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ORIGINAL RESEARCH

ADRB2, brain white matter integrity and cognitive ageing in the Lothian Birth Cohort 1936

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Abstract The non-synonymous mutations arg16gly (rs1042713) and gln27glu (rs1042714) in the adrenergic β-2 receptor gene (*ADRB2*) have been associated with cognitive function and brain white matter integrity. The current study aimed to replicate these findings and expand them to a broader range of cognitive and brain phenotypes. The sample used is a community-dwelling group of older people, the Lothian Birth Cohort 1936. They had been assessed cognitively at age 11 years, and undertook further cognitive assessments and brain diffusion MRI tractography in older age. The sample size range for cognitive function variables was $N = 686$–765, and for neuroimaging variables was $N = 488$–587. Previously-reported findings with these genetic variants did not replicate in this cohort. Novel, nominally significant associations were observed; notably, the integrity of the left arcuate fasciculus mediated the association between rs1042714 and the Digit Symbol Coding test of information processing speed. No significant associations of cognitive and brain phenotypes with *ADRB2* variants survived correction for false discovery rate. Previous findings may therefore have been subject to type 1 error. Further study into links between *ADRB2*, cognitive function and brain white matter integrity is required.

Keywords Intelligence · White matter · Cognitive ageing · Diffusion MRI · Tractography · *ADRB2* · Processing speed

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Introduction

The adrenergic β-2 receptor gene (*ADRB2*) is widely expressed in the brain where it plays many roles including signal transduction of adrenaline, noradrenaline and to a lesser extent dopamine (Brodde 2008; Dohlman et al. 1991). Two single nucleotide polymorphisms (SNPs), rs1042713 which causes an arg16gly amino acid substitution, and rs1042714 which causes a gln27glu amino acid substitution, affect adrenergic receptor sensitivity (Cagliani et al. 2009). Arg16gly and gln27glu polymorphisms have been significantly associated at $p < 0.05$ (hereafter simply

'associated') with increased risk of neurodevelopmental disorder (Cheslack-Postova et al. 2007) and, separately, with differences in cardiovascular phenotypes such as diastolic blood pressure (Snieder et al. 2002).

Bochdanovits et al. (2009) tested rs1042713 and rs1042714 in two Dutch samples of 391 young (mean age 12.7 years) and 409 adult (36.7 years) participants assessed on Dutch adaptations of the Wechsler Adult Intelligence Scale-III^{UK} (WAIS-III^{UK}). For rs1042713, the 16gly (G allele) was associated with lower performance IQ scores in the young Dutch sample only. They also assessed the Lothian Birth Cohort 1936 (LBC1936) which comprised 1063 older adults with relevant data. They were tested on the Moray House Test No.12 (MHT; a general intelligence-type test) at two ages, namely 11 and 70 years, and the Matrix Reasoning subtask from the standard WAIS-III^{UK} also at age 70 years. Matrix Reasoning was significantly associated with both rs1042713 (standardised $\beta = 0.07$; hereafter β) and rs1042714 ($\beta = 0.08$) positively and additively in the direction of the 16gly and 27glu (G) alleles, respectively. The rs1042713 SNP was also associated with age 70 MHT ($\beta = 0.07$), and rs1042714 with age 11 MHT ($\beta = 0.07$).

In a subsample consisting of 162 LBC1936 participants who had by that time undergone diffusion MRI tractography as well as cognitive assessments (Penke et al. 2010a), the rs1042714 G allele was significantly associated with reduced fractional anisotropy (FA) ($\beta = -0.19$) in the left arcuate fasciculus indicating lower white matter integrity. In the splenium of corpus callosum the G allele was associated with higher FA ($\beta = 0.16$) and lower mean diffusivity (MD) ($\beta = -0.17$), indicating greater integrity. This allele was associated with higher age 70 MHT and age 73 Matrix Reasoning performance, both with ($\beta = 0.24$ and $\beta = 0.23$) and without ($\beta = 0.19$ and $\beta = 0.23$) controlling for childhood intelligence as assessed by the MHT. These data therefore indicate that variation in the *ADRB2* gene may have an effect on the change in cognitive function between childhood and older age. In addition, Penke et al. (2010a) found that the integrity of the splenium correlated positively with Matrix Reasoning and MHT performance. These neuroimaging and cognitive variables were each associated with the G allele of rs1042714. Penke et al. (2010a) further reported that controlling for splenium integrity attenuated the relationship between rs1042714 and both MHT and Matrix Reasoning adjusted for age 11 cognitive ability, indicating that this tract partially mediated the SNP-cognitive ageing associations (Sobel mediation test p values = 0.058 and 0.077). Penke et al. reported relatively large effect sizes (β) for an association study of common SNPs, and it is important to attempt replication in a larger sample.

Bochdanovits et al. (2009) suggested that the G alleles of rs1042713 and rs1042714 could have been under positive selection for higher cognitive ability in humans, whereas Penke et al. (2010a) noted that the G allele of rs1042714 appears to be protective against age-related cognitive decline (Deary et al. 2009). In the current study we investigate: (i) whether the results of Penke et al. (2010a) can be replicated in the larger, full LBC1936 sample; while (ii) extending the number of cognitive domains and white matter tracts tested for association with *ADRB2* SNPs, in further exploratory analyses.

