Behav Genet (2010) 40:146–156
DOI 10.1007/s10519-009-9318-4

ORIGINAL RESEARCH

White Matter Integrity in the Splenium of the Corpus Callosum is Related to Successful Cognitive Aging and Partly Mediates the Protective Effect of an Ancestral Polymorphism in *ADRB2*

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Received: 20 February 2009 / Accepted: 21 November 2009 / Published online: 20 January 2010

Abstract It has recently been reported that the evolutionarily ancestral alleles of two functional polymorphisms in the β_2-adrenergic receptor gene (*ADRB2*) were related to higher cognitive ability in the 70 year old participants of the Lothian Birth Cohort 1936 (LBC1936). One emerging important factor in cognitive aging is the integrity of white matter tracts in the brain. Here, we used diffusion tensor MRI-based tractography to assess the integrity of eight white matter tracts in a subsample of the LBC1936. Higher integrity of the splenium of the corpus callosum predicted better cognitive ability in old age, even after controlling for IQ at age 11. Also, the ancestral allele of one *ADRB2* SNP was associated with both splenium integrity and better cognitive aging. While the effects of the SNP and splenium integrity on cognitive aging were largely independent, there was some evidence for a partial mediation effect of *ADRB2* status via splenium integrity.

Keywords Cognitive aging · Diffusion tensor MRI · White matter tractography · Splenium corpus callosum · *ADRB2* · Comparative genomics

Edited by William Kremen.

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Introduction

Tracking molecular genetic causes for heritable differences in complex, dimensional traits such as cognitive ability and cognitive aging has proven difficult so far (Deary et al. 2009a, b; Manolio et al. 2009). Recently, more attention has focused on different approaches to identify candidate functional polymorphisms influencing these complex traits in the genome (Deary et al. 2004). A rather novel approach is provided by comparative genomics, which allows the identification of genes that have been under positive selection in a lineage and were thus probably involved in diverging evolution between species. Such genes can be detected by the ratio of non-synonymous to synonymous nucleotide substitutions that emerge for different genetic loci when comparing the genomes of related species, e.g. humans and chimpanzees (Harris 2008).

A comparative genomic approach is usually taken to detect species-typical adaptations that have become genetically unimorphic because they have been fixated by natural selection. However, genes that show signs of positive selection in cross-species comparisons might still show functional polymorphisms in one or both species

today, and these might contribute to the genetic variance between individuals in traits of interest (Thomas and Kejariwal 2004). Based on this assumption, several studies have examined functional polymorphisms in genes that show signatures of positive selection that are expressed in the brain, and tested them for associations with cognitive ability and related traits in modern humans. For example, it has been reported that the *MCHP1* and *ASPM* genes (both associated with primary microcephaly, a neurodevelopmental disorder characterized by dramatic reduction in cortical volume) show signatures of recent positive selection (Evans et al. 2005; Mekel-Bobrov et al. 2005). Subsequently, several studies have looked for links of these genes with current individual differences in either brain size (which shows a robust phenotypic and genetic correlation with general cognitive ability; McDaniel 2005; Miller and Penke 2007) or cognitive, reading or language abilities (Woods et al. 2006; Bates et al. 2008; Mekel-Bobrov et al. 2007). However, none of these studies found significant associations with variants in these two genes. More recently, Bochdanovits et al. (2009) reported, in this journal, a list of 28 SNPs in 22 brain-expressed genes with signatures of positive selection. Two functional SNPs (rs1042713 and rs1042714) in the β_2-adrenergic receptor gene *ADRB2* stood out as they were significantly associated with cognitive ability test scores. However, the pattern of results was complex: the derived, human-specific allele of the rs1042713 SNP was associated with increased performance IQ in Dutch teenagers, but unrelated with cognitive ability in Dutch middle-aged adults, and associated with decreased cognitive ability in the 70-year-old subjects comprising the Lothian Birth Cohort 1936 (LBC1936) from Scotland (Deary et al. 2007). Furthermore, whereas the rs1042714 SNP was not tested in the Dutch cohorts because it was not in Hardy–Weinberg equilibrium, the derived allele was again associated with decreased cognitive ability in the Scottish cohort.

The *ADRB2* gene on chromosome 5 encodes the β_2-Adrenergic receptor, which is a member of the G protein-coupled receptor superfamily and is part of the catecholamine system, where it acts as a receptor for adrenaline, noradrenaline and dopamine. Within the coding region of the intronless *ADRB2* gene, there are two non-synonymous SNPs: a substitution of the ancestral G for a derived A in codon 16 (rs1042713), which encodes for the amino acid glycine rather than the arginine (Arg16–Gly), and a substitution of the ancestral G for a derived C at codon 27 (rs1042714), which codes for glutamic acid rather than glutamine (Gln27–Glu). These two variants modulate receptor activity (Cockcroft et al. 2000; Johnson 2006). The opposing effects of *ADRB2* polymorphisms on cognitive ability in younger and older samples in the article by Bochdanovits et al. (2009) might imply that it is more closely related to individual differences in normal cognitive aging than to lifelong cognitive ability differences. Variability in *ADRB2* has also been associated with autism (Cheslack-Postava et al. 2007) and memory consolidation (see Bochdanovits et al. 2009). Additionally, the hypoperfusion of the cerebral white matter in multiple sclerosis is proposed to act through astrocytic β2-adrenergic receptors (De Keyser et al. 2008). However, the exact effects of *ADRB2* on the central nervous system are generally not well understood.

