Expression of HDAC2 but Not HDAC1 Transcript Is Reduced in Dorsolateral Prefrontal Cortex of Patients with Schizophrenia

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Supporting Information

ABSTRACT: Postmortem brain studies support dysregulated expression of the histone deacetylase enzymes, HDAC1 and HDAC2, as a central feature in diseases including schizophrenia, bipolar disorder, and depression. Our objective was to investigate HDAC expression in a large postmortem sample set representing healthy and disease brains. We used >700 well-characterized samples from patients diagnosed with schizophrenia (n = 175), major depressive disorder (n = 135), and bipolar disorder (n = 61) to measure HDAC1 and HDAC2 transcript levels by quantitative real-time PCR in dorsolateral prefrontal cortex (DLPFC) and caudate compared to control samples. HDAC expression was calculated relative to the geometric mean of β-2-microglobulin, β-glucuronidase, and β-actin. In adult-age DLPFC, HDAC2 was decreased by 34% in schizophrenia samples compared to controls (p < 10−4). HDAC2 was significantly upregulated in major depressive disorder samples by 17% versus controls (p = 0.002). Neither smoking history nor therapeutic drugs impacted HDAC2 levels and no HDAC1 patient-control differences were observed. In caudate, HDAC levels were unchanged between patient and control groups. In control DLPFC, age fetal week 14 to 97 years (n = 326), both HDAC1 and HDAC2 levels sharply declined around birth and stabilized thereafter. Using by far the largest postmortem sample set on this topic, our major finding (decreased HDAC2 transcript) showed notable specificity in disease (schizophrenia but not major depressive disorder), HDAC subtype (HDAC2 but not HDAC1) and brain region (DLPFC but not caudate). These differences shape understanding of regional components of neural circuitry in the diseased brain and set a benchmark to quantify HDAC density and distribution using in vivo neuroimaging tools.

KEYWORDS: Epigenetics, chromatin, schizophrenia, mood disorders unipolar, mood disorders bipolar, neuropsychiatry

Chromatin modifying enzymes, particularly histone deacetylase (HDAC) family members, maintain a central presence in research on mechanisms underlying neuropsychiatric disease on the basis of postmortem brain tissue analysis, animal models, and large-scale genome wide sequencing from patient samples. Surprisingly, even for major psychiatric diseases including schizophrenia, bipolar disorder, and depression, only a handful of small-scale experiments demonstrate altered HDAC expression in the human brain.

Foundation studies provided early evidence, albeit from small cohorts, that dysregulated expression and activity of HDAC enzymes may represent a fundamental difference between the diseased versus healthy brain. For the class I subtype HDAC1, this evidence comprised one report on transcript microarray data from postmortem DLPFC (n = 16–27/group) and another on individual transcript quantities (n = 7/group) in GABA-ergic neurons from schizophrenia, bipolar disorder and control sample cohorts. Postmortem evidence further demonstrated that HDAC2 protein levels may be altered in the nucleus accumbens from depressed patients and in the hippocampus of Alzheimer’s disease patients, where cognitive deficits exemplify a comorbidity of many psychiatric diseases. However, no study has investigated if altered HDAC expression in the brain is consistently dysregulated within a disease population.

Last year, genome-wide analysis demonstrated that the activity of chromatin modifying enzymes and specifically, the
HDAC2 Levels Are Downregulated in DLPFC from Schizophrenia Samples and Upregulated in Major Depressive Disorder Samples. Transcript levels of HDAC1 and HDAC2 were first measured by quantitative PCR in cDNA prepared from postmortem human DLPFC from brain donors without history of psychiatric illness (controls), and from patients diagnosed with SCZ, BP, or MDD. The results showed that HDAC2 transcript levels were significantly decreased by 34% in DLPFC samples from patients with schizophrenia compared to controls (p < 0.002) with no significant difference observed in BP samples. HDAC1 transcript levels were not significantly different in any diagnosis group compared to control samples. Significant differences in MDD (15–17% decreases observed in the total cohort compared to SCZ (p = 0.002) or BP sample groups (p = 0.01). Caudate HDAC expression scatter plots including bars for mean ± SD illustrate relative HDAC expression results from a subset of Ctrl (n = 69), SCZ (n = 54), and BP (n = 44) samples. Analysis of DLPFC results from this subset recapitulated the HDAC2-selective decreases observed in the total cohort. Caudate was also assayed from these same donors with no significant differences (p < 0.05) detected for HDAC2 or HDAC1 transcript levels in SCZ or BP groups compared to controls.

