ORIGINAL ARTICLE

Corticosteroids and Regional Variations in Thickness of the Human Cerebral Cortex across the Lifespan

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Abstract

Exposures to life stressors accumulate across the lifespan, with possible impact on brain health. Little is known, however, about the mechanisms mediating age-related changes in brain structure. We use a lifespan sample of participants ($n = 21\,251$; 4–97 years) to investigate the relationship between the thickness of cerebral cortex and the expression of the glucocorticoid- and the mineralocorticoid-receptor genes (NR3C1 and NR3C2, respectively), obtained from the Allen Human Brain Atlas. In all participants, cortical thickness correlated negatively with the expression of both NR3C1 and NR3C2 across 34 cortical regions. The magnitude of this correlation varied across the lifespan. From childhood through early adulthood, the profile similarity (between NR3C1/NR3C2 expression and thickness) increased with age. Conversely, both profile similarities decreased with age in late life. These variations do not reflect age-related changes in NR3C1 and NR3C2 expression, as observed in 5 databases of gene expression in the human cerebral cortex (502 donors). Based on the co-expression of NR3C1 (and NR3C2) with genes specific to neural cell types, we determine the potential involvement of microglia, astrocytes, and CA1 pyramidal cells in mediating the relationship between corticosteroid exposure and cortical thickness. Therefore, corticosteroids may influence brain structure to a variable degree throughout life.

Introduction

Throughout the human lifespan, exposures to life stressors accumulate with possible consequences for brain structure and function, including mental health. Cumulative exposure to stress and passing of time, namely aging, are intimately linked. Stress has been associated with accelerated aging particularly in the form of telomere shortening and age-related epigenetic modifications (Epel et al. 2004; Shalev et al. 2013; Haussmann and Heidinger 2015; Gassen et al. 2017). Additionally, aging may result in a dysregulation of the hypothalamic-adrenal pituitary (HPA) axis and reduced ability to adapt to stressors; this phenomenon is commonly marked by a prolonged recovery time in older adults (Sapolsky et al. 1986; Ferrari et al. 2001; Seeman et al. 2001).

Glucocorticoids, the main mediators of the stress response, are a class of corticosteroids with intracellular receptors capable of both genomic (i.e., transcriptional) and non-genomic (e.g., membrane associated) activity (Prager and Johnson 2009; Menke et al. 2012; Liston et al. 2013; Niwa et al. 2013; Arloth et al. 2015; Gassen et al. 2017; Zannas and Chrousos 2017). Within the brain, there are 2 highly homologous corticosteroid receptors through which glucocorticoids act: the abundant glucocorticoid receptor (GR), encoded by the NR3C1 gene, and the less abundant mineralocorticoid receptor (MR), encoded by the NR3C2 gene (Arriza et al. 1988). It is known that MR has a 10-times greater affinity for glucocorticoids than GR (Reul and De Kloet 1985; Arriza et al. 1988). This difference in receptor affinity results in a dose effect whereby MR and GR are occupied, respectively, at low and high glucocorticoid levels. Although highly lipophilic, the passage of corticosteroids across the blood brain barrier is partially inhibited by the efflux transporter, P-glycoprotein (Geerling and Loewy 2009). The crossing of some corticosteroids (e.g., cortisol and aldosterone) is more hindered than others (e.g., corticosterone; Geerling and Loewy 2009). Due to higher concentrations, glucocorticoids outcompete mineralo-corticoids for MR binding in brain tissue (Yongue and Roy 1987; Arriza et al. 1988; Geerling and Loewy 2009). Moreover, MR is thought to be constitutively occupied with high nuclear concentration even at basal circulating levels of corticosteroids (Reul and De Kloet 1985; Gesing et al. 2001). Activation of MR increases neuronal excitability and elicits anti-apoptotic/neuroprotective cellular effects. Conversely, GR activation can decrease neuronal excitability and cause pro-apoptotic/deleterious cellular effects (Almeida et al. 2000; Crochemore et al. 2005; Prager and Johnson 2009; Sapolsky 2015). Thus, acting via ligand-bound corticosteroid receptors, glucocorticoid exposure may induce changes in brain structure detectable with magnetic resonance imaging (MRI).

The variation in corticosteroid receptor gene expression may result in differing susceptibility to glucocorticoid exposure. In a previous study of the adolescent brain, we showed that age-related decreases in cortical thickness were negatively correlated with the expression of NR3C1 across 34 regions of the cerebral cortex (Wong et al. 2017). We have also reported that this relationship appears stronger in female adolescents living in a potentially stressful social environment (Parker et al. 2017). It is well established that cortical thinning occurs during adolescence and continues into adulthood (Sowell et al. 2007; Tamnes et al. 2010). This cortical thinning may, in

Table 1 Cohort and gene expression source characteristics

Cohort Participant Demographics			
Cohort	Participants (n)	Median age (range)	Sex (%Male)
HRC[a,c]	1107 (454)	12.0 (6–18)	60.8
SYS (Adolescents)[d]	987	14.8 (12–19)	48.5
IMAGEN[a,d]	1823 (1203)	14.9 (12–22)	47.7
BIL&GIN[d]	453	24.0 (18–56)	48.8
HCP[e]	1200	29 (22–37)	45.6
LCBC[a,c]	1755 (986)	36.6 (4–93)	40.5
SYS (Parents)[d]	541	49.7 (36–65)	44.9
SHIP&TREND[d]	3021	52.9 (21–90)	47.3
DLBS[e]	315	54.3 (20–89)	37.1
RS[b,d]	5720 (11 600 sim.)	63.0 (45–100) [64.1 (46–94) sim]	44.6
SALD[e]	494	64.0 (19–80)	37.9
MAS[d]	358	64.5 (25–97)	28.9
FHS[b,d]	999 (1000 sim.)	64.0 (41–93) [64.1 (41–92) sim]	41.8
ASPS_Fam[d]	332	68.1 (38–84)	39.2
OATS[d]	403	69.2 (65–97)	34.5
OASIS[a,e]	671 (389)	69.5 (42–95)	39.5
3C_Dijon[d]	436	72.2 (65–83)	42.0
LBC1936[d]	636	72.7 (71–74)	52.8
Gene Expression Databases			
Source	Donors (n)	Median Age (range)	Sex (%Male)
Allen Human Brain Atlas	6	42.5 (24–57)	83.3
BrainCloud	206	36.3 (4–78)	68.5
BrainEAC	134	57.9 (16–102)	73.9
BrainSpan	14	20.2 (4–40)	57.1
GTEx	142	57.9 (25–80)	69.7