The current study aims to shed some light on the effects of *ADRB2* on cognitive functioning in old age by taking an imaging genetics approach. In imaging genetics, associations between polymorphisms and brain parameters derived from neuroimaging are studied, based on the assumption that individual differences in brain structure, chemistry and function are closer to gene function than differences that are measured by cognitive tests (Mattay et al. 2008). A plausible neurobiological substrate for individual differences in cognitive ability and cognitive aging is the integrity of axonal fibre tracts in the brain, the so-called white matter. This is because it is unlikely that single areas in the brain are responsible for general cognitive functioning. Instead, cognitive ability probably represents the orchestrated functioning of different brain areas, which requires intact white matter tracts to allow for information transfer between areas (especially between frontal and parietal-temporal areas, Jung and Haier 2007). White matter tracts are also prone to age-related decline (Sullivan and Pfefferbaum 2006), making them good candidates for neurobiological correlates of cognitive aging (O'Sullivan et al. 2001, 2004; Deary et al. 2006). Again, this is especially true for white matter tracts with connections to frontal regions (Sullivan and Pfefferbaum 2006). On the other hand, it has been argued that, in case of age-related decline of brain structure, cognitive deficits can be compensated by the adaptive recruitment of contralateral brain areas for the affected functions (Cabeza 2002; Park and Reuter-Lorenz 2009). In this case, white matter tracts that allow information transfer between the hemispheres are especially crucial for successful compensation.

White matter integrity can be studied in vivo using diffusion tensor magnetic resonance imaging (DT-MRI), which measures the mobility of water molecules (Beaulieu 2002). DT-MRI provides two scalar metrics of white matter integrity, namely the mean diffusivity ($\langle D \rangle$), which measures the magnitude of water diffusion, and fractional anisotropy (FA), which indicates the directional coherence of diffusion (Basser and Pierpaoli 1996). In regions of the brain with highly organised myelinated structures, such as the corpus callosum, water diffusion will be highly restricted and dependent on fibre direction, and so $\langle D \rangle$ will be low and FA high. Alterations in axonal microstructure will change the magnitude and directional coherence of water molecule diffusion, which will be reflected in the

measured ⟨D⟩ and FA values. Additionally, several studies of pathologies have investigated whether the eigenvalues ($\lambda 1$, $\lambda 2$ and $\lambda 3$) of the apparent water diffusion tensor obtained from DT-MRI can be used to differentiate impaired myelination from axonal injury (Harsan et al. 2006; Song et al. 2002; Tyszka et al. 2006). Since the axial ($\lambda ax = \lambda 1$) and radial ($\lambda rad = \{\lambda 2 + \lambda 3\}/2$) diffusivities represent water diffusion parallel and perpendicular to the axonal fibres, their results of increased cross-fibre diffusion in the presence of impaired myelination suggest that λrad may be an indicator of myelin loss while λax may be an indicator of axonal integrity (Bastin et al. 2009).

In a subsample of the LBC1936, in which Bochdanovits et al. (2009) found an association between *ADRB2* and cognitive ability, we used DT-MRI quantitative tractography (Bastin et al. 2008; Clayden et al. 2007) to assess the integrity of three bilateral white matter tracts that connect frontal and posterior cerebral areas, as well as two parts of the corpus callosum, which is the main interhemispheric white matter connection in the brain. The LBC1936 is unusually valuable in that childhood IQ scores of its members are available from the Scottish Mental Survey of 1947 (Deary et al. 2007). We investigated associations of the two functional *ADRB2* polymorphisms and the three well-established haplotypes they form (Diatchenko et al. 2006) with the integrity of the eight individual white matter tracts that, according to what has been proposed in the literature, are most likely to underlie higher cognitive functioning and cognitive aging (i.e. those plausibly involved in frontal-parietotemporal integration processes or contralateral compensation). Wherever significant associations were found, we also tested for relationships of tract integrity values with cognitive ability and lifetime cognitive change, as well as for mediating effects of tract integrity on gene-ability links.

