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A GWAS-Derived Polygenic Score for Interleukin-1β is Associated with Hippocampal Volume in Two Samples

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Abstract

Accumulating research suggests that the pro-inflammatory cytokine interleukin-1β (IL-1β) has a modulatory effect on the hippocampus, a brain structure important for learning and memory as well as linked with both psychiatric and neurodegenerative disorders. Here, we used an imaging genetics strategy to test an association between an IL-1β polygenic score and hippocampal volume in two independent samples. Our polygenic score was derived using summary statistics from a recent genome-wide association study (GWAS) of circulating cytokines that included IL-1β (N=3,309). In the first sample of 512 non-Hispanic Caucasian university students (274 women, mean age 19.78 ± 1.24 years) from the Duke Neurogenetics Study, we identified a significant positive correlation between IL-1β polygenic scores and hippocampal volume. This positive association was successfully replicated in a second sample of 7,960 white British volunteers (4,158 women, mean age 62.63±7.45 years) from the UK Biobank. Our results lend further support in humans, to the link between IL-1β and the structure of the hippocampus.

Keywords

Interleukin-1β (IL-1 β); inflammation; structural MRI; hippocampus; brain volume; polygenic score; single nucleotide polymorphism

Introduction

The hippocampus, a key brain structure supporting learning and memory, has been implicated in the pathophysiology of both psychiatric and neurodegenerative disorders. For example, smaller hippocampal volume has been noted in schizophrenia (van Erp et al., 2016), depression (Schmaal et al., 2016), and bipolar disorder (Hibar et al., 2016), as well as in neurodegenerative disorders such as Alzheimer's disease (Bobinski et al., 1999). More

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Conflict of interest: The authors declare no competing financial or other interests.

Data availability

The required procedures for obtaining the DNS data are detailed in our website https://www.haririlab.com/projects/procedures.html. The UK Biobank data requires contacting the UK Biobank team directly, through http://www.ukbiobank.ac.uk.

broadly, smaller hippocampal volume has been associated with poorer cognitive function in healthy adults (Zhu, Chen, Dang, Dong, & Lin, 2017). Thus, advancing the understanding of the factors that contribute to individual differences in hippocampal volume, can shed light on both normal and abnormal function.

It is now clear that inflammation has far-reaching modulatory effects on the central nervous system (Miller, Haroon, Raison, & Felger, 2013; Yirmiya & Goshen, 2011). Amongst these, the pro-inflammatory cytokine interleukin (IL)-1β, which can affect the physiology of most cells and is a key mediator of autoinflammatory, autoimmune, infectious, and degenerative diseases (Garlanda, Dinarello, & Mantovani, 2013), may be particularly important for understanding hippocampal structure. First, receptors for IL-1β are highly expressed in the dentate gyrus (Ban, Milon, Prudhomme, Fillion, & Haour, 1991; Loddick, Liu, Takao, Hashimoto, & De Souza, 1998), where neural stem cells reside in the adult mammalian brain (Gage, 2000). Second, IL-1β has been shown to affect neurogenesis, synaptic strengthening, and long term potentiation (LTP) in the hippocampus (Avital et al., 2003; Bellinger, Madamba, & Siggins, 1993; Goshen et al., 2008; Green & Nolan, 2012; Katsuki et al., 1990; Wu, Montgomery, Rivera-Escalera, Olschowka, & O'Banion, 2013). All of these processes can affect volume. For example, in animal models, interrupting IL-1β signaling, by a deletion of IL-1 receptor type 1 or by administration of IL-1 receptor antagonist (IL-1Ra), blocks the antineurogenic effect of stress on the hippocampus (Koo & Duman, 2008). Further, increasing IL-1β signaling, by exogenous administration of this cytokine, mimics the effect of stress, and decreases hippocampal cell proliferation (Koo & Duman, 2008). In humans, Zunszain et al., (2012) demonstrated that IL-1β directly inhibits neurogenesis in hippocampal progenitor cells in vitro.

It is notable that while high levels of IL-1β are usually associated with deleterious effects on the hippocampus, this cytokine has also been shown to support normal brain function, by affecting neurogenesis, LTP, learning, and memory. Such salubrious effects seem to depend on the target organ, expression level/dose, and timing (reviewed in Donzis & Tronson, 2014; Spulber, Bartfai, & Schultzberg, 2009). For instance, one study in mice showed that LTP is associated with an increase in IL-1β gene expression in hippocampal cells and that IL-1Ra led to a reversible inhibition of LTP (Schneider et al., 1998). Another study found that a 30-minute IL-1β (1 ng/mL) administration impaired N-methyl-D-aspartate (NMDA) receptor dependent LTP, but not NMDA receptor independent LTP, in mouse hippocampal slices (Hoshino, Hasegawa, Kamiya, & Morimoto, 2017).

Despite the vast literature demonstrating the effects of IL-1β on hippocampal volume and studies showing that IL-1β levels are moderately to highly heritable (Brodin et al., 2015; De Craen et al., 2005), to our knowledge, the genetic influences of IL-1β on hippocampal volume in humans have only been previously shown in one candidate gene study (Raz, Daugherty, Bender, Dahle, & Land, 2015). In a sample of 80 individuals, Raz et al. found that the T allele of the single nucleotide polymorphism (SNP) rs16944 in the IL-1β gene was associated with smaller hippocampal volume. Notably however, candidate gene studies suffer from low replicability rates (e.g., Avinun, Nevo, Knodt, Elliott, & Hariri, 2018), and more specifically, findings regarding the biological functionality of rs16944 have not been consistent across studies (e.g., Chen et al., 2006; Iacoviello et al., 2005).

