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RESEARCH ARTICLE

Association of RDoC dimensions with *post mortem* brain transcriptional profiles in Alzheimer's disease

Weiqian Jiang[1] | **Jonathan Vogelgsang**[1] | **Shu Dan**[1] | **Peter Durning**[1] | **Thomas H. McCoy**[2] | **Sabina Berretta**[1] | **Torsten Klengel**[1]

[1]Department of Psychiatry, Harvard Medical School, McLean Hospital, Belmont, Massachusetts, USA

[2]Center for Quantitative Health, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Torsten Klengel, Department of Psychiatry, Harvard Medical School, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.
Email: tklengel@mclean.harvard.edu

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Abstract

INTRODUCTION: Neuropsychiatric symptoms are common in people with Alzheimer's disease (AD) across all severity stages. Their heterogeneous presentation and variable temporal association with cognitive decline suggest shared and distinct biological mechanisms. We hypothesized that specific patterns of gene expression associate with distinct National Institute of Mental Health Research Domain Criteria (RDoC) domains in AD.

METHODS: Post-mortem bulk RNA sequencing of the insula and anterior cingulate cortex from 60 brain donors, representing the spectrum of canonical Alzheimer's disease neuropathology, was combined with natural language processing approaches based on the RDoC Clinical Domains to uncover transcriptomic patterns linked to disease progression.

RESULTS: Distinct sets of >100 genes ($P_{\text{false discovery rate}} < 0.05$) were specifically associated with at least one clinical domain (cognitive, social, negative, positive, arousal). In addition, dysregulation of immune response pathways was shared across domains and brain regions.

DISCUSSION: Our findings provide evidence for distinct transcriptional profiles associated with RDoC domains suggesting that each dimension is characterized by sets of genes providing insight into the underlying mechanisms.

KEYWORDS
Alzheimer's disease, gene expression, machine learning, natural language processing, Research Domain Criteria

Highlights

- *Post mortem* brain tissue investigations are critically important for Alzheimer's disease (AD) research.
- Neuropsychiatric symptoms in AD are common and an important aspect of AD.

Weiqian Jiang, Jonathan Vogelgsang, Sabina Berretta, and Torsten Klengel contributed equally to this study.

- Categorical phenotypes are commonly used, but insufficiently describe the heterogenous presentation of AD.
- Using natural language processing (NLP) of *post mortem* brain donor health records provides insight into dimensional phenotypes of AD.
- We provide evidence for distinct RNA expression profiles associated with NLP-derived Research Domain Criteria clinical domain scores.

1 | BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in dementia. While advanced stages of AD are characterized by severe cognitive impairment, varying degrees of neuropsychiatric symptoms (NPS) including depression, agitation, aggression, and apathy can be present across the entire spectrum of AD.[1,2] NPS can lead to accelerated disease progression, increased caregiver burden, and earlier death. Treatment of these symptoms with medications used for non-neurodegenerative psychiatric disorders is based on the largely unchallenged assumption that their biological underpinnings are equivalent. Neuropathologically, AD is characterized by extracellular plaques of misfolded amyloid beta (Aβ) aggregates and intracellular neurofibrillary tangles (NFTs) formed by paired helical filaments of hyperphosphorylated tau protein.[3] While deposition of Aβ and NFTs are considered neuropathological hallmarks of AD, studies on transcriptional changes in AD using *post mortem* brain tissue suggest the dysregulation of multiple cellular pathways including synaptic dysfunction, gliosis, demyelination, and inflammation leading to neuronal loss.[4–6] Bridging between canonical and molecular changes on one side and symptoms on the other is particularly challenging, even more so in the context of clinical, genetic, and neuropathological heterogeneity among persons with AD.[7]

Most large-scale transcriptional studies focus on extensively studied brain regions such as the hippocampus, anterior cingulate cortex, and prefrontal cortex.[4–6,8] In contrast, the insula, which is located deep within the lateral sulcus that separates the temporal from the parietal and frontal lobes, remains largely understudied. It has been traditionally viewed as a paralimbic or limbic integration cortex integrating visceral information.[9] Recently, imaging studies have sparked considerable interest in investigating the role of the insular cortex in the context of emotion, pain, decision making, motor control, and social functions.[10] The insular cortex is connected to a wide variety of brain regions including the frontal, anterior cingulate, and parietal cortex; limbic areas such as the amygdala, hypothalamus, and entorhinal cortex; and to sensorimotor brain regions.[11] The central role of the insular cortex in relevant circuits is supported by several neuroimaging studies suggesting its involvement in AD and AD-related NPS.[12,13] However, transcriptomic studies investigating molecular mechanisms underlying pathological alterations of the insular cortex in AD remain scarce.