Methods

Sample and procedure

The LBC1936 comprises 1091 surviving participants of the Scottish Mental Survey 1947 (SMS1947) who undertook medical and cognitive testing at a mean age of 70 years (see Deary et al. 2007, for full details on participant recruitment). Participants lived independently in the community around the city of Edinburgh, Scotland, and were able to travel to the Wellcome Trust Clinical Research Facility in Edinburgh. At a mean age of approximately 72 years, surviving members of the LBC1936 are, at the time of writing, visiting the Wellcome Trust Clinical Research Facility a second time to undergo cognitive re-testing, structured medical interviews, and the SFC Brain Imaging Research Centre for neuroimaging.

The current study was based on a subsample of 162 participants (90 men, 72 women) who were right-handed, showed no signs of dementia according to self-reports and Mini-Mental State Examination scores (Folstein et al. 1975) (all had scores greater 23), and for whom genotyping and white matter tractography had been successfully performed to date. At the second follow-up assessment, this subsample had a narrow age range of 70.9–72.7 years, with a mean age of 71.7 years (SD = .3 years). All were Caucasian. Their years of full-time education ranged between 9 and 20, with the average and median being 11.0 years (SD = 1.4 years).

ADRB2 genotyping and genetic analyses

Genomic DNA was isolated from whole blood and genotyped for the *ADRB2* SNPs rs1042713 and rs1042714 using KASPar by Kbiosciences (Herts, UK). rs1042713 and rs1042714 are in high linkage disequilibrium with each other in the LBC1936 sample ($r^2 = .465$, $D' = 1$, 95% CI 0.98–1.0) (Barrett et al. 2005). Both SNPs are in Hardy–Weinberg equilibrium (exact SNP test $p > .10$). For the pilot sample used in the current study, the minor allele frequencies are .38 (rs1042713) and .45 (rs1042714). Linear regression analysis investigated the additive effect of each SNP on the phenotype variables, co-varying for gender and age in days at testing using PLINK (Purcell et al. 2007). Conditional haplotype-based association testing was also performed with PLINK software. For the haplotype analysis, standardised residualised scores were calculated for phenotypic values to incorporate age at time of testing and gender, using linear regression.

White matter tractography

DT-MRI was performed on 162 participants on a GE Signa LX 1.5T MRI clinical scanner using a self-shielding gradient set with maximum gradient strength of 33 mT m^{-1}, and eight channel head array coil. Echo-planar diffusion-weighted images ($b = 1{,}000$ s mm^{-2}) were acquired in 64 non-collinear directions, along with seven T2-weighted images ($b = 0$ s mm^{-2}). Seventy-two contiguous axial slices of 2 mm thickness were acquired with a field of view of 256 × 256 mm and matrix size of 128 × 128, giving a resolution of 2 × 2×2 mm^3. Repetition time was 16.5 s and echo time 95.5 ms, producing a total scan time of approximately 20 min.

Datasets were converted into Analyze format (Mayo Foundation, Rochester, MN, USA) and pre-processed using FSL tools (FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk/) to extract the brain, remove bulk motion and eddy current induced artefacts and estimate diffusion tensor parameters (Basser et al. 1994). We used the BEDPOST/ProbTrack tractography algorithm (Behrens et al. 2007) with a two-fibre

model and 5,000 streamlines to reconstruct tracts of interest. An automatic tract selection method with good reproducibility (Clayden et al. 2009), based on a model of tract topology (Bastin et al. 2008; Clayden et al. 2007), was used to generate equivalent tracts of interest in each subject. This technique optimises the choice of seed point for tractography by estimating the best matching tract from a series of candidates against a reference tract which was derived from a digital human white matter atlas (Hua et al. 2008), as described by Muñoz Maniega et al. (2008). The topological tract model was also used to reject any false positive connections (Clayden and Clark 2009). Eight white matter pathways in the brain that are thought to be related to cognitive functioning in old age were segmented in this way, specifically callosal fibres (genu and splenium of the corpus callosum) and frontal white matter connections bilaterally (cingulum bundles, uncinate fasciculus and arcuate fasciculus) (Fig. 1). For each subject, the seed point that produced the best match tract to the reference for each of the eight pathways was determined, with the resulting tractography mask applied to each subject's $\langle D \rangle$, FA, λax, and λrad volumes. Tract-averaged mean values for these parameters were calculated and used in all subsequent analyses. Since λax and λrad are mathematically dependent on $\langle D \rangle$, we tested for any distinctive pattern of relationships of these two parameters with other variables only if they showed a significant association with $\langle D \rangle$. After visual inspection, a small proportion ($\leq$7%) of the segmented tracts were excluded from further analysis by a researcher who was blind to all other study variables. These exclusions were made on the basis of aberrant or truncated pathways, which did not represent anatomically plausible representations of the tracts of interest.

