Supplementary Information (SI) for

Genetic Underpinnings of Risky Behaviour Relate to Altered Neuroanatomy

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Supplementary Methods

1. Measures

1.1. Main risky behaviour measure

We closely follow the methods of ref 1 to derive a measure of risky behaviour based on participants' self-reports across the drinking, smoking, driving, and sexual domains.

Specifically, we use the following UK Biobank variables:

- Number of alcoholic drinks per week (Data-Fields: 1558, 1568, 1578, 1588, 1598, 1608, 5364, 4407, 4418, 4429, 4440, 4451, 4462)
- Ever smoking (Data-Field 20116, 1249, 1239)
- Frequency of driving faster than the motorway speed limit (Data-Field 1100)
- \bullet Lifetime number of sexual partners (Data-Field 2149)¹

The full description of each Data-Field can be found in the online data showcase of the UKB (http://biobank.ctsu.ox.ac.uk/crystal/search.cgi). The annotated STATA code used to derive all behavioural phenotypes and control variables can be found in our pre-registered analysis plan

(https://osf.io/qkp4g/).

All variables above were measured on at least one of 3 occasions: (1) the initial assessment visit, (2) the first repeat assessment visit, and (3) the imaging visit. Data from (2) and (3) are only available for a subset of the original sample. In cases where participants provided answers across more than one visit, we compute the average of their reports.

To obtain a measure that captures the common variance in risky behaviour shared across domains, we perform principal component analysis (PCA) on *N* = 315,855 UKB participants and extract the first principal component (PC) as our main outcome of interest for this study (referred to as "risky behaviour"). Compared to experimental procedures that elicit risk tolerance, selfreported measures exhibit higher external validity and test-retest reliability³⁻⁵. Furthermore, by

 1 Self-reports of the number of sexual partners have been implicated in risky behaviours related to alcohol abuse (i.e., binge drinking) and unprotected sex, specifically in young adults 2, irrespective of gender or sexual orientation.

extracting the first principal component of the four risky behaviours, we reduce measurement noise due to the aggregation of signals across various measures, while capturing behavioural tendencies across domains that are independent of idiosyncratic differences in the four specific behaviours. The PCA summary statistics are available in Supplementary Table 1, and the component loadings are available in Supplementary Table 2. The first PC explained about 37% of the variance in the different phenotypes of risky behaviours in the sample, and it was the only PC that positively loaded on all of four phenotypes. Data distribution was assumed to be normal but this was not formally tested.

While the GWAS by Linnér et al. (2019)¹, was primarily based on a meta-analysis of two very crude, noisy, single-item measures of risk taking that were available in the two largest samples (UKB and 23andMe, which had slightly different questions on risk taking), this choice (in the GWAS) was made to maximize the sample size for genetic discovery, following the logic outlined in ref 6, i.e., that in genetic discovery studies, sample size typically trumps phenotypic accuracy in terms of statistical power. (The supplementary material of ref 6 includes a mathematical derivation that illustrates this). In the current work, we also wanted to maximize statistical power, albeit the situation here is different, as the sample size was exogenously determined by the UKB. Thus, the only means to increase statistical power was via increasing the quality of the phenotypic measurement. We decided to focus on the first PC of the four risky behaviours introduced in Linnér et al. (2019) for the following reasons: (1) It is available for a large part of the scanned subsample. (2) Linnér et al. (2019) showed that this first PC has a higher SNP-based heritability than any of the general risk-taking measures or individual phenotypes, which is partly because the first PC is less affected by random measurement error than any input variable considered separately. (3) The high heritability of the first PC suggests that similar genetic factors influence risk taking across various domains, making this a promising trait to study in connection with other biomarkers such as brain anatomy. (4) This variable has been studied in the literature, limiting our degrees of freedom for the current study. (5) GWAS results for this variable were readily available.⁶

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1.2 Control Variables

All of our analyses systematically control for several genetic, socio-demographic and anthropometric factors that could potentially confound the observed associations [e.g. sex⁷, height⁸ and genetic population structure⁹]. Specifically, we use the following control variables, as provided by the UKB:

- Age at the time of brain scan (Data-Field 21003)
- Birth year (Data-Field 33)
- Sex (self reported and genetically identified, Data-Fields 31 & 22001, dummy coded)
- Height (Data-Field 50)
- Handedness (Data-Field 1707, categorical variable: Right-handed, Left-handed, ambidextrous, N/A)
- Sex x birth year interactions (binned into fields containing at least 20 participants each)
- The first 40 PCs of the genetic data (Data-Field 22009)
- Total intracranial volume (TIV), derived using the CAT12 toolbox from T1 images.

