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Cerebellar brain volume accounts for variance in cognitive performance in older adults.

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Abstract

Introduction: Frontal lobe atrophy is implicated in patterns of age-related cognitive decline. However, other brain areas, including the cerebellum, support the work of the frontal lobes and are also sensitive to the effects of ageing. A relationship between cerebellar brain volume and cognitive function in older adults is reported, but no study has separated variance associated with cerebellar gray matter volume and cerebellar white matter volume; and no study has examined whether or not brain volume in the cerebellum is related to cognitive function in older adults after statistical control for frontal lobe volume of gray and white matter.

Method: We used voxel based morphometry (VBM) and structural equation modelling (SEM) to analyse relations between general cognitive ability (G) and volume of gray and white matter in frontal areas and cerebellum in a sample of 228 older adults (121 males and 107 females).

Results: Results indicate that gray matter volume in the cerebellum predicts G, even when total intracranial volume (TICV) and gray and white matter volumes in frontal lobes are statistically controlled. However, results differ for males and females, with males showing a stronger relationship between brain volume in the cerebellum and G.

Conclusions: Results are discussed in light of neurological models of cognitive ageing and the significance of the cerebellum in models of cognitive functioning.

1. Introduction

There is mounting evidence that cognitive functions are supported by the neocerebellum containing the phylogenetically more recent cerebellar regions (Cabeza & Nyberg, 2000; Desmond & Fiez, 1998; Ito, 2008; Timmann & Daum, 2007). Functional imaging research provides evidence for cerebellar activity during a broad range of cognitive activities including: rule-based word-generation (Petersen et al., 1989), mental imagery (Parsons et al., 1995; Ryding et al., 1993), cognitive flexibility (Kim et al., 1994), sensory discrimination (Gao et al., 1996), motor learning (Jenkins et al., 1994; Rauch et al., 1995), verbal memory (Grasby et al., 1994), and working memory (Hayter et al, 2007; Klingberg et al., 1995).

Neuroanatomical evidence suggests that the prefrontal cortex and lateral cerebellum are the last structures to develop during maturation and the first to undergo involution in later life (Allman et al., 1993; Arenberg, 1987; Grady et al., 1999; Haug, 1991; Raz et al., 2001). Potentially, the cerebellum works in conjunction with the frontal and pre-frontal cortex in the modulation of behaviour (Schmahmann, 1996) but the mechanism of such possible interaction is less clear (Ito, 2008; Timmann & Daum, 2007). The frontal lobes are thought to support executive control processes, that is, a sub-set of cognitive skills requiring effortful attention and the ability to manage one's thoughts, memories and actions in accordance with task-relevant goals (Chudasama & Robbins, 2006; Mohr, Goebel, & Linden, 2006; Stuss & Alexander, 2007; Stuss & Benson, 1984). Executive function declines throughout middle to late adulthood and frontal lobe atrophy may play a central role in these patterns of age-related cognitive decline (West, 1996). The cerebellum may support the resource and capacity base of the

frontal lobes by modulating the speed, variability, and automaticity of information processing operations (Hogan, 2004; Ito, 1993; Leiner, Leiner, & Dow, 1989, 1991; Ramnani, 2006; Schmahmann, 2003, 2004), which in turn may facilitate executive control and general cognitive ability (Craik and Anderson, 1999; Salthouse, 1996).

In order to understand how the cerebellum might work in conjunction with the frontal lobes in the modulation of behaviour, it is potentially useful to examine the effect of ageing on both the frontal lobes and the cerebellum and to model these effects conjointly when examining brain-behaviour relations. While this strategy of analysis can extend to other brain areas that play a role in patterns of ageing cognition (e.g., the temporal lobes), the current study focuses on general cognitive ability (G) and the hypothesised role of cerebellar-frontal lobe associations with G (Hogan, 2004).