HRC, Brazilian High Risk Cohort for Psychiatric Disorders; SYS, Saguenay Youth Study; BIL&GIN, Brain Imaging of Lateralization by the Groupe d'Imagerie Fonctionnelle; LCBC, Lifespan Changes in Brain and Cognition; HCP, Human Connectome Project; SHIP&TREND, Study of Health in Pomerania and SHIP-TREND; DLBS, Dallas Lifespan Brain Study; RS, Rotterdam Study; SALD, Southwest University Adult Lifespan Dataset; MAS, Memory and Aging Study; FHS, Framingham Heart Study; ASPS_Fam, Austrian Stroke Prevention Study Family Cohort; OATS, Older Australian Twin Study; OASIS, Open Access Series of Imaging Studies; 3C_Dijon, The 3 City Study—Dijon location; LBC1936, Lothian Birth Cohort.

[a]Longitudinal studies where participants n in brackets (column 2) represent the subsample of participants with more than 1 scan.
[b]Simulated data were used for both the Rotterdam and Framingham study. Therefore, number of participants and median age (and ranges) will have both an observed sample value and a simulated value. Sim, based on simulated data.
[c]Collaborating cohort outside of the BRIDGET Consortium.
[d]Cohorts included in the BRIDGET Consortium.
[e]Cohorts with open access data.

part, be due to age-related reductions in dendritic and synaptic complexity (Huttenlocher 1979; Nakamura et al. 1985; Kolb et al. 2003; Selemon 2013; Koss et al. 2014), a structural modification also linked to glucocorticoid exposure (Vyas et al. 2002; Cook and Wellman 2004; Liston and Gan 2011; Liston et al. 2013). Therefore, typically developing adolescents may exhibit glucocorticoid-associated changes in cortical thickness. It is still unknown if this association exists outside of the adolescent period.

The present investigation aims to examine the lifespan association between corticosteroids and brain structure, namely cortical thickness, using inter-regional variations in cortical expression of NR3C1 and NR3C2 as a proxy of inter-regional variations in response to corticosteroids. Here we use a large, multi-cohort, lifespan sample (n = 21 251; age 4–97 years) of individuals to investigate the relationship between the inter-regional profile of cortical thickness, estimated from MRI, and the inter-regional profile of NR3C1 and NR3C2 expression, obtained from the Allen Human Brain Atlas. With cumulative exposure to glucocorticoids with aging, we hypothesize that cortical thickness may become more strongly associated with the distribution of NR3C1 and NR3C2 cortical expression across the lifespan. Furthermore, we investigate neural cell types that may be involved in mediating the relationship between glucocorticoid exposure and cortical thickness. Finally, we examine whether expression of NR3C1 and NR3C2 in the human cerebral cortex varies across the lifespan, using data from 502 post-mortem donor brains (4–102 years of age).

Materials and Methods

Participants

A group of 18 international cohorts (14 cross-sectional), with a combined total of 21 251 participants (54.9% female), contributed data for this study. All cohorts contributed demographic (age and sex) and neuroimaging data from cognitively healthy participants across the lifespan (age range, 4–97 years). All included participants had at least 1 T1-weighted brain scan. Basic demographic and cohort details can be found in Table 1.
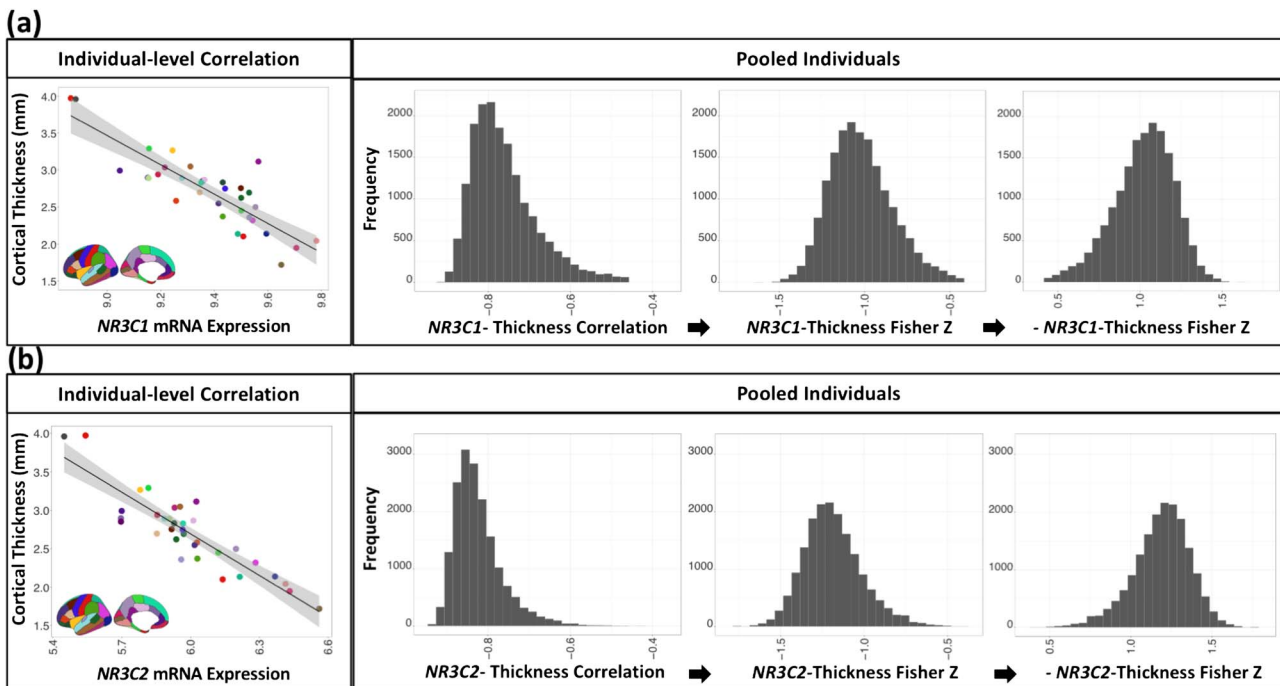
Figure 1. Creation of the *NR3C1*- (*a*) and *NR3C2*- (*b*) Thickness Similarity measure. Each measure starts from an individual-level correlation between regional cortical thickness (in each of the 34 regions) and gene expression. Since gene expression is obtained from the Allen Human Brain Atlas, these values are constant across all individuals. The individual-level correlations are pooled, Fisher-Z transformed, and then multiplied by negative 1 (inverted).