Cognitive testing

A general measure of cognitive ability or IQ (*Moray House Test No. 12*; MHT) had been administered when participants were aged 11, when they took part in the SMS1947 (Scottish Council for Research in Education 1949). It was re-administered in this sample during a follow-up at a mean age of almost 70 years, using the same instructions and the same 45-min time limit. At a second follow-up at a mean age of 72 years, Matrix Reasoning, a test of non-verbal reasoning from the WAIS-III^{UK} (Wechsler 1998), was administered. These were the two cognitive tests that showed significant associations with *ADRB2* in the full LBC1936 sample at age 70 (Bochdanovits et al. 2009).

Statistical analyses

Outliers ($\pm$3 SD) were removed from all studied variables. Gender and age in days at testing were statistically controlled in all analyses.

Results

Associations of *ADRB2* with white matter tract integrity

Due to missing data, the sample size for these analyses varied between 149 and 162. Linear additive effects of the alleles were assumed, an assumption that was confirmed by general linear models. Since the two SNPs under study were in relatively strong linkage disequilibrium and the eight white matter tract integrity values showed substantial positive intercorrelations (mean r's = .27 and .36 for FA and $\langle D \rangle$, respectively), resulting in a single principal component, we refrained from statistical corrections for multiple testing, which would have been overly stringent in this case. The haplotypes were estimated from the full sample of LBC1936 with successful genotyping for *ADRB2* SNPs (n = 1,031), but associations were tested in the current sample (n = 162). We only compared the ancestral GG haplotype (frequency: 47.4%) against all others, of which the AC (34.3%) and the GC (18.6%) haplotypes were the most common. This comparison

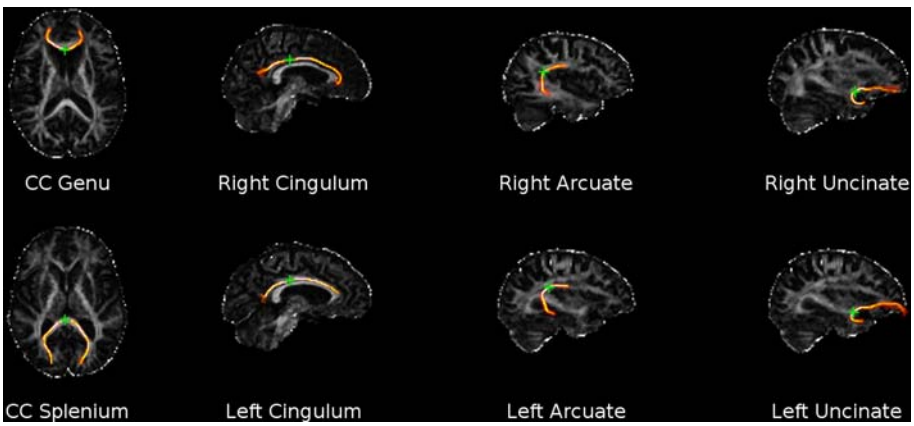

Fig. 1 *White* matter tract segmentations obtained in one participant. Seed points are marked with a *green cross*, tracts are projected into the plane of the seed point

Table 1 Associations of two *ARDB2* SNPs with two DTI-based indices for eight white matter tracts

		rs1042713		rs1042714	
		FA	⟨D⟩	FA	⟨D⟩
Left arcuate fasciculus	β	.14	−.05	**−.19**	.07
	p	.067	.535	**.013**	.380
Right arcuate fasciculus	β	.07	−.02	−.08	.10
	p	.389	.809	.286	.172
Left cingulum bundle	β	.00	−.05	−.09	.11
	p	.972	.496	.223	.136
Right cingulum bundle	β	−.02	.03	.02	.03
	p	.773	.697	.768	.723
Left uncinate fasciculus	β	.07	.04	−.07	.01
	p	.358	.643	.401	.868
Right uncinate fasciculus	β	.06	−.01	−.05	.03
	p	.434	.873	.496	.670
Splenium corpus callosum	β	−.04	.11	**.16**	**−.17**
	p	.596	.143	**.043**	**.026**
Genu corpus callosum	β	−.08	.08	.03	.00
	p	.279	.285	.689	.973

Note: Gender and age in days are statistically controlled in all analyses. Positive beta weights indicate effects of the ancestral G alleles for rs1042713 and rs1042714. All betas are fully standardized. Associations significant at $p < .05$ are printed in bold face. FA, fractional anisotropy; ⟨D⟩, mean diffusivity

strategy was based on the rationales that (1) the comparison of the ancestral against any derived haplotype is theoretically meaningful given the history of recent evolutionary selection on this gene, and (2) the ancestral G alleles of both SNPs were the ones associated with higher cognitive functions in previous analyses of this sample (Bochdanovits et al. 2009).

Results for the associations of the two *ADRB2* SNPs and their haplotype with the two main DT-MRI parameters (FA and ⟨D⟩) for the eight tracts are shown in Table 1. None of the white matter tract integrity values was associated significantly with the rs1042713 SNP. The rs1042714 SNP, however, showed significant associations with the left arcuate fasciculus FA (but not ⟨D⟩), as well as the splenium of the corpus callosum FA and ⟨D⟩. The directions of the effects indicate that the derived C allele was associated with greater white matter integrity in the left arcuate fasciculus, whereas it was the ancestral G allele that was associated with reduced white matter integrity in the splenium of the corpus callosum.