To date, most transcriptomic studies focus on the comparison between normative individuals and people with either early- or late-onset AD.[8] Single-nucleus RNAseq studies have provided significant insight into AD pathology by revealing distinct gene expression patterns in multiple cell types.[14] Although very informative, categorical diagnosis comparison designs may not be well suited to account for interindividual heterogeneity in symptom presentation, particularly regarding comorbid NPS. To overcome these limitations, we previously applied a natural language processing (NLP) algorithm to records of donors with and without AD to provide dimensional phenotyping within the context of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC).[15]

In this study, we performed a RNAseq analysis in the anterior insula (aINS; BA16) and dorsal anterior cingulate cortex (dACG; BA32), focusing on a dimensional approach based on the NIMH RDoC domain matrix. Using a generalized linear regression model, we show that transcriptomic changes associated with dimensional RDoC clinical domain scores provide a deeper and more nuanced insight into the underlying molecular correlates of dimensional symptoms presentation in AD. Importantly, our results suggest common and distinct molecular mechanisms across RDoC domains and brain regions.

2 | METHODS

2.1 | Experimental subjects

All tissue samples and medical records were obtained from the Harvard Brain Tissue Resource Center (HBTRC; operating under the Mass General Brigham McLean Institutional Review Board [IRB]). The subject cohort ($n = 60$) available for this study included brain donors representing the full spectrum of Braak & Braak neuropathological stages, thus representing the neuropathological AD progression from Braak & Braak stages 0 to II (unaffected controls) to stages III and IV (mild to moderate AD pathology) and stages V and VI (severe AD pathology).[16] Available medical records from health-care professionals who provided treatment to the donor were retrieved with the authorization by the legal next of kin. These records include detailed neurological and psychiatric assessments, records pertaining to other medical treatments, and nursing and hospice reports. Only donors with sufficient medical records and a life diagnosis by a qualified clinician were included. Judgment on the adequate number of medical records was made by experienced clinicians focusing on the ability to document and verify symptom development and progression over time. Donors with significant psychiatric conditions diagnosed during adolescence,

or early- or mid-adulthood were not included. Similarly, we excluded donors with non-AD neurological diagnoses.

Medical records in hard copies were scanned into computer-readable text files using optical character recognition. Text files were processed using RDoC-based NLP algorithms to obtain quantitative measures of clinical domain scores, as described by McCoy et al.[15] (https://github.com/thmccoy/CQH-Dimensional-Phenotyper). Access to donors' medical records and other sensitive data was restricted to IRB-authorized investigators; all other investigators contributing to this study were given access to de-identified data, according to the Health Insurance Portability and Accountability Act (HIPAA) regulations. Detailed metadata information for each sample is given in Data S1 in supporting information. A summary of the cohort subject basic data by RNAseq batch is included in Data S2 in supporting information and individual scores in each domain are given in Data S3 in supporting information.

2.2 | Tissue preparation, RNAseq library preparation, sequencing, and processing of RNAseq data

The dACG (BA32) and the aINS (BA16) were isolated from flash-frozen human *post mortem* brain tissue samples and RNA was extracted using the Agilent Absolutely RNA miniprep kit. RNA library preparation and sequencing were conducted at Azenta Life Sciences and RNAseq data were processed and analyzed using the bcbio-nextgen Bulk RNA-seq pipeline (https://github.com/bcbio/bcbio-nextgen; see supporting information for details).

