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Early Developmental Gene Enhancers Affect Subcortical Volumes in the Adult Human Brain

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Abstract: Genome-wide association screens aim to identify common genetic variants contributing to the phenotypic variability of complex traits, such as human height or brain morphology. The identified genetic variants are mostly within noncoding genomic regions and the biology of the genotype–phenotype association typically remains unclear. In this article, we propose a complementary targeted strategy to reveal the genetic underpinnings of variability in subcortical brain volumes, by specifically selecting genomic loci that are experimentally validated forebrain enhancers, active in early embryonic development. We hypothesized that genetic variation within these enhancers may affect the development and ultimately the structure of subcortical brain regions in adults. We tested whether variants in forebrain enhancer regions showed an overall enrichment of association with volumetric variation in subcortical structures of >13,000 healthy adults. We observed significant enrichment of genomic loci that affect the volume of the hippocampus within forebrain enhancers (empirical $P = 0.0015$), a finding which robustly passed the adjusted threshold for testing of multiple brain phenotypes (cutoff of $P < 0.0083$ at an alpha of 0.05). In analyses of individual single nucleotide polymorphisms (SNPs), we identified an association upstream of the *ID2* gene with rs7588305 and variation in hippocampal volume. This SNP-based association survived multiple-testing correction for the number of SNPs analyzed

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but not for the number of subcortical structures. Targeting known regulatory regions offers a way to understand the underlying biology that connects genotypes to phenotypes, particularly in the context of neuroimaging genetics. This biology-driven approach generates testable hypotheses regarding the functional biology of identified associations. *Hum Brain Mapp 37:1788–1800, 2016.*

Key words: functional genomics; gene enhancer; GWAS; hippocampus; neurodevelopment; subcortical volume

INTRODUCTION

Global research efforts are underway to determine how genomic variants contribute to variation in brain volume in the general population. Altered volumes of brain regions are associated with neurodegenerative [Jack et al., 2011] and neuropsychiatric disorders [Videbech and Ravnkilde, 2004; van Erp et al., 2015]. Current Genome-Wide Association Screening (GWAS) studies connect common genetic variants known as single nucleotide polymorphisms (SNPs) with phenotypic variations in brain imaging data in cohorts of healthy individuals [Bis et al., 2012; Stein et al., 2012; Cai et al., 2014; Guadalupe et al., 2015]. However, most SNPs identified by GWAS are within noncoding regions and their biological functions remain unclear. We employed a hypothesis-driven strategy involving preselection of SNPs within genomic regions of experimentally defined biological function. We found that the selected SNPs are significantly enriched for association with hippocampal volume. This approach can help to generate testable follow-up hypotheses about the underlying genotype–phenotype correlation.

It is challenging to predict and test the consequences of single nucleotide changes in genomic regions that do not encode proteins or regulatory RNA molecules [Visel et al., 2009b]. Nevertheless, a vast amount of noncoding DNA is thought to play some functional role, for example by regulating gene expression as promoters or enhancers. These regions are bound by regulatory proteins such as transcription factors (TFs) to directly influence gene expression and single nucleotide changes within these regions can affect gene expression [Spitz and Furlong, 2012].

A complementary strategy to genome-wide association screening is to look specifically for association within genomic regions that are predicted to be functional; for example by targeting regions known to be bound by a particular TF or marked by a given epigenetic modification. The approach was adopted in a study focusing on the genomic distribution of cell-type-specific regulatory regions in hematopoietic cells. These regions were enriched for the presence of genetic variants associated with hematological traits such as platelet count, while no enriched association was detected for unrelated traits such as body mass index (BMI) [Paul et al., 2013]. Another study applied a similar approach to publicly available functional datasets and found enriched association across a range of human traits and disorders, including Crohn's disease and height [Pickrell, 2014]. Thus, a priori knowledge of the functional characteristics of genomic regions may help in selecting subsets of genomic variants for association testing. To our knowledge, no prior study has systematically integrated information about functional brain enhancers with genetic data in human individuals. In the current study, we analyzed publicly available data from the Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) consortium, a neuroimaging genetics initiative that combines GWAS statistics from 50 cohorts spread worldwide, with a total combined sample size of 30,717 individuals [Thompson et al., 2014]. The ENIGMA consortium recently presented GWAS findings on seven subcortical volumes and intracranial volume [Hibar et al., 2015]. Five genetic variants were significantly associated with the volumes of the hippocampus and putamen. These SNPs mapped within noncoding regions of the genome and their functional roles are largely unknown. We hypothesized that polymorphisms located within experimentally validated brain enhancers, with established impacts on early neural development may be enriched for association with volumetric changes in subcortical brain structures. A valuable source of enhancers is the VISTA browser, which reports the tissue-specificity of about two thousand potential enhancers. Genomic elements tested in VISTA were chosen for their conservation across species and/or enhancer-specific chromatin marks in brain tissue [Visel et al., 2008, 2009a]. Their potential to reproducibly drive expression of a reporter gene was tested at an early developmental timepoint in the mouse brain [Visel et al., 2007]. VISTA contains 309 enhancers that drive expression in the embryonic forebrain; the developmental origin of the subcortical regions analyzed in adults by the ENIGMA consortium. Here, we integrate ENIGMA meta-analysis data with information on VISTA forebrain enhancer regions to assess for genetic effects on normal variation in subcortical brain volumes, using gene-set and SNP-based approaches.