For the two tracts that showed significant associations, we also tested the effect of rs1042714 on the two directional diffusion parameters λax and λrad. In the case of the left arcuate fasciculus only, λrad, but not λax, showed a trend toward being significantly associated with the SNP ($\beta = .13$, $p = .083$ and $\beta = -.04$, $p = .587$, respectively). This very tentatively suggests a slightly stronger effect of the polymorphism on myelination than on axonal integrity, even though the difference between the two coefficients is not statistically significant ($p > .10$). For the callosal splenium, both λax and λrad showed significant relationships of similar effect size with rs1042714 ($\beta = -.16$, $p = .042$ and $\beta = -.17$, $p = .024$, respectively), indicating that both impaired myelination and axonal decline of the splenium are associated with the derived C allele.

The GG haplotype was associated with lower FA ($p = .014$) and higher λrad ($p = .020$) in the left arcuate fasciculus, as well as higher FA ($p = .025$) and lower ⟨D⟩ ($p = .006$), λrad ($p = .007$) and λax ($p = .014$) in the splenium of the corpus callosum. Thus, the haplotype analyses exactly replicated the pattern of results found for the rs1042714 SNP.

Associations of *ADRB2* with cognitive functioning

As a check, we re-tested the associations between the two *ADRB2* SNPs and cognitive tests that were found in the full LBC1936 sample at age 70 (Bochdanovits et al. 2009) in the current subsample (Table 2, left side). There was a significant association of rs1042713 with higher Moray House Test IQ at age 70 and WAIS-III Matrix Reasoning at age 70 in the full sample, but it failed to reach significance in the subsample. This seems to be due to the lower statistical power of the current analyses, as the effect sizes were very similar. As in the full sample, rs1042714 showed a significant association with Matrix Reasoning. In addition, it was related to Moray House Test IQ at age 70 (but not at age 11) in the current subsample. The directions of all of the effects indicate that the ancestral G allele is related to better cognitive ability.

When the SNP associations with cognitive ability in old age are statistically controlled for childhood IQ (Moray House Test at age 11), they are indicative of how the SNPs relate to cognitive aging (i.e. lifetime cognitive change). These results are shown in the lower part of Table 2. As can be seen, rs1042713 was not related to cognitive aging, but rs1042714 showed significant associations with both IQ at age 70 and Matrix Reasoning at age 72. Again, it was the ancestral G allele that was protective against age-related cognitive decline.

Again, the haplotype analyses exactly replicated the pattern of results found for the rs1042714 SNP, with the ancestral GG haplotype being associated with higher IQ at age 70 ($p = .044$) and a higher matrix reasoning score at age 72 ($p = .002$), but not with IQ at age 11 ($p = .975$). Also, the GG haplotype was associated with higher age 70 IQ ($p = .030$) and better age 72 matrix reasoning ($p = .002$) after controlling for age 11 IQ.

Table 2 Correlations of cognitive ability tests with *ADRB2* SNPs and four indicators of splenium corpus callosum white matter integrity

		ADRB2		Splenium corpus callosum			
		rs1042713	rs1042714	FA	⟨D⟩	λrad	λax
Moray house test IQ at age 11	*r*	.09	.00	.00	.01	.01	.02
	p	.307	.962	.963	.895	.936	.811
Moray house test IQ at age 70	*r*	.10	**.24**	**.19**	**−.22**	**−.22**	**−.21**
	p	.233	**.003**	**.023**	**.008**	**.009**	**.012**
WAIS III matrix reasoning at age 72	*r*	.12	**.23**	**.19**	**−.22**	**−.22**	**−.20**
	p	.145	**.003**	**.022**	**.008**	**.007**	**.014**
Controlling for IQ at age 11							
Moray house test IQ at age 70	*r*	.07	**.19**	**.22**	**−.26**	**−.25**	**−.25**
	p	.431	**.008**	**.009**	**.002**	**.002**	**.003**
WAIS III matrix reasoning at age 72	*r*	.11	**.23**	**.19**	**−.23**	**−.23**	**−.22**
	p	.209	**.003**	**.020**	**.006**	**.005**	**.010**

Notes: Gender and age in days are statistically controlled in all analyses. Positive correlations indicate effects of the ancestral G alleles for rs1042713 and rs1042714. Associations significant at $p < .05$ are printed in bold face. FA, fractional anisotropy; ⟨D⟩, mean diffusivity

Relationships between white matter tract integrity and cognitive functioning

For all of the following analyses, the sample was limited to participants who had complete records of all relevant genetic, neuroimaging and cognitive data ($n = 146$, 83 men, 63 women). The left arcuate fasciculus showed no significant correlations with any of the cognitive measures (all p's $> .10$) and was thus not considered further.