Polygenic scores that aggregate information from across the genome to summarize genome-wide genetic influences on an outcome of interest, have been successfully used in previous research to model individual differences (e.g., Domingue, Belsky, Conley, Harris, & Boardman, 2015; Domingue, Liu, Okbay, & Belsky, 2017; Stephan, Sutin, Luchetti, Caille, & Terracciano, 2018). A recent study conducted separate genome-wide analyses of circulating blood levels of 41 cytokines, including IL-1β, in up to 8,293 adult Finns from three independent population cohorts (Ahola-Olli et al., 2017). Using meta-analysis of the associations from each cohort, and after controlling for sex, age, genetic ancestry, and body mass index (BMI), the authors found 27 genome-wide significant SNPs for one or more cytokines. Specifically, the sample used for the analysis of IL-1β included 3,309 individuals from two studies: the Cardiovascular Risk in Young Finns Study and the FINRISK study. No genome-wide significant SNPs were found for IL-1β, possibly due to the stringent correction for multiple comparisons using a significance threshold of $p<(5*10–8)/41$. However, genome-wide statistical significance is not a prerequisite for leveraging GWAS summary statistics to model individual differences in target phenotypes. In fact, polygenic scores based on summary statistics of all available SNPs irrespective of nominal significance (i.e., $p=1$) have been shown to account for most of the variance in the phenotype of interest (Dudbridge, 2013; Ware et al., 2017).

Here, we used summary statistics from the above study to generate polygenic scores to model potential individual differences in circulating levels of IL-1β. There are two main advantages to this approach. First, accurate measures of IL-1β levels are not readily available to researchers as the human IL-1β may not directly cross the blood brain barrier, requiring highly invasive sampling of cerebrospinal fluid (reviewed in Banks, 2005). Second, polygenic scores, reflecting inherent differences between individuals, more readily allow for speculation regarding the directionality of effects than direct measures of contemporaneous IL-1β levels that can reflect differences that precede or follow changes in hippocampal volume.

Based on the available literature, we hypothesized that higher polygenic IL-1β scores, which putatively correlate with higher circulating levels of the pro-inflammatory cytokine, would be associated with smaller hippocampal volume. We tested our hypothesis in two independent samples: 1) 512 non-Hispanic Caucasian university students from the Duke Neurogenetics Study; and 2) 7,960 adult white British volunteers from the UK Biobank. In the analyses of both samples, in addition to sex, age, and ethnicity, we also included socioeconomic status (SES), stress, and BMI, as covariates of no interest because of prior links between these measures and brain volume (Gunstad et al., 2008; Hackman, Farah, & Meaney, 2010; Lupien, McEwen, Gunnar, & Heim, 2009) as well as inflammation (Pollitt et al., 2008; Silverman & Sternberg, 2012; Tam, Clement, Baur, & Tordjman, 2010).

Materials and methods

Participants

Our first sample consisted of 512 self-reported non-Hispanic Caucasian participants (274 women, mean age 19.78±1.24 years) from the Duke Neurogenetics Study (DNS) who were not genetically related and for whom there was complete data on genotypes, structural MRI,

and all covariates detailed below. All procedures were approved by the Duke University Medical Center Institutional Review Board, and participants provided informed written consent before study initiation. All participants were free of the following study exclusions: 1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

Current and lifetime DSM-IV (the Diagnostic and Statistical Manual of Mental Disorders) Axis I or select Axis II disorders (antisocial personality disorder and borderline personality disorder), were assessed with the electronic Mini International Neuropsychiatric Interview (Lecrubier et al., 1997) and Structured Clinical Interview for the DSM-IV Axis II subtests (First, Gibbon, Spitzer, Williams, & Benjamin, 1997), respectively. Importantly, neither current nor lifetime diagnosis were an exclusion criterion, as the DNS seeks to establish broad variability in multiple behavioral phenotypes related to psychopathology. Of the 512 participants with data included in our analyses, 114 individuals had at least one past or current DSM-IV diagnosis, including 65 with alcohol use disorders, 19 with non-alcohol substance use disorders, 26 with major depressive disorders, 16 with bipolar disorders, 13 with panic disorder (no agoraphobia), 12 with panic disorder including agoraphobia, 5 with social anxiety disorder, 8 with generalized anxiety disorder, 6 with obsessive compulsive disorder, and 3 with eating disorders. However, no participants, regardless of diagnosis, were taking any psychoactive medication during or at least 14 days prior to their participation.

Our second sample, consisted of 7,960 white British participants (4,158 women, mean age 62.63±7.45 years), with complete genotype, structural MRI, and covariate data from the UK Biobank (www.ukbiobank.ac.uk; Sudlow et al., 2015), which includes over 500,000 participants, between the ages of 40 and 69 years, who were recruited within the UK between 2006 and 2010. Participants in the imaging sample of the UK Biobank were excluded if they had any metal inside their body or an implanted medical device that could create imaging artefacts or pose a risk during MRI, if they were likely to find it difficult to lie still, or if they were unlikely to tolerate the imaging due to reported claustrophobia. The UK Biobank study has been approved by the National Health Service Research Ethics Service (reference: 11/NW/0382), and our analyses were conducted under UK Biobank application 28174.