METHODS AND MATERIALS

VISTA Enhancer Browser of Experimentally Validated Enhancer Fragments

The VISTA enhancer browser is a collection of experimentally validated noncoding fragments of the human and mouse genomes that exhibit enhancer activity [Visel et al., 2007]. Potential enhancers were predicted based on ChIP-

seq experiments or evolutionary conservation. The selected noncoding fragments were cloned in front of a minimal promoter and the LacZ reporter gene. The resulting constructs were injected into the pronucleus of mouse embryos and reimplanted into foster mothers. Developing embryos were stained for reporter gene expression at embryonic day 11.5 (E11.5). Noncoding fragments that drive reproducible reporter gene expression in multiple ($\geq$5) embryos are defined as positive enhancers. If no reproducible staining was detected in seven individual embryos, the noncoding fragment was regarded as negative. Thus, the database represents a collection of functional enhancers and their tissue of activity in developing embryos.

ENIGMA Meta-Analyzed Neuroimaging GWAS of Subcortical Brain Volumes

The ENIGMA consortium conducts harmonized analyses that combine neuroimaging genetics data from over 50 cohorts worldwide to search for common gene variants that are associated with brain structure and function. ENIGMA2 describes the second project of this consortium, which tested associations of 8.5 million SNPs with the variance in volumes of the nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, thalamus, and the intracranial volume, measured from brain MRI [Hibar et al., 2015]. The discovery sample for ENIGMA2 consisted of 13,171 subjects of European ancestry. The ENIGMA consortium also had access to a replication set of 17,546 subjects and reported on a total of 30,717 individuals. Subjects were scanned at the individual sites using brain MRI and the resulting images were processed in a standard way across all sites. The volumetric measures of all subcortical structures were corrected for age, sex, genetic homogeneity and intracranial volume. At each site, genotypes were obtained from commercially available platforms and imputed to the reference panel 1000genomes v1.3 using scripts provided by the ENIGMA working group. GWAS was performed at each site, and the meta-analysis of all 50 cohorts was performed centrally using the software package METAL [Willer et al., 2010]. Here, we use the meta-analyzed summary *P*-values of the 13,171 subjects obtained from the discovery sample. The remaining 17,000 subjects from ENIGMA2 lack meta-analyzed genome-wide statistics and were thus unavailable for use in the present study.

Selecting SNPs Within Human Enhancers

A list of enhancers, including their genomic coordinates (human genome build hg19) and their tissue of activity, was downloaded from the VISTA enhancer browser (Version 19, September 2014) [Visel et al., 2007]. We filtered all human enhancer elements with a reproducible forebrain activity at embryonic stage E11.5. The forebrain is the developmental origin of the subcortical regions analyzed by ENIGMA. We removed nine enhancer elements located on chromosome X, as this chromosome was not included in the ENIGMA2 data. Four enhancers (hs322, hs1354, hs998, and hs1597) contained within larger enhancers were deleted to obtain a nonredundant list of 296 loci with a mean size of 1,936 bp (standard deviation of 941 bp). Enhancer boundaries are not well defined, and flanking regions can be critical for the stability of an enhancer's activity [Ludwig et al., 2011]. We intersected the genomic enhancer regions, including 500 bp flanking regions with the genomic positions of all markers present in the meta-analyzed GWAS files of ICV-adjusted subcortical volumes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus) from ENIGMA2. From this, we derived a list of 2,082 SNPs and indels, which represent noncoding genetic variants with a potential impact on enhancer activity. We refer to these variants as *enhancer SNPs*.