Correlations with cognitive tests for the splenium of the corpus callosum are listed in Table 2 (right side). Greater white matter integrity, as indicated by all four parameters (FA, ⟨D⟩, λax, and λrad), was related to higher IQ and Matrix Reasoning scores in old age, but not to childhood IQ. When controlling for childhood IQ, all eight correlations that indicated a relationship between higher splenium integrity and more successful cognitive aging were significant. Pairwise comparisons of λax and λrad correlations revealed that they were not statistically different in any of the analyses (all p's $> .10$), thus providing no indication that either impaired myelination or loss of axonal integrity clearly stood out as the more important causal mechanism.

Mediation analysis

Because the *ADRB2* rs1042714 polymorphism showed significant relationships with callosal splenium integrity and both cognitive tests in old age, and because splenium integrity was also significantly linked to both cognitive test scores, it is appropriate to test whether the gene-cognitive ability link is mediated by splenium integrity (Baron and Kenny 1986). Since all relationships with old-age cognitive ability remained virtually unchanged when controlling for childhood ability, it is likely that the *ADRB2* and white matter effects were more related to cognitive aging than to the lifetime stable trait of cognitive ability. Therefore, we also statistically controlled for age 11 IQ in the mediation analyses.

The results of these mediation analyses are depicted in Fig. 2. Controlling for splenium integrity (as indicated by ⟨D⟩, results for the other three parameters were similar) reduced the relationship of rs1042714 with age 70 IQ from .19 to .15 (a reduction of the explained variance by 37.67%, Sobel test statistic $= 1.89$, $p = .058$), and the relationship with age 72 Matrix Reasoning from .23 to .20 (explained variance reduced by 24.39%, Sobel test statistic $= 1.77$, $p = .077$). Thus, there was a statistical trend toward splenium integrity mediating one quarter to one-third of the effect of the *ADRB2* polymorphism on lifetime cognitive aging.

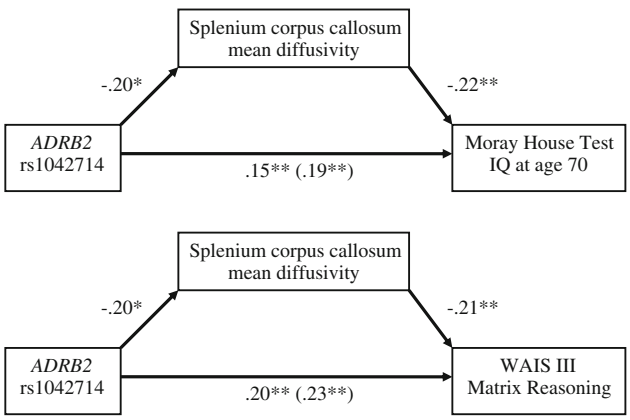

Fig. 2 Results for the analyses of the mediator role of splenium corpus callosum white matter integrity in the association between the *ADRB2* rs1042714 SNP and cognitive abilities in old age, controlling for gender, age in days and IQ at age 11. Values are standardized betas, values in brackets are betas before controlling for splenium integrity. * $p < .05$, ** $p < .01$

Confounding effects of health history

The ancestral G allele of the rs1042714 SNP has been associated with increased risk of ischemic stroke (Stanzione et al. 2007), high systolic blood pressure (Gjesing et al. 2007), and type-2 diabetes (Pinelli et al. 2006, but see Gjesing et al. 2007). However, all effects we reported here remained virtually unchanged after controlling for self-reported histories of these three conditions or of cardiovascular diseases (only 13 subjects (8%) had diabetes and six (3.7%) ever had a stroke in this generally healthy sample). This indicates that the protective effects of the G allele for white matter integrity and healthy cognitive aging were independent of other potential detrimental effects it might have on physical health in this sample. However, the current sample was relatively healthy and it is unclear if this result generalises to populations with more variance in health conditions.

Discussion

A recent study has found protective effects on old-age cognitive ability for two functional polymorphisms in *ADRB2,* a gene that codes for a catecholamine receptor in the brain and shows signatures of positive evolutionary selection (Bochdanovits et al. 2009). Following up a subsample of the cohort in which this original association was discovered (the LBC1936), we found a link of one *ADRB2* polymorphism and an *ADRB2* haplotype to the integrity of white matter in the splenium of the corpus callosum, which in turn tended toward partly mediating *ADRB2*-cognitive aging associations. We also found some scattered evidence that the same *ADRB2* SNP and haplotype relate to the integrity of the arcuate fasciculus, a white matter tract that connects the frontal lobe to parieto-temporal regions (Jung and Haier 2007). However, since this result was only found for the left, but not the right fasciculus, did not replicate consistently across different DT-MRI parameters, and arcuate fasciculus integrity was generally unrelated to cognitive ability measures, this result may be a chance finding.