Table 1. Demographic and DLPFC Sample Details

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<td>32.9 ± 18.4</td>
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<td>RIN (DLPFC), mean ± SD</td>
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Figure 1. HDAC2, but not HDAC1, is profoundly decreased in the DLPFC from patients with schizophrenia. (A) Box plots illustrate HDAC2 transcript levels were significantly decreased by 34% in DLPFC samples from patients with SCZ compared to Ctrls (p < 0.002). A significant, 17% increase was also detected in MDD samples compared to Ctrls (p = 0.002) with no significant difference observed in BP samples. (B) HDAC1 transcript levels were not significantly different in any diagnosis group compared to Ctrl samples. Significant differences in MDD (15–17% differences) were observed when compared to SCZ (p < 0.01) or BP sample groups (p = 0.01). (C and D) HDAC expression scatter plots including bars for mean ± SD illustrate relative HDAC expression results from a subset of Ctrl (n = 69), SCZ (n = 54), and BP (n = 44) samples. Analysis of DLPFC results from this subset recapitulated the HDAC2-selective decreases observed in the total cohort (C and D, left panels). Caudate was also assayed from these same donors with no significant differences (p < 0.05) detected for HDAC2 or HDAC1 transcript levels in SCZ or BP groups compared to controls (C and D, right panels).
MDD; donor demographics and DLPFC sample details are shown in Table 1. For each transcript, relative expression was normalized to the geometric mean of three housekeeping genes: B2M, GUSB, and ACTB. These normalizing genes were utilized on the basis of prior work in postmortem brain demonstrating favorable low variance;16 relative quantification normalized to the geometric mean of three genes is a conservative and recommended method to reduce bias introduced by a single normalizing gene.17

Comparison of HDAC transcript levels from adult-age samples (≥18 years old) across psychiatric disease diagnosis groups revealed a significant difference of HDAC2 in the DLPFC with diagnosis as the primary factor (R² = 0.21, p = 10⁻¹⁵). Posthoc testing revealed a statistically significant, 34% ANCOVA-corrected decrease in HDAC2 from SCZ samples compared to controls; F (3, 566) = 61.05, Tukey HSD p < 10⁻⁴ (Figure 1A). Covariates known to impact postmortem transcript levels were clarified as significant (p < 0.05) and applied in a multifactorial linear model of HDAC2 expression as a function of disease diagnosis. The covariates applied and additional percent variance described by each were: RNA integrity, RIN (6.7%); race (6.9%); pH (5.1%); smoking status (2.2%); age at death (4.4%); and sex (1.4%). Correction for transcript measurements collected in two data sets was also applied (6.9% variance), as well as a conservative correction for postmortem interval, which revealed marginal significance (p = 0.10) within samples from the BP group alone. Overall, the model provided a collective measurement of 33.21% variance, a level consistent with prior postmortem transcript investigation.18 By similar comparison, a significant increase of 17% for HDAC2 expression was detected in MDD samples compared to controls, Tukey HSD p = 0.002. No significant changes were detected for BP samples compared to controls (p = 0.8).

HDAC1 transcript measurements across diagnosis groups and control samples were also compared similarly by ANCOVA, with no significant differences detected; F(3, 561) = 3.94 (Figure 1B).

Given that the schizophrenia cohort demonstrated the most profound differences in HDAC levels compared to controls, we wanted to investigate the extent of these changes in another brain region. The caudate nucleus was identified in elegant functional neuroimaging studies to provide a remarkable 74% classification accuracy to distinguish schizophrenia patients from controls on the basis of increased specialization to the right versus left hemisphere.18 Prior reports have provided insight that decreases in caudate volume and activity may contribute to schizophrenia symptoms including deficits in language processing, speech recognition20 and delusions of reference.21 Therefore, we justified interrogating caudate samples for levels of HDAC1 and HDAC2, and on the basis of sample availability, measured transcript levels in a subset of samples from control (n = 69), SCZ (n = 54), and BP (n = 44) groups.

ANCOVA comparison in caudate revealed no significant diagnosis group differences for HDAC2, F(2,152) = 1.62 or HDAC1, F(2,152) = 3.42; (Figure 1C and D, “Caudate”). Analysis of DLPFC data collected from this sample subset (a fraction of data presented in Figure 1) recapitulated changes found from the full sample compliment with the SCZ group demonstrating a significant decrease in HDAC2, but not HDAC1 (Figure 1C and D, “DLPFC”). No significant correlations were found between levels of HDAC1 or HDAC2 in the caudate to DLPFC, or for correlations of HDAC1 to HDAC2 within either the caudate or DLPFC.