We carry out an additional analysis that further controls for the following socio-economic and cognitive outcomes (provided by the UKB):

- Educational attainment (Data-Field 6138)
- A 13-item measure of fluid IQ (Data-Fields 20016 and 20191)
- Zip-code level measure of the Townsend social deprivation index (Data-Field 189)
- Household income (Data-Field 738)
- Number of household members (Data-Field 709)
- Place of birth, binned in 100 clusters based on North and East birth location coordinates (Data-Fields 129 and 130). Clusters were calculated using the *k*-means algorithm, which minimizes within-cluster variances (squared Euclidean distances) of *k* = 100 clusters with 10,000 iterations after random seeding.

The empirical distributions of the main variables used in our main analysis and the correlations between them are depicted in Figure 1B and Extended Data Figure 1 and 2. Data distributions were assumed to be normal but this was not formally tested.

1.3 Imaging-derived Phenotypes (IDPs)

1.3.1 T1 MRI Image Processing

Our voxel-level analysis uses T1-weighted structural brain MRI images in NIFTI format provided by the UKB (data field 20252). The images were acquired using 3-T Siemens Skyra scanners, with a 32-channel head coil (Siemens, Erlangen, Germany), with the following scanning parameters: repetition time = 2000 ms; echo time = 2.1 ms; flip angle = 8° ; matrix size = $256 \times$ 256 mm; voxel size = $1 \times 1 \times 1$ mm; number of slices = 208.

We preprocessed the data using the Computational Anatomy Toolbox (CAT; www.neuro.unijena.de/cat/) for SPM (www.fil.ion.ucl.ac.uk/spm/software/spm12/), a fully automated toolbox for deriving neuroanatomical measurements at voxel and ROI levels. Image pre-processing used the default setting of CAT12 (accessible online at http://www.neuro.uni-jena.de/cat12/CAT12- Manual.pdf). Images were corrected for bias-field inhomogeneities, segmented into gray matter, white matter, and cerebrospinal fluid (CSF), spatially normalized to the MNI space using linear and non-linear transformations, and were modulated to preserve the total amount of signal in the original image during spatial normalization (the specific SPM-processing parameters can be found in the pre-registered document on OSF https://osf.io/qkp4g/). We applied spatial smoothing with 8-mm Full-Width-at-Half-Maximum (FWHM) Gaussian kernel for the segmented, modulated images for grey matter volume (GMV). Finally, to ensure that only voxels that likely contain grey matter enter the analyses, we constructed a brain mask based on the average of all GMV images. Specifically, following standard VBM procedures (see SPM/CAT12

http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) we thresholded the average of all brain images at 250 GMV intensity units. The resulting image was binarized and applied as a pre-mask to all individual images before running analyses. Additionally, on an individual level, we excluded all voxels that exhibited a lower grey matter volume than .1 from the analyses (see standard

parameters of SPM/CAT12 http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). Data distributions were assumed to be normal but this was not formally tested. To illustrate the results of the GMV analyses, we used a standard MNI brain template based on Fonov et al $(2011)^{10}$.

1.3.2 Region of interest (ROI)-level IDPs Processed by the UKB

We use all of the GMV IDPs that were processed and provided by the UKB [for details see ref 11]. These IDPs include GMV of 139 ROIs derived using parcellations from the Harvard-Oxford cortical and subcortical atlases, and Diedrichsen cerebellar atlas. Data distributions were assumed to be normal but this was not formally tested.

1.3.3 Additional ROI-level IDPs

Based on our voxel-level results (see 2.1), we extracted 5 additional ROI-level IDPs that quantified GMV in anatomical substructures that were not derived by the UKB. These ROIs were extracted bilaterally from unbiased masks and included the dorsolateral prefrontal cortex (dlPFC; BA 46), hypothalamus, posterior hippocampus, ventro-anterior insula and ventromedial prefrontal cortex (vmPFC). For the dlPFC, ventro-anterior insula and vmPFC masks, we used recent functional parcellations based on resting state data. The dlPFC mask was derived using the Sallet Dorsal Frontal resting state connectivity-based parcellation (cluster 7/BA46)¹². Functionally, this area exhibits coupling with the frontal-parietal network (incl. anterior cingulate cortex, parietal cortex and inferior parietal lobe), as well as with the vmPFC. Anatomically, its boundaries show resemblance to BA 46 — an area functionally related to executive function that shows distinct cytoarchitectonic properties.