Socioeconomic status (SES)

Prior research has reported associations between SES and brain volume (Hackman et al., 2010). In the DNS, we controlled for possible SES effects using the “social ladder” instrument (Adler, Epel, Castellazzo, & Ickovics, 2000), which asks participants to rank themselves relative to other people in the United States (or their origin country) on a scale from 0–10, with people who are best off in terms of money, education, and respected jobs, at the top (10) and people who are worst off at the bottom (0).

In the UK Biobank, we used the Townsend deprivation index, which was assessed at recruitment, as a means to control for SES. The Townsend deprivation index is a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership,

and household overcrowding. It was calculated before participants joined the UK Biobank and was based on the preceding national census data, with each participant assigned a score corresponding to the postcode of their home dwelling. Scoring was reversed so that high values represented high SES.

Body mass index (BMI)

Prior research has reported associations between BMI and brain volume (Gunstad et al., 2008). In both DNS and UK Biobank samples, BMI was calculated based on the height and weight of the participants. In the DNS, this calculation was based on imperial system values (pounds/inches^2*703), while in the UK Biobank the metric system was used (kg/m^2). For the UK Biobank we used the BMI from the imaging assessment visit.

Recent life stress

Prior research has reported associations between stress and hippocampal volume (Lupien et al., 2009). In the DNS, we controlled for the effects of life stress during the year prior to assessment using a summation of 38 negatively valenced items (as described in Avinun et al., 2017; Nikolova, Bogdan, Brigidi, & Hariri, 2012) from the Life Events Scale for Students (LESS; Clements & Turpin, 1996).

In the UK Biobank, life stress during the two years prior to imaging was assessed based on a count of 6 stressful events (illness of participant, illness of a close relative, death of a partner/spouse, death of a close relative, marital separation/divorce, and financial difficulties).

Race/Ethnicity

Because self-reported race and ethnicity are not always an accurate reflection of genetic ancestry, an analysis of identity by state of whole-genome SNPs was performed in PLINK (Purcell et al., 2007). The first two multidimensional scaling components within the non-Hispanic Caucasian subgroup were used as covariates in analyses of data from the DNS. The decision to use only the first two components was based on an examination of a scree plot of the eigenvalue of each component.

For analyses of data from the UK Biobank, only those who were ‘white British’ based on both self-identification and a principal components analysis of genetic ancestry were included. Additionally, the first 10 multidimensional scaling components received from the UK Biobank’s team were included as covariates as previously done (e.g., Whalley et al., 2016).

Genotyping

In the DNS, DNA was isolated from saliva using Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP

data, the HumanOmniExpress (N=326) or HumanOmniExpress-24 (N=186; Do et al., 2011; Eriksson et al., 2010; Tung et al., 2011).

In the UK Biobank, samples were genotyped using either the UK BiLEVE (N=775) or the UK Biobank axiom (N=7,185) array. Details regarding the UK Biobank's quality control can be found elsewhere (Bycroft et al., 2017).

Quality control and polygenic scoring

For genetic data from both the DNS and UK Bionbank, PLINK v1.90 (Purcell et al., 2007) was used to perform quality control analyses and exclude SNPs or individuals based on the following criteria: missing genotype rate per individual >.10, missing rate per SNP >.10, minor allele frequency <.01, and Hardy-Weinberg equilibrium p<1e-6. Additionally, in the UK Biobank, quality control variables that were provided with the dataset were used to exclude participants based on a sex mismatch (genetic sex different from reported sex), a genetic relatedness to another participant, and outliers for heterozygosity or missingness.

Polygenic scores were calculated using PLINK's (Purcell et al., 2007) "--score" command based on published SNP-level summary statistics from a recent GWAS that included IL-1β blood levels as an outcome of interest (Ahola-Olli et al., 2017). SNPs from the IL-1β GWAS were matched with SNPs from the DNS and UK Biobank datasets. For each SNP the number of the alleles (0, 1, or 2) associated with IL-1β blood levels was multiplied by the effect estimated in the GWAS. The polygenic score for each individual was an average of weighted IL-1β-associated alleles. All SNPs that could be matched with SNPs from the DNS or UK Biobank were used regardless of effect size and significance in the original GWAS, as previously recommended and shown to be effective (Dudbridge, 2013; Ware et al., 2017). A total of 428,481 SNPs in the DNS and 567,256 SNPs in the UK Biobank were included in the respective polygenic scores. The approach described here for the calculation of the polygenic score was successfully used in previous studies (e.g., Domingue et al., 2015; Domingue et al., 2017; Stephan et al., 2018).

Structural MRI

In the DNS, data were collected at the Duke-UNC Brain Imaging and Analysis Center using one of two identical research-dedicated GE MR750 3T scanners (General Electric Healthcare, Little Chalfont, United Kingdom) equipped with high-power high-duty cycle 50-mT/m gradients at 200 T/m/s slew rate, and an eight-channel head coil for parallel imaging at high bandwidth up to 1 MHz. T1-weighted images were obtained using a 3D Ax FSPGR BRAVO with the following parameters: TR = 8.148 ms; TE = 3.22 ms; 162 axial slices; flip angle, 12°; FOV, 240 mm; matrix =256×256; slice thickness = 1 mm with no gap; and total scan time = 4 min and 13 s.