HDAC expression, particularly of HDAC1 and HDAC2, has long been implicated in the mechanisms underlying schizophrenia, bipolar disorder, and depression2–4,12 and, on the basis of preclinical research with small molecule HDAC inhibitors, represents a set of targets with demonstrated therapeutic relevance. This is the first study to measure the gene expression of an epigenetic enzyme in a large (>700 total samples) and well-characterized cohort of human postmortem brain samples, including disease groups comprising SCZ, BP and MDD. We found strong evidence that the levels of HDAC2 transcript in the DLPFC of SCZ samples were decreased compared to controls. This effect was statistically significant (p < 10⁻⁴) and robust, with a 34% HDAC2 deficit that remained significant after correction for a number of covariates relevant in postmortem brain and psychiatric disease research. We also found a significant upregulation of HDAC2 transcript in the DLPFC of MDD samples (17% increase).

In contrast, we showed no differences in either HDAC1 or HDAC2 in caudate between control and SCZ samples. As the relevance of the caudate in the neuropathology and phenomenology of schizophrenia is well recognized, we interpret that our findings indicate that the changes in HDAC2 in the DLPFC of schizophrenia patients do not summarize brain-wide changes in epigenetic enzyme expression.

The relationship between mRNA and protein is complex and cognate levels are often poorly correlated.22,23 Nevertheless, given the large HDAC2 change we observed in the SCZ group, we used Western blotting to measure relative DLPFC protein expression of HDAC1 and HDAC2 in a subset of SCZ and control samples (n = 10/group). Specific samples (similar in age and sex) were selected as representative of the median DLPFC HDAC2 transcript levels for their diagnosis group. Quantitation of HDAC density was expressed on the basis of immunoreactivity from recombinant HDAC standards and normalized to GAPDH. No differences were observed between control and SCZ samples for HDAC1 or HDAC2 protein levels in this subset (Supporting Information Figure 1).

Our examination of HDAC2 protein levels in a small sample subset by Western blot did not recapitulate group-level transcriptional changes observed in DLPFC from SCZ vs controls. Prior studies highlight the well-known issue of transcript/protein disparity.2,23 Although extensive work has been done to understand critical factors in postmortem transcript measurements,22 less is known about postmortem effects on epigenetic proteins (e.g., HDACs), associated
posttranslational modifications (e.g., nitrosylation in the case of HDAC2), or the status of interaction with other essential proteins in complex. Nevertheless, tools are emerging to obtain highly sensitive and quantitative HDAC expression data at the protein level using LC-MS/MS as well as in the living brain, using positron emission tomography with the radiotracer [18F]Martinostat or its analogue, [18F]MGS-3.

**Disease-Relevant Covariates Have Limited Impact on HDAC Expression in DLPFC.** Smoking Status. A history of smoking was documented for ~25% of the control group (Table 2: 150 nonsmokers to 51 smokers), was modestly elevated in MDD and BP groups and had a prevalence of 71% in the SCZ group (48 nonsmokers to 116 smokers), consistent with nicotine use as a comorbidity of psychiatric disease. ANCOVA testing revealed no significant effect of smoking on HDAC2 or HDAC1 transcript levels in the DLPFC for any diagnosis group; (e.g., HDAC2, F(5, 575) = 31.28). Exemplified in Table 2, the magnitude of differences in DLPFC HDAC2 levels was equivalent in subgroups of nonsmokers and smokers from each diagnosis and control group (e.g., SCZ nonsmokers and smokers revealed decreases in HDAC2 by 38.2% and 37.6%, respectively compared to matched controls). In the subset of control samples where nicotine and cotinine were measured (subset of control samples where nicotine and cotinine were 37.6%, respectively compared to matched controls). In the con

| Table 3. Impact of Therapeutics on HDAC2 Transcript Levels in DLPFC |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | control         | schizophrenia   | bipolar disorder | major depressive disorder |
|                                 | antidepressant  | antidepressant  | antidepressant  | antidepressant  |
| AD negative: n HDAC2 level      | n = 210, 0.744  | n = 129, 0.484  | n = 27, 0.823   | n = 38, 0.815   |
| AD positive: n HDAC2 level      | n = 43, 0.482   | n = 30, 0.821   | n = 42, 0.813   |                 |
| % change neg vs pos             | <1%             | <1%             | <1%             |                 |
| AP negative: n HDAC2 level      | n = 210, 0.782  | n = 63, 0.453   | n = 40, 0.807   | n = 74, 0.811   |
| AP positive: n HDAC2 level      | n = 110, 0.502  | n = 17, 0.857   | n = 6, 0.860    |                 |
| % change neg vs pos             | 6.2%, not significant | 6.04%, not significant | 10.8%, not significant |                 |