Testing Enrichment of Association With Subcortical Volumes

ENIGMA2 tested for the association of 8.5 million genome-wide markers against volumes of seven subcortical brain structures. 2,082 of these markers were located within forebrain enhancer regions. For each of these markers we converted their association *P*-values into *z*-scores. Note that we could not specify a priori whether a particular allele of a SNP within an enhancer should lead to an increase or decrease in the activity of the relevant enhancer. Moreover, increases in gene expression may be correlated with either an increase or decrease in volume of a structure, depending on the nature of the gene product; both directions of effect are possible in principle, given what is known about mechanisms by which genes influence brain morphology. Thus, because we did not have prior hypotheses regarding direction of effect, we converted the *P*-values to right-tailed *z*-scores. These *z*-scores were then summed to calculate a "forebrain enhancer" test statistic. This was repeated for each of the tested brain phenotypes.

The probability of observing a similar (or greater) test statistic was determined by sampling 2,082 markers from 296 random genomic regions from the rest of the ENIGMA2 results. For each of the 296 forebrain enhancer regions, a randomly sampled genomic region of similar length was selected (with a difference no greater than 1,000 bp), which included at least the same number of markers as the original one. We chose the generated regions to be of similar size to avoid repetitive parts of the genome, such as telomeres or centromeres. We note that since the ENIGMA results are obtained via a large-scale meta-analysis of GWAS statistics from many different populations, we are unable to determine the precise linkage disequilibrium (LD) structure that would most appropriately match the enrichment analyses. Thus, our permutation approach assumes that the LD structure of the enhancer regions is broadly characteristic of the rest of the genome. From this set of new selected regions,

2,082 markers were used to calculate the new randomly generated set statistic. This was repeated ten thousand times. The *P*-value for the enrichment is the result of dividing the number of randomly generated test statistics that are higher than the observed test statistic by the number of permutations (10,000). The seven phenotypes are correlated, and we determined that the effective number of independent phenotypes is six, using the Matrix Spectral Decomposition, matSpD software [Nyholt, 2004]. We accounted for multiple testing by Bonferroni correction for this effective number of independent phenotypes. Thus, at an alpha of 0.05, the *P*-value threshold for significant enrichment was 0.0083.

Testing Enrichment of Association With Unrelated Human Traits as a Control

As noted above, our permutation approach for assessing enrichment assumes that enhancer regions do not deviate substantially in LD structure, as compared to the rest of the genome. Therefore, we performed additional control experiments to discount the possibility that evidence of enrichment might be an artifact of unusual LD patterns. We downloaded the meta-analyzed GWAS summary statistics for BMI [Speliotes et al., 2010], height [Lango Allen et al., 2010] and waist-to-hip ratio (WHR) [Heid et al., 2010] from the Genetic Investigation of Anthropometric Traits (GIANT) consortium. We used the Galaxy web-based platform [Giardine et al., 2005; Blankenberg et al., 2010; Goecks et al., 2010] to add the SNP's genomic locations (hg19) and carried out enrichment analysis as described above. Based on Bonferroni correction for use of three control phenotypes, at an alpha of 0.05 the *P*-value threshold for significant enrichment in these analyses was 0.017.

Association of Individual Enhancer SNPs With Subcortical Volumes

SNPs within the same enhancer are in close proximity, and often in LD, so not independent from each other. We therefore wanted to determine the effective number of independent SNPs in the SNP-based association tests. Since the original genotypes for all subjects were not centrally collected by ENIGMA they were unavailable for the present study. Therefore, we calculated the effective number of tested SNPs from a large subset of ENIGMA for which genotypes were available to us: the Brain Imaging Genetics (BIG) cohort of the Cognomics initiative [Guadalupe et al., 2014]. This cohort contributed approximately 10% of the subjects to the ENIGMA2 discovery sample and consists of healthy subjects of European ancestry. Using the Genetic Type I Error Calculator [Li et al., 2012], we determined that the number of effectively independent tests performed when assessing associations for the 2,082 enhancer SNPs was 770.

We evaluated the evidence for association between enhancer SNPs (spread across 296 enhancers) and variation in the seven subcortical volumes analyzed in ENIGMA2. As noted above, analyses with matSpD [Nyholt, 2004] indicated that the effective number of independent phenotypes is six. We derived an appropriate significance threshold based on Bonferroni correction, taking into consideration both the effective number of tested SNPs and the effective number of independent phenotypes. At an alpha of 0.05, the significance threshold for a SNP was 1.08×10^{-5}.

Analysis of eQTL Effects in Adult Brain Samples

We used the BRAINEAC eQTL database [Ramasamy et al., 2014] to investigate if rs7588305 is associated with expression changes in adult human hippocampal samples. Using the webtool we obtained eQTL association *P*-values for the queried SNP to expression probes of surrounding genes in different brain areas. We corrected the *P*-values for the number of probes that the rs7588305 SNP was correlated with to determine if the SNP represents an eQTL for one of the surrounding genes.