Substantive clues about the importance of connectivity and interaction between multiple cortical and sub-cortical sites comes from studies of sub-cortical dementia (Albert et al., 1974; Filley et al., 1989; Grafman et al., 1990; Gunning-Dixon & Raz, 2000; Junque et al., 1990; Rao et al., 1989), but little is known about the relationship between cognition and cerebellar volumes in healthy older adults. In a notable exception, MacLullich and colleagues (MacLullich et al., 2004) observed significant correlations between size of the neocerebellar areas of the vermis and several cognitive tests in a sample of healthy elderly men. However, MacLullich and colleagues did not assess the relative contribution of brain volume in frontal regions in accounting for cognitive performance, nor did they separate out the effects of gray matter volume and white matter volume in their analysis – an important distinction in light of research demonstrating a relationship between white matter atrophy and cognitive decline (Gunning-Dixon & Raz,

2000; Medina et al., 2006; Murray et al., 2005). Furthermore, MacLullich and colleagues examined the relationship between brain area (not volume) in the cerebellum and cognition in males only, and in light of recent evidence pointing not only to a reduction in the size of the cerebellum over the adult lifespan but also to gender differences in the size of the cerebellum (Raz et al., 2001) and gender differences in the rate of cell loss in the cerebellum with age (Xu et al., 2000), we argue that it is important to model the relationship between frontal lobe volume, brain volume in the cerebellum and cognitive performance in both males and females separately. Specifically, research suggests that the cerebellum shrinks proportionally more with age in men than women (Xu et al., 2000). Therefore, in samples of healthy older males and females matched on age, education, and childhood intelligence, we might expect that any observed relationship between cerebellar volume and G would be stronger for males than females, that is, after statistically controlling for gender differences in total intracranial volume (TICV).

In the present study, we used voxel based morphometry (VBM) and structural equation modelling (SEM) to analyse relations between general cognitive ability (G) and volume of gray and white matter in both frontal lobes and the cerebellum in a large sample of males and females (N = 228) who are participating in the Aberdeen Longitudinal Study of Cognitive Ageing (Murray et al., 2005). Males and females were matched on age, education, and childhood intelligence. We used VBM to first establish whether or not there is any relationship between brain volume and G. We then used Multi-Group SEM to examine the direct and indirect effects on G of both gray and white matter brain volume in the cerebellum and the frontal lobes while controlling for total intracranial volume (TICV). We used multiple indicators of G and cereballar volume in

our SEM analysis, and as part of our analysis we tested for measurement invariance for G, across both males and females. We predicted gender invariance in G and thus specified an a priori multi-group measurement model with a single latent variable and equal factor loadings for males and females. Also, given the conclusion by Raz and colleagues (2001) that age-related reduction in the cerebellum is uniform, we defined and tested two *a priori* measurement models that used a single latent variable to represent cerebellar gray matter volume and cerebellar white matter volume, again with equal factor loadings for males and females (see SEM Results Section, Models 1 - 3). In Model 4 we combined the three measurement models into a fuller path analysis which specified *a priori* relations between the core independent and dependent variables of interest. Consistent with the findings of MacLullich and colleagues, we hypothesized a direct effect on G of brain volume in the cerebellum, and we expected this effect to be stronger in males when compared with females. As part of our effort to ensure rigorous testing of the relationship between cerebellar brain volume and G, our VBM analysis examined the relationship between G and brain volume across the whole brain (i.e., without reference to any *a priori* hypothesis and by using statistical controls that correct for multiple comparisons in the analysis of brain-behaviour relations). Similarly, in our SEM analysis of the effect on G of brain volume in the cerebellum we controlled for both brain volume in the frontal lobes and TICV. Finally, in light of the role of the frontal lobes in age-related reduction in G (West, 1996; Hedden & Gabrieli, 2004), we remained open to the possibility that any effect of the volume of cerebellum on G would vanish in the context of statistical controls for frontal lobe volume.

2. Methods

2.1 Participants

We recruited, from the local community, volunteers who were all born in 1936 between 2000 and 2001. All had participated in the Scottish Mental Survey of 1947 when about 95% of children born in 1936 and at school in Scotland on 1st June 1947 were tested. 986 of the 1823 Aberdeen city children, who sat the test in 1947, were traced to an address in North East Scotland. The 986 who were traced were linked to local general medical practices. General practitioners were selected at random to help with the study and agreed to invite by post 647 local residents who could be matched exactly by birth name and date of birth with entries in the Scottish Mental Survey (1947) archive. From these 647, 506 (75%) volunteered to participate in a long-term follow up study of brain ageing and health and, among these 506, 22 did not complete their first assessment. Participants with an initial Mini-Mental State Examination (MMSE) score <23 were excluded from the cohort, scores of 23 and over suggesting that volunteers retained in the samples were not dementia sufferers. Refusal to take part was significantly associated with lower childhood mental ability scores ($p<.05$). Between April 2004 and April 2006 (at mean age 68.7 years, SD .8 years), a subgroup (N=320) was invited at random to undergo an MRI examination; 248/320 (77%) agreed to MRI and 248 image datasets were obtained. Those for whom imaging was obtained had significantly higher childhood mental ability and a significantly higher current mental ability (measured using Raven's progressive Matrices) than those who declined imaging ($p<.05$). These procedures were approved by the regional Research Ethics Committee. Written informed consent was obtained for the study.