of three common antidepressants (sertraline, citalopram/escitalopram, and fluoxetine) and four common antipsychotics (risperidone, olanzapine, haloperidol and clozapine). Samples lacking therapeutic treatment evidence were not included in analyses. Each treatment subgroup was relatively small in size (n = 2−37; Supporting Information Figure 2), with the largest subgroup sizes identified for antidepressants in MDD (Supporting Information Figure 2A and C) and for antipsychotics in SCZ (Supporting Information Figure 2B and D). ANCOVA comparison of each of the common AD drugs across diagnostic groups and controls revealed no apparent impact on transcript levels of HDAC1 or HDAC2 in DLPFC. Within-diagnosis group comparison only revealed marginal significance when comparing MDD samples with (n = 7) and without (n = 73) evidence of escitalopram/citalopram; F(1, 67) = 3.86, p = 0.054. ANCOVA adjusted mean values for HDAC1 or HDAC2 in DLPFC indicate MDD samples with evidence of escitalopram/citalopram treatment had ~20% higher transcript levels compared to MDD samples without. Subgroups divided on the basis of common AP drug toxicity evidence (Supporting Information Figure 2B and D) revealed no difference in HDAC1 or HDAC2 levels in DLPFC for common antipsychotic drugs, (p = 0.57−0.97). In each diagnosis group, only a fraction of samples had positive evidence for lithium (n = 2−4) or valproate (n = 7−11) treatment (Supporting Information Figure 2E); given small group sizes, correlation with HDAC levels was not tested. Despite the caveat of small subgroup sizes (valproate treatment; Supporting Information Figure 2E), we used t tests to compare within-SCZ or -BP diagnosis group levels of HDAC1 or HDAC2 between samples with positive and negative evidence of treatment with valproate, an HDAC inhibitor. No significant differences in HDAC levels were found based on valproate treatment; p = 0.64−0.97.

Overall, we did not detect the effects of factors relevant in psychiatric disease research including smoking status and antidepressant and antipsychotic treatment with HDAC2 in the DLPFC. A limitation of postmortem tissue research is that antemortem medication status, as indicated by toxicology, only represents medications that were consumed within the last hours/day prior to death and therefore may underestimate the effect of therapeutics on gene expression. This may provide some explanation for results previously shown by others in mice and in a small cohort (n = 10) of human postmortem samples that therapeutics impact HDAC expression. Nevertheless, we have a high degree of confidence in our measurement of HDAC transcript levels as we were able to take advantage of large-scale sample groups (n = 61−210/ group in DLPFC) and rich sample detail to apply statistical correction on the basis of covariates that have previously been
demonstrated as influential in postmortem transcript studies, including RNA integrity (RIN), brain pH and age at death.\textsuperscript{16}

Expression of HDAC1 and 2 in the DLPFC Are Powerfully Correlated with Age during Development. Relative expression of HDAC1 and HDAC2 transcripts were additionally measured in DLPFC from subjects with no known psychiatric disease diagnosis spanning fetal week 14 to 97 years of age. HDAC expression means ± standard deviation (SD) were calculated in 10 age groups including fetal (14–20 weeks), infant (0–1 year); child (1–10 years) and decade-limited age groups thereafter (Figure 2). Pearson’s correlation revealed a

\begin{align*}
\text{HDAC1:} & F(1,316) = 11.46, r = -0.187, p = 8 \times 10^{-4} \quad \text{and} \quad \text{HDAC2:} F(1, 305) = 62.17, r = -0.411, p < 10^{-13}. \\
\text{The most evident change in} & \text{ HDAC1 (Figure 2A) and HDAC2 (Figure 2B) expression was during the perinatal period, with a large decrease between the fetal and infant age groups for both transcripts. Dramatic changes in the expression of genes at birth, including HDAC1 and HDAC2 have been previously observed in DLPFC by independent transcript quantification methods.} \text{ Further, these findings are consistent with the critical nature of HDAC expression in development and histone acetylation in aging.}^1,14,31 \text{ Among adult samples (≥18 years of age), we did not find a significant correlation of HDAC expression with age for either HDAC1 or HDAC2; Pearson’s correlation revealed no significant linear correlation between adult age and expression of HDAC1: } F(1, 207) = 1.098; r = -0.076; p = 0.30 \text{ or expression of HDAC2: } F(1, 208) = 1.29; r = -0.079, p = 0.26.
\end{align*}