Neuroimaging

For each participant, cortical thickness was estimated for 34 cortical regions (left hemisphere) using the FreeSurfer pipeline with the Desikan–Killiany Atlas (Desikan et al. 2006). We used left hemisphere values of cortical thickness to ensure compatibility with gene expression data available in the Allen Human Brain Atlas (left hemisphere only, see below). Note that inter-regional profiles of cortical thickness in the right hemisphere are virtually identical to those in the left hemisphere; in a sample of 2091 participants (3514 scans), we observed a strong correlation between the left and right inter-regional profiles ($r = 0.99$). Specifics on MRI protocol and FreeSurfer version can be found in Supplementary Table S1.

Gene Expression

The Allen Human Brain Atlas provides mRNA expression from multiple regions of the left hemisphere of 6 donor brains (age 24–57 years, 1 female); mRNA was quantified using Agilent microarrays, and each brain sample was mapped to MNI coordinates (Supplementary, Hawrylycz et al. 2012; Mazziotta et al. 2001). Using these data, French and Paus (2015) mapped gene expression to the 34 cortical regions parcellated using the Desikan–Killiany Atlas. Briefly, 1) probe expression values ($n = 58\,692$) were averaged at the gene level ($n = 20\,737$), 2) Freesurfer V5.3 was run on the MNI152 template to map sample coordinates to Desikan–Killiany Atlas regions, with anatomical annotations helping to increase the number of correctly mapped samples, 3) each donor had between 6 and 100 samples per region; therefore, gene expression values were averaged at the regional level resulting in a single expression value for each of the cortical region ($n = 34$), and 4) across the 6 donors, median gene expression was

calculated for each brain region. The final result is a single gene expression (median) value for each of the 34 regions.

Given the lifespan nature of our study, we examined whether *NR3C1* and *NR3C2* expression varies with age. To do so, we obtained mRNA expression values from the following (additional) sources of gene expression in the human brain: BrainCloud (Supplementary, Colantuoni et al. 2012; Jaffe et al. 2015), Brain eQTL Almanac (BrainEAC; Trabzuni et al. 2011), BrainSpan (Li et al. 2018), and Genotype Tissue Expression (GTEx; Ardlie et al. 2015). Each source acquired tissue samples from human post-mortem donor brains. The extent of tissue sampling ranges from a single cortical region (BrainCloud) to 34 cortical regions (Allen Human Brain Atlas). When applicable, we excluded donors younger than 4 years of age (the youngest age in the in vivo MRI dataset). Across these datasets, the age span was from 4 to 102 years. General demographics of each source can be seen in Table 1. A description of each database and information on data acquisition can be found in Supplementary Table S2.

NR3C1- and NR3C2-Cortical Thickness Similarity

We assessed the degree of similarity in inter-regional profiles of gene expression (Allen Human Brain Atlas) and inter-regional profiles of cortical thickness (procedure depicted in Fig. 1). For each participant, the 34 regional cortical thickness values were correlated with *NR3C1* expression (Allen Human Brain Atlas). By design, values of cortical thickness varied across participants while values of gene expression remained constant. Next, a Fisher-Z transformation was applied to all correlation coefficients. For ease of interpretation, the Fisher-Z values were then multiplied by negative 1; a higher value represents a greater

similarity between inter-regional profiles of cortical thickness and gene expression. The resulting values were then termed *NR3C1*-Thickness Similarity. The same procedure was followed for *NR3C2* resulting in a distribution of *NR3C2*-Thickness Similarities (Fig. 1b). It is important to note that variations in the *NR3C1*- and *NR3C2*-Thickness Similarity are solely due to individual variations in the inter-regional profiles of cortical thickness. The same (reference) values of *NR3C1* and *NR3C2* expression (Table S3) are used in all individual-level correlations between cortical thickness and gene expression across the 34 cortical regions.

For the Framingham Heart Study (FHS) and the Rotterdam Study (RS), gene thickness similarities were simulated from sex-stratified and age-binned individual-level values to comply with local data-sharing regulations. The simulation procedure is outlined in Supplementary Table S4. Similarities in simulated and observed gene-thickness similarities were evaluated using Kolmogorov–Smirnov tests of the distributions as well as by a comparison of age coefficients (procedure outlined in Supplementary Table S4). Age coefficients, from fitting observed and simulated data, were highly comparable (Supplementary Table S5; Supplementary Figs S1 and S2).

Co-expression of *NR3C1* and *NR3C2* Genes with Cell-Specific Genes

We compared co-expression of *NR3C1* and *NR3C2* with gene panels specific to the following 9 neural cell types, as identified by Zeisel et al. (2015): astrocytes, CA1 pyramidal cells, endothelial cells, ependymal cells, interneurons, microglia, mural cells, oligodendrocytes, and S1 pyramidal cells. Included cell-specific genes had to pass a 2-stage filter for reliability of gene expression profiles across the cerebral cortex, as described by Shin et al. (2017). A resampling approach was used to test for significance in co-expression profiles between *NR3C1* (or *NR3C2*) and the panel of genes specific to a cell type. For each cell-specific panel of genes, a random sample, equal in size to the gene-panel, was selected from all the genes in the Allen Human Brain Atlas that passed the 2-stage filtering ($n = 2511$). Expression of each gene in the random sample was then correlated with expression of the gene of interest (*NR3C1* or *NR3C2*) and the mean correlations coefficient was calculated (test statistic). This random sampling and averaging of correlation coefficients was repeated 10 000 times for each panel of genes. The distribution of the resulting mean values, 10 000 per 9 cell-specific gene-panels, comprised an empirical null distribution. The proportion of the null distribution of means that exceed the observed mean correlations of *NR3C1* (or *NR3C2*) with the true cell-specific panel genes were used for a 2-sided *P* value at an FDR corrected alpha = 0.05.