Methods

Sample and procedure

The LBC1936 is a cohort of 1091 community-dwelling older adults most of whom completed the MHT of verbal reasoning as part of the Scottish Mental Survey of 1947 (SMS1947) at a mean age of 11 years. The recruitment and testing of this sample has been described in detail elsewhere (Deary et al. 2007, 2011). All of the LBC1936 participants were born in 1936 and most resided in the Lothian area of Scotland when recruited at age 70 years (SD = 0.83). In the first wave of the LBC1936 study (Wave 1), at around age 70, they were retested on the MHT in addition to other detailed cognitive, sociodemographic and physical assessments (Deary et al. 2007, 2011). The sample was generally healthy; no participants reported dementia. Around 3 years later, at a mean age of about 73 years (SD = 0.71), 866 members of the cohort returned for re-testing in the second wave of the study (Wave 2). At this point, participants also underwent detailed structural brain MRI (Wardlaw et al. 2011). At both waves, participants were screened for cognitive impairment with the Mini Mental State Exam (MMSE), with scores under 24 indicating possible dementia (Folstein et al. 1975). Participants received medical and cognitive assessments at the Wellcome Trust Clinical Research Facility (http://www.wtcrf.ed.ac.uk), and brain MRI at the Brain Research Imaging Centre (http://www.bric.ed.ac.uk), both located at the Western General Hospital, Edinburgh. Diagnoses of clinical conditions were elicited via interview. Clinical vascular conditions asked about included high blood pressure, diabetes, stroke, high cholesterol and any cardiovascular pathology. All subjects gave written, informed consent.

Cognitive assessment

Moray house test (MHT)

This was completed in 1947 at a mean age of 11 years and again at a mean age of 70 years in Wave 1. This assessment has a 45-min time limit and includes 76 questions with a predominance of verbal reasoning items, with some

numerical and visuospatial items also included (Deary et al. 2007).

Assessment of cognitive domains

The tests completed at a mean age of 73 years in Wave 2 are described by Deary et al. (2007). In brief, the cognitive domains assessed were as follows. Working memory was assessed with Digit Span Backwards and Letter Number Sequencing from the WAIS-III^{UK} (Wechsler 1998a). Processing speed was assessed using Digit Symbol Coding and Symbol Search from the WAIS-III^{UK}, Simple reaction time (RT), and Four-Choice RT via a self-contained device (Cox et al. 1993), and a psychophysical visual discrimination task called Inspection Time (Deary et al. 2007). Verbal declarative memory was assessed with the Verbal Paired Associates I and II, and Logical Memory I and II tests from the Wechsler Memory Scale-III III^{UK} (WMS-III^{UK}; Wechsler 1998b). Visuospatial ability and memory were assessed with Block Design and Spatial Span from the WAIS-III^{UK} and WMS-III^{UK} respectively. Abstract reasoning was assessed using Matrix Reasoning from the WAIS-III^{UK}.

Data reduction was applied to the cognitive test scores using principal components analyses (PCA) which produced the following summary cognitive variables. First, 'general intelligence' (g) included the six non-verbal Wechsler subtests of Digit Span Backwards, Matrix Reasoning, Letter-Number Sequencing, Block Design, Symbol Search and Digit Symbol Coding. Second, 'processing speed' (g_{Speed}) included Symbol Search, Digit Symbol Coding, Simple RT, Four-Choice RT and Inspection Time. The derivation of these was described by Luciano et al. (2009). Third, a 'memory' factor (g_{Memory}) was formed from Logical Memory, Spatial Span, Verbal Paired Associates, Letter-Number Sequencing and Digit Span Backwards. The derivation of this variable was described by Houlihan et al. (2010). Strictly speaking PCA does not generate latent underlying 'factors', but this usage is common and is adopted here. In each case, we tested for the existence of a large first unrotated component that could be used to form scores for the three variables. Inspection of eigenvalues and scree-plots suggested that a single component should be extracted from the data in each of the three analyses. The first unrotated principal component scores in each domain accounted for the variance as follows: 50.1 % for general intelligence, 49.8 % for processing speed and 53.6 % for memory. All individual test scores had moderate to high loadings on their respective first unrotated principal components.

Diffusion MRI and Tractography Analysis

Participants underwent whole brain diffusion MRI acquired using a GE Signa HorizonHDxt 1.5 T clinical scanner (General Electric, Milwaukee, USA) equipped with a self-shielding gradient set (33 mT m^{-1} maximum gradient strength) and manufacturer supplied 8-channel phased-array head coil (Wardlaw et al., 2011). The protocol consisted of 7 T2-weighted ($b = 0$ s mm^{-2}) and sets of diffusion-weighted ($b = 1000$ s mm^{-2}) axial single-shot spin-echo echo-planar (EP) volumes acquired with diffusion gradients applied in 64 non-collinear directions. Seventy-two contiguous slices of 2 mm thickness were collected with a field of view of 256 × 256 mm and acquisition matrix of 128 × 128, giving 2 mm isotropic voxel resolution.