2.2 Cognitive testing

Tests were selected to assess the major domains of cognitive ability, and to be age sensitive. All the tests used load on what Carroll describes as the 'general cognitive factor' (Carroll, 1993). We had a very good fitting single factor model for both males and females, which suggests that all tests used load on a general cognitive factor (see below). The composite score used (G) is the factor weighted sum of the scores on the three measures.

2.21 Non-verbal reasoning. Raven's Standard Progressive Matrices (Raven, Court, & Raven, 1977) were used as a measure of nonverbal reasoning. This test is one of the best individual tests with respect to loadings on the general cognitive ability factor (Carroll, 1993). There are 60 items organized in 5 groups of 12. Participants were allowed 20 min to complete the test. The number of correctly completed items comprised the score.

2.22 Short- and long-term memory. The Rey Auditory Verbal Learning Test (AVLT; Lezak, 1995, pp. 438–446) assessed short-term and longer term memory and learning. Participants were given 5 trials to learn a list of 15 words. They were asked to recall as many of the words as possible immediately after hearing each repetition of the list. At the conclusion of these 5 trials, a list of 15 new words was read to them. The participants were asked to recall as many of these new words as possible immediately after the list was read. Distraction was then provided by structured discussion with the tester for 5 min. Following this, participants were asked to recall as many of the original list's 15 words as

possible without its being read to them again. The sum of the scores from each part of the test was used as the total AVLT score.

2.23 Speed of information processing. The Digit Symbol subtest of the Wechsler Adult Intelligence Scale—Revised (WAIS–R; Wechsler, 1981) was used as an indicator of speed of information processing (Salthouse, 1996). The test involves participants in substituting symbols for numbers according to an explicit code. It was administered as instructed in the test manual. The score was the number of correct substitutions made in 90 s.

2. 3 Imaging

Image datasets were obtained between April 2004 and April 2006, when the participants had a mean age of 68.7 years (SD .8 years). Each participant was scanned using a 1.5 T GE NVi MR scanner (General Electric Medical Systems, Milwaukee, WI, USA) and a quadrature head coil. A 3D T1 weighted sequence (SPGR) was used with a TR of 20 ms, a TE of 6 ms, a flip angle of 35 degrees, a field of view of 24 cm, and a slice thickness of 1.6 mm. The sequence acquired 124 contiguous slices into matrices of 256x256. A single excitation was used. Of the imaging data sets 7 were considered unusable due to participant movement. Results of cognitive tests were not available for 10 participants. This resulted in a sample of 228 (121 male).

2. 4 Image analysis

The T1 data was processed using SPM2 (Wellcome Dept. of Cognitive Neurology, London, England http://www.fil.ion.ucl.ac.uk). Each data set was automatically segmented into three images representing the probability that any voxel contained gray matter (GM), white matter (WM) and CSF. This was done using optimised voxel based morphometry (VBM) implemented using the SPM2 code (Good et al., 2001). The segmented data were smoothed with a Gaussian smoothing kernel of 10mm full width at half maximum.

2. 5 Total Brain volume and customized study specific template

Total GM, WM and CSF volumes were calculated using the sum of all segmented voxels for each tissue type, in 'native' non-normalized space. The total intracranial volume was calculated as the sum of all three tissue types (including the cerebellum). A customized study specific T1 template was created by first registering all image data sets to the standard template provided within the SPM software. A mean of the registered individuals was then created to create the customized study specific T1 template.

2.6 Volumes of Interest (VOI)

As part of our analysis, we interrogated our data using the assumption that there are specific brain locations associated with cognition. In order to do this, we defined volumes of interest associated with these assumptions. A frontal lobe VOI was initially defined using the Wake Forest Pick atlas tool. The Wake forest frontal lobe VOI was first inspected for registration against the study specific T1 template created for the VMB analysis. The VOI was manually edited so that the VOI boundaries outline the frontal

lobe defined by the boundary with central sulcus, lateral sulcus and the corpus callosum. T1 template was registered to an individual's T1 MRI data set. The transformations required for this were then applied to the VOI. The VOI was then manually edited, adding and removing voxels, where appropriate to create an individual VOI. This was then used to extract the frontal lobe GM and WM volumes from the segmented T1 data sets in 'native' non-normalized space.