To generate regional measures of brain volume, anatomical images for each subject were first skull-stripped using ANTs (Klein et al., 2009), then submitted to Freesurfer's (Version 5.3) recon-all with the "-noskullstrip" option (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999), using an x86_64 linux cluster running Scientific Linux. The gray and white matter boundaries determined by recon-all were visually inspected using FreeSurfer QA Tools (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools) and determined to be sufficiently

accurate for all subjects. Volume measures for the hippocampus from each participant's aseg.stats file were averaged across hemispheres. Estimated Total Intracranial Volume (eTIV) was used to quantify intracranial volume (ICV).

In the UK Biobank, imaging data were collected on a Siemens Skyra 3T, with a standard Siemens 32-channel RF receive head coil, and preprocessed with FSL packages (the FMRIB Software Library; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Segmentation of T1-weighted structural images into subcortical structures was done using FIRST (FMRIB's Integrated Registration and Segmentation Tool; Patenaude, Smith, Kennedy, & Jenkinson, 2011). Additional information on the imaging processing pipeline conducted for the UK Biobank can be found elsewhere (Alfaro-Almagro et al., 2018; Miller et al., 2016; online documentation: biobank.ctsu.ox.ac.uk/crystal/docs/brain_mri.pdf). Here as well, left and right hippocampal volumes were averaged to create a mean volume variable. ICV was estimated based on the sum of white matter, gray matter and ventricular cerebrospinal fluid volumes.

Statistical analyses

Mplus version 7 (RRID:SCR_015578; Muthén & Muthén, 2007) was used to conduct linear regression analyses. In both samples the covariates of no interest included: participants' sex (coded as 0=males, 1=females), age (in the DNS 18–22 years were coded as 1–5), ethnicity components, BMI, SES, recent life stress, and intracranial volume. Maximum likelihood estimation with robust standard errors, which is robust to non-normality, was used in the regression analyses. Standardized results for these analyses are presented.

Results

Descriptive statistics and correlations between study variables are presented in Table 1 and Table 2, respectively. IL-1β polygenic scores were positively and significantly associated with SES in both samples, therefore the findings below are reported with and without SES as a covariate. The polygenic scores did not differ between men and women (DNS: F[1, 510] = .642, p=.42; UK Biobank: [1, 7958] = .021, p=.88).

The analysis in the DNS sample revealed that IL-1β polygenic scores significantly predicted hippocampal volume, so that higher scores were associated with larger volume (without SES: β=.078, SE=.037, p=.036; with SES: β=.075, SE=.037, p=.044). Of the covariates, only ICV was significantly associated with hippocampal volume (β=.626, SE=.044, p<.001). The R^2 of the model with SES was .425 (SE=.03, p<.001). Comparing the R^2 of the model with the IL-1β polygenic score to the R^2 of a model without it, indicated that the variance explained by the polygenic score was small (R^2=.005). In the UK Biobank analysis, IL-1β polygenic score was also positively and significantly associated with hippocampal volume (without SES: β=.023, SE=.010, p=.020; with SES: β=.022, SE=.010, p=.021). Of the covariates, other than ICV (β=.425, SE=.014, p<.001), both age (β=−.177, SE=.010, p<.001) and stress (β=−.025, SE=.010, p=.010) negatively predicted hippocampal volume. The R^2 of the model with SES was .248 (SE=.01, p<.001). Comparing the R^2 of the model with the IL-1β polygenic score to the R^2 of a model without it, indicated that the variance explained by the polygenic score was small (R^2=.001).

As post-hoc analyses we tested each hemisphere separately with the same covariates, including SES. This was done to examine whether one hemisphere was driving the observed associations. In the DNS the effect was stronger and only significant in the left hippocampus (LEFT: β=.109, SE=.039, p=.005; RIGHT: β=.024, SE=.036, p=.503). In the UK Biobank, the effect was also only significant in the left hippocampus (LEFT: β=.022, SE=.010, p=.025; RIGHT: β=.018, SE=.010, p=.072).

Additionally, in the DNS we were able to test whether a DSM-IV diagnosis, as determined by a structured clinical interview, biased the findings. With the addition of a variable indicating a DSM-IV diagnosis (0-no diagnosis; 1-at least one DSM-IV diagnosis) as a covariate, the positive association of the IL-1β polygenic score with hippocampal volume remained significant (β=.074, SE=.037, p=.047).

Discussion

Here we report that a polygenic score for circulating levels of the pro-inflammatory cytokine IL-1β, based on summary statistics from a recent GWAS, is associated with hippocampal volume in two independent samples: the DNS, which consists of 18–22 year old university students, and the UK Biobank, which consists of 45–78 year old volunteers. Contrary to our hypothesis, which was based on previous research demonstrating that high IL-1β levels suppress neurogenesis (Goshen et al., 2008; Koo & Duman, 2008; Zunszain et al., 2012), we found that higher IL-1β polygenic scores, which have been associated with increased levels of this pro-inflammatory cytokine, were associated in both samples with larger hippocampal volume.