We extracted GMV from the vmPFC using a parcellation of the medial wall of the prefrontal cortex, based on resting state functional coupling¹³. Specifically, we extracted GMV from 14m $-$ an area linked to cost-benefit integration in value-based decision-making¹⁴⁻¹⁷, which maintains strong positive coupling with hypothalamus, ventral striatum, and amygdala¹⁸. The hypothalamus mask was derived from a high-resolution atlas of human subcortical brain nuclei¹⁹. The posterior hippocampus mask was derived according to recent recommendations for long-axis segmentation of the hippocampus in human neuroimaging²⁰. We labeled hippocampal voxels

posterior to the coronal plane at *y* = -21 in MNI space (which corresponds to the uncal apex of the parahippocampal gyrus), as posterior hippocampus. To ensure spatial precision across participants, we used a minimum 80% likelihood of each voxel being in the anatomical structure for all of the aforementioned masks. The ventro-anterior insula mask was derived following a recent parcellation of the insula based on a resting state functional connectivity analysis by ref 21, which reported that this brain region showed functional coactivation with limbic areas including amygdala, ventral tegmental area (VTA), superior temporal sulcus, and posterolateral orbitofrontal cortex. The raw mask was thresholded at *z* = 10.

1.4 Polygenic Risk Score (PRS) for Risky behaviour

We use the genetic data provided by the UKB to construct a polygenic risk score (PRS) for risky behaviour. As a first step, we rerun the genome-wide association study (GWAS) of risky behaviour (the same measure used in the current study) as reported in ref 1 after excluding the 18,796 genotyped individuals with usable T1 NIFTI structural brain images (UKB field 20252) and all of their relatives up to the third degree (defined using the KING coefficient²² based on a pairwise coefficient >0.0442). The final GWAS sample includes 297,025 individuals of European ancestry. We use BOLT-LMM version 2.3.2²³ to perform GWAS with linear mixed models (LMM), which outperforms linear regression in terms of statistical power and controlling for relatedness²⁴.

Next, we perform quality control (QC) of the GWAS results using a standardized QC protocol, described in detail in ref 1. This protocol removes rare and low-quality single-nucleotide polymorphisms (SNPs) based on minor allele frequency (MAF) < 0.001, imputation quality (INFO) < 0.7, and SNPs that could not be aligned with the Haplotype Reference Consortium (HRC) reference panel. After QC, a total of 11,514,220 SNPs remains in the GWAS summary statistics. Thereafter, we calculate for each participant *i* a PRS, S_i , by weighting his or her genotype across SNPs (*j*), g_{ij} , by the corresponding regression coefficients, β_i estimated in the GWAS described above. Thus, the PRS is a linear combination of genetic effects, calculated as:

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$$
S_i = \sum_{j=1}^M \beta_j g_{ij},
$$

where the set of SNPs, *M*, is restricted to the consensus genotype set of 1.4 million SNPs established by the International HapMap 3 Consortium²⁵, which has been successfully employed for polygenic prediction in many previous studies. Furthermore, the PRS is constructed only with autosomal, bi-allelic SNPs with *MAF* > 0.01 and *INFO* > 0.9 in the UKB. The resultant PRS is based on a total of *M*=1,176,729 SNPs. The PRS is then standardized to mean zero and unit variance in the prediction sample. Data distribution was assumed to be normal but this was not formally tested.

1.5 Genetic Correlations of Risky behaviour

We rely on the results of the risky behaviour GWAS to estimate genetic correlations between this phenotype and 85 other traits, using bivariate LD Score regression²⁶. The estimates are reported in Supplementary Table 3. For this purpose, we query the "GWAS ATLAS"²⁷ to identify publicly archived GWAS results that we consider relevant. We supplement the publicly available GWAS with a soon-to-be published GWAS on diet composition²⁸. Notably, the collected traits span across many different outcomes, including the anthropometric, behavioural, cognitive, psychiatric, medical, and socioeconomic domains.