While the size of our study sample must be considered small for a genetic association study, it is rather large for a tractography study. In the nascent field of imaging genetics, studies like ours are considered sufficiently powered, based on the assumption that in vivo brain measures are intermediate or endophenotypes of cognition, which are expected to be much closer to genetic effects and probably of simpler genetic structure than cognitive or behavioural test scores (Mattay et al. 2008). However, this assumption might not generally hold for all kinds of endophenotypes and it is still unclear if it is true for neurological measures (Flint and Munafò 2007). In any case, even if neuroimaging studies are nowadays usually limited in their sample sizes, they are certainly a promising approach to shed some light on the mechanisms that underlie cognition (Green et al. 2008) and especially helpful in explaining correlative findings that do not lend themselves easily to experimental studies in model organisms. Note also that the gene-cognition association we report here has not been newly established in this sample, but has already been shown in the seven times larger full sample of the LBC1936.

Besides the fairly large sample for an imaging study, another advantage of the current study is the use of state-of-the-art tractography techniques, which allowed us to quantify the integrity of eight individual white matter tracts accurately. Thus, we were able to test the disconnection hypothesis of cognitive aging as directly as currently possible. However, although tractography has proved to be a useful tool for assessing changes in white matter integrity, it does have limitations with regard to spatial localization. The results of the current study could be due to effects related to other white matter regions or even non-white matter structures, producing a secondary effect in the region of the splenium; however, this would be hard to unravel. Another limitation is the use of tract-averaged water diffusion parameters which ignore the potential variability of tract integrity along the fibre path. A tract profiling method could have been used to investigate this effect, although it would only provide qualitative information as tracts were segmented without previous standard space normalisation and can vary significantly in length between individuals making it difficult to identify homologous points in all tracts.

Furthermore, the narrow age cohort-design of our study made it possible for us to separate cohort effects and age differences from individual differences in aging (Hofer and Sliwinski 2001), and the availability of childhood IQ scores for all participants allowed us to disentangle cognitive aging effects from individual differences caused by the underlying stability of lifelong cognitive ability. In contrast, other studies of the neurological foundations of cognitive aging almost exclusively rely on snap-shots of individuals in age-heterogeneous cross-sectional samples (but see Deary et al. 2006).

Our main finding that an *ADRB2* variant and the integrity of the splenium corpus callosum have partly overlapping effects on cognitive aging is notable in several ways. First of all, even though we studied two *ADRB2* SNPs in relatively strong linkage disequilibrium, associations with white matter integrity and cognitive aging were limited to one of them (rs1042714) and the haplotype they defined. With regard to the associations with cognition, this appeared to be a power problem, since, as noted earlier, the effects sizes for rs1042713 were similar to those found in the full LBC1936 sample (Bochdanovits et al. 2009). With regard to the white matter integrity associations, however, there was no indication for a trend of the ancestral

rs1042713 allele. Thus, this could mean that it is not the rs1042714 polymorphism itself that affects splenium integrity, but a different genetic variant which we did not genotype directly, but which is in stronger linkage disequilibrium with rs1042714 than with rs1042713. This is also supported by the fact that the significant haplotype associations mirrored the rs1042714 results completely.

A further interesting aspect of our findings is that it was an ancestral, not a derived, *ADRB2* allele that had protective effects against cognitive and splenium white matter decline. This seems counter-intuitive at first glance, given that the derived allele shows signatures of positive selection based on human-chimp-comparisons (Bochdanovits et al. 2009), and given the various positive associations that have been found for the derived allele with autism (Cheslack-Postava et al. 2007) and health-related phenotypes (Gjesing et al. 2007; Pinelli et al. 2006; Stanzione et al. 2007). On second sight, however, such antagonistic effects are what should be expected for derived alleles that are still variable today, despite positive selection acting on them recurrently, since the human and chimpanzee lineages split 6–7 million years ago (Harris 2008). Evolutionary selection is very efficient in fixating genes with exclusively positive effects over time spans as short as 10,000 years (Keller and Miller 2006a, b), which means that selective effects favouring the ancestral *ADRB2* allele had to be present all the time since the novel mutations first spread in the human lineage, or else we would not be able to observe standing genetic variation. The protective effects in old age that we identified might be part of what keeps the *ADRB2* polymorphisms in evolutionary equilibrium in the current Scottish population. However, such antagonistic pleiotropic trade-offs tend to be evolutionarily unstable in the long run (Roff and Fairbairn 2007), and this might imply that the effects of the rs1042714 polymorphism that we found in a Scottish population do not replicate in other populations because this locus might already be close to fixation in some (see Penke et al. 2007a, b). This is also in line with a recent molecular population genetic study that suggests ADRB2 is either under balancing selection or in the midst of a recent selective sweep (Cagliani et al. 2009). Indeed, Bochdanovits et al. (2009) found the rs1042714 SNP to be out of Hardy–Weinberg equilibrium in two Dutch populations, and the derived C allele has already reached 88.2% prevalence in Han Chinese, 91.0% prevalence in North American Na-Dene Indians, and fixation in South American Quechua people (Kidd 2009). A possible interpretation of this pattern is that the benefits in old-age which we found for the ancestral rs1042714 polymorphism in this study were too weak in these other populations to counter-act selection for the evolutionarily novel allele.