While high levels of IL-1β may adversely affect neurogenesis, they have been shown to increase gliogenesis (Chen et al., 2013; Crampton, Collins, Toulouse, Nolan, & O'Keeffe, 2012). In other words, IL-1β may reduce neurogenesis, not by increasing cell death, but by affecting cell fate determination and promoting the differentiation of neural progenitor cells into glial cells (Crampton et al., 2012). Furthermore, nonpathological/physiological levels of IL-1β have been shown to support neurogenesis in transgenic mice that overexpress human soluble IL-1Ra (Spulber, Oprica, Bartfai, Winblad, & Schultzberg, 2008) and in rats treated with IL-1Ra (Bachstetter et al., 2011). Additional processes that may explain the observed positive association between IL-1β polygenic scores and hippocampal volume, are the effects of IL-1β on LTP (Avital et al., 2003) and dendritic spine size (Goshen et al., 2009). Mice with impaired IL-1 signaling are characterized by deficits in memory function, reduced LTP, and reduced dendritic spine size (Avital et al., 2003; Goshen et al., 2008; Goshen et al., 2007; Yirmiya, Winocur, & Goshen, 2002), suggesting that certain levels of IL-1β are required for normal brain function. It is possible that the higher levels of IL-1β, as modeled by the polygenic score, are within an optimal range that leads to an advantageous function of this cytokine in promoting synaptic integrity and plasticity. Further studies, combining genetic, immune, and structural brain measurements during various stages in development are needed to shed light on the processes that may underlie the positive association between IL-1β polygenic scores and hippocampal volume.

Although our study has several strengths, including the use of two independent samples with markedly different characteristics (e.g., young university students versus older community volunteers) and a GWAS-derived functionally informed polygenic score, it is not without limitations. First, similar to other studies that rely on samples of university students and/or volunteers, neither the DNS nor the UK Biobank (Fry et al., 2017) represent the general population. Similarly, it should be kept in mind that we restricted our analyses to non-Hispanic Caucasians. As a result, further studies are needed to test the generalizability of our findings. Second, we did not examine specific hippocampal subregions, such as the dentatge gyrus, which may exhibit preferential sensitivity to variability in IL-1β signaling (Ban et al., 1991; Loddick et al., 1998). Such subregional analyses require higher resolution structural data. Third, the IL-1β GWAS only included 3,309 individuals, which limits the power to identify all meaningfully associated SNPs. As has been observed with other phenotypes (e.g., educational attainment; Plomin & von Stumm, 2018), vastly larger GWASs will be needed to develop more precise polygenic scores for IL-1β. Lastly, as cytokine levels were not measured in our samples, we were not able to validate the functionality of the IL-1β polygenic score or examine how it correlates with other pro-inflammatory markers. Such data are necessary for better understanding the underlying mechanism of our observed associations, which cannot establish a causative role of IL-1β levels in hippocampal volume. It should be noted that levels of inflammatory cytokines, including IL-1β, increase with age (Brüünsgaard & Pedersen, 2003) and that this cytokine has been shown to affect brain processes in an age dependent manner (Bachstetter et al., 2011; Griffin et al., 2006; Spulber et al., 2008). Consequently, the processes that underlie the links between the IL-1β polygenic score and hippocampal volume may differ between the samples and require further research. Additionally, as the polygenic score included SNPs that span the entire genome, the related processes may not only affect circulating IL-1β levels differently across the lifespan, but also include pathways that do not involve direct effects of IL-1β. These limitations notwithstanding, our results further support the association between IL-1β and hippocampal volume in humans and motivate additional research on the links between an IL-1β polygenic score, inflammation, and brain volume.

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REFERENCES

Adler NE, Epel ES, Castellazzo G, & Ickovics JR (2000). Relationship of subjective and objective social status with psychological and physiological functioning: Preliminary data in healthy, White women. Health Psychology, 19(6), 586. [PubMed: 11129362]

Ahola-Olli AV, Würtz P, Havulinna AS, Aalto K, Pitkänen N, Lehtimäki T, … Seppälä I (2017). Genome-wide association study identifies 27 loci influencing concentrations of circulating cytokines and growth factors. The American Journal of Human Genetics, 100(1), 40–50. [PubMed: 27989323]

Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JL, Griffanti L, Douaud G, … Vallee E (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. Neuroimage, 166, 400–424. [PubMed: 29079522]

Avinun R, Nevo A, Knodt AR, Elliott ML, & Hariri AR (2018). Replication in Imaging Genetics: The Case of Threat-Related Amygdala Reactivity. Biological Psychiatry, 84(2), 148–159. 10.1016/j.biopsych.2017.11.010 [PubMed: 29279201]

Avinun R, Nevo A, Knodt AR, Elliott ML, Radtke SR, Brigidi BD, & Hariri AR (2017). Reward-Related Ventral Striatum Activity Buffers against the Experience of Depressive Symptoms Associated with Sleep Disturbances. The Journal of Neuroscience, 37(40), 9724–9729. 10.1523/jneurosci.1734-17.2017 [PubMed: 28924013]

Avital A, Goshen I, Kamsler A, Segal M, Iverfeldt K, Richter-Levin G, & Yirmiya R (2003). Impaired interleukin-1 signaling is associated with deficits in hippocampal memory processes and neural plasticity. Hippocampus, 13(7), 826–834. [PubMed: 14620878]