Gene-Thickness Similarities that Increase with Age in Late Life: Post-hoc Analysis

After observing a decline in both *NR3C1*- and *NR3C2*-Thickness Similarities in late life, we investigated which other genes show an age-related increase in association with cortical thickness during the same time-period. In a subsample of participants greater than 68 years old (start of *NR3C1*-Thickness Similarity decline), the profiles of all 2511 genes that pass the 2-stage consistency filtering were correlated with the profile of cortical thickness. Next, we determined which of the gene-thickness similarities increase with age. This was accomplished by cal-

culating the mean of each gene-thickness similarity and the age-associated slope, derived from linear models adjusting for sex and scanner site. There are 2 cases where the gene-thickness similarity would on average increase with age: 1) if the mean gene-thickness similarity was greater than zero and the slope was positive or 2) if the mean gene-thickness similarity was less than zero and the slope was negative. After identifying those gene-thickness similarities that met either of the 2 criteria, we conducted a gene ontology (GO) enrichment analysis. The 2511 genes with consistent cortical profiles were used as the background gene set, and GO group size was restricted to < 300 genes.

Statistical Analysis

To determine the effect of age on cortical thickness in each of the 34 regions, we used generalized additive mixed models (GAMMs; *mgcv* package in R Wood 2006) with a cubic spline smoothing terms for age. Sex and scanner site were included as fixed effects. GAMM fitting is well suited for estimating non-linear trajectories—such as thickness estimates across the lifespan—and is robust to changes in modeled parameters such as age range (Storsve et al. 2014; Fjell et al. 2015; Vandekar et al. 2015). To adjust for repeated measures and participant kinship, random effects for participant ID and family ID were included. We then tested the association between age and the *NR3C1*- and *NR3C2*-Thickness Similarity with outliers defined as greater than 3 standard deviations (SDs) from the mean. To fit the lifespan trajectories, we again used a GAMM with sex and scanner site included as fixed effects and participant ID and family ID as random effects. The same procedure was used to test the association between age and *NR3C2*-Thickness Similarity. We compared *NR3C1*-Thickness Similarity with *NR3C2*-Thickness Similarity by 1) overall mean and 2) rate of change with age using first derivatives of the GAMM functions (*gratia* package in R), in early (<28 years; peak in *NR3C2*-Thickness Similarity) and late life (>68 years; initial-decline in *NR3C1*-Thickness Similarity). To determine significance of these comparisons, we used bootstrapped test statistics (10 000 iterations) where a Gene-Thickness Similarity label was randomly assigned to each participant prior to calculating the test statistics. Due to limited overlap in sampled regions, *NR3C1* and *NR3C2* expression from all 5 gene expression databases were scaled and pooled by cerebral lobe (frontal, parietal, temporal, and occipital). Within each of the lobes, we used linear mixed effect models with fixed effects for age and sex as well as random effects for donor ID. All statistical analyses were performed using R v3.5.1 (https://www.r-project.org/), and reported significance values ($P < 0.05$) are FDR corrected.

Results

A total of 21 251 participants, with 30 143 T1-weighted scans, were included in this study. Age ranged from 4.12 to 97.13 years (mean = 49.56, SD = 23.38), and females comprised 54.86% of the sample (Table 1).

Group-Level Analysis: Cortical Thickness and *NR3C1* (*NR3C2*) Expression

Only studies that provided true estimates of cortical thickness for each individual were included in this group-level analysis.

This sample subset included 13 793 participants (45.0% male) with an age range between 4.12 and 97.13 [mean age = 38.41 (±24.05) years]. All 34 cortical regions exhibited age-related variation in thickness across the lifespan (Supplementary Fig. S3; Supplementary Table S6). Across these cortical regions, we observed a strong negative correlation between NR3C1 expression and the group mean cortical thickness ($R^2 = 0.70$, $P < 0.001$) as well as NR3C2 expression and the group mean cortical thickness ($R^2 = 0.83$, $P < 0.001$; Supplementary Fig. S3).

Individual-Level Analysis: Cortical Thickness and NR3C1 (NR3C2) Expression

All participants exhibited a negative correlation between cortical thickness and NR3C1 (NR3C2) expression across the 34 cortical regions (Fig. 1). Thus, consistent with the group-level pattern, cortical regions with high NR3C1 (NR3C2) expression are thinner than regions with low expression.

Age-Related Changes in the NR3C1 (NR3C2) Thickness Similarity

As explained above, each participant's correlation coefficient (thickness by gene expression across 34 regions) was Fisher-Z transformed and multiplied by negative 1; a higher value represents a greater similarity between inter-regional profiles of cortical thickness and gene expression. The NR3C1-Thickness Similarity varied in strength across the lifespan ($F_{(7,30\,143)} = 243.8$, $P < 0.001$; Fig. 2a). From childhood through early adulthood, we observe an age-related increase in the NR3C1-Thickness Similarity. Therefore, the inter-regional profile of cortical thickness became more similar to the inter-regional profile of NR3C1 expression. This trend peaked at 30 years after which a relative plateau is observed (Fig. 2a). At 68 years, we begin to see a monotonic decrease in NR3C1-Thickness Similarity. Thus, in late life, the inter-regional profile in cortical thickness departs from the inter-regional profile of NR3C1 mRNA expression. Across the lifespan, males had greater NR3C1-Thickness Similarity than females (beta = 4.39e-03, $P = 0.021$).