2.3 | Differential expression analysis over clinical domain scores

Scores for RDoC-based clinical domains were derived using NLP algorithms as previously described in Vogelgsang et al.[17] The clinical domain scores of all donors were binned between 0 and 1, in 0.1 intervals and considered on a dimensional scale from 0 (lower limit) to 1 (upper limit; Data S3). Note that higher scores indicate more severe symptoms (e.g., more severe cognitive impairment); thus, a positive correlation between gene expression and clinical domain scores indicates that higher gene expression is associated with greater symptom severity. Differential gene expression analyses in the aINS and dACG for over dimensional scores for each of the five clinical domains using the filtered gene set was performed by ImpulseDE2.[18]

After filtering, normalized counts were used in a principal component analysis (PCA) to identify potential covariates. The first five principal components (PCs) were correlated with known technical and biological variables, resulting in significant correlations for neuropathological Braak & Braak stage, brain region, sex, age, RNA Integrity Number (RIN), and sequencing batch, but not *post mortem* interval (PMI; Figure S1 in supporting information illustrates the relationship between PCs and covariates). To further explore residual unknown sources of variation including the influence of changing cell type composition, medication, and comorbidities, surrogate variable analysis[19] was used, which yielded two significant surrogate variables (SVs) correlated with the first five PCs. Subsequently, we explored the relevance of these covariates across the RDoC cognition domain for each brain region and found that sex, sequencing batch, and Braak & Braak status showed significant associations, while age, RIN, PMI, SV1, and SV2 were not significantly associated across the dimension (Data S1 and S2 provide raw data and statistical analysis of the relationship between covariates and RDoC domains).

Thus, the final model to identify genes progressively regulated along the axis from low to high clinical domain scores in ImpulseDE2 included sex and sequencing batch as covariates. Braak & Braak stage was not included due to collinearity with the clinical domain scores. Statistical significance of differential expression was defined at $P_{false\ discovery\ rate(\mathrm{FDR})} < 0.05$.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and Google Scholar. While *post mortem* brain tissue research is critically important and successful, studies focusing on dimensional phenotyping of neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) in combination with molecular profiling remain scarce. The relevant literature is appropriately cited.
2. **Interpretation**: Our approach to combine natural language processing (NLP) of *post mortem* brain donor electronic health records (EHRs) in combination with RNA sequencing led to the identification of distinct RNA expression profiles associated with dimensional Research Domain Criteria (RDoC) clinical domain scores, indicating distinct molecular mechanism associated with NPS in AD.
3. **Future directions**: The article provides proof of concept for the use of EHR and NLP in *post mortem* molecular brain research. Future studies (a) will refine NLP analyses to provide more granular phenotypes of NPS beyond RDoC domain scores and (b) can be combined with other molecular readouts to provide a better understanding of the underlying mechanisms of NPS in AD.

2.4 | Functional enrichment analysis

A one-tailed hypergeometric test was conducted for pathway enrichment analysis using Metascape.[20] We included multiple databases such as Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), Reactome, and Wikipathway, separately for up- and down-regulated differentially expressed genes (DEGs) from the dimensional analyses. Statistical significance was defined at $P_{\mathrm{FDR}} < 0.05$.