Bachstetter AD, Morganti JM, Jernberg J, Schlunk A, Mitchell SH, Brewster KW, … Bickford PC (2011). Fractalkine and CX3CR1 regulate hippocampal neurogenesis in adult and aged rats. Neurobiology of Aging, 32(11), 2030–2044. [PubMed: 20018408]

Ban E, Milon G, Prudhomme N, Fillion G, & Haour F (1991). Receptors for interleukin-1 (α and β) in mouse brain: Mapping and neuronal localization in hippocampus. Neuroscience, 43(1), 21–30. 10.1016/0306-4522(91)90412-H [PubMed: 1833666]

Banks WA (2005). Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Current Pharmaceutical Design, 11(8), 973–984. [PubMed: 15777248]

Bellinger FP, Madamba S, & Siggins GR (1993). Interleukin 1β inhibits synaptic strength and long-term potentiation in the rat CA1 hippocampus. Brain research, 628(1–2), 227–234. [PubMed: 8313151]

Bobinski M, De Leon M, Wegiel J, Desanti S, Convit A, Saint Louis L, … Wisniewski H (1999). The histological validation of post mortem magnetic resonance imaging-determined hippocampal volume in Alzheimer's disease. Neuroscience, 95(3), 721–725.

Brodin P, Jojic V, Gao T, Bhattacharya S, Angel CJL, Furman D, … Butte AJ (2015). Variation in the human immune system is largely driven by non-heritable influences. Cell, 160(1–2), 37–47. [PubMed: 25594173]

Brüünsgaard H, & Pedersen BK (2003). Age-related inflammatory cytokines and disease. Immunology and Allergy Clinics, 23(1), 15–39.

Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, … O'Connell J (2017). Genome-wide genetic data on~ 500,000 UK Biobank participants. bioRxiv, 166298.

Chen E, Xu D, Lan X, Jia B, Sun L, C Zheng J, & Peng H (2013). A novel role of the STAT3 pathway in brain inflammation-induced human neural progenitor cell differentiation. Current molecular medicine, 13(9), 1474–1484. [PubMed: 23971732]

Chen H, Wilkins LM, Aziz N, Cannings C, Wyllie DH, Bingle C, … Cork MJ (2006). Single nucleotide polymorphisms in the human interleukin-1B gene affect transcription according to haplotype context. Human Molecular Genetics, 15(4), 519–529. [PubMed: 16399797]

Clements K, & Turpin G (1996). The life events scale for students: validation for use with British samples. Personality and Individual Differences, 20(6), 747–751.

Crampton SJ, Collins LM, Toulouse A, Nolan YM, & O'Keeffe GW (2012). Exposure of foetal neural progenitor cells to IL-1β impairs their proliferation and alters their differentiation–a role for maternal inflammation? Journal of neurochemistry, 120(6), 964–973. [PubMed: 22192001]

Dale AM, Fischl B, & Sereno MI (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage, 9(2), 179–194. [PubMed: 9931268]

De Craen A, Posthuma D, Remarque E, Van Den Biggelaar A, Westendorp R, & Boomsma D (2005). Heritability estimates of innate immunity: an extended twin study. Genes and Immunity, 6(2), 167. [PubMed: 15674372]

Do CB, Tung JY, Dorfman E, Kiefer AK, Drabant EM, Francke U, … Langston JW (2011). Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. PLoS Genetics, 7(6), e1002141. [PubMed: 21738487]

Domingue BW, Belsky DW, Conley D, Harris KM, & Boardman JD (2015). Polygenic influence on educational attainment: New evidence from the National Longitudinal Study of Adolescent to Adult Health. AERA open, 1(3), 2332858415599972.

Domingue BW, Liu H, Okbay A, & Belsky DW (2017). Genetic heterogeneity in depressive symptoms following the death of a spouse: Polygenic score analysis of the US Health and Retirement Study. American Journal of Psychiatry, 174(10), 963–970. [PubMed: 28335623]

Donzis EJ, & Tronson NC (2014). Modulation of learning and memory by cytokines: signaling mechanisms and long term consequences. Neurobiology of Learning and Memory, 115, 68–77. [PubMed: 25151944]

Dudbridge F (2013). Power and predictive accuracy of polygenic risk scores. PLoS Genetics, 9(3), e1003348. [PubMed: 23555274]

Eriksson N, Macpherson JM, Tung JY, Hon LS, Naughton B, Saxonov S, … Mountain J (2010). Web-based, participant-driven studies yield novel genetic associations for common traits. PLoS Genetics, 6(6), e1000993. [PubMed: 20585627]

First MB, Gibbon M, Spitzer RL, Williams JBW, & Benjamin LS (1997). Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II) Washington, DC: American Psychiatric Press.