A similar lifespan trajectory was observed for the NR3C2-Thickness Similarity (Fig. 2b; age, $F_{(7,30\,087)} = 217.8$, $P < 0.001$). Maturation of the cerebral cortex also resembled the distribution of NR3C2 mRNA expression where NR3C2-Thickness Similarity increased in early life (peak at age 27.9 years), plateaued in midlife, and declined after 59.9 years. Females had a greater NR3C2-Thickness Similarity than males (beta = 2.01e-02, $P < 0.001$).

Differences in NR3C1- and NR3C2-Thickness Similarity

Despite the strong correlation between NR3C1 and NR3C2 expression across the 34 cortical regions ($R^2 = 0.75$, $P < 0.001$), the 2 genes differed in the strength of association with cortical thickness. On average, the NR3C2-Thickness Similarity was stronger than the NR3C1-Thickness Similarity (mean$_{difference}$ = 0.15, $P < 0.001$) indicating that—across the 34 cortical regions—cortical thickness correlates more strongly with NR3C2 (than NR3C1) expression. The first derivatives of the GAMM lifespan trajectories (Supplementary Fig. S5) were used to compare the rate of change in NR3C1- and NR3C2-Thickness Similarity during the first few decades (increasing similarity) and past few decades (decreasing similarity) of the lifespan. The NR3C1-Thickness Similarity had a steeper

age-related increase in participants < 28 years (mean$_{difference}$ = 2.34e-3, $P < 0.001$). Thus, changes in cortical thickness appeared to be more strongly associated with the distribution of NR3C1 early in life. Conversely, participants > 68 years displayed no difference in the rate of age-related decline in NR3C1- and NR3C2-Thickness Similarity (mean$_{difference}$ = 8.98e-4, $P = 6.41e-2$).

Lifespan Variation in NR3C1 and NR3C2 Expression

A total of 502 donor brains (66.93% male) were included in this analysis. Donor age ranged from 4 to 102 years (mean = 47.25, SD = 20.19). Lobar NR3C1 expression did not change with age (Fig. 3a). For NR3C2, only the frontal lobe displayed age-related increases in expression, which appear to be confined to the early years (Fig. 3b).

Additional analysis of age-related changes in gene expression was conducted for each sampled region of the 5 databases (Supplementary Tables S8 and S9). None of the cortical regions sampled displayed age-related changes in NR3C1 expression. Expression of NR3C2 increased with age in 5 sampled regions and decreased with age in 2 regions.

Co-expression of NR3C1 and NR3C2 with Cell-Specific Genes

Both NR3C1 and NR3C2 were co-expressed negatively with the majority of genes specific to astrocytes (74% and 72%, respectively), CA1 pyramidal cells (72% for both), and microglia (69% and 71%, respectively). Of the 3 cell types, CA1 pyramidal genes had the strongest negative co-expression with both NR3C1 and NR3C2 (Table 2).

Gene-Thickness Similarities that Increase with Age in Late Life

In older participants (age > 68) both NR3C1- and NR3C2-Thickness Similarities decreased with age. Other biological processes (non-corticosteroid mediated) may be involved. Therefore, we tested for gene-thickness similarities that increase with age in older participants. Of the 2511 genes with consistent cortical profiles, 455 exhibited an increased gene-thickness similarity with age. After conducting a GO enrichment analysis on these 455 genes, no GO terms survived FDR correction. The top 10 GO terms can be found in Supplementary Table S10.