Predicting Transcription Factor Binding Events

To predict the effect of rs7588305 alleles on TF binding events, we performed a motif analysis using the MATCH algorithm, set to minimize false positives [Kel et al., 2003]. As the source for position weight matrices we used the commercially available Transfac2014.4 motif library. We predicted the binding events for a 51-nucleotide long genomic fragment centered on rs7588305, which was downloaded from the UCSC Genome Browser human genome version 19 (hg19). We predicted binding events for both the major and minor alleles.

RESULTS

Developmental Brain Enhancers Are Significantly Enriched for Association With Hippocampal Volume

The *a priori* selection of functional genomic regions (Fig. 1, Supporting Information Table I) allowed us to test for enriched genetic association among all enhancer elements as a group. We hypothesized that the group of enhancers contains a significant number of SNPs with subthreshold associations, which we could detect by comparing the enhancer regions to random genomic regions. Using a permutation approach, we detected significantly enriched association of the enhancer region set with hippocampal volume (empirical $P = 0.0015$, passing our predesignated threshold of $P < 0.0083$ based on Bonferroni correction for multiple brain phenotypes). Additionally, we detected nominally significant enrichment in the nucleus accumbens, putamen, and thalamus ($P = 0.016$, $P = 0.048$, and $P = 0.016$, respectively) that did not pass multiple testing correction for the number of subcortical volumes that were analyzed (Table I). This result supports the hypothesis that experimentally validated

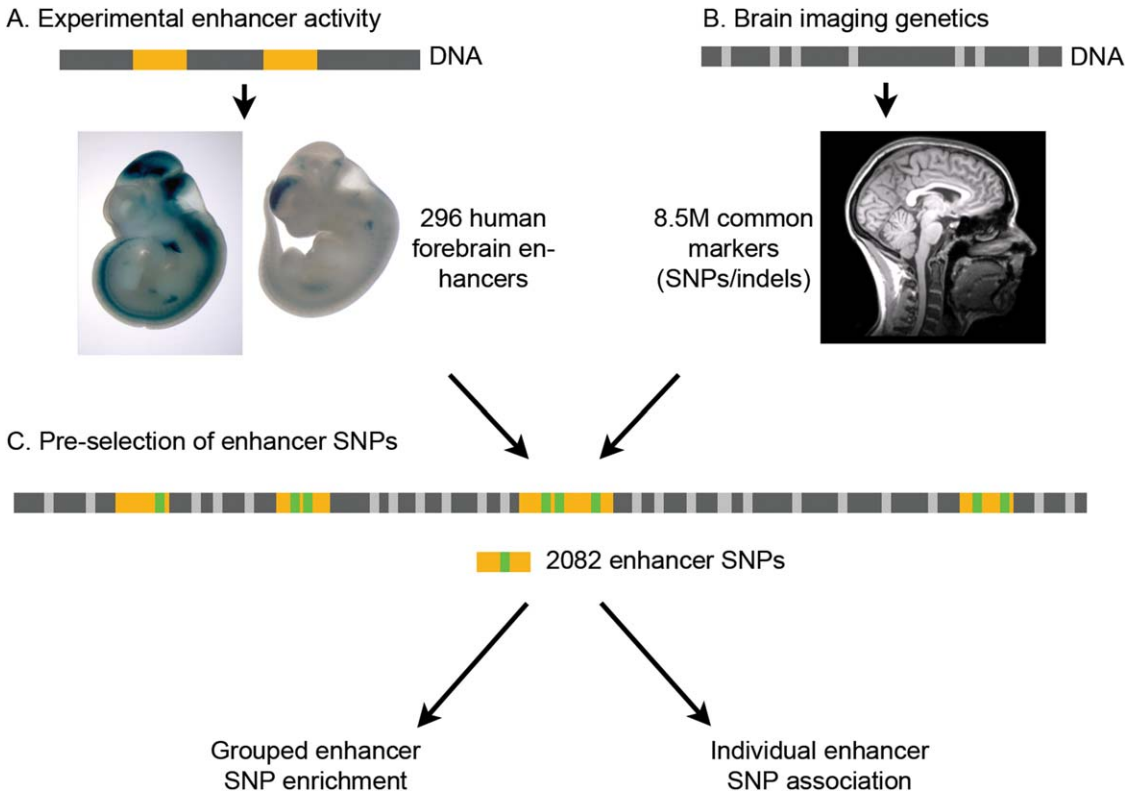

Figure 1.