We find moderate to strong genetic correlations between our main measure and a range of phenotypes that are considered risky behaviours, including ever consuming cannabis $(r_g = 0.72)$; *SE* = 0.03), self-employment (r_g = 0.52; *SE* = 0.30), and age at first sexual experience (r_g = -0.54; *SE* = 0.02). Our measure of risky behaviour is also genetically correlated with a range of mental disorders including bipolar disorder (r_g = 0.23; *SE* = 0.03), major depressive disorder (r_g = 0.22; $SE = 0.03$), and schizophrenia ($r_g = 0.17$; $SE = 0.02$). Finally, risky behaviour is genetically correlated in the expected direction with the personality traits of conscientiousness $(r_g = -0.25;$ *SE* = 0.10) and extraversion $(r_g = 0.34; SE = 0.05)$.

2. Pre-registration of Analysis Plan and Unplanned Deviations

We pre-registered our analysis plan on Open Science Framework (OSF, https://osf.io/qkp4q/). Our pre-registered plan specifies the construction of the dependent variable, the control variables, the inclusion criteria and quality controls, the VBM analyses and the main ROI-level analyses.

We deviated from the pre-registered plan in several cases, which are outlined in the following. These deviations occurred when the computational burden of following the preregistered plan was unexpectedly high, and when alternative measures that we were not aware of at the time of the pre-registration were made available by the UKB. Specifically, we decided not to use alternative segmentations of the cortex (e.g. Hammer's atlas) as robustness checks for our ROI-level analysis because of the significant computational burden in deriving those measures. Instead, based on the voxel-level analysis, we derived additional ROIs only when they were not derived in sufficient granularity in the IDPs provided by the UKB (see 1.3.3).

Similarly, we did not derive cortical thickness (CT) measures because of the high computational burden using FreeSurfer, which is the gold standard in cortical thickness estimation. While other means to derive CT would have been available (e.g. CAT toolbox), they would provide relatively lower quality data and would not allow analyses of subcortical areas. Additionally, the UKB was expected to release CT measures derived from FreeSurfer before this work was finalized (see the UKB Data Showcase website for public announcements). The lack of CT measures has also led us to decide to postpone the conduct of an additional pre-registered multivariate analysis.

Finally, our pre-registered plan states that we would run additional robustness checks to control for potential neurotoxic effects of excessive alcohol intake. Upon examining the data for a different project that is focused on the effects of alcohol intake on the brain, we observed effects that were mainly driven by individuals who were heavy drinkers. We therefore decided to deviate from our original plan and exclude all participants who qualified as current or former regular heavy drinkers. However, we also provide additional analyses that include weekly alcohol intake and smoking habits as a covariate (see Extended Data Figure 6). Finally, the pre-registered

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analysis of white-matter volume is not reported here, because we decided to focus our manuscript on GMV differences.

Supplementary Discussion

Our study highlights the importance of using large samples to study associations of neuroanatomy with complex behavioural traits. The largest effect we identify for the relationship between any cluster of voxels and risky behaviour is Δ*R*2 = 0.6% (see Supplementary Table 4). It would require more than 1,750 participants to have 90% statistical power at a liberal *p*-value threshold of 0.05 (uncorrected) to identify effects of this magnitude. This is a lower bound for the required sample size for such studies that does not reflect the upward bias in our effect size estimate due to the statistical "winner's curse", and the need to correct for multiple testing. Previous large-scale VBM studies ($N > 1000$) with other behavioural phenotypes²⁹ found effect sizes of similar magnitude and suggest that large samples are a prerequisite to detect such an association reliably. Of note, the largest previous study of risk tolerance employed a sample of 108 participants³⁰ and would have only 12% power to detect $\Delta R^2 = 0.6\%$ at $\alpha = 0.05$ (uncorrected).

A possible limitation of our study is that, the specific features of the component phenotypes (e.g., smoking) rather than their first PC (risky behaviour) could have driven the associations we report (quantified via standardized regression coefficients). To further investigate this possibility, we repeat our ROI-based analysis with the individual phenotypic measures (instead of their first PC) as outcome variables (see Supplementary Table 6). We find that 22 out of 23 ROIs are significantly associated with more than one phenotype (the exception is IX Cerebellum (r), which is significantly associated only with the number of sexual partners, yet the standardized coefficient denoting its relationship with the first PC is greater in magnitude than the coefficient denoting its relationship with the number of sexual partners). Furthermore, the standardized coefficients quantifying the relationships between the ROIs and the individual

phenotypes are either smaller than or at the same order of magnitude as the coefficients quantifying their relationship with the first PC.