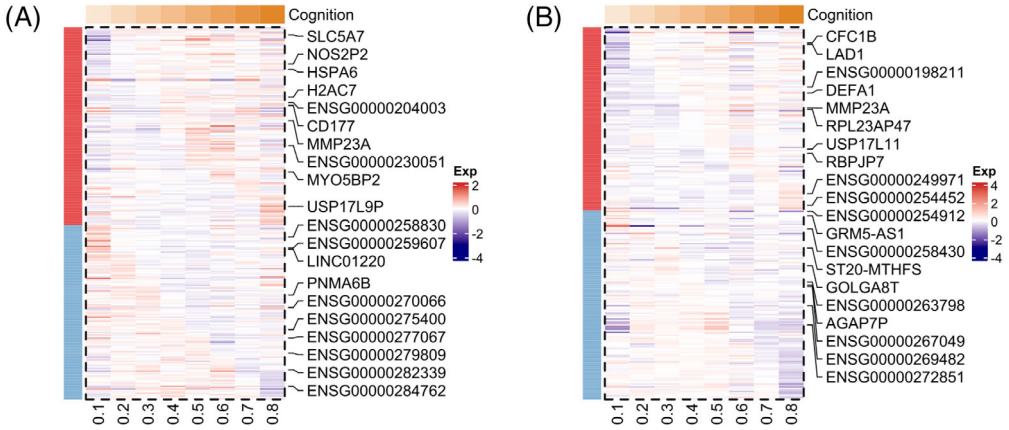

FIGURE 1 Transcriptional signature of dimensional RDoC cognition profiling. A, Heatmap showing gene expression signatures of all DEGs ($P_{nominal} < 0.05$) with a significant up- or downregulated pattern over increasing RDoC cognition values in the dACG. The top 10 up- or downregulated DEGs (all $P_{FDR} < 0.05$) are labeled. Bar colors on the left side indicate whether genes are clustered in an increasing (red) or decreasing (blue) trajectory. B, Heatmap showing gene expression of DEGs ($P_{nominal} < 0.05$) with a significant up- or downregulated pattern over increasing RDoC cognition values in the aINS. Top 10 up- or downregulated monotonous DEGs (all $P_{FDR} < 0.05$) are labeled. dACG, dorsal anterior cingulate cortex; DEG, differentially expressed gene; FDR, false discovery rate; RDoC, Research Domain Criteria.

3 | RESULTS

3.1 | Differential gene expression in aINS and dACG as a function of dimensional cognition scores

Previously, we used NLP algorithms to obtain cognition scores and showed that they are significantly associated with neuritic plaque load across all lobes of the brain.[17] The correlation of this classical neuropathological hallmark of AD with compelling evidence for a direct relationship to cognition[16,21] and cognition scores provided evidence for the feasibility and validity of *post mortem* dimensional phenotyping of brain donor electronic health records beyond categorical diagnoses.

Because the donor cohort available for this study only partially overlaps with the prior one,[17] we again tested the association between neuritic plaque load and cognitive symptom burden. As expected, the cohort analyzed here showed a significant association between neuritic plaque load across all lobes and cognition scores, as well as a significant association of Braak & Braak stages with cognition scores (Data S4 in supporting information).

To investigate the underlying molecular changes associated with dimensional cognition burden, we regressed cognition scores over gene expression in the dACG and aINS of all donors, representing the full spectrum of Braak & Braak stages (from 0 to VI) using ImpulseDE2.[18] In the aINS, 109 DEGs at $P_{FDR} < 0.05$ showed a monotonous increase or decrease of expression across cognition score (Figure 1A Data S5 in supporting information). Out of these 109 genes, 67 genes were positively correlated with more severe cognitive impairment. Top hits included genes involved in innate immune response, such as *CD177* and *HSPA6*. The remaining 42 genes were negatively correlated with cognition scores. These included *PNMA6B*, a member of paraneoplastic Ma antigen family, which is associated with immune-related diseases and neurological disorders,[22] alongside a large number of non-coding RNAs (ncRNAs) and pseudogenes.

In dACG, 107 DEGs ($P_{FDR} < 0.05$) showed a monotonous increased or decreased expression in association with cognition scores (Figure 1B, Data S5). Among the 48 genes with increased expression associated with more severe cognition scores, *LAD1* and *MMP23A* were the top hits, with a strong positive correlation with cognitive impairment. Similar to the aINS, top downregulated DEGs primarily belong to the less known group of pseudogenes or ncRNAs, with a total of 59 genes showing significant negative correlation with cognition severity.

3.2 | Differential gene expression in aINS and dACG as a function of clinical domain scores

Next, we focused on the arousal regulatory, negative valence, positive valence, and social systems domain scores. As expected, all domains were highly intercorrelated (Pearson $r = 0.88 \pm 0.04$). As shown in Figure 2A and Data S5, each clinical domain was associated with distinct sets of DEGs (all $P_{FDR} < 0.05$). In the aINS, DEGs were detected in association with arousal (56 genes increased; 45 genes decreased), negative valence (40 genes increased; 56 decreased), positive valence (61 genes increased; 61 genes decreased), and social domain (61 genes increased; 49 genes decreased). Similar number of DEGs were detected in dACG in association with arousal (42 genes increased; 52 genes decreased), negative valence (65 genes increased; 60 genes decreased), positive valence (46 increased; 55 genes decreased) and social domain (55 genes increased and 65 genes decreased (Figure 2B and Data S5). Notably, a large number of DEGs in aINS and dACG were uniquely associated with one domain with moderate to minimal