Overview of enhancer SNP association study. In this study we used two independent datasets. (**a**) Genomic regions of forebrain enhancers as determined in transgenic E11.5 mouse embryos and (**b**) association of common genetic variants with the volumetric variation of subcortical brain structures, determined by MRI. (**c**) Preselecting SNPs within enhancer regions allowed us to investigate associations that do not pass genome-wide significance. We used two complementary strategies testing for enriched occurrence of association signals within the group of enhancer regions, and looking for association of individual enhancer SNPs.

forebrain enhancer regions from early developmental timepoints contain a significant number of genetic variants associated with the size of adult subcortical brain structures.

Within each permutation the SNPs were randomly generated, but had to be located in genomic regions of similar SNP density to the enhancer regions. Genomic regions with low SNP density may have a different overall LD structure from that of the enhancer regions and may skew the observed enrichment. Indeed, if we did not limit the genomic distribution of the randomly generated SNPs, we detect a more significant enrichment for the forebrain enhancer regions within the hippocampus ($P < 0.0006$).

TABLE I. Enrichment of enhancer SNP association

Brain structure	Enrichment *P*-value
Accumbens	0.016
Amygdala	0.068
Caudate	0.076
Hippocampus	0.0015
Pallidum	0.075
Putamen	0.048
Thalamus	0.016

Our hypothesis was that specifically forebrain enhancers are enriched for association with subcortical volumes. To assess if the detected enrichment could instead be due to a more general enrichment in enhancer regions, we generated a list of VISTA enhancers that are active in tissues other than the brain. We obtained a comparable number of nonbrain enhancers (320 enhancers, Supporting Information Table II). We calculated the enrichment of association with hippocampal volume using the same approach as for the forebrain enhancer set and found that the control enhancer regions were not significantly enriched for association with hippocampal volume ($P = 0.95$). These findings suggest that the enrichment we detected within forebrain enhancers reflect functional links between these enhancer sequences and their tissue of activity.

Enhancers may function in more than one tissue and many of the forebrain enhancers are also active in other parts of the developing embryo, such as the neural tube

TABLE II. Most significant individual SNP associations in each subcortical brain structure

Brain structure	Enhancer ID	Enhancer SNP	Allele 1 [A1]	Allele 2 [A2]	*P*-value	Effect of A2 (mm^3/allele)	StdErr effect
Accumbens	hs1578	rs139118507	A	C	5.65E−04	−18.16	5.27
Amygdala	hs1300	rs149826134	A	G	9.50E−04	−31.75	9.61
Caudate	hs1362	rs17710617	T	C	8.79E−05	20.66	5.27
Hippocampus	hs1527	rs7588305	C	G	2.88E−05	−21.73	5.20
Pallidum	hs1636	rs36058915	—	T	1.18E−04	7.73	2.01
Putamen	hs1300	rs149826134	A	G	1.33E−04	−88.06	23.04
Thalamus	hs200	rs34415491	A	—	1.29E−04	−26.76	6.99

(79/296 enhancer regions), limbs (33/296), eye (19/296), or heart (5/296) (Supporting Information Table III). However, we wanted to determine if the forebrain enhancers are specifically enriched for neuronal traits and exclude that the enrichment is caused by factors other than the biological link. We downloaded GWAS summary statistics for BMI, height and WHR from the GIANT consortium and repeated the enrichment analysis. We detected no enrichment for BMI, height, or WHR ($P = 0.06$, $P = 0.99$, or $P = 0.97$ respectively, none approaching predesignated threshold of $P < 0.017$ for control phenotypes). This finding supports the view that the significant enrichment of forebrain enhancers with hippocampal volume reflects specific effects, rather than being an artifact e.g. of the particular LD structure of the regions being studied.

Suggestive Association of an Enhancer SNP Upstream of ID2 With Variation in Hippocampal Volume

In parallel we analyzed the individual enhancer SNPs for association with the seven subcortical volumes. After adjusting our significance threshold for the effective number of tested SNPs and the effective number of independent phenotypes, no individual SNP met the strictest significant threshold (Table II and Supporting Information Table IV). Nonetheless, the strongest evidence of association was between hippocampus volume and SNP rs7588305, which had an unadjusted *P*-value of 2.9×10^{-5} (Fig. 2a and Table II). This association remained significant after correcting for the effective number of tested SNPs ($P = 0.022$ after Bonferroni correction), but not after further correction for the number of subcortical brain regions investigated (adjusted $P = 0.13$). Rs7588305 has a minor allele frequency (MAF) of 0.45. The SNP is located in the enhancer hs1527, which according to the VISTA enhancer browser is active in the forebrain, hindbrain, midbrain, and neural tube (Fig. 2b). In the genome this enhancer is approximately 38 kb upstream of the closest gene *ID2* (Fig. 2d), which is involved in transcriptional regulation [Ferrer-Vicens et al., 2014]. *ID2* expression overlaps hs1527 enhancer activity in the forebrain and midbrain at the same embryonic period (Fig. 2c). However, we could not find supportive expression quantitative trait loci (eQTL) association between rs7588305 and *ID2* in a dataset of human adult hippocampal expression data [Ramasamy et al., 2014].