Finally, we compared the NR3C1- and NR3C2-Thickness Similarities with those calculated for all other genes that pass the 2-stage consistency filtering (n_{other} = 2509). To do so, we generated individual-level gene-thickness profile similarities for all 2511 genes (2509 plus NR3C1 and NR3C2). Next we calculated average gene-thickness profile similarities for each gene within 3 age groups: young (age < 27 years; n = 8080), middle-aged (age 27–60 years; n = 9171), and elderly (age > 60 years; n = 12 892). The distribution of the 2511 values of the average gene-thickness profile similarities can be seen in Figure S6. Among the negatively correlated genes, NR3C1 ranked 140, 25, and 44 for the young, middle-aged, and elderly groups, respectively (the top 12%; Fig. S6, dotted line). The NR3C2-Thickness Similarity ranked 1, 1, and 7 for the young, middle-aged, and elderly groups, respectively (the top 1%; Fig. S6, solid line).
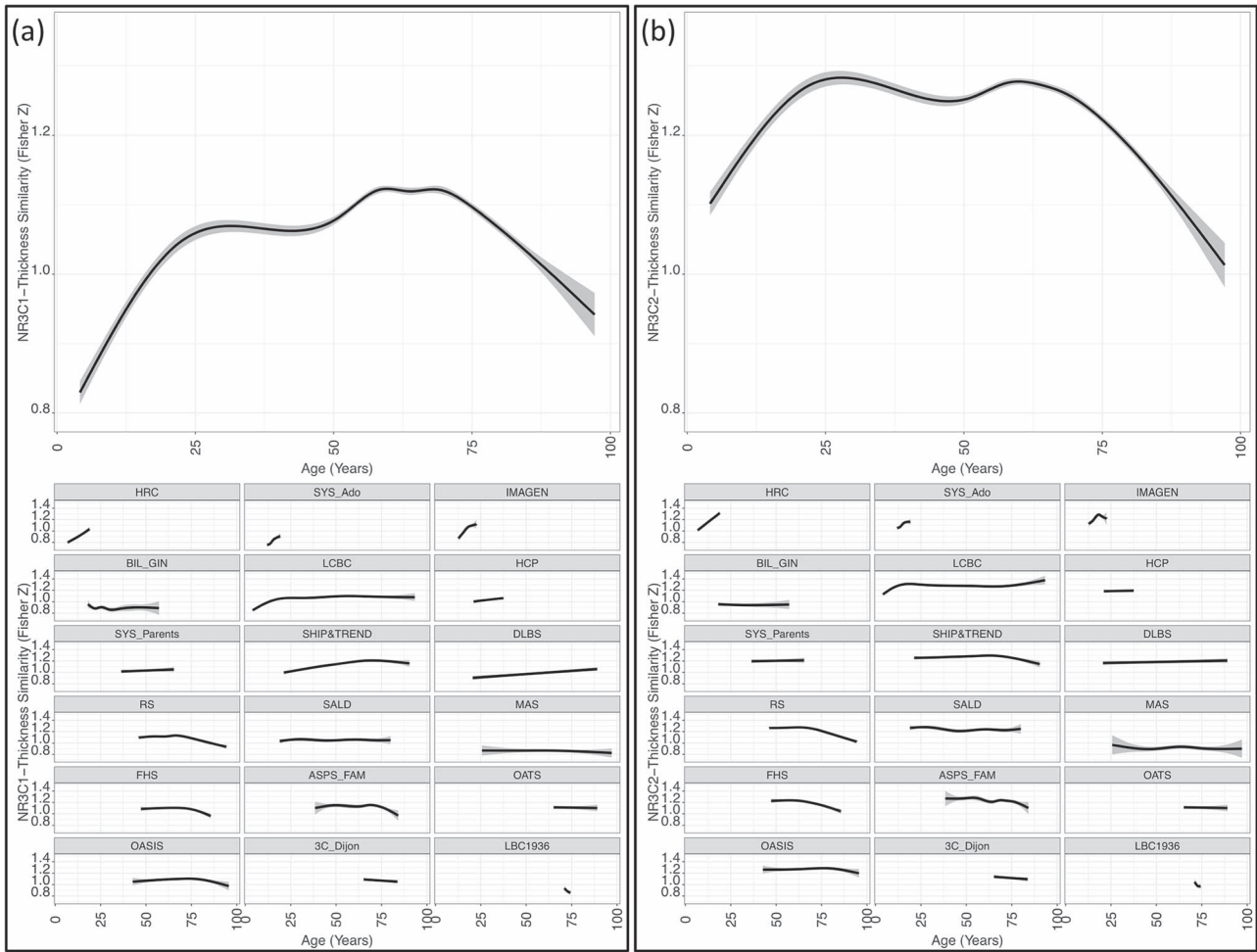
Figure 2. *NR3C1*- and *NR3C2*-Thickness Similarity lifespan trajectories modeled using GAMM analysis with a cubic spline smoother for age. The 95% confidence intervals (CIs) are shown in gray. For visualization with the inclusion of data points see Supplementary Figure S4. Both gene similarities show similar lifespan trajectories. (*a*) Top: The *NR3C1*-Thickness Similarity increases rapidly during the first 2 decades of life before peaking at age 30 years. In contrast, at age 68 years there is a monotonic decline with age. Bottom: *NR3C1*-Thickness Similarity by age modeled in each study separately. Study-specific statistics can be found in Supplementary Table S7. (*b*) The *NR3C2*-Thickness Similarity increases rapidly during the first 2 decades of life before peaking at age 27.9. By age 59.9 years a monotonic decrease in *NR3C2*-Thickness Similarity occurs. Bottom: *NR3C2*-Thickness Similarity by age modeled in each study separately. Study-specific statistics can be found in Supplementary Table S7. HRC, Brazilian High Risk Cohort for Psychiatric Disorders; SYS, Saguenay Youth Study; BIL_GIN, Brain Imaging of Lateralization by the Groupe d'Imagerie Fonctionnelle; LCBC, Lifespan Changes in Brain and Cognition; HCP, Human Connectome Project; SHIP&TREND, Study of Health in Pomerania and SHIP-TREND; DLBS, Dallas Lifespan Brain Study; RS, Rotterdam Study; SALD, Southwest University Adult Lifespan Dataset; MAS, Memory and Aging Study; FHS, Framingham Heart Study; ASPS_Fam, Austrian Stroke Prevention Study Family Cohort; OATS, Older Australian Twin Study; OASIS, Open Access Series of Imaging Studies; 3C_Dijon, The 3 City Study - Dijon location; LBC1936, Lothian Birth Cohort 1936.

Table 2 Inter-regional co-expression of *NR3C1* and *NR3C2* with cell-specific genes

Cell type	Genes (n)	NR3C1			NR3C2		
		Avg. r	p	Corrected p (FDR)	Avg. r	p	Corrected p (FDR)
Astrocyte	54	−0.34	2.00E-04	9.00E-04	−0.34	2.00E-04	9.00E-04
CA1 pyramidal	103	−0.26	1.00E-04	9.00E-04	−0.28	1.00E-04	9.00E-04
Endothelial	57	0.11	1.97E-01	2.53E-01	0.09	2.98E-01	3.83E-01
Ependymal	84	−0.11	1.33E-01	1.99E-01	−0.08	2.36E-01	3.54E-01
Interneuron	100	0.01	8.53E-01	8.53E-01	−0.02	8.29E-01	8.29E-01
Microglia	48	−0.27	5.70E-03	1.71E-02	−0.28	2.90E-03	8.70E-03
Mural	25	−0.11	4.13E-01	4.65E-01	−0.12	3.57E-01	4.02E-01
Oligodendrocyte	60	0.15	6.92E-02	1.25E-01	0.11	1.74E-01	3.13E-01
S1 Pyramidal	73	0.17	3.32E-02	7.47E-02	0.11	1.55E-01	3.13E-01