The diffusion MRI data were preprocessed using FSL tools (FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk) to extract the brain, remove bulk patient motion and eddy current induced artefacts, and generate parametric maps of water diffusion tensor parameters MD and FA. These biomarkers measure the magnitude and directional coherence of water molecule diffusion in vivo, and since water molecules diffuse preferentially along the principal fibre direction, can be used to assess white matter structural integrity (Pierpaoli et al. 1996). Specifically, MD takes low and FA high values in healthy, structurally intact white matter, but rise or fall respectively in diseased tissue. Underlying tractography connectivity data were generated using BedpostX/ProbTrackX with the default settings of a two-fibre model per voxel, and 5000 probabilistic streamlines with a fixed separation of 0.5 mm between successive points (Behrens et al. 2007).

Twelve tracts-of-interest were identified using probabilistic neighbourhood tractography, a novel approach for automatic and reproducible tract segmentation (Clayden et al. 2007), as implemented in the TractoR package for fibre tracking analysis (Clayden et al. 2011; http://www.tractor-mri.org.uk). Tracts assessed were the genu and splenium of corpus callosum, and bilateral anterior thalamic radiations, rostral cingulum bundles, arcuate, uncinate and inferior longitudinal fasciculi. Tract masks generated by this method were overlaid on the MD and FA parametric maps and tract-averaged values of these biomarkers, weighted by the connection probability, determined for each tract in every subject.

To ensure that the segmented tracts were anatomically plausible representations of the fasciculi-of-interest, a researcher visually inspected all masks blind to the other study variables and excluded tracts with aberrant or truncated pathways. In general, probabilistic neighbourhood tractography was able to segment the twelve tracts-of-interest reliably in the majority of subjects, with tracts that did not meet quality criteria, such as truncation or failing to follow the expected path, ranging from 0.3 % for the splenium of corpus callosum to 16 % for the left anterior thalamic radiation, with a mean of 5 %. To permit PCA on these

data, participants with up to two missing values from specific tracts had data replaced with the mean value for that tract.

PCA was conducted on the tract-averaged water diffusion parameters for these twelve pathways, giving clear single-factor models for FA (g_{FA}) and MD (g_{MD}) that accounted for 38.8 and 39.4 % of the overall variance respectively. This indicates that the integrity of white matter tracts is to a substantial degree shared among different tracts throughout the brain, suggesting potential common causes (Lopez et al. 2012). These general white matter integrity factors have been found to be associated with cognitive abilities in this sample (Penke et al. 2010b, 2012).

ADRB2 genotyping

ADRB2 SNPs rs1042713 and rs1042714 were genotyped from DNA isolated from whole blood by KBiosciences (http://www.kbioscience.co.uk) using their proprietary genotyping assay, KASPar.

Statistical analyses

We first attempt to replicate the results reported by Bochdanovits et al. (2009) and Penke et al. (2010a) using the same cognitive measures and covariates. In a second step, we then conduct exploratory analyses on a broader range of cognitive measures and white matter tracts to test further associations between *ADRB2* SNPs, neurostructural indicators, and cognitive ability as well as lifetime cognitive change.

Participants were excluded if they reported being ambidextrous or left-handed at either wave, had MMSE scores below 24 or not completed at Wave 2, reported diagnosis of dementia, or failed genotyping for rs1042713 or rs1042714. Outliers of more than 3 standard deviations from mean values were removed from all cognitive variables. One participant was removed from analysis because of a discrepancy between their directly genotyped *ADRB2* data (as described above) and genome wide association study (GWAS) data which were also available for the current sample. Removing this participant did not affect any final results and this paper reports only directly genotyped data as performed by KBioscience. All associations were controlled for gender in addition to age in days at time of cognitive and neuroimaging assessment. Penke et al. (2010a) reported that associations that controlled for age and gender were unchanged when vascular risk factors were entered as covariates. Any influence of vascular pathologies such as high blood pressure on genotype-phenotype associations may have been different in the larger sample used here ($n = 866$) compared with the smaller sample used by Penke et al. ($n = 162$). The current study therefore included associated vascular covariates in exploratory analyses as part of the final model in this larger sample unless otherwise specified. To examine the effects of *ADRB2* upon lifetime cognitive change, cognitive task scores from age 73 were controlled for age 11 MHT score.

In the current study, PLINK (Purcell et al. 2007; http://pngu.mgh.harvard.edu/~purcell/plink) provided summary statistics for minor allele frequencies and was used to perform tests of Hardy–Weinberg equilibrium. Haploview provided linkage disequilibrium statistics (Barrett et al. 2005; http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview). Data were otherwise analysed with the Predictive Analytics SoftWare (PASW, version 17; http://www-01.ibm.com/software/uk/analytics/spss) statistics programme. Mediation analysis was used to test the indirect effect of the predictor variable (*ADRB2*) upon the outcome (cognitive function), through the hypothesised mediator (white matter integrity). Mediation analysis was run using the INDIRECT bootstrapping macro (Preacher and Hayes, 2008). In a simple example mediation model, variable X's effects on variable Y can be either direct or indirect via variable M. Path A represents the effect of X on M, while path B represents the effect of M on Y, partialling out the effect of X. The direct effect of X on Y is represented by path C. The indirect effect can then be quantified as the combined product of paths A and B. The bias-corrected bootstrapping point estimate coefficients that are reported here each reflect this indirect product (Preacher and Hayes 2008). These point estimate coefficients are unstandardised and averaged over 5000 bootstrap estimates (Preacher and Hayes 2008). Bias-corrected bootstrapping has an advantage over percentile bootstrapping in that it corrects for any skew in the population, including the bias created by the central tendency of the estimate (Efron and Tibshirani 1993; Fritz and MacKinnon 2007). To protect against type 1 error, the false discovery rate (FDR) was used to estimate the number of significant findings controlling for multiple testing (Benjamini and Hochberg 1995). An Excel macro (Pike 2011) was used to conduct classical one-stage FDR based on *ADRB2* associations with white matter integrity and cognitive function.