Using the prior knowledge that rs7588305 is located within a forebrain enhancer, we identified a suggestive association of this SNP with hippocampal volume. If this SNP itself (rather than others in LD) is mediating this association, then complementary data should support a functional role. For example, the alternative allele of this SNP might affect the activity of the surrounding enhancer caused by differential binding of TFs. In order to assess such possibilities, we used in silico analyses to test if the change from major to minor allele would affect known TF binding sites. The differential motif analysis of the surrounding genomic fragment predicted a gain of six new motifs and a loss of five motifs for the minor allele (Supporting Information Table V). Among these predicted differences we found two ubiquitously expressed general TFs that are involved in chromatin structure and looping, CTCF and p300 (Supporting Information Fig. 1). The minor allele of rs7588305 gained a binding motif for CTCF—a general TF that stabilizes chromatin loops and is generally found in structural chromatin loops that either block enhancer promoter interactions or are active enhancer loops [Ong and Corces, 2014]. The second change for the minor allele was the loss of a p300-binding motif. P300 is a transcriptional coactivator that is found at active enhancer–promoter loops and increases transcription of the target gene [Chan and La Thangue, 2001]. The motif analysis of the rs7588305 SNP is thus consistent with the view that the allelic state of this SNP could be associated with changed activity of the enhancer. The variant could potentially decrease the activity of the enhancer, given that the binding site for the co-activator p300 is lost. However, CTCF function is highly dependent on context, and the effect of a gained CTCF binding site is difficult to predict. Thus, to determine the direction of effect of the minor allele would require future experiments, for example using cellular models.

DISCUSSION

The advent of GWAS has allowed for the high-throughput characterization of genetic variants in large cohorts of human subjects. In a comprehensive resource of SNP-trait association

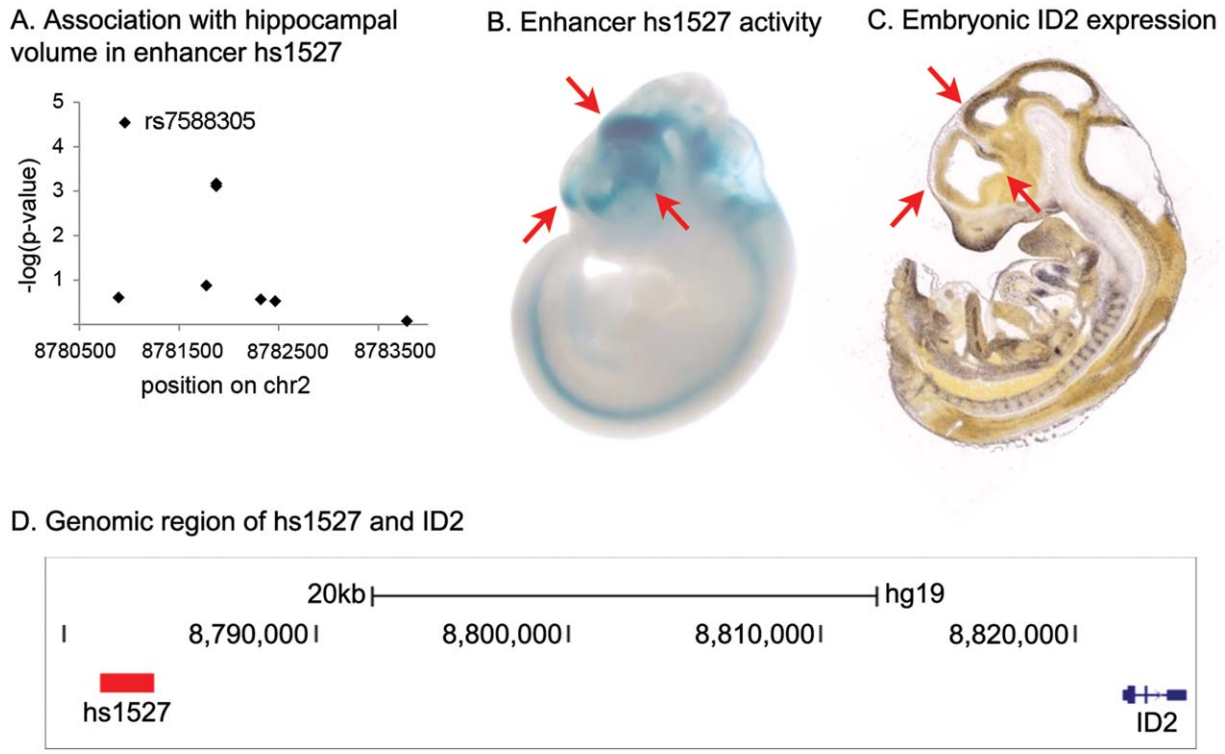

Figure 2.