The cerebellar vermis was divided into four regions of interest (VOIs). These were created by first drawing ROIs on the mid-saggital slice of the customised T1 template. The first ROI included the lingula and lobulus centralis and was bordered by the superior medullary velum and the preculminate fissure. This area corresponds to lobules I–III in the nomenclature of Larsell and Janssen (1972). The second ROI was bordered by the preculminate fissure and the primary fissure, and included the culmen (lobules IV and V). The declive, folium, and tuber (lobules VI and VII) made up the third ROI, which was bordered by the primary fissure and the prepyramidal fissure. The boundaries of the fourth ROI were the prepyramidal fissure and the inferior medullary velum. It contained the pyramis, uvula, and nodulus (lobules VIII–X). For each ROI the upper and lower borders met at the apex of the fourth ventricle. These ROIs were then copied into adjacent sagittal slices to the left and right of the mid slice creating VOIs representative of the ROIs 1.8cm thick and centred on the mid slice. Volume of gray matter and volume of white matter was computed for all four ROIs, from the segmented images, in native space using a registration, review and manual editing approach similar to that described for the frontal lobe.

3. Results

Descriptive statistics and gender difference t-test statistics are reported in Table 1.

Insert Table 1 around here

3.1 VBM

First we modelled the regional association between gray matter (GM) volume and G with gender as a co-factor and age at imaging as a co-variable and tested for a positive association between GM and G. Here we found clusters of voxels predominantly in the frontal lobe and cerebellum. Each cluster contained only voxels that were significant after correction for multiple comparison (False Detection Rate $p<0.02$). In order to avoid false positives brought about by noise only clusters >30 voxels (~0.25 mls) were considered significant. Selecting an extended threshold to filter the statistical maps involves choosing between a threshold that is large enough to eliminate values brought about by noise and a threshold that small enough so as not to eliminate small structures you may be interested in. Given some of the small structure in the cerebellum vermis are central to our study we selected 30 voxels as a reasonable compromise between these two concerns.

The locations of the clusters are shown in Figure 1. The statistical details are shown in Table 2. A similar analysis of white matter found no significant associations.

Insert Figure 1 around here

In an analysis of the males separately we found that all of the locations identified previously were again significant after FDR correction for multiple comparisons with the exception of the right inferior frontal gyrus, the right insula, and the splenium of the corpus callosum. The GM differences identified in the splenium are confusing, since the splenium is a white matter structure and this may represent adjacent GM. Its apparent mis-location may have been brought about by a combination of non perfect segmentation and/or registration and the degree of smoothing used. The right inferior frontal gyrus, the right insula, and the splenium of the corpus callosum did however have FDR corrected probabilities of $p<.1$. No new locations were identified as being significantly associated with G (FDR corrected $p<.02$, cluster size >30 voxels,). Separate analysis of women showed that only left inferior frontal gyrus was significantly associated with G (FDR corrected $p<.02$, cluster size >30 voxels). No new locations were identified as being significantly associated with G.

No significant associations were found between G and the regional WM volumes in males or females. Although we found several GM significant regions in men, but not women, analysis revealed no significant differences (FDR $p<.02$) between the sexes for the regional volume association with G.

Insert Table 2 around here

3.2. Structural Equation Models

Following the guidelines suggested by Hoyle and Panter (1995), the goodness of fit for each model (both measurement and structural) is assessed using the chi-square, the Goodness of Fit Index (GFI: Jöreskog & Sörbom, 1981), the Incremental Fit Index (IFI: Bollen, 1989), and the Comparative Fit Index (CFI: Bentler, 1990). A non-significant chi-square ($p \leq 0.05$ level) and values greater than 0.95 for the GFI, IFI and CFI are considered to reflect acceptable model fit. In addition, the Root Mean Square Error of Approximation (RMSEA: Steiger,1990) with 90% confidence intervals (90%CI) was reported, where a value less than 0.05 indicates close fit and values up to 0.08 indicate reasonable errors of approximation in the population (Jöreskog & Sörbom, 1993).