All initially-reported p values are raw (and we then apply FDR-adjustment), β coefficients are standardised (and are equivalent to semi-partial r correlations), and p values <0.05 are considered nominally significant. Linear regression analyses tested the additive effects of *ADRB2* rs1042713 and rs1042714 SNP G alleles upon white matter and cognitive variables. All associations are reported in the direction of these alleles.

Results

Of the 866 members of the cohort who returned for cognitive testing in Wave 2, SNP data were obtained from 765

(rs1042713) and 762 (rs1042714) individuals. From this group, neuroimaging data were obtained from 650 and 647 subjects, respectively.

Minor allele frequencies in the sample for rs1042713 were A = 34 %, and for rs1042714 G = 48 %. Genotype frequencies for rs1042713 were AA = 11 %, AG = 46 % and GG = 43 %, and for rs1042714 GG = 23 %, GC = 50 % and CC = 27 %. Exact tests performed in PLINK confirmed that rs1042713 ($p = 0.52$) and rs1042714 ($p = 0.91$) were individually in Hardy–Weinberg equilibrium. Both SNPs were in high linkage disequilibrium in LBC1936, however ($r^2 = 0.47$, D′ = 1.00, CI = 0.98–1.00).

Attempted replication of previous findings

Replication of previous results by Bochdanovits et al. (2009) and Penke et al. (2010a) was attempted first. Bochdanovits et al. examined Matrix Reasoning scores at age 70 and MHT scores at ages 11 and 70, while Penke et al. examined MHT at age 70 and Matrix Reasoning at age 73 both adjusted and unadjusted for age 11 cognitive ability. For comparison, Table 1 shows association statistics (β coefficients and p values) as reported by Bochdanovits et al. and Penke et al., and also when re-tested in the present sample.

In a larger number of the LBC1936 tested at mean age 70 years ($n = 1063$; Wave 1), Bochdanovits et al. (2009) reported associations between *ADRB2* SNPs and abstract reasoning tasks, controlling for age and gender. When tested again in the current subsample of participants that underwent repeat cognitive testing in Wave 2, there were no significant associations between rs1042713 and rs1042714 with MHT or Matrix Reasoning at age 70, or MHT at age 11 years (Table 1). The effect sizes were similar to those found by Bochdanovits et al. but non-significant. The current study included right-handed participants only. To test for this as a source of discrepancy, the original data (Wave 1) of Bochdanovits et al. were re-analysed in right-handed participants only ($n = 954$). With an otherwise identical analytic strategy, the findings by Bochdanovits et al. remained at or very close to statistical significance except for one association; namely rs1042714 and age 11 MHT. Another source of discrepancy may be selective attrition of more cognitively impaired individuals from Wave 1 to Wave 2 of testing in old age. Independent samples t-tests showed that in right-handed participants, those who attended both Waves 1 and 2 ($n = 866$)—compared with those who attended Wave 1 only—had higher scores on age 11 MHT (mean [M] = 50.16, standard deviation [SD] = 11.00 vs. M = 47.62 SD = 10.53, $t = -2.89$, $p = 0.004$, Cohen's $d = 0.24$), age 70 MHT (M = 65.22, SD = 7.55 vs. M = 62.80, SD = 8.66, $t = -3.59$, $p < 0.001$, Cohen's $d = 0.30$) and age 70 Matrix Reasoning (M = 13.92, SD = 5.03 vs. M = 12.27, SD = 5.14, $t = -4.15$, $p = < 0.001$, Cohen's $d = 0.32$).

The previous pilot study on the subsample of the present cohort that had been brain scanned at that time ($n = 162$) reported seven significant associations (Penke et al. 2010a), which are shown here in Table 1. In the current full sample, all seven associations were markedly reduced in effect size. Only the one between rs1042714 and left arcuate fasciculus FA ($\beta = -0.12$, $p = 0.006$) was still significant and the one between rs1042714 and age 73 Matrix Reasoning ($\beta = 0.07$, $p = 0.053$) showed a statistical trend. This trend attenuated when age 11 MHT score was added as a covariate ($\beta = 0.05$, $p = 0.116$). Because there were no significant associations with splenium of corpus callosum FA or MD, replicating the mediation reported by Penke et al. was not attempted.