Fischl B, Sereno MI, & Dale AM (1999). Cortical surface-based analysis: II: inflation, flattening, and a surface-based coordinate system. Neuroimage, 9(2), 195–207. [PubMed: 9931269]

Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, … Allen NE (2017). Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. American Journal of Epidemiology, 186(9), 1026–1034. [PubMed: 28641372]

Gage FH (2000). Mammalian neural stem cells. Science, 287(5457), 1433–1438. [PubMed: 10688783]

Garlanda C, Dinarello C, & Mantovani A (2013). The interleukin-1 family: back to the future. Immunity, 39(6), 1003–1018. [PubMed: 24332029]

Goshen I, Avital A, Kreisel T, Licht T, Segal M, & Yirmiya R (2009). Environmental enrichment restores memory functioning in mice with impaired IL-1 signaling via reinstatement of long-term potentiation and spine size enlargement. The Journal of neuroscience: the official journal of the Society for Neuroscience, 29(11), 3395–3403. [PubMed: 19295146]

Goshen I, Kreisel T, Licht T, Weidenfeld J, Ben-Hur T, & Yirmiya R (2008). Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Molecular psychiatry, 13(7), 717. [PubMed: 17700577]

Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, … Yirmiya R (2007). A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology, 32(8), 1106–1115. 10.1016/j.psyneuen.2007.09.004 [PubMed: 17976923]

Green H, & Nolan Y (2012). Unlocking mechanisms in interleukin-1β-induced changes in hippocampal neurogenesis—a role for GSK-3β and TLX. Translational Psychiatry, 2(11), e194. [PubMed: 23168994]

Griffin R, Nally R, Nolan Y, McCartney Y, Linden J, & Lynch MA (2006). The age-related attenuation in long-term potentiation is associated with microglial activation. Journal of Neurochemistry, 99(4), 1263–1272. [PubMed: 16981890]

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, & Gordon E (2008). Relationship between body mass index and brain volume in healthy adults. International Journal of Neuroscience, 118(11), 1582–1593. [PubMed: 18853335]

Hackman DA, Farah MJ, & Meaney MJ (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. Nature Reviews Neuroscience, 11(9), 651. [PubMed: 20725096]

Hibar D, Westlye LT, van Erp TG, Rasmussen J, Leonardo CD, Faskowitz J, … Agartz I (2016). Subcortical volumetric abnormalities in bipolar disorder. Molecular Psychiatry, 21(12), 1710. [PubMed: 26857596]

Hoshino K, Hasegawa K, Kamiya H, & Morimoto Y (2017). Synapse-specific effects of IL-1β on long-term potentiation in the mouse hippocampus. Biomedical Research, 38(3), 183–188. [PubMed: 28637953]

Iacoviello L, Di Castelnuovo A, Gattone M, Pezzini A, Assanelli D, Lorenzet R, … Amore C (2005). Polymorphisms of the interleukin-1β gene affect the risk of myocardial infarction and ischemic stroke at young age and the response of mononuclear cells to stimulation in vitro. Arteriosclerosis, Thrombosis, and Vascular Biology, 25(1), 222–227.

Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, & Smith SM (2012). FSL. Neuroimage, 62(2), 782–790. [PubMed: 21979382]

Katsuki H, Nakai S, Hirai Y, Akaji K. i., Kiso Y, & Satoh M (1990). Interleukin-1β inhibits long-term potentiation in the CA3 region of mouse hippocampal slices. European journal of pharmacology, 181(3), 323–326. [PubMed: 2166677]

Klein A, Andersson J, Ardekani BA, Ashburner J, Avants B, Chiang M-C, … Hellier P (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage, 46(3), 786–802. [PubMed: 19195496]

Koo JW, & Duman RS (2008). IL-1β is an essential mediator of the antineurogenic and anhedonic effects of stress. Proceedings of the National Academy of Sciences, 105(2), 751–756.

Lecrubier Y, Sheehan DV, Weiller E, Amorim P, Bonora I, Sheehan KH, … Dunbar GC (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. European Psychiatry, 12(5), 224–231.

Loddick S, Liu C, Takao T, Hashimoto K, & De Souza E (1998). Interleukin-1 receptors: cloning studies and role in central nervous system disorders. Brain Research. Brain Research Reviews, 26(2–3), 306. [PubMed: 9651547]

Lupien SJ, McEwen BS, Gunnar MR, & Heim C (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews Neuroscience, 10(6), 434. [PubMed: 19401723]

Miller AH, Haroon E, Raison CL, & Felger JC (2013). Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depression and Anxiety, 30(4), 297–306. [PubMed: 23468190]

Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, … Andersson JL (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nature Neuroscience, 19(11), 1523. [PubMed: 27643430]

Muthén LK, & Muthén BO (2007). Mplus User's Guide Los Angeles, CA: Muthén & Muthén.

Nikolova YS, Bogdan R, Brigidi BD, & Hariri AR (2012). Ventral striatum reactivity to reward and recent life stress interact to predict positive affect. Biological Psychiatry, 72(2), 157–163. [PubMed: 22534456]

Patenaude B, Smith SM, Kennedy DN, & Jenkinson M (2011). A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage, 56(3), 907–922. [PubMed: 21352927]

Plomin R, & von Stumm S (2018). The new genetics of intelligence. Nature Reviews Genetics

Pollitt R, Kaufman J, Rose K, Diez-Roux AV, Zeng D, & Heiss G (2008). Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood. Journal of Epidemiology and Community Health, 62(6), 484–491. [PubMed: 18477746]

Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, … Daly MJ (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. The American Journal of Human Genetics, 81(3), 559–575. [PubMed: 17701901]

Raz N, Daugherty AM, Bender AR, Dahle CL, & Land S (2015). Volume of the hippocampal subfields in healthy adults: differential associations with age and a pro-inflammatory genetic variant. Brain Structure and Function, 220(5), 2663–2674. [PubMed: 24947882]

Schmaal L, Veltman DJ, van Erp TG, Sämann P, Frodl T, Jahanshad N, … Niessen W (2016). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. Molecular Psychiatry, 21(6), 806–812. [PubMed: 26122586]

Schneider H, Pitossi F, Balschun D, Wagner A, Del Rey A, & Besedovsky H (1998). A neuromodulatory role of interleukin-1β in the hippocampus. Proceedings of the National Academy of Sciences, 95(13), 7778–7783.