The enhancer SNP rs7588305 is associated with reduced hippocampal volume and is located upstream of the *ID2* gene. Plot (**a**) shows association *P*-values with hippocampal volume. Plotted are all enhancer SNPs within hs1527 according to their position on human chromosome 2. The rs7588305 SNP is at position 8,780,959 and has a *P*-value of 2.88×10^{-5}. (**b**) Representative transgenic mouse embryo injected with the hs1527 construct. Picture downloaded from the VISTA enhancer database (http://enhancer.lbl.gov/cgi-bin/imagedb3.pl?form=presentation&show=1&experiment_id=1527&organism_id=1) [Visel et al., 2007]. The hs1527 enhancer activity is detected at embryonic stage E11.5 in parts of the forebrain, midbrain and neural tube as shown by the blue reporter gene staining. (**c**) *ID2* gene expression in a mouse embryo at stage E11.5, detected with in situ hybridization. Picture downloaded from the Allen Developing Mouse Brain Atlas (http://developingmouse.brain-map.org/experiment/siv?id=100072835&imageId=101217794&initImage=ish, Website: © 2015 Allen Institute for Brain Science.). *ID2* expression overlaps hs1527 enhancer activity in the forebrain and midbrain (red arrows in b and c). (**d**) UCSC genome browser (https://genome.ucsc.edu) showing the genomic location of the hs1527 enhancer upstream of the *ID2* gene.

data from multiple GWAS studies, collated by the National Institutes of Health (NIH), more than 90% of SNP associations map to noncoding regions [Welter et al., 2014]. A substantial number of these SNPs are in genomic regions with regulatory functions, such as enhancers. Thus, preselecting functionally tested enhancers may help to detect biological links between genetic variants and phenotypic traits. Here we investigated the association of common variation in well-defined developmental forebrain enhancers with volumetric measures of subcortical regions in a meta-analyzed study of 13,000 adult subjects. For hippocampus volume, we found a significant overall enrichment of association within enhancer regions that was robust to multiple-testing, as well as suggestive individual association of one enhancer SNP. Therefore, this study shows how functional data can help to detect trait-associated genetic variants. Our approach also generates testable hypotheses relating noncoding SNPs to an observed trait of interest.

High-throughput studies have documented the functions of noncoding DNA across a range of tissues and cell lines by characterizing genome-wide distribution of chromatin modifications and/or TF interactions [Encode, 2012; Barrett et al., 2013]. The resulting public databases allow predictions to be made regarding the regulatory activity of a genomic fragment. They thus provide useful tools to determine the functionality of trait-associated noncoding SNPs, and how they relate to the phenotype of interest [Boyle et al., 2012; Ward and Kellis, 2012]. Crucially, in most GWAS efforts these data are only exploited in a post hoc manner, to assess SNP associations that meet genome-wide significance. Our method is unbiased with respect to the functional regions and our results therefore include subthreshold associations of SNPs with smaller effect sizes.

Targeted studies of single genomic regions indicate that variants in noncoding DNA are related to variation in normal

brain volume and risk for psychiatric illness. For example, a rare variant implicated in autism was found in an enhancer that is active during forebrain development [Poitras et al., 2010]. The variant that may increase risk for autism alters binding of regulatory TFs and reduces enhancer activity in the developing forebrain [Poitras et al., 2010]. Another study focused on an enhancer that underwent accelerated evolution on the human lineage, after splitting from that of chimpanzees [Boyd et al., 2015]. In mouse models, the human version of this enhancer prolongs forebrain growth and increases the size of the developing neocortex [Boyd et al., 2015]. This supports our finding that human gene enhancers help explain how noncoding SNPs contribute to variation in brain volume.