Table 1 Linear *ADRB2* SNP associations with cognitive function in two previous reports compared with the present sample

Previous report	SNP (G alleles)	Cognitive task	β (p)	Present sample ($n = \sim 765$) β (p)
Bochdanovits et al. (2009); ($n = 1063$)	rs1042713	Matrix reasoning (age 70)	0.07 (0.020)	0.05 (0.154)
		Moray house test (age 70)	0.07 (0.025)	0.04 (0.240)
	rs1042714	Matrix reasoning (age 70)	0.08 (0.014)	0.06 (0.124)
		Moray house test (age 11)	0.07 (0.023)	0.06 (0.109)
Penke et al. (2010a); (n = 162)	rs1042714	Moray house test (age 70)	0.24 (0.003)	0.03 (0.400)
		Adjusted for age 11 IQ	0.19 (0.008)	0.00 (0.982)
		Matrix reasoning (age 73)	0.23 (0.003)	0.07 (0.053)
		Adjusted for age 11 IQ	0.23 (0.003)	0.05 (0.116)
		Left arcuate fasciculus FA	−0.19 (0.013)	−0.12 (0.006)*
		Splenium corpus callosum FA	0.16 (0.043)	0.01 (0.803)*
		Splenium corpus callosum MD	−0.17 (0.026)	−0.02 (0.567)*

Note. Gender and age at time of assessment statistically controlled. All beta values are standardized. All associations are in the direction of *ADRB2* SNP G alleles. *$n = \sim 650$

Exploratory analyses

Vascular risk factors

Controlling for age and gender, linear regression analyses showed an association between rs1042713 and self-reported diagnosis of high blood pressure ($\beta = 0.09, p = 0.019$), and a trend toward an association with rs1042714 ($\beta = 0.07$, $p = 0.067$). Neither SNP was associated with self-reported diabetes, stroke, high cholesterol or cardiovascular disease. The following analyses therefore controlled for high blood pressure in addition to age, gender and (where applicable in cognitive analyses only) age 11 MHT score.

ADRB2 and white matter tract integrity

Fifty-two separate tests of association between *ADRB2* SNPs and white matter integrity variables were conducted (Table 2), of which four were nominally significant at the $p < 0.05$ level. For rs1042713, there were associations with lower FA of the left arcuate fasciculus ($\beta = -0.10$, $p = 0.021$) and right anterior thalamic radiation ($\beta = -0.09, p = 0.025$). For rs1042714 there were associations with lower left arcuate fasciculus FA ($\beta = -0.11$, $p = 0.007$) and higher MD ($\beta = 0.09$, $p = 0.037$). None of the associations survived FDR correction.

ADRB2 and cognitive performance

In exploratory analyses, we examined a range of cognitive phenotypes at age 73, as well as MHT performance at ages 11 and 70 only, at first unadjusted and then adjusted for age 11 ability. The attempted replication of findings reported by Bochdanovits et al. and Penke et al. (above) controlled for age, gender and (where applicable) age 11 intelligence. Controlling for age, gender and additionally for high blood pressure, no significant associations were evident in the present analyses between *ADRB2* SNPs and g, g_{Speed} and g_{Memory}. Table 3 shows the associations between *ADRB2* SNPs and specific cognitive task scores, not adjusted for age 11 MHT scores. There was no evidence of association between *ADRB2* and specific memory or visuospatial tasks. The *ADRB2* SNP rs1042713 showed a nominally significant association with better performance on Simple RT, in the direction of the G allele ($\beta = -0.09$, $p = 0.010$). The rs1042714 polymorphism was also associated with better Simple RT ($\beta = -0.08$, $p = 0.035$) and Matrix Reasoning performance ($\beta = 0.07$, $p = 0.041$), in the direction of the G allele.

Additionally controlling for age 11 MHT scores in order to test for associations with lifetime cognitive change, Table 4 shows that the *ADRB2* SNP rs1042714 showed a nominally significant association with poorer processing speed (g_{Speed}; $\beta = -0.07$, $p = 0.045$). When tests of association were conducted with specific processing speed tasks, rs1042713 was associated with faster Simple RT ($\beta = -0.09$, $p = 0.025$) but worse Symbol Search performance ($\beta = -0.07$, $p = 0.044$). The rs1042714 polymorphism was associated with worse performance on Digit Symbol Coding ($\beta = -0.09$, $p = 0.010$) and Symbol Search ($\beta = -0.08$, $p = 0.022$) tests. Note that when age 11 MHT scores were controlled for, the nominally

Table 2 Linear *ADRB2* SNP associations with white matter integrity parameters, fractional anisotropy (FA) and mean diffusivity (MD)

White matter tract	rs1042713 (G allele)				rs1042714 (G allele)			
	Fractional anisotropy		Mean diffusivity		Fractional anisotropy		Mean diffusivity	
	β (p)	*N*	β (p)	*N*	β (p)	*N*	β (p)	*N*
General factor (g_{MD} or g_{FA})	−0.08 (0.072)	531	0.02 (0.638)	531	−0.07 (0.086)	529	0.03 (0.554)	529
Genu of the corpus callosum	−0.06 (0.152)	570	0.01 (0.773)	570	−0.05 (0.284)	568	0.01 (0.774)	568
Splenium of the corpus callosum	0.01 (0.837)	586	0.01 (0.836)	586	0.01 (0.772)	584	−0.02 (0.582)	584
Left arcuate fasciculus	**−0.10 (0.021)**	**562**	0.06 (0.148)	562	**−0.11 (0.007)**	**560**	**0.09 (0.037)**	**560**
Right arcuate fasciculus	−0.06 (0.211)	512	−0.01 (0.913)	512	−0.08 (0.079)	509	0.04 (0.359)	509
Left uncinate fasciculus	−0.03 (0.528)	502	−0.05 (0.305)	502	−0.03 (0.531)	500	0.00 (0.938)	500
Right uncinate fasciculus	−0.05 (0.210)	555	0.06 (0.198)	555	−0.06 (0.146)	553	0.07 (0.124)	553
Left anterior thalamic radiation	−0.05 (0.285)	488	0.02 (0.641)	488	0.00 (0.929)	486	0.02 (0.603)	486
Right anterior thalamic radiation	**−0.09 (0.025)**	**567**	0.07 (0.102)	567	−0.06 (0.123)	564	0.01 (0.793)	564
Left rostral cingulum	−0.08 (0.073)	567	0.04 (0.357)	567	−0.07 (0.100)	565	0.02 (0.716)	565
Right rostral cingulum	−0.02 (0.589)	574	0.00 (0.983)	574	−0.04 (0.346)	572	−0.03 (0.495)	572
Left inferior longitudinal fasciculus	0.03 (0.540)	586	−0.06 (0.134)	586	−0.06 (0.150)	584	0.01 (0.867)	584
Right inferior longitudinal fasciculus	−0.07 (0.072)	587	0.02 (0.610)	587	−0.07 (0.072)	587	0.02 (0.610)	587