Silverman MN, & Sternberg EM (2012). Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Annals of the New York Academy of Sciences, 1261(1), 55–63. [PubMed: 22823394]

Spulber S, Bartfai T, & Schultzberg M (2009). IL-1/IL-1ra balance in the brain revisited–evidence from transgenic mouse models. Brain, behavior, and immunity, 23(5), 573–579.

Spulber S, Oprica M, Bartfai T, Winblad B, & Schultzberg M (2008). Blunted neurogenesis and gliosis due to transgenic overexpression of human soluble IL-1ra in the mouse. European Journal of Neuroscience, 27(3), 549–558. [PubMed: 18279308]

Stephan Y, Sutin AR, Luchetti M, Caille P, & Terracciano A (2018). Polygenic Score for Alzheimer Disease and cognition: The mediating role of personality. Journal of Psychiatric Research

Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, … Landray M (2015). UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Medicine, 12(3), e1001779. [PubMed: 25826379]

Tam C, Clement K, Baur L, & Tordjman J (2010). Obesity and low-grade inflammation: a paediatric perspective. Obesity Reviews, 11(2), 118–126. [PubMed: 19845868]

Tung JY, Do CB, Hinds DA, Kiefer AK, Macpherson JM, Chowdry AB, … Wojcicki A (2011). Efficient replication of over 180 genetic associations with self-reported medical data. PLoS ONE, 6(8), e23473. [PubMed: 21858135]

van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, … Dale AM (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Molecular Psychiatry, 21(4), 547. [PubMed: 26033243]

Ware EB, Schmitz LL, Faul JD, Gard A, Mitchell C, Smith JA, … Kardia SL (2017). Heterogeneity in polygenic scores for common human traits. bioRxiv, 106062.

Whalley HC, Adams MJ, Hall L, Clarke T-K, Fernandez-Pujals AM, Gibson J, … Davies G (2016). Dissection of major depressive disorder using polygenic risk scores for schizophrenia in two independent cohorts. Translational Psychiatry, 6(11), e938. [PubMed: 27801894]

Wu MD, Montgomery SL, Rivera-Escalera F, Olschowka JA, & O'Banion MK (2013). Sustained IL-1β expression impairs adult hippocampal neurogenesis independent of IL-1 signaling in nestin+ neural precursor cells. Brain, behavior, and immunity, 32, 9–18.

Yirmiya R, & Goshen I (2011). Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain, behavior, and immunity, 25(2), 181–213.

Yirmiya R, Winocur G, & Goshen I (2002). Brain interleukin-1 is involved in spatial memory and passive avoidance conditioning. Neurobiology of Learning and Memory, 78(2), 379–389. [PubMed: 12431424]

Zhu B, Chen C, Dang X, Dong Q, & Lin C (2017). Hippocampal subfields' volumes are more relevant to fluid intelligence than verbal working memory. Intelligence, 61, 169–175.

Zunszain PA, Anacker C, Cattaneo A, Choudhury S, Musaelyan K, Myint AM, … Pariante CM (2012). Interleukin-1β: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. Neuropsychopharmacology, 37(4), 939. [PubMed: 22071871]

Table 1.

Descriptive statistics of study variables.

	DNS				UK Biobank			
	Min	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**
Age	18.00	22.00	19.78	1.24	45.00	78.00	62.63	7.45
BMI	16.30	39.15	22.30	2.84	14.20	53.04	26.67	4.43
Stress	0.00	18.00	2.49	2.25	0.00	4.00	0.49	0.70
SES	2.00	10.00	7.35	1.43	−6.26	9.16	4.97	2.58
Intracranial volume ^	−2.46	3.01	0.00	1.00	−3.02	3.77	0.00	1.00
Hippocampal volume ^	−3.89	3.04	0.00	1.00	−4.80	4.54	0.00	1.00
IL-1β polygenic score ^	−2.46	2.63	0.00	1.00	−3.63	4.06	0.00	1.00

^ Standardized values.

Table 2.

Correlations between study variables.

	DNS						UK Biobank					
	IL-1B polygenic score	**Age**	**SES**	**Recent life stress**	**BMI**	**ICV**	**IL-1β polygenic score**	**Age**	**SES**	**Recent life stress**	**BMI**	**ICV**
IL-1β polygenic score	1						1					
Age	−.008	1					−.021$^{\wedge}$	1				
SES	.099*	.115**	1				.024*	.083**	1			
Recent life stress	−0.038	−.091*	−.125**	1			0	−.147**	−.068**	1		
BMI	−0.077$^{\wedge}$	.022	−0.079$^{\wedge}$	0.017	1		−0.011	−.031**	−0.071**	.077**	1	
ICV	0.03	−.01	.114*	−0.037	.115**	1	0.007	−.163**	0.026*	−0.026*	.067**	1
Hippocampal volume	.097*	0.017	.122**	−0.016	0.075	.645**	.030**	−.241**	0.011	−0.012	.023*	.466**

Note.

$^{\wedge}$ p<.10

* p<.05

** p<.01