3.21 Measurement models

A series of one factor models was used to assess the dimensional structure of 1) General cognitive ability (measured using three indicators: Raven's Progressive Matrices, the Auditory Verbal Learning Test, and Digit Symbol), 2) cerebellar gray matter volume (measured with 4 indicators: Vermis I-III, IV-V, VI-VII, and VIII-X), and 3) cerebellar white matter volume (measured with 4 indicators: Vermis I-III, IV-V, VI-VII, and VIII-X). In the first of the measurement models general cognitive ability was well described by reference to a single factor measurement model where the factor loadings were constrained to be invariant across males and females, χ^2 $(df = 1, N = 228) = 0.15$, $p = .698$, GFI = 1.00, IFI = 1.00, CFI = 1.00, RMSEA = 0.000 (90%CI, 0.000 – 0.129). Cerebellar gray matter (Cg) volume was similarly well described by reference to a single factor measurement model where the factor loadings were constrained to be invariant across

males and females, χ^2 *(df* = 1, *N* = 228) = 1.07, *p* = .301, GFI = 0.99, IFI = 1.00, CFI = 1.00, RMSEA = 0.018 (90%CI, 0.000 – 0.178). Cerebellar white matter (Cw) volume was also well described using this single factor measurement model, χ^2 *(df* = 5, *N* = 228) = 6.85, *p* = .232, GFI = 0.98, IFI = 0.99, CFI = 0.99, RMSEA = 0.040 (90%CI, 0.000 – 0.107). These results highlight the factorial invariance for our three measurement models and suggest that it was reasonable to use composite indexes for cerebellar gray matter volume, and cerebellar white matter volume within a path analytic structure examining the relations between brain volume in the cerebellum and general cognitive ability. Composite scores for Cg and Cw were generated, separately, by computing the sum of volumes across the four lobes of the cerebellum. However, given that our three indicators of G were measured on three distinct scales, we retained the one factor G measurement model in the overall structural model used to examine the effect on G of brain volume in the cerebellum and frontal lobes (see *Structural Models* below). In the G measurement model the factor loadings were invariant, but the intercepts indicated that the means relating to the observed measures differed. Males had a higher score on the Raven's Matrices but on the other two measures (Digits and Avltot), females had the higher scores. (See also the results reported in Table 1).

3.22 Structural Models

An analysis was undertaken of the direct and indirect effects on general cognitive ability (G) of brain volume in the cerebellum and the frontal lobes while controlling for total intracranial volume (TICV). In order to maximise statistical power a multi-group approach was taken to the analysis of gender, and a large number of measurement invariant restrictions were placed on the model. These included factor loading, intercepts,

variances and covariances and regression effects. Constraining these parameters not only permits a test for invariance but also enhances the statistical power of the model. In the first path model all direct effects, covariances, means and variances for the exogenous measures were constrained to be equal across the groups, with the exception of the intercepts for the measure of Raven's Matrices within the G factor. All sources of residual variance and intercepts relating to endogenous structural measures were permitted to vary across genders. This model failed to adequately describe the data ($\chi^2(df = 47, N = 228) = 174.841$, $p = 0.001$, TFI = 0.646, CFI = 0.622; RMSEA = 0.154 (90%CI, 0.130 - 0.179). Following an examination of the residuals, parameter estimates and fit statistics a number of modifications were introduced. The means for all of the exogenous measures were permitted to be different between the groups and the effect from cerebellar gray matter (Cg) to G was also allowed to differ. This provided a good fit for the data ($\chi^2(df = 41, N = 228) = 39.673$, $p = 0.5296$, TFI = 1.0, CFI = 1.0; RMSEA = 0.00 (90%CI, 0.00 – 0.061).

In the path model the intercepts for G and TICV were statistically different between the sexes. Females had a higher intercept value on G and a lower value on TICV, indicating that females had scored higher on the G factor and lower on TICV. However, males tended on average to score higher on the measure of Raven's Matrices, but lower on the other two measures; hence the factor representing G is only partially invariant. Within this context it is also evident that the effect from Cg to G is only statistically significant for the males. However, in the context of the current model, if the female effect from Cg to G was of the same size as that for females, we would have a statistical power above 80% to detect such an effect.