Note. Gender, diagnosis of high blood pressure and age at time of MRI statistically controlled. All beta values are standardized. Associations significant at $p < 0.05$ are printed in bold-face. All associations are in the direction of *ADRB2* SNP G alleles

Table 3 Linear *ADRB2* SNP associations with cognitive abilities, not adjusted for age 11 cognitive ability

Cognitive measure	rs1042713 (G allele)		rs1042714 (G allele)	
	β (p)	*N*	β (p)	*N*
Moray house test: age 11[a]	0.07 (0.070)	717	0.06 (0.109)	712
Moray house test: age 70	0.05 (0.188)	756	0.03 (0.345)	753
General factor: intelligence (g)	0.01 (0.787)	751	−0.01 (0.846)	748
Digit span backwards	0.02 (0.633)	765	0.02 (0.608)	763
Matrix reasoning	0.06 (0.106)	764	**0.07 (0.041)**	**761**
Block design	0.01 (0.850)	761	−0.03 (0.447)	758
Letter-number sequencing	0.02 (0.531)	763	0.00 (0.958)	760
General factor: processing speed (g_{Speed})	−0.01 (0.813)	716	−0.04 (0.243)	714
Digit symbol coding	−0.03 (0.337)	761	−0.07 (0.060)	758
Symbol search	−0.03 (0.347)	759	−0.05 (0.147)	756
Simple reaction time (s)	**−0.09 (0.010)**	**751**	**−0.08 (0.035)**	**748**
Four choice reaction time (s)	0.04 (0.280)	759	0.05 (0.156)	756
Inspection time total	−0.01 (0.877)	737	−0.01 (0.772)	735
General factor: memory (g_{Memory})	0.01 (0.741)	735	−0.01 (0.879)	733
Logical memory	0.03 (0.442)	758	−0.00 (0.917)	756
Verbal paired associates	−0.01 (0.818)	741	−0.02 (0.643)	738
Spatial span	−0.10 (0.787)	762	0.02 (0.622)	759

Note. Age at time of testing, gender and high blood pressure statistically controlled. All beta values are standardised. Associations significant at $p < 0.05$ are printed in bold-face

[a] Controlling for age at time of testing and gender only. All associations are in the direction of *ADRB2* SNP G alleles

Table 4 Linear *ADRB2* SNP associations with cognitive abilities, adjusted for age 11 cognitive ability

Cognitive measure	rs1042713 (G allele)		rs1042714 (G allele)	
	β (p)	*N*	β (p)	*N*
Moray house test: age 70	0.00 (0.873)	710	0.00 (0.957)	705
General factor: intelligence (g)	−0.04 (0.159)	705	−0.05 (0.097)	700
Digit span backwards	−0.03 (0.455)	717	−0.02 (0.580)	712
Matrix reasoning	0.03 (0.419)	716	0.06 (0.101)	711
Block design	−0.03 (0.321)	713	−0.06 (0.102)	708
Letter-number sequencing	−0.01 (0.783)	716	−0.03 (0.400)	711
General factor: processing speed (g_{Speed})	−0.04 (0.258)	671	**−0.07 (0.045)**	**667**
Digit symbol coding	−0.06 (0.087)	714	**−0.09 (0.010)**	**709**
Symbol search	**−0.07 (0.044)**	**712**	**−0.08 (0.022)**	**707**
Simple reaction time (s)	**−0.09 (0.025)**	**704**	−0.06 (0.092)	699
Four choice reaction time (s)	0.05 (0.152)	713	0.07 (0.054)	708
Inspection time total	−0.02 (0.559)	690	−0.03 (0.427)	686
General factor: memory (g_{Memory})	−0.04 (0.202)	689	−0.05 (0.111)	685
Logical memory	−0.02 (0.612)	711	−0.05 (0.173)	707
Verbal paired associates	−0.04 (0.293)	695	−0.04 (0.318)	690
Spatial span	−0.03 (0.449)	715	−0.01 (0.866)	710

Note. Age at time of testing, gender, high blood pressure and age 11 Moray house test score statistically controlled. All beta values are standardised. Associations significant at $p < 0.05$ are printed in bold-face. All associations are in the direction of *ADRB2* SNP G alleles

significant associations between rs1042714, Matrix Reasoning and Simple RT in Table 3 attenuated to non-significance (Table 4).