Finally, the splenium of the corpus callosum might not be the most obvious candidate for a white matter tract that relates to aging of general cognitive functioning. This is a widespread assumption because general intelligence is assumed to be more dependent on the integration of frontal and posterior cortical areas (Jung and Haier 2007), and the white matter tracts connecting to frontal areas have been found to be especially prone to aging effects (O'Sullivan et al. 2001; Sullivan et al. 2001; Sullivan and Pfefferbaum 2006). However, several studies have implied a role of the corpus callossum in the intelligence functions of young adults, which is apparently increasing with age (Allin et al. 2007; Hutchinson et al. 2009; Luders et al. 2007). Also, age-related decline in splenium integrity has been reported (Abe et al. 2002; Bhagat and Beaulieu 2004; Chepuri et al. 2002; Head et al. 2004; Madden et al. 2008; Ota et al. 2006; Pfefferbaum et al. 2000, 2005; Pfefferbaum and Sullivan 2003; Salat et al. 2005; Sullivan et al. 2006), as well as age-related correlations between splenium integrity and measures of cognitive speed (Madden et al. 2004; Sullivan et al. 2001) and task switching performance (Madden et al. 2008). Thus, even though aging effects with possible consequences for cognitive functioning are less prominent in posterior than in anterior white matter, they are clearly evident in the splenium, too.

While the major white matter fibres of the splenium run between the two occipital cortices, it also entails fibres that provide interhemispheric connections between parieto-temporal association cortices, which have been implicated in long-term memory (Hasegawa 2000) and attention processes (Banich 1998). A possible role for the splenium in age-related cognitive decline is suggested by compensation theories of cognitive aging (Cabeza 2002; Dennis and Cabeza 2008; Kennedy and Raz 2009; Park and Reuter-Lorenz 2009). According to these theories, the brains of people who have suffered from decline in systems with primary roles in cognitive functioning (e.g. fronto-parietal white matter tracts) can compensate for these losses by the functional bilateral recruitment of brain areas with hitherto only indirect relations to general cognitive ability. While some authors proposed, on largely theoretical grounds, that interhemispheric transfer is more important for these compensation processes if it occurs between anterior than between posterior cortical areas (Park and Reuter-Lorenz 2009), this assumption is challenged by recent evidence that implicates posterior white matter, including the callosal splenium, in the compensation of age-related cognitive decline (Kennedy and Raz 2009; Madden et al. 2008). Madden and colleagues also found that water diffusion perpendicular to the direction of the splenium fibres (λrad) was more important for its effects on age-related cognitive decline than diffusion in axonal direction (λax), suggesting a stronger role of impaired myelination than axonal loss. This somewhat contradicts our finding of equally strong contributions of λrad and λax to the splenium effects, a difference

that might be resolved by future studies. In any case, our study adds to the accumulating evidence that posterior white matter structures play a role in cognitive aging.

Conclusion

Both the ancestral G allele of the rs1042714 SNP in the *ADRB2* gene and white matter integrity in the splenium of the corpus callosum had protective effects on cognitive aging in a Scottish cohort. These two effects were largely independent, and thus likely have largely independent mechanistic underpinnings. In the case of the *ADRB2* polymorphism, the mechanism might be more related to memory consolidation, while the splenium effects might be related to individual differences in compensatory recruitment of contralateral association cortices that affect attention and long-term memory. To the degree that splenium integrity mediated the effects of the *ADRB2* polymorphism, this gene-brain-cognition link might be related to their shared effect on memory processes. However, more research is needed to clarify the causal pathways that are suggested by the current results.

Acknowledgments LP, SMM and CM are funded by the UK Medical Research Council. LP, AJG, and the LBC1936 data collection were supported by the Disconnected Mind project (www.disconnectedmind.ed.ac.uk) funded by Help the Aged and Research into Ageing. JMW is part-funded by the Scottish Funding Council as part of the SINAPSE Collaboration. We thank the study secretary Paula Davies, Janie Corley and Ross Henderson for data collection and data entry; the nurses, radiographers and other staff at the Wellcome Trust Clinical Research Facility and the SFC Brain Imaging Research Centre (www.sbirc.ed.ac.uk) where the data were collected; and the staff at Lothian Health Board and at the SCRE Centre, University of Glasgow. The work was undertaken within The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Well-being Initiative. Funding from the BBSRC, EPSRC, ESRC and MRC is gratefully acknowledged.

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