Insert Table 3 around here

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4. Discussion

The findings of the current study extend those of MacLullich et al. (2004), who observed a relationship between the neocerebellar vermian areas and cognitive performance. The results of our multi-group SEM analysis revealed a significant relationship between cerebellum gray matter volume (GM) and general cognitive ability (G) in men but not women. The VBM analysis also revealed a relationship between GM and G in men but not women. VBM analysis also identified multiple GM regions associated with G in the full sample that are in part consistent with other reports of an association between GM and intelligence. These included BA 47 bilaterally (Colom, Jung, & Haier, 2006; Frangou, Chitins, & Williams, 2004), BA 10 (Colom et al., 2006; Frangou et al., 2004; Gong et al., 2005; Haier, Jung, Yeo, Head, & Alkire, 2004) and BA 13 (Colom et al., 2006). Furthermore, the anterior cingulate volume (BA 25), postulated to be an early marker in Alzheimer's dementia (AD) by Johnson et al. (2000), and significantly associated with G in our sample, was shown to be smaller in AD when compared to mild cognitively impaired (MCI) subjects (Karas et al., 2004). Similarly, the superior temporal gyrus (BA 13) was found to be smaller in groups of MCI subjects who subsequently develop dementia (Karas et al., 2008). By virtue of their age alone, our sample is at risk of imminent cognitive decline attributable to dementia and these findings may therefore represent a dementia prodrome. At the same time, our participants were without dementia at the time of testing, and correlations between brain volume and G observed

may simply represent covariation in the range of normal ability. Our VBM results show associations in the vermis region 3 previously reported by MacLullich and colleagues (MacLullich et al., 2004). In general, our VBM results are consistent with most published literature.

Although we predicted that the relationship between cerebellar volume and G would be stronger in men when compared with women, the results of our multi-group SEM revealed no significant relationship between cerebellar volume and G in women when frontal lobe volume and TICV were statistically controlled. This finding was observed in the context of strong statistical power to observe any such effect if it existed. Notably, controlling for total intracranial volume, the women in our sample had significantly higher proportions of both frontal gray matter and cerebellar gray matter volume when compared with men. Furthermore, the women had higher levels of overall cognitive functioning than men. Thus, while it is possible that some portion of the men in our sample are at risk of imminent cognitive decline attributable to dementia and have possibly already experienced some neural degeneration, it may be that the women in our sample are a high performing group who have experienced no substantial neural degeneration. As such, it is possible that cerebellar gray matter volume will emerge as a significant predictor of general cognitive ability for the women in our sample as they age. This interpretation is also consistent with findings from previous research which suggest that the cerebellum shrinks proportionally more with age in men than women (Xu et al., 2000).

None of our analyses has found a robust association between the white matter volume and G. This was somewhat unexpected since in previous studies using a similar

cohorts of subjects (The Aberdeen Birth Cohort of 1921) we found associations between white matter volumes and cognition (Staff et al, 2006) and white matter hyperintensities and cognition (Leaper et al., 2001). This apparent contradiction can be explained by the differences in the cohort. The previously published cohort was scanned between 79 and 80 years old whereas the present sample was scanned between 67 and 69 years. It can be expected that a significant amount of atrophy will occur in our sample over the coming decade brought about by ageing, the environment and underlying disease. It may well be that the associations found previously are a consequence of these processes and that in the current sample these effects have not yet influenced white matter volume and cognition.

Of interest in the context of our SEM analysis is that there was no significant relationship between frontal lobe volume and general cognitive ability (G). Specifically, the direct path between frontal lobe volume and G in both males and females is non-significant and, although a significant relationship between frontal lobe volume and TICV is present, the indirect influence of frontal lobe volume on G (via TICV) is non-significant. This raises the issue of what unmeasured variables might predict G. It may be that we need greater disaggregation of measures (e.g., to model the influence of several frontal areas on G). What this paper does is address some pertinent questions while raising a number of substantive issues that remain to be answered

There are many mechanisms through which the cerebellum may support the work of the frontal lobes, and in particular the information processing demands linked to performance on tests of general cognitive ability. As noted in the introduction, research points to a role for the cerebellum in the following three functions: the speed of

information processing, the variability of information processing, and the development of automaticity through learning and practice. Each of these functions may be critical for understanding general cognitive ability and the cognitive performance of older adults more generally (Hogan, 2004). For example, researchers have consistently observed a relationship between the speed of information processing and age-related declines in memory and reasoning ability (Cerella, 1990; Salthouse, 1996). While researchers continue to investigate the brain mechanisms associated with this relationship (Hogan et al., 2006) there is much scope for new research efforts that examine the contribution of the cerebellum.