Linear regression models were used to explore associations between white matter tracts and cognitive measures that both showed nominally significant associations with

Table 5 Associations between age 73 cognitive and white matter measures that are each associated with *ADRB2*

White matter tract	Symbol search		Digit symbol coding		Simple reaction time		General processing speed factor (g_{Speed})		Matrix reasoning[a]	
	β (p)	*N*	β (p)	*N*	β (p)	*N*	β (p)	*N*	β (p)	*N*
Right anterior thalamic radiation (FA)	0.08 (0.062)	549	**0.13 (0.001)**	**549**	**−0.10 (0.024)**	**541**	**0.12 (0.003)**	**524**	**0.09 (0.038)**	**588**
Left arcuate fasciculus (FA)	0.05 (0.199)	546	**0.12 (0.001)**	**547**	−0.05 (0.273)	540	**0.12 (0.004)**	**522**	−0.00 (0.985)	584

Note. Age at time of testing, gender, high blood pressure and age 11 Moray House Test score statistically controlled. All beta values are standardised. Associations significant at $p < 0.05$ are printed in bold-face

[a] Not adjusted for age 11 cognitive ability

ADRB2 variants. As shown in Table 5, Simple RT was associated with FA of the right anterior thalamic radiation ($\beta = -0.10$, $p = 0.024$). The rs1042713 G allele was associated with both of these variables. Of the measures associated with the rs1042714 G allele, FA of the left arcuate fasciculus was associated with Digit Symbol Coding ($\beta = 0.12$, $p = 0.001$) and g_{Speed} ($\beta = 0.012$, $p = 0.004$). With FDR correction for all reported tests, the association between left arcuate fasciculus FA and Digit Symbol Coding remained statistically significant (FDR-adjusted $p = 0.048$). None of the other associations between white matter integrity and cognitive function survived FDR correction.

Neuroimaging and cognitive variables that both showed nominally significant associations with *ADRB2* SNPs were examined further (Fig. 1). Note that all genotype-phenotype associations attenuated to non-significance when corrected for FDR and this mediation analysis is therefore only exploratory. Bootstrapping statistics indicated that the association between rs1042713 and Simple RT was significantly mediated by right anterior thalamic radiation FA (bootstrapping point estimate coefficient <0.001 [95 % CIs: <0.001 & 0.002]), because the bootstrapping confidence interval span did not contain zero (Preacher and Hayes 2008). Left arcuate fasciculus FA was found to significantly mediate the association between rs1042714 and Digit Symbol Coding (bootstrapping point estimate coefficient = −0.207 [95 % CIs: −0.519 & −0.043]), but not g_{Speed}.

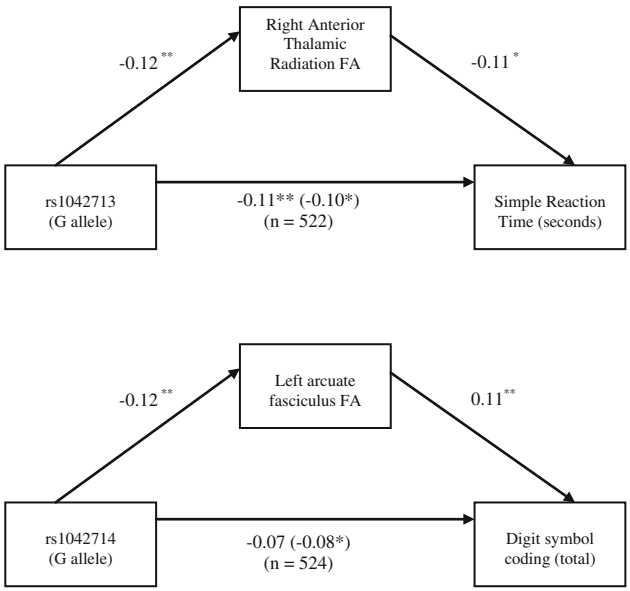

Fig. 1 Mediation analyses of the role of white matter integrity in the association between *ADRB2* SNPs and cognition, controlling for age, gender, diagnosis of high blood pressure and age 11 cognitive ability. *Note*. Associations shown represent linear regressions between each variable. Note this mediation is in the context of attenuation to non-significance when corrected for multiple comparisons (FDR). All beta values are standardised. *FA* fractional anisotropy. Values in *brackets* are betas before controlling for white matter integrity. All associations are in the direction of *ADRB2* SNP G alleles. $*p < 0.05$, $**p < 0.01$

Discussion

In an earlier report employing the full LBC1936 sample and using Wave 1 data, (Bochdanovits et al. 2009), *ADRB2* SNPs were associated with cognitive tests performed at mean age 70 years. Specifically, rs1047213 and rs1042714 were associated with performance on two cognitive tests, namely Matrix Reasoning and the MHT. In a subsample study of the LBC1936 tested at mean age 73 years (Penke et al. 2010a), associations were found for rs1042714 with cognitive ability and particularly cognitive change from childhood to older age that were mediated by white matter integrity in the splenium of the corpus callosum. In the present study of only right-handed participants who completed cognitive testing, the majority of whom also underwent diffusion MRI, and with identical covariates, these associations with cognitive function and white matter integrity did not replicate.

