene et al. 1993), and induces corresponding left/right shifts of attention (Nicholls et al. 2008). There is evidence in early development for a number-space mapping (de Hevia and Spelke 2010) and a general magnitude representation shared between the dimensions of space, number and time (Lourenco and Longo 2010). In adults, a common fronto-parietal network supporting processing of these three dimensions has been proposed (Walsh 2003), and is supported by studies showing all three dimensions are similarly affected by saccadic compression (Burr et al. 2010). Thus the spatial mapping required by visuospatial WM tasks and the mental number line mapping required by number comparison and arithmetical tasks may recruit similar neural populations.

Although the effects were small, the fact that neuroimaging data could significantly improve arithmetical outcome prediction compared to behavioural measures may be related to the intermediate phenotypes concept put forwards in the imaging genetics literature (Meyer-Lindenberg and Weinberger 2006). The suggestion is that neuroimaging measures may be more sensitive to individual differences by being closer to the biological substrate. Dyscalculia and poor performance in arithmetic are quite specifically associated with dysfunction of the IPS. Imaging data, which contrasts well-matched conditions in terms of visual stimuli and motor responses, can provide information on a subpart of the components that add to a behavioural WM score, e.g. processes of maintenance of information over a delay, and can provide localised measures of corresponding brain function. In addition, imaging data may reflect physiological or neural properties that might provide information about future capacity, e.g. number of neurons, or measures of structural maturity (synaptic connectivity strength and myelination), that are the basis of future cognitive development. In the present study, IPS activation during visuospatial WM may thus reflect the potential of local neural resources for supporting future arithmetical development.

Note that, although our participants where overall typically developing, it is likely that our results have validity for children with larger arithmetical deficits or dyscalculia, as it has been suggested that the genetic components of mathematics learning disability are likely to be the same as those underlying individual differences in mathematics achievement (Kovas et al. 2007). Moreover, the results obtained here in a large age range suggest that some behavioural and brain measures are good predictors of future arithmetical performance throughout development. Further work may identify whether some measures may be more specific to young age groups, for the development of tests permitting the early identification of children at risk of poor arithmetical outcome.

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Tables

Table 1: Multiple regression predicting arithmetical performance at T2 using age, reasoning (RavenZ) and working memory measures (Dot Matrix, Backwards Digit, 3-back) in the behavioural sample (N = 246).

	B	*SE*	*β*
Step 1: R^2 = .642***			
Constant	1.95	0.11	
T1 Age^{-1}	-258.8	12.4	-.80***
Step 2: ΔR^2 = .130***			
Constant	-1.04	0.32	
T1 Age^{-1}	-102.2	16.9	-.32***
T1 $Raven_Z$	0.30	0.07	.21***
T1 Dot Matrix	0.03	0.01	.23***
T1 Backwards Digit	0.03	0.01	.15**
T1 3-back	0.04	0.01	.14***

** $P < 0.01$, *** $P \leq 0.001$

Table 2: Multiple regression predicting arithmetical performance at T2 using age, whole-brain and left IPS WM – Control ROIs mean activation in the fMRI sample (N = 46).

	B	*SE*	*β*
Step 1: R^2 = .687***			
Constant	1.68	0.18	
T1 Age^{-1}	-199.8	20.3	-.83***
Step 2: ΔR^2 = .003			
Constant	1.79	0.25	
T1 Age^{-1}	-207.6	23.7	-.86***
T1 Whole-brain WM-Control	-0.13	0.19	-.06
Step 3: ΔR^2 = .051**			
Constant	2.02	0.25	
T1 Age^{-1}	-229.8	23.3	-.95***
T1 Whole-brain WM-Control	0.50	0.28	.26[†]
T1 Left IPS WM-Control	-0.51	0.18	-.44**

[†] $P < 0.1$ ** $P < 0.01$, *** $P \leq 0.001$

Table 3: Multiple regression predicting arithmetical performance at T2 using age, reasoning and WM behavioural measures, and whole-brain and left IPS WM – Control ROIs mean activation in the fMRI sample (N = 46).

	Step 1: R^2 = .687			Step 2: ΔR^2 = .101**			Step 3: ΔR^2 = .001			Step 4: ΔR^2 = .025*		
	B	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*	*B*	*SE*	*β*
Constant	1.68	0.18		0.57	0.94		0.7	1.03		0.64	0.98	
T1 Age^{-1}	-199.8	20.3	-.83***	-107.5	31.6	-.45**	-113.5	36.8	-.47**	-139.9	37.0	-.58***
T1 $Raven_Z$				0.24	0.10	.27*	0.23	0.11	.27*	0.16	0.11	.18
T1 Dot Matrix				0.04	0.01	.37**	0.04	0.01	.37**	0.04	0.01	.36**
T1 Backwards digit				-0.02	0.02	-.11	-0.02	0.02	-.11	-0.02	0.01	-.11
T1 3-back				-0.02	0.04	-.05	-0.02	0.04	-.05	0	0.04	-.01
T1 Whole-brain WM-Control							-0.06	0.18	-.03	0.4	0.27	.20
T1 Left IPS WM-Control										-0.38	0.17	-.33*

* $P < 0.05$, ** $P < 0.01$, *** $P \leq 0.001$

Captions

Figure 1: Scatterplot of arithmetical performance of T2 as a function of age at T1. The line represents a fit of the data as a function of age^{-1}, which was found to be a better fit of the development of arithmetical performance than functions of age or ln(age).

Figure 2: Representation of the ROIs used in the fMRI analyses. (A) Coronal and transverse slices: the whole-brain contrast of the WM – Control conditions is represented in yellow and was performed using FDR correction ($P < 0.05$); the IPS ROIs are represented in blue and were 8 mm radius spheres centered on coordinates obtained by Cohen-Kadosh et al. (Cohen Kadosh et al. 2008) in a meta-analysis of fMRI studies of numerical representation (left IPS: -31 -54 46; right IPS: 37 -50 43). (B) Render of the whole-brain main effect and IPS ROIs on a surface-based human atlas (see Materials and Methods).

Figure 1

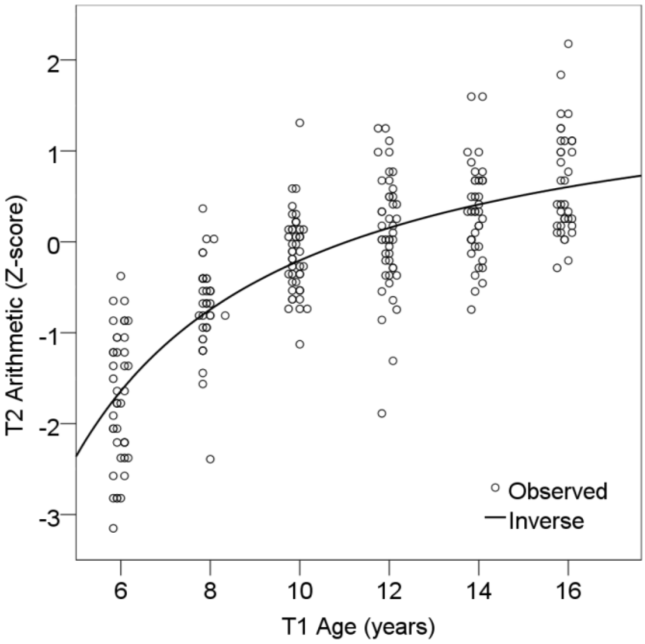

Figure 2