Much remains to be done to understand fully how the frontal lobes and the cerebellum might interact during the performance of selected cognitive tasks. Some excellent examples of research that address this question are now in the literature (Balsters & Ramnani, 2008), the results of which suggest that the prefrontal-projecting zones in the human cerebellum process the abstract content of information embedded within sensory cues and thus facilitate not only the motor performance dimension of performance tasks, but also the symbolic processing component. Extending the strategy used in the current study, we suggest the application of structural equation modelling techniques to the analysis of combined MRI/fMRI and cognitive performance data in both younger and older adults. Given the hypothesised role of the cerebellum in learning (Ito, 2008), we believe it would be particularly interesting to examine changes in the fMRI – performance relation in prefrontal and lateral cerebellum over the course of learning trials in younger and older adults. More generally, functional brain changes associated with performance on a variety of age-sensitive cognitive tasks can be used as

endogenous variables in an effort to understand the relationship between levels of activation in frontal areas and levels of activation in the cerebellum. This data can be combined with MRI data in an effort to understand the relationship between both structural and functional brain changes and cognitive ageing. Although SEM might be fruitfully used in this context for the purpose of comparing alternative models, one caveat for future use of SEM is the issue of sample size and statistical power necessary to test complex models of brain-behaviour relations. In the current study, we were fortunate enough to have access to a relatively large sample for the purpose of modelling relatively complex relations. However, if as noted earlier further disaggregation of measures is needed to clarify the hypothesised role of cerebellar-frontal lobe associations with G, and if MRI and fMRI measures are to be combined in this modelling effort, then increasingly large samples and increasing efforts to generate standardized measurement techniques and collect data across different laboratories will be needed.

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Table 1: Descriptive statistics and gender differences

		Mean	*SD*	*t-value*	*p*
Age (years)	male	68.69	0.67		
	female	68.69	0.66	0.03	0.977
Mini-Mental State Examination	male	28.90	1.14		
	female	28.92	1.29	0.09	0.926
Moray house score (age 11 years)	male	44.73	10.57		
	female	45.94	10.45	0.87	0.384
Education (years)	male	11.12	2.30	0.03	0.975
	female	11.12	1.89		
Raven's Progressive Matrices	male	39.03	7.71		
	female	37.45	7.72	1.55	0.123
Digit Symbol	male	43.66	10.90		
	female	48.15	10.52	3.15	0.002
Auditory Verbal Learning Test	male	58.01	14.00		
	female	67.97	13.57	5.44	0.001
General Cognitive Ability	male	140.70	24.95		
	female	153.57	25.41	3.92	0.001
Total Intercranial Volume	male	1741.77	132.10		
	female	1532.10	121.73	12.41	0.001
Frontal Gray Matter Volume [a]	male	94.29	6.17		
	female	97.18	5.61	3.67	0.001
Frontal White Matter Volume	male	81.36	5.77		
	female	79.85	6.62	1.84	0.067
Cerebellum Gray Matter Volume - Total	male	50.61	6.33		
	female	56.61	7.19	6.70	0.001
Cerebellum White Matter Volume - Total	male	13.26	2.22		
	female	14.22	2.46	3.09	0.002
Cerebellum Gray Matter Volume - lobules I–III	male	0.82	0.10		
	female	0.89	0.11	4.97	0.001
" " - lobules IV - V	male	1.41	0.16		
	female	1.46	0.15	2.22	0.027
" " - lobules VI - VIII	male	2.35	0.27		
	female	2.60	0.29	6.48	0.001
" " - lobues IX - X	male	1.62	0.25		
	female	1.82	0.29	5.50	0.001
Cerebellum White Matter Volume - lobules I–III	male	0.13	0.03		
	female	0.12	0.04	2.93	0.004
" " - lobules IV - V	male	0.06	0.02		
	female	0.06	0.02	2.74	0.007
" " - lobules VI - VIII	male	0.26	0.06		

	female	0.26	0.07	0.98	0.326
" " - lobues IX - X	male	0.18	0.05		
	female	0.18	0.07	0.34	0.732

[a] Frontal lobe and cerebellar volumes are proportional to total intracranial volume (volume x 1000 / TICV).

Table 2: A summary of the gray matter VBM/SPM result showing the regions of the brain that have a significant positive correlation with G. These results were produced with an FDR multiple comparison correction of $p<.02$ and a cluster threshold of >30 voxels. [m] indicates those areas that have a significant positive correlation in men with G at the same significance level. [f] indicates those areas that have a significant positive correlation in women with G at the same significance level.