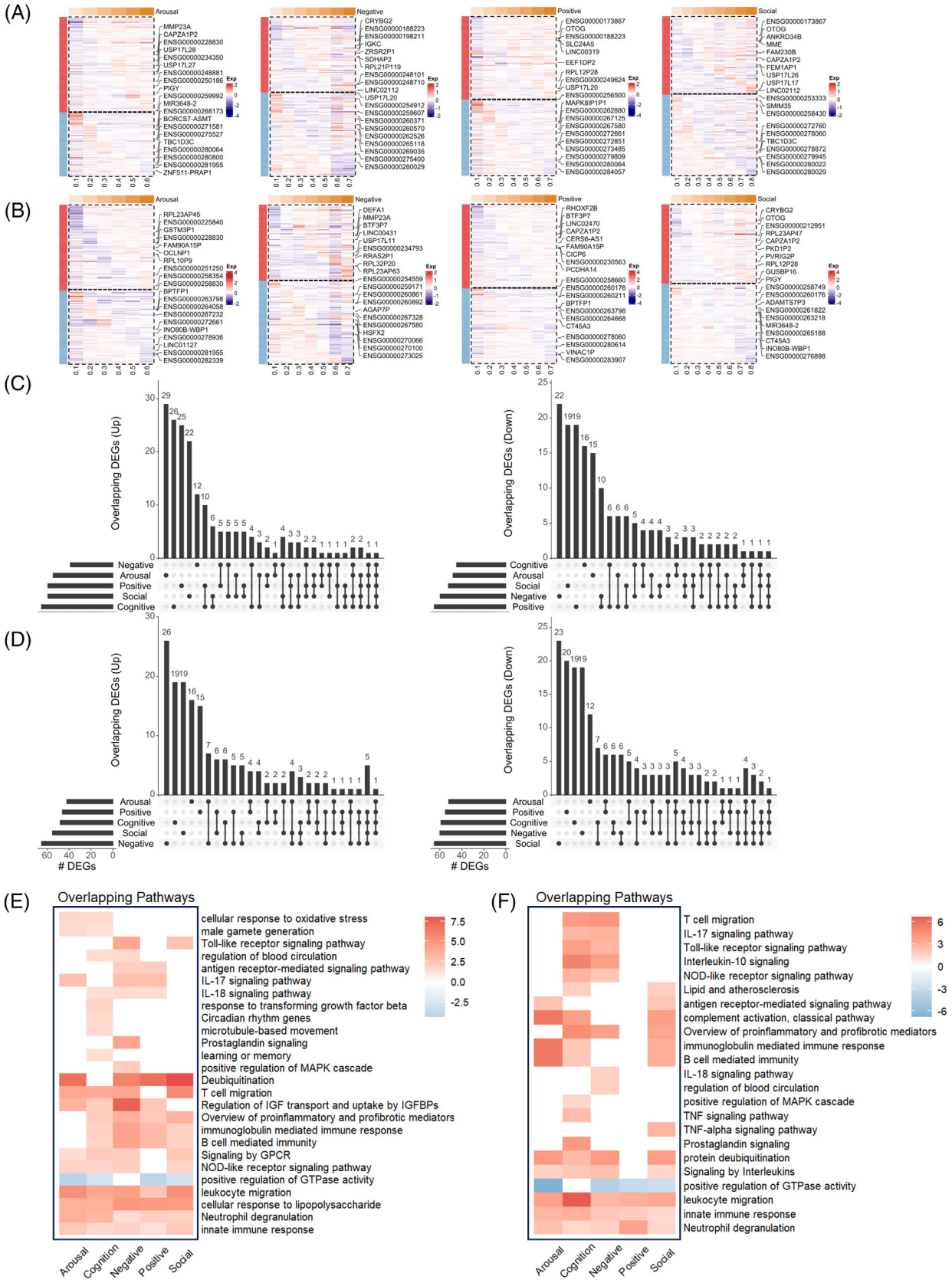

FIGURE 2 Identification of gene expression programs as a function of distinct RDoC domains. A, Heatmaps showing expression trajectories of up- or downregulated DEGs ($P_{nominal} < 0.05$) over increasing RDoC domain values separated for arousal, negative, positive, and social in the dACG. Top 10 up- or downregulated DE genes (all $P_{FDR} < 0.05$) labeled. B, Heatmaps showing analogous expression pattern in the aINS, separated for arousal, negative, positive, and social. C, Upset plots showing the overlap of DEGs of each RDoC domain, for increasing (left) and decreasing (right)

overlap between domains (Figure 2C,D; Data S5 and S6 in supporting information).

3.3 | Pathway enrichment in aINS and dACG as a function of clinical domain scores

Last, we assessed functional pathways across all clinical domains in aINS and dACG. Across both brain regions and all clinical domains, we found a predominating enrichment of pathways related to immune system functions. Enrichment analyses in the aINS revealed multiple pathways associated with innate immune responses shared across the five domains (Figure 2E, Data S7 in supporting information), including neutrophil degranulation, lipopolysaccharide (LPS) response, and leukocyte migration, supporting the notion that immune dysregulation is a driving factor for AD disease progression across all clinical domains investigated. In contrast to the broad association of innate immune response pathways with all clinical domains, other functional pathways were unique to a specific domain or a subset of domains. Specifically, pathways associated with the cognition domain included those involved in learning and memory, microtubule-based movement, circadian rhythm, and response to transforming growth factor beta (TGF-β). Moreover, pathways related to sex hormones were unique to the arousal, cognition, and negative domain. As an example, FSHB (beta subunit of follicle-stimulating hormone) was specifically increased in domain arousal and cognition. This hormone has been shown to accelerate Aβ and tau deposition in neurons and to impair cognition in an AD rodent model,[23] and sex steroid hormones have been associated with AD onset as well as progression.[24] Very similar shared biological processes were detected among the five domains in BA32 (Figure 2F, Data S7). Unique pathways, including complement activation—shared by the RDoC domains of arousal, cognition, and social processes—have been associated with Aβ clearance in Alzheimer's disease.[25]