We identified an enhancer SNP that has a within-phenotype significant association with hippocampal volume. The SNP is contained within the enhancer hs1527 and positioned upstream of the inhibitor of DNA binding 2 (*ID2*) gene. *ID2* is expressed in the embryonic mouse forebrain and in regions of adult rat brain, including the hippocampus [Kitajima et al., 2006]. The expression pattern of *ID2* overlaps with the regions of hs1527 enhancer activity (Fig. 2b,c). *ID2* enhances cell proliferation [Iavarone et al., 1994] and promotes axon growth in primary rat neurons [Lasorella et al., 2006]. In human neuronal cell lines, *ID2* is directly regulated by MECP2 [Peddada et al., 2006]. Disruptions of the *MECP2* gene cause Rett syndrome, a neurodevelopmental disorder characterized by severe intellectual disability and microcephaly [Amir et al., 1999]. Accordingly, *ID2* expression was higher in postmortem brain samples from subjects with Rett Syndrome [Peddada et al., 2006]. The absence of association between rs7588305 and *ID2* expression in adult human hippocampal samples, as measured by the Braineac eQTL database, does not discount an effect on enhancer activity in embryonic tissue. Differential *ID2* expression during embryonic development may be sufficient to lead to volumetric changes in the adult, which agrees with the role of the gene in cell-proliferation and neurogenesis. Future studies of *ID2* function in neurodevelopment may link this gene to hippocampal development.

A benefit of preselecting genetic variants based on functional information is that specific testable hypotheses are generated for follow-up studies. For example, motif analysis using the major and minor alleles of rs7588305 predicted differential binding of CTCF and p300, two ubiquitously expressed proteins involved in chromatin loop formation and transcriptional regulation. The minor allele lacks the motif for p300, a general mediator for enhancer activity, and gains a motif for CTCF, which may affect enhancer loop formation. The shifted binding of these two general chromatin associated factors could conceivably alter the activity of the hs1527 enhancer, a hypothesis that can be tested with future experiments in cellular models, which would also enable the direction of effect to be determined.

Here, we determined if a set of functionally validated enhancers, active during early brain development, was enriched for association with volumetric differences in subcortical brain structures in human adults. We found significant enrichment with hippocampal volume and nominal significance for the nucleus accumbens, pallidum, and thalamus. The selected forebrain enhancers contained an increased number of common genetic variants with subthreshold associations. The observed enrichment in the hippocampus was found with forebrain enhancers, but was not detectable for nonbrain enhancers. In order to exclude that the effects reflected unusual LD structure of the forebrain enhancers, or some other artifact, we performed additional control analyses of other human traits, including BMI, height and WHR, and did not observe enrichment. This finding implies that early developmental enhancer activity has an impact on adult hippocampal volume. During the human lifespan more than 80% of all genes ($\geq$20,000) are expressed in the developing and adult human brain [Kang et al., 2011], and each active gene promoter is in contact with several enhancers [Sanyal et al., 2012; Jin et al., 2013]. Tens of thousands of enhancers may guide the coordinated expression of genes during development. Indeed, more than 80,000 noncoding genomic regions show histone marks indicative of active enhancers in brain tissue [Vermunt et al., 2014]. The VISTA enhancer database likely represents only a fraction of enhancers that act during human brain development, and genetic variants in unsampled enhancers may also contribute to subcortical volumes. This could likely have limited our ability to detect enrichment beyond the hippocampus. Future testing of all existing brain enhancers may increase the power to identify enrichment of associations.

Another current limitation is that the VISTA database characterizes enhancer activity at E11.5 and anatomically annotates this activity only to the general forebrain region. An annotation with respect to specific adult subcortical areas is not possible at this early embryonic period. It is crucial to look at the most relevant tissue for association studies of enhancers, so more detailed anatomical annotations of enhancer activities at later time points would improve the approach. This may enable mapping of more direct connections from enhancer activity to adult neuroimaging data.

In this study we focused on experimentally validated enhancer elements, because these give a robust set of regions with clear functional links to defined human tissues. The method we have employed may be expanded to study tissue-specific histone modifications as they become more readily available [Vermunt et al., 2014; Roadmap Epigenomics et al., 2015]. A benefit of these datasets may be their more fine-grained anatomical description and sampling across several developmental time points.

In summary, we demonstrated genotype–phenotype connections between early neurodevelopmental enhancers and the volumes of adult subcortical brain regions in a dataset of over 13,000 people. As with all genetic association studies, replication of these findings should be sought in independent samples of a similar size where matched genome-wide genotyping and brain measures are available. Comparable analyses

of enhancer SNPs in cohorts of patients with neurodevelopmental disorders have the potential to link early embryonic enhancer activity to disease processes. Our study illustrates a novel method for integrating functional genomic and phenotypic data to identify the biological underpinnings of highly heterogeneous traits, including neuropsychological traits. Our method can be applied to other sets of functional noncoding genomic elements to connect the function of the regions to studied phenotypes of interest.

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