Studies clarifying molecular components—and confounding effects—of brain disease are essential in making meaningful, pragmatic gains in understanding and advanced treatment development.\textsuperscript{32} Investigation of large-scale sample sets provides a powerful advantage to identify conserved biochemical signatures that may help discriminate psychiatric disease patient groups on the basis of gene expression\textsuperscript{33} and protein modification.\textsuperscript{34} Prior findings and our current work provide an important comparator for emerging personalized-medicine approaches identifying disease deficits via induced pluripotent stem cells (e.g., ref 34) or by in vivo neuroimaging (e.g., ref 18) with a goal to develop an integrated and accurate understanding of the healthy and diseased brain, including epigenetic regulatory components.\textsuperscript{35}

Early reports identified that transcriptional differences in HDAC1 were present in small postmortem SCZ cohorts compared to controls.\textsuperscript{7,8} Narayan and colleagues used microarray methods to identify differential gene expression in the schizophrenic DLPFC, implicating HDAC1 via pathway analysis.\textsuperscript{40} However, there are significant limitations in the sensitivity of microarray transcriptomics as used in prior studies compared to qRT-PCR, as we have applied herein. Further, the scale of the numerous prior studies featured substantially fewer individual samples per patient group (~n = 20) and investigated a variety of regions comprising frontal cortex compared to our current large-scaled, DLPFC-focused study. This may be the reason that HDAC isoforms including HDAC2 did not emerge with distinct SCZ-related expression (see ref 37 and references therein). Future examination of HDAC transcript levels should take advantage of methods with even greater sensitivity (e.g., RNA-Seq).

Importantly, we note here that HDAC mRNA and protein expression is not expected to be uniform throughout the brain: as Broide and colleagues demonstrated by in situ hybridization in the rodent brain; as existing reports show for HDAC transcript and protein expression in human postmortem brain tissue; and as our recent in vivo positron emission tomography imaging with the radiotracer \textsuperscript{11}C/Martinostat demonstrates for healthy subjects.\textsuperscript{2,3} Despite the high sequence homology between HDAC1 and HDAC2, our observation that only HDAC2 is decreased in SCZ DLPFC indicates that expression—at least at the transcript level—is regulated independently. The role of localized expression and activity of HDAC subtypes has already been linked to neuro-glial development\textsuperscript{35,38} and behavioral changes in rodents.\textsuperscript{7,8,30,12}

Additionally, HDAC1 and HDAC2 are known to function in larger protein complexes with distinct activities. For example, in rodent models the CoREST complex, which contains HDAC1 and 2, contributes to hippocampal neuron excitability,\textsuperscript{47} while the distinct NuRD-HDAC1/2 complex enhances synaptic connectivity in the cerebellum.\textsuperscript{41} Regional HDAC expression differences are therefore likely to contribute to refined and region-specific control over transcription and neural signaling. Thus, a major next step in defining the epigenetic underpinnings of brain disease is to understand the expression of HDAC complexes throughout the healthy and diseased brain, in vivo and clarify their specific regulatory impact on gene expression and brain function.

\section*{METHODS}

\textbf{Human Post-mortem Brain Tissue Collection.} Post-mortem brains were collected at the Human Brain Collection Core (HBCC), National Institute of Mental Health (NIMH), with informed consent.
from the legal next of kin according to the National Institutes of Health Institutional Review Board and ethical guidelines under protocol (90-M-0142), and at the Brain and Tissue Bank for Developmental Disorders of the National Institute of Child Health and Human Development (under contracts N01-HD-4-3368 and N01-HD-4-3368). Clinical characterization, neuropathological screening, toxicological analyses and dissection of the DLPEC and caudate were performed as previously described.16,33 (Additional methods are available in the Supporting Information.)

Quantitative Real-Time PCR. Total RNA was extracted from DLPEC and caudate as previously described.16 Expression levels of HDAC1 and HDAC2 were measured in the postmortem DLPEC samples and a subset of caudate samples using quantitative real-time PCR on the ABI Prism 7900 sequence detection system with 384-well format (Applied Biosystems, Carlsbad, Calif.) using Taqman assays Hs00606262_g1 for HDAC1 and Hs00231032_m1 for HDAC2. (Additional methods are available in the Supporting Information.)

Statistical Analyses. Comparisons between groups were made by analyses of covariance (ANCOVAs) for each normalized transcript expression level, with diagnosis and antemortem medication as independent variables. (Additional methods are available in the Supporting Information.)

■ ASSOCIATED CONTENT

Research Article

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acschemneuro.6b00372.

Additional methodological details (tissue sample information, quantitative real-time PCR, antemortem medication, Western blotting, and statistical analysis), figure showing Western blotting experiments against HDAC1 and HDAC2 in the DLPEC of a subset of SCZ and samples and controls, and figure showing common therapeutics detected in postmortem samples (PDF)

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Notes
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■ REFERENCES