4 | DISCUSSION

Historically, investigations of AD placed emphasis on the pathogenesis of canonical findings such as NFTs and senile plaques. Although the relevance of Aβ and tau proteinopathies is uncontroversial, growing evidence supports the contribution of additional molecular pathways such as immune regulation, oxidative stress, insulin signaling and lipid metabolism, synaptic regulation, and sex hormone signaling.[26]

The relationship between AD neuropathology and dysregulation of molecular pathways on the one hand and AD symptomatology on the other hand has been predominantly investigated in the context of categorical diagnosis frameworks and with strong emphasis on cognitive impairment. Over the last decade, efforts have been made to overcome these limitations by establishing dimensional models of human cognition, behavior, and emotions that are based on neurobiological or behavioral phenotypes such as RDoC or the hierarchical taxonomy of psychopathology (HiTOP). Dimensional phenotyping across diagnostic entities is a promising approach to identify molecular mechanisms behind distinct symptoms and syndromes. Distinct neuropathological and molecular patterns may, at least in part, account for the heterogenous clinical presentation of neuropsychiatric disorders including AD.[27]

We previously reported an association of NLP-derived cognitive scores with hallmark neuropathological findings supporting the validity of NLP-based methodologies to obtain quantitative measures of functional RDoC domains from *post mortem* health records.[17] Here we link dimensional clinical domain scores to bulk RNAseq data on 101 *post mortem* brain samples from aINS and dACG to test the hypothesis that gene expression signatures are associated with dimensional phenotype constructs derived from *post mortem* brain donor health records. Indeed, our results provide evidence for distinct gene expression signatures associated with each clinical domain and brain region, potentially facilitating future research into more granular phenotypes and molecular mechanisms beyond categorical diagnoses. Our data also suggest immune-related transcriptional changes as a common underlying mechanism across all domains and brain regions.