Avg.r, average correlation coefficient; FDR, false discovery rate corrected.
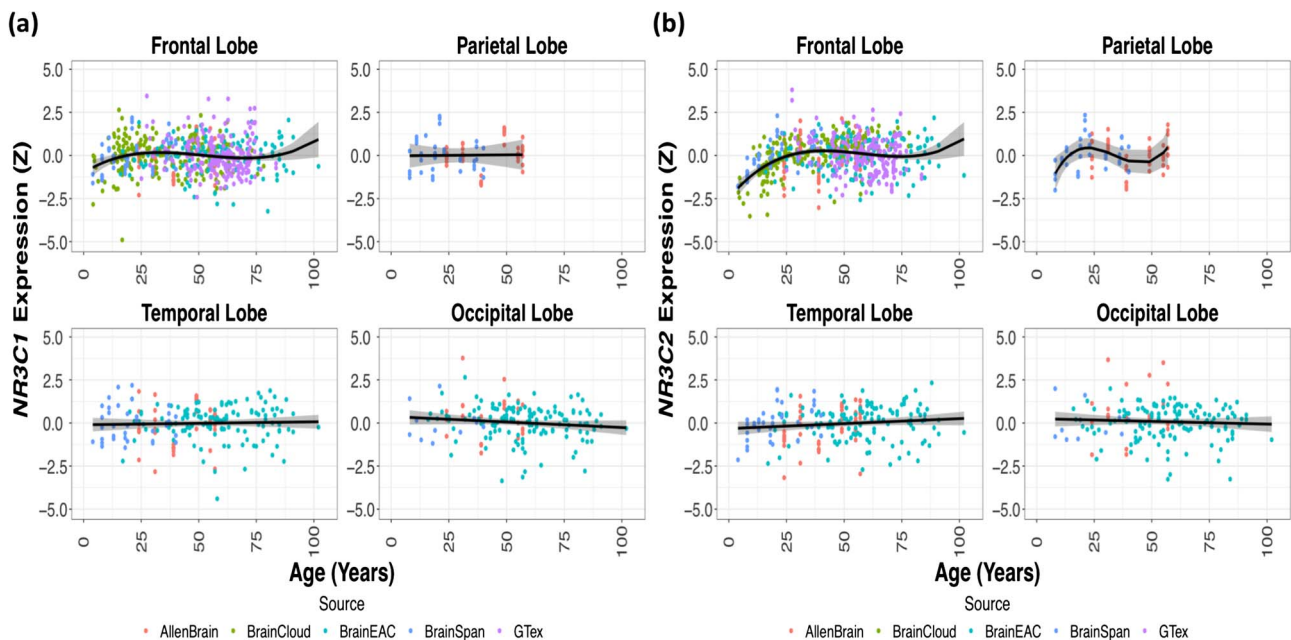
Figure 3. Age-related variation in NR3C1 and NR3C2 mRNA expression from 5 pooled sources of human post-mortem gene expression databases (plotted with a cubic smoother). (*a*) Expression of NR3C1 mRNA in the 4 cerebral lobes. Age did not predict NR3C1 expression in any of the cortical lobes (Frontal: $F_{(3,493)} = 3.64$, $P = 0.15$; Parietal: $F_{(1,19)} = 0.01$, $P = 0.95$; Occipital: $F_{(1,146)} = 2.32$, $P = 0.78$; Temporal: $F_{(1,139)} = 0.21$, $P = 0.95$). Models with linear age terms fit all regions except the frontal lobe, which had a cubic age term. (*b*) Expression of NR3C2 mRNA in the 4 cerebral lobes. Age did not predict NR3C2 expression in the Parietal ($F_{(3,19)} = 2.16$, $P_{FDR} = 2.80e-01$), Occipital ($F_{(1,146)} = 0.51$, $P = 6.46e-01$), or Temporal ($F_{(1,139)} = 2.41$, $P = 2.80e-01$) lobes. A cubic age term did predict NR3C2 expression in the Frontal lobe ($F_{(3,493)} = 25.74$, $P = 2.00e-14$).

Discussion

With a large sample of 21 251 participants, we investigated the relationship between the inter-regional profile of cortical thickness and the inter-regional profile of corticosteroid receptor gene (NR3C1 and NR3C2) expression across the lifespan. In all 34 cortical regions, cortical thickness was associated strongly with age. This is consistent with previous lifespan studies (Salat et al. 2004). Additionally, we show that the cortical profile of NR3C1 and NR3C2 mRNA expression was negatively correlated with the profile of cortical thickness. Previous human studies report associations between glucocorticoid exposure and thinner cortex (Kremen et al. 2010; Davis et al. 2013). Moreover, remodeling of dendritic and synaptic architecture is involved in both typical aging (Huttenlocher 1979; Nakamura et al. 1985; de Brabander et al. 1998) and glucocorticoid-associated (Liston and Gan 2011) cortical thinning. Although we cannot rule out the involvement of mineralocorticoids in shaping cortical thickness, this is unlikely for several reasons. Compared with glucocorticoids, mineralocorticoids have much lower plasma levels and more restricted passage across the blood brain barrier; for these reasons, glucocorticoids outcompete mineralocorticoids in their binding to GR and MR in brain tissue (Reul and De Kloet 1985; Yongue and Roy 1987; Arriza et al. 1988; Rupprecht et al. 1993; Geerling and Loewy 2009). Here we present some evidence that the overlapping mechanisms of age- and glucocorticoid-related cortical thinning may be mediated by the 2 corticosteroid receptors.

The NR3C1-Thickness Similarity was on average stronger in males than in females. This is consistent with our previous study in which the inter-regional profile of age-related decreases in cortical thickness showed a nominally stronger similarity in male ($R^2 = 0.46$) versus female ($R^2 = 0.30$) adolescents (Wong et al.

2017). It is of note that, in the same study, the strongest decreases in cortical thickness were found in cortical regions with high expression of both AR and NR3C1 genes. This synergistic action of AR and NR3C1 might be absent in case of NR3C2. This may contribute to the opposite pattern of sex differences in the case of the NR3C2-Thickness Similarity (Female>Male).

Our co-expression investigation of cell-specific genes and NR3C1/NR3C2 help explain mechanisms involved in glucocorticoid-associated cortical thinning. The majority of genes associated with CA1 pyramidal cells, microglia, and astrocytes are co-expressed negatively with both NR3C1/NR3C2. Our previous study of adolescents used a similar technique and identified the same 3 cell types as associated with cortical thickness and thinning (Shin et al. 2017). The association of genes specific to CA1 pyramidal cells with NR3C1 and NR3C2 supports the potential role of reduced dendritic complexity in age- and glucocorticoid-related variations in cortical thickness. Areas with greater dendritic complexity will likely require more astrocyte support; dexamethasone, a synthetic glucocorticoid, has been shown to block differentiation of astrocytes (Sabolek et al. 2006). Activation of microglia is also negatively regulated by glucocorticoids (Rivest 2009). The potential reduction in astrocyte density and inactivation of microglia in regions with high NR3C1 and NR3C2 expression may contribute to the observed thinner cortex in these regions.