Cluster Location	Brodmann Area	x, y, z	FDR corrected p	Cluster Size
Left Inferior Frontal Gyrus & Insula [m,f]	47, 13	-38,18,-6	.002	821
Superior &Medial Frontal Gyrus [m]	10	-2, 66, 6	.002	717
Anterior Cingulate [m]	25	10, 20, 4	.004	489
Left Inferior Frontal Gyrus	47	-50, 40, -12	.005	42
Left Inferior Lateral Cerebellum [m]	NA	-24, -56, -50	.005	963
Right Insula	13	44, 10, -6	.007	261
Right Inferior Lateral Cerebellum [m]	NA	30, -66, -54	.007	761
Left Superior Temporal Gyrus [m]	13	-48, -42, 18	.008	75
Right Inferior Frontal Gyrus	NA	58, 32, 10	.010	35
Vermis ROI 3 [m]	NA	-2, -76, -22	.011	38
Splenium of the Corpus Callosum *	NA	20, -50, 10	.011	72

*The splenium is a white matter structure; this cluster may represent adjacent GM. Its apparent mis-location may have been brought about by a combination of non-perfect segmentation and/or registration and the degree of smoothing used.

Table 3. Model 4 estimates for females and males

			Estimate	S.E.	C.R.	P
Constrained factor loadings						
Raven's		G	1.000	0.000	--------	-------
Digits		G	0.953	0.199	4. 786	0.001
AVLT		G	1. 395	0.271	5.154	0.001
Constrained direct effects						
TICV	<---	Frontal Gray	.036	.005	7.232	0.001
TICV	<---	Frontal White	.042	.005	9.203	0.001
TICV	<---	Cerebellum Gray	.136	.048	2.817	0.005
TICV	<---	Cerebellum White	-.0.418	0.239	-1.753	0.080
G	<---	Cerebellum White	-3.773	2.271	-1.661	0.097
G	<---	Frontal Gray	0.019	0.050	.375	0.708
G	<---	Frontal White	-0.054	0.050	-1.074	0.283
G	<---	TICV	0.683	0.630	1.083	0.279
Direct effect for females						
G	<---	Cerebellum Gray	.292	0.615	.474	0.635
Direct effect for males						
G	<---	Cerebellum Gray	1.264	0.571	2.213	0.027
Correlations between the exogenous measures (standardized)						
Cerebellum Gray	←-→	Frontal Gray	0.343	0.058	5.877	0.001
Cerebellum Gray	←-→	Frontal White	0.307	0.060	5.121	0.001
Cerebellum Gray	←-→	Cerebellum White	0.442	0.053	8.283	0.001
Frontal Gray	←-→	Frontal White	0.618	0.041	15.116	0.001
Frontal Gray	←-→	Cerebellum White	0.099	0.066	1.507	0.132
Frontal White	←-→	Cerebellum White	0.387	0.056	6.868	0.001
Means for females						
Cerebellum Gray			10.376	0.116	89.606	0.001
Cerebellum White			0.964	0.024	39.856	0.001
Frontal Gray			148.733	1.306	113.842	0.001
Frontal White			122.408	1.432	85.497	0.001
Means for males						
Cerebellum Gray			10.816	0.109	99.332	0.001
Cerebellum White			1.155	0.023	50.764	0.001
Frontal Gray			164.036	1.229	133.516	0.001
Frontal White			141.789	1.346	105.314	0.001

	Estimate	S.E.	C.R.	P
Intercepts for females				
TICV	3.849	0.596	6.461	0.001
Raven's	14.736	8.119	1.815	0.070
G	16.683	8.222	2.029	0.042
Intercepts for males				
TICV	4.602	0.650	7.083	0.001
Raven's	22.411	7.854	2.854	0.004
G	0.000	0.000	-------	-------
Constrained intercepts				
Digits	27.173	8.014	3.391	0.001
AVLT	35.534	11.129	3.193	0.001
Constrained variances				
Cerebellum Gray	1.435	0.134	10.677	0.001
Cerebellum White	0.063	0.006	10.677	0.001
Frontal Gray	182.640	17.106	10.677	0.001
Frontal White	219.332	20.542	10.677	0.001

Figures

Figure 1. The gray matter VBM/SPM result showing the regions of the brain that have a significant positive correlation with G. These results were produced with an initial statistical threshold of $p<.001$ and a cluster threshold of 30 voxels. Each cluster contains at least one voxel which has a corrected cluster level significance of $p<.02$ (FDR corrected).