Results of linear regression models across all clinical domains in both brain regions yielded between $n = 94$ and $n = 125$ DEGs associated with one of the domains (Data S5). Comparisons of up- or downregulated DEGs showed only a moderate level of overlap between clinical domains, suggesting that each domain is associated with a specific set of non-overlapping and overlapping DEGs (Figure 2C,D). Notably, immune response pathways were robustly dysregulated across all clinical domains. These findings contribute to growing evidence for a critical role of immune signaling factors in AD and suggest their pervasive contribution to the overall clinical presentation of this disorder.

Specifically, we detected a substantial number of FDR-significant DEGs with an increasing or decreasing expression pattern over cognition scores in aINS ($n = 109$ DEGs) and dACG ($n = 107$ DEGs; Figure 1A,B). In the aINS, a subset of genes was uniquely differentially expressed in association with the cognitive domain (upregulated $n = 26$, downregulated $n = 16$, Figure 2C, Data S7) including *H2AC7* and *LCN2* (both upregulated). *H2AC7*, a H2A histone protein variant, is involved in regulating cell cycle processes. Interestingly, reactivation of cell cycle–related genes and DNA double-strand breaks are early pathological hallmarks of AD, and eventually lead to neuronal

genes, in the aINS. Overlapping DEGs are indicated by intersecting lines among different domains. D, Upset plots showing overlapping DEGs for each RDoC domain, for increasing (left) and decreasing (right) genes, in the dACG. E, Heatmap showing overlapping and distinct regulatory pathways for each RDoC domain in aINS and dACG (F). Colors indicate whether pathways are up- (red) or downregulated (blue), and color depths represent significance levels of the enriched pathways. aINS, analysis in the anterior insula; dACG, dorsal anterior cingulate cortex; DEG, differentially expressed gene; FDR, false discovery rate; RDoC, Research Domain Criteria.

loss.[28] *LCN2* is involved in a wide range of biological processes such as regulation of iron homeostasis, inflammation, cell death, survival, differentiation, and migration.[29] LCN2 in the brain has been implicated in cognition and behavior while increased levels of LCN2 are associated with age-related central nervous system diseases such as AD and Parkinson's disease (PD).[30] In the dACG, a total of 38 genes were uniquely differentially expressed with the cognitive domain (upregulated $n = 19$, downregulated $n = 19$, Figure 2D, Data S7). Top hits include *LAD1* and *MMP23A*, which showed a strong positive correlation with cognition scores. LAD1 is involved in cell anchoring and adhesion and MMP23A is one of the matrix metalloproteinase (MMP) family engaged in cell adhesion and matrix degradation in the extracellular matrix (ECM), enhancing immune cell migration and inflammatory response.[31]

DEGs that are uniquely up- or downregulated over specific clinical domains may shed light on underlying molecular mechanisms of NPS in AD. For example, *PINX1* and *HSPA7* showed a unique signature of increased expression over the arousal domain in the aINS. *PINX1* can inhibit the activity of telomerase, which is protective against reactive oxygen species production and oxidative stress at different stages of AD pathology.[32] Interestingly, telomerase activity is also associated with circadian oscillation under the control of CLOCK-BMAL1 heterodimers,[33] a molecular mechanism fundamental to the arousal domain. *HSPA7* is a member of the human Hsp70 family and overexpression of Hsp70 can have protective effects on neurons in AD.[34] *AMIGO3* is among genes uniquely associated with the positive domain in the aINS. *AMIGO3* triggers the inhibition of oligodendrocyte precursor cell maturation, myelin production, and neurite outgrowth.[35] Similarly, we found *NPAS4* showing a unique positive association with the positive domain in the aINS. *NPAS4* encodes a transcription factor that regulates a number of downstream genes such as *BDNF*, *NARP*, and *KCNA1*, which mediate diverse effects of synaptic modulation and experience-dependent memory formation.[36] Two other genes uniquely upregulated in association with the social domain in the aINS are *NME8* and *E2F8*. *NME8*, encoding TXNDC3, is involved in cytoskeletal function and axonal transport and identified as a late-onset AD risk gene from genome-wide association studies and meta-analyses.[37] E2F8 is a member of E2F transcription factor family that regulate the transition from G1 to S phase, and an aberrant activation of neuronal cell cycle has also been postulated as a mechanism of neuronal loss in AD.[38] Last, interleukin (IL) 6, a major inflammatory marker, showed an increasing expression pattern in association with the negative domain in the aINS. This is consistent with previous meta-analyses showing positive association between inflammatory markers and depression.[39]