In the first few decades of life, a steeper increase in NR3C1-Thickness Similarity, compared with NR3C2, suggests the involvement of glucocorticoid-associated GR activation in shaping cortical maturation. Similarly, our previous work, in an adolescent sample, revealed a negative association between NR3C1 mRNA expression and age-related decreases in cortical thickness (Parker et al. 2017; Wong et al. 2017). Therefore, stress may potentially play a role in the typical cortical

thinning observed in early life. From childhood through to early adulthood, there is a combination of a rapid decline in cortical thickness (Gogtay et al. 2004; Raznahan et al. 2010; Tamnes et al. 2010) concurrent with a unique blend of novel stress exposures and increases in stress- and sex-hormone production (Lupien et al. 2009; Eiland and Romeo 2013). The increased glucocorticoid exposure may produce GR-mediated reductions in neuronal excitation, dendritic and synaptic architecture, and, to a lesser extent, cellular apoptosis (Almeida et al. 2000; Crochemore et al. 2005; Radley 2005; Cerqueira et al. 2007; Prager and Johnson 2009). On the other hand, the constitutively occupied MR has been shown to be neuroprotective, to be anti-apoptotic, and to increase neuronal excitability (Almeida et al. 2000; Crochemore et al. 2005; Prager and Johnson 2009). With the transcription rate of the MR less than that of GR (Arriza et al. 1988; Rupprecht et al. 1993), the net response may lead to a relative reduction in dendritic and synaptic complexity. Alterations in synapse and dendritic spine formation have been associated with circadian peaks in circulating glucocorticoids (potential GR role); conversely, maintenance of those structural-alterations occurred during troughs/low levels of circulating glucocorticoids (potential MR role; Liston and Gan 2011; Liston et al. 2013). In addition, an MR:GR balance is suggested to be critical for healthy neuronal activity (Sousa et al. 2008; Oitzl et al. 2010); this may extend to shaping and maintaining age-related changes in cortical thickness.

Glucocorticoid exposure may play a role in shaping brain maturation but brain aging may be governed by different biological processes. In midlife, we observed little change in NR3C1- or NR3C2-Thickness Similarity. There are several potential reasons: by midlife, 1) there may be adequate stressor coping and maintenance of an MR:GR balance; 2) a ceiling effect may occur, limiting the degree of similarity between cortical thickness and NR3C1/NR3C2 distribution; or 3) competing biological processes may interfere with age-related increases in NR3C1- and NR3C2-Thickness Similarity. In the seventh decade, the maintenance of a strong NR3C1- or NR3C2-Thickness Similarity begins to decline. That is, the inter-regional profile of cortical thickness no longer resembles the distribution of the GRs mRNA expression as tightly as during midlife. Dysregulation of the HPA axis and a decrease in sensitivity to glucocorticoids are evident during aging (Sapolsky et al. 1986; Ferrari et al. 2001; Seeman et al. 2001). This may disrupt the midlife-maintenance mechanisms mentioned above (reason 1). In a study of stress-associated gene expression, young rats exposed to the same thermic stressor as older rats exhibited differential gene expression. Specifically, older rats had a less induction of stress-response genes and an increase in oxidative stress-associated genes (Zhang et al. 2002). Oxidative stress, denoted by the cellular accumulation of free-radical by-products, is closely linked to aging (Lee et al. 2000; Terman and Brunk 2006). Moreover, neuro-inflammation is strongly associated with aging (Lee et al. 2000). These are 2 late life biological processes that may alter the strength of association between the profile of cortical thickness and the profile of NR3C1 (or NR3C2). Therefore, senescence is linked to disruption of many biological processes, beyond the dysregulation of the HPA axis, all of which may impact the patterned changes in cortical thickness.

Here we used gene expression data, sampled from different regions of the human cerebral cortex and deposited in 5 separate databases with over 500 post-mortem donor brains, to show that the expression of NR3C1 and, with a few exceptions, also of NR3C2 do not change with age. This rules out the potential confounding effect of age-related changes in gene expression driving observed variations in NR3C1- or NR3C2-Thickness Similarity with age. Previous studies have shown an increase in NR3C1 mRNA expression in cerebral cortex with age (Perlman et al. 2007; Sinclair et al. 2011). Our results may vary due to differences in sample size, age range, and brain regions sampled. Additionally, unlike previous studies, age was modeled as continuous variable in our analysis. Also, increase in NR3C1 and/or NR3C2 expression with age would likely result in a lifespan strengthening of both the NR3C1- and NR3C2-Thickness Similarity, which was not observed.

We acknowledge that there are various methods used for mapping gene expression data to a brain atlas space. Arnatkevic̆iūtė et al. (2019) have reviewed a number of approaches (including the approach employed here) used for relating gene expression data from the Allen Human Brain Atlas to various neuroimaging datasets. As pointed out by Arnatkevic̆iūtė et al. (2019), while valid, our original approach did not include probes unassigned to an annotated gene and did not filter probe expression based on their intensity. On the other hand, we applied strict consistency criteria (profile similarity across donors and atlases), which have minimized possible technical sources of noise in the expression data.

Conclusions

The aim of this study was to determine the association between corticosteroids and cortical thickness across the lifespan. This was accomplished by using a large sample of participants in conjunction with human post-mortem gene expression data from several publicly available databases. The 2 corticosteroid receptors may be involved in shaping the profile of cortical thickness early in the lifespan. In midlife, there is a relative maintenance of a strong association between cortical thickness and corticosteroid receptor expression across the cerebral cortex. In late life, this association deteriorates. The results suggest that corticosteroids may influence brain structure to a varying degree throughout life and, as such, may contribute to age- and stress-related variations in cognitive functioning and mental health.

Supplementary Material

Supplementary material is available at *Cerebral Cortex* online.

Notes

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