While our study is larger and more representative than any previous investigation of the topic, and although we control for various potential confounds and replicate our findings in an independent sample, it was conducted in a population of UK individuals of European descent that were over 40 years old at the time of measurement, which limits the generalizability of our results to other populations. Moreover, our results do not exclude the possibility of bias due to other unobserved variables that our analyses do not account for. With the rise of large publicly available data sets [e.g. ref 31], we hope that future studies will be able to test the generalizability of our findings to populations of different ethnicities and age groups (e.g., adolescents).

Finally, while our analyses identify distinct brain areas that mediate gene-phenotype associations for risky behaviour (i.e., putamen, hypothalamus and dlPFC), they do not provide evidence for their causal relationship. For instance, it is possible that a person's genetic disposition would lead them to select into environments that influence both risky behaviour and features of brain anatomy.

Supplementary Table 1 | Eigenvalues of the four Principal Components of Risky Behaviours

Supplementary Table 2 | Eigenvectors of the four Principal Components of Risky Behaviours

Supplementary Table 3 | Genetic correlations (r_g) between risky behaviour (GWAS *N* = 297,025) and 85 traits, estimated using bivariate LD Score regression. All *P* values are based on two-sided statistical tests.

Supplementary Table 4 | Association between risky behaviour and grey matter volumes (GMV) in clusters of voxels (*N* = 12,675). Depicted are the summarized regression statistics per cluster. Δ*R*² indicates the marginal increase in variance explained compared to a model that excludes GMV from the respective cluster. The corresponding coordinates of the peak activation in each cluster can be found in Extended Data Figure 3.

Supplementary Table 5 | Effect sizes (standardized betas) and 95% confidence interval (uncorrected) of associations between risky behaviour and grey matter volumes (GMV) in 23 ROIs, with and without controlling for cognitive and socioeconomic outcomes $(N = 11,864)$. Additional controls include education years, fluid IQ, zip-code level social deprivation, household income, number of household members, birth location. Both models include all standard controls. The sample size of the analysis with additional controls is reduced due to missing data for some variables. *FWE-rate of 5%; **FWE-rate of 1%.

Supplementary Table 6 | Effect sizes (standardized betas) and the corresponding 95% confidence interval (uncorrected) of the associations between grey matter volumes in 23 ROIs and individual phenotypes of risky behaviour (*N*=12,675). Models include all of the standard control variables. *FWE-rate of 5 %; **FWE-rate of 1%.

Supplementary Table 7 | Effect sizes (standardized betas) and the corresponding 95% confidence intervals (uncorrected) of the associations between risky behaviour and grey matter volume in 23 ROIs, with and without controlling for current drinking level (binned in deciles) and current smoking level (binned in 3 categories). Both models include all of our standard controls (*N* = 12,675). *FWE-rate of 5 %; **FWE-rate of 1%.

Supplementary Table 8 | Effect sizes (standardized betas) and the corresponding 95% confidence intervals (uncorrected) of the associations between risky behaviour and ROI-level imaging-derived phenotypes (IDPs) of grey matter volume (GMV) in the replication sample (*N* = 13,004) and original sample (*N*=12,675). All beta coefficients are consistently negative across samples and 21 of 23 ROIs identified in the original analysis replicate (corrected for multiple testing using a permutation test, see Methods). *FWE-rate of 5%; **FWE-rate of 1%.

Supplementary Table 9 | Summary of studies used for the meta-analysis of fMRI studies on risky behaviours (provided by Neurosynth). Neurosynth uses text mining techniques to search through published articles for certain keywords (here: 'risky') and then quantifies how important the keyword is in any particular published article, relative to all other searched articles. Specifically, Neurosynth uses a metric (i.e. 'loading') to quantify how often the key word (here: 'risky') was used in the respective article relative to all other articles in this meta-analysis. Its value ranges from 0 to 1 and increases proportionally with the number of times a word appears in the respective published article. Neurosynth typically uses a cutoff of .05 for articles to be included in the meta-analysis. For further information see ref 32.

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Supplementary Notes

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