The effect sizes reported by Penke et al. were not found here and Bochdanovits et al. reported small coefficients, suggesting that associations may be sensitive to changes in sample size; specifically selection effects, restriction of

range and random fluctuation. Compared with the associations reported by Bochdanovits et al., the effect sizes reported here are similar but slightly smaller, and with a smaller sample size did not attain statistical significance. The current study differed from Bochdanovits et al. in two ways: the earlier report assessed participants that attended Wave 1 and included left, right and ambidextrous-handed participants, whereas the current study included only right-handed individuals that attended Wave 2. One previous association that was reported by Bochdanovits et al. attenuated when analysis examined only right-handed participants, suggesting that this is a partial source of discrepancy between the two reports. There is also evidence that another source of discrepancy may be selective attrition of more cognitively impaired individuals between Waves 1 and 2. It is important to note that Bochdanovits et al. reported opposing associations for the rs1042713 G allele; in the deleterious direction for younger participants, but in the protective direction for older participants. Their findings were therefore not unambiguous. Failure to replicate Penke et al. may reflect the limited number of participants in the original study compared to the current report. It is therefore possible that previous findings were type 1 errors.

In exploratory analysis of a range of age 73 white matter and cognitive phenotypes as well as MHT scores at ages 11 and 70, after controlling for gender, high blood pressure and age in days, rs1042713 was associated with faster Simple RT in the direction of the G allele. For rs1042714, associations were found with faster Simple RT and greater Matrix Reasoning performance in the direction of the G allele. After controlling for age 11 MHT scores, association between rs1042713 and faster Simple RT remained statistically significant in addition to an association with lower Symbol Search performance. When also adjusted for age 11 MHT scores, rs1042714 showed significant associations with lower Digit Symbol Coding, Symbol Search and g_{Speed} scores however previous associations with Simple RT and Matrix Reasoning attenuated to non-significance, indicating those effects were specific to cross-sectional ability at age 73 rather than cognitive ageing. In terms of white matter integrity, the G allele of rs1042713 was associated with lower FA of the left arcuate fasciculus and right anterior thalamic radiation tracts, while the G allele of rs1042714 was associated with lower FA/MD in the left arcuate fasciculus. When adjusted for multiple testing using FDR, all associations attenuated to non-significance.

A large number of association tests were conducted, and all significant associations attenuated once corrected for multiple testing using FDR. Whereas there are likely to be type-1 errors in the current study, given the number of associations conducted, it is also possible that correction for multiple testing is rejecting modest but true signals (Williams and Haines 2011). Cognitive and water diffusion tensor phenotypes are individually highly correlated as indicated by the g, g_{Speed}, g_{Memory}, g_{MD}, and g_{FA} factors, which means that each association test does not represent an independent observation. This can make correction for multiple testing overly conservative (Nyholt 2001). The current study therefore requires replication in independent cohorts.

Bearing in mind that our correction for multiple testing could have been overly conservative, we explored, using bootstrapping, mediation of associations between *ADRB2* and cognitive task performances by specific white matter tracts where the uncorrected p-levels were indicative of such links. We emphasise that these analyses were cautiously exploratory in the context of genotype-phenotype associations that were non-significant when corrected for FDR. However, we think they could provide indications for future studies.

The relationship between rs1042714 and Digit Symbol Coding attenuated when left arcuate fasciculus FA was controlled for. This may suggest partial mediation (Salthouse 2010). Integrity of the arcuate fasciculus has been associated with performance on different cognitive domains (Schmithorst et al. 2005) and has been suggested to underlie parieto-frontal cortical integration, a proposed foundation of higher cognitive ability (Jung and Haier 2007; Deary et al. 2010). The mediation reported here may therefore reflect the general role that this tract plays in subserving cognitive functioning in addition to the high sensitivity of the Digit Symbol Coding task in detecting even subtle cognitive dysfunction (Lezak et al. 2004). The association between rs1042713 and Simple RT showed evidence of being mediated by FA of the right anterior thalamic radiation tract. The strength of association between rs1042713 and Simple RT did not attenuate when relevant white matter integrity measures were controlled for however, and instead strengthened. This does not suggest true partial mediation; rather, these measures suppressed the relationship between rs1042713 and Simple RT (MacKinnon et al. 2000). It is counter-intuitive for the same allele to associate with faster Simple RT but lower integrity in associated white matter tracts. This suggests that this direct SNP-cognitive task association may instead be mediated by other related but distinct brain measures, for example integrity of the superior longitudinal fasciculus white matter tract which was not assessed here. It is also possible that this counter-intuitive finding reflects a spurious association, as reflected by its attenuation when corrected for FDR.

Summary

The current study examined healthy older adults that were cognitively assessed at age 11 years and again in older age. *ADRB2* previously showed significant associations with

cognitive ageing mediated by white matter tract integrity in a pilot study of the LBC1936 cohort. These associations were not replicated in this larger sample from the same cohort. Novel three-way associations were evident between *ADRB2* G alleles and specific cognitive and white matter tract integrity measures; however, all associations attenuated to non-significance upon correction for multiple testing. This correction could be considered conservative, so further research on functional *ADRB2* SNPs in large, independent samples is needed.

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