Several FDR-significant up- and downregulated genes were uniquely associated with individual clinical domains in the dACG. For example, *CNTF*, encoding a neurotrophic factor involved in neurotransmitter synthesis and neurite outgrowth, was uniquely upregulated in the social domain. *PINX1* was upregulated across the positive domain but downregulated across the cognitive and negative domain in the dACG. Interestingly it shows a unique upregulation with arousal in BA16 (see above). *SLC5A1*, encoding the sodium/glucose cotransporter SGLT1 and *LCN2*, encoding a glycoprotein expressed in reactive microglia and astrocytes in AD, were uniquely associated with the positive domain in our cohort.[40] Genes associated with the negative domain and prior evidence for a role in AD included *IL1RL1*, *LIF*, and *FGB*.[41,42]

Although the number of overlapping DEGs across clinical domains was small (Figure 2C,D), these genes could point to molecular mechanisms that influence a broader set of symptoms in AD. Common upregulated genes across all domains (including the cognitive domain) in the aINS indicate the overall activation of processes related to immune activation, which is an important mechanism contributing to AD pathogenesis and progression. For example, we found *CXCL10*, a chemokine that can mediate immune activation by binding to its receptor *CXCR3* and activate and recruit leukocytes.[43] We also found *MUC13*, which promotes nuclear factor kappa beta activity and leads to increased production of IL-8.[44] On the other hand, as a subtype of mucins, mature MUC13 can provide numerous glycosylation sites with its N-terminus located on the cell surface, and N-linked glycosylation has been recently reported to affect the progression of AD.[45] In total, we detect $n = 70$ genes upregulated at $P_{FDR} < 0.05$ across at least two domains. In contrast, $n = 70$ downregulated genes at $P_{FDR} < 0.05$ are shared across at least two domains (Data S6).

In the dACG, several genes including *USP17L11*, *USP17L17*, *USP17L26*, and *USP17L28* were upregulated across different clinical domains. They belong to the deubiquitinating enzyme family of genes and are involved in regulating the removal of ubiquitin molecules from proteins.[46] Ubiquitin proteasome system impairment and mitochondrial dysfunction have been implicated as hallmarks of aging and associated with neurodegenerative diseases such as AD and PD.[47,48] Notably, *MT-RNR2*, encoding the polypeptide humanin, is also upregulated across the cognitive, arousal, and social domain in the dACG.[49] In total, we detect $n = 66$ genes upregulated at $P_{FDR} < 0.05$ across at least two domains. In contrast, $n = 78$ downregulated genes at $P_{FDR} < 0.05$ are shared across at least two domains (Data S6).

At the level of regulatory pathways, we found a more congruent profile with shared pathways related to the innate immune response defining upregulated gene profiles, and GTPase activity defining downregulated gene profiles across domains and (Figure 2E,F Data S7). This contrasting result compared to the regulation of individual genes may reflect the overall strong impact of immune dysregulation, vesicle trafficking, and cell cycle regulation in AD progression.

In summary, the use of NLP-derived dimensional phenotypes may provide more specific insight into the underlying biology of AD. Each clinical domain score was associated with a distinct pattern of DEGs with a limited number of DEGs shared across domains. However, changes across clinical domains may be driven by shared functional pathways with a focus on immune system dysregulation.

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CONFLICT OF INTEREST STATEMENT

Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

RNAseq data are available through the GEO accession number GSE261050. The code of the analyses is available at the Klengel Lab GitHub page under https://github.com/klengellab/RDoC_RNAseq.

CONSENT STATEMENT

All tissue samples and medical records were obtained from the Harvard Brain Tissue Resource Center (HBTRC; operating under the Mass General Brigham McLean Institutional Review Board). *Post mortem* brain tissue research is not considered human research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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