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Subtypes of Insomnia Disorder Identified by Cortical Morphometric Similarity Network

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ABSTRACT

Insomnia disorder (ID) is a highly heterogeneous psychiatric disease, and the use of neuroanatomical data to objectively define biological subtypes is essential. We aimed to examine the neuroanatomical subtypes of ID by morphometric similarity network (MSN) and the association between MSN changes and specific transcriptional expression patterns. We recruited 144 IDs and 124 healthy controls (HC). We performed heterogeneity through discriminant analysis (HYDRA) and identified subtypes within the MSN strength. Differences in MSN between subtypes and HC were compared, and clinical behavioral differences were compared between subtypes. In addition, we investigated the association between MSN changes and brain gene expression in different ID subtypes using partial least squares regression to assess genetic commonalities in psychiatric disorders and further performed functional enrichment analyses. Two distinct subtypes of ID were identified, each exhibiting different MSN changes compared to HC. Furthermore, subtype 1 is characterized by objective short sleep, impaired cognitive function, and some relationships with major depressive disorder and autism spectrum disorder (ASD). In contrast, subtype 2 has normal objective sleep duration but subjectively reports poor sleep and is only related to ASD. The pathogenesis of subtype 1 may be related to genes that regulate sleep rhythms and sleep–wake cycles. In contrast, subtype 2 is more due to adverse emotion perception and regulation. Overall, these findings provide insights into the neuroanatomical subtypes of ID, elucidating the relationships between structural and molecular aspects of the relevant subtypes.

1 | Introduction

Insomnia disorder (ID) is a common sleep disorder that affects 30%–35% of people worldwide (Morin and Benca 2012; Morin et al. 2015). The main characteristics of ID include sleep difficulty, poor physical and mental health, and impaired daytime functioning (Ballesio et al. 2019; Brownlow, Miller, and Gehrman 2020; Kyle, Morgan, and Espie 2010; Ohayon 2002). Recently, an increasing number of studies have found that ID is a highly heterogeneous psychiatric disease (Benjamins et al. 2017; Zhang, Sun, Li, Fan, et al. 2023). Although researchers are beginning to focus on the delineation of insomnia subtypes, most are based on clinical symptoms or personal traits and, therefore, are highly subjective and inaccurate (Bjorøy et al. 2020; Blanken et al. 2019; Perlis et al. 1997; Rezaie et al. 2018). In contrast, using neuroanatomical data to define biological subtypes objectively is essential for further understanding the disease.

Many studies have been devoted to examining the specific brain structural abnormalities of ID by using magnetic response imaging (MRI). Some voxel-based morphometry studies have identified abnormal gray matter volumes (GMVs) in

Summary

- Revealing two distinct subtypes of insomnia based on morphometric similarity network.
- Revealing the association between morphometric similarity network changes and specific transcriptional expression patterns in each subtype.
- Two subtypes exhibit different sleep problems and daytime function.

ID (Altena et al. 2010; Neylan et al. 2010; Riemann et al. 2007). In addition, many studies have found abnormalities in cortical structural connectivity in patients with ID. Structural connectivity abnormalities correlate with sleep quality and executive function performance (Suh et al. 2016; Zhao et al. 2015). More importantly, recent studies have revealed significant differences in structural connectivity patterns across five different insomnia subtypes, classified based on patients' levels of distress as well as their unique profiles of personality and mood traits (Bresser et al. 2024). These findings support the hypothesis that ID is associated with connectivity abnormalities. However, specific patterns of brain connectivity abnormalities and corresponding biological explanations are still lacking.

As far as we know, there is only one recent study to identify biological subtypes of ID by using objective neuroanatomical data (Zhang, Sun, Li, Fan, et al. 2023). In that study, we identified two distinct neuroanatomical subtypes of ID based on regional GMVs using heterogeneity through discriminant analysis (HYDRA), a novel machine-learning approach (Varol, Sotiras, and Davatzikos 2017). Here, GMVs were the volumes of brain gray matter with unit of cm^3. One subtype was characterized by widely distributed decreased GMVs and more impaired daytime functioning. In contrast, the other subtype showed increased GMVs in the right superior temporal gyrus and more sleep disturbance. However, our previous study had several limitations—first, the small sample size (the number in the ID group is 56). Second, the measures used in the study were subjective questionnaires and lacked objective explanatory measures (e.g., sleep-related parameters and broad neuropsychological–behavioral assessments), significantly impeding a deeper understanding of the subtypes. Finally, only a single structural feature (GMVs) was used, which may not be sufficient to capture structural anomalies fully. In contrast, an individual-level whole-brain morphometric similarity network (MSN) combines multiple MRI parameters to quantify similarities among various cortical regions (Seidlitz et al. 2020, 2018), potentially leading to improved classification. Due to the successful application of MSN in depression (Li et al. 2021) and schizophrenia (Morgan et al. 2019; Yao et al. 2023), we thought it was worth to extend in the field of ID.

Some studies proposed that ID is potentially influenced by genetic risk factors (Jansen and Watanabe 2019; Madrid-Valero et al. 2021). For example, twin studies have found an average heritability of ~37% for ID (Madrid-Valero et al. 2021). Genome-wide association studies have also determined a heritability of approximately 7% (Jansen and Watanabe 2019). However, we know little about the biological processes by which genetic factors affect ID. Genetic factors are thought to significantly influence psychiatric disease by shaping human brain connectivity (Arnatkeviciute et al. 2021). With the advent of the Allen Human Brain Atlas (AHBA) (Hawrylycz et al. 2012), brain transcriptional expression atlases provide a bridge connecting the brain connectomes with biological functions (Fornito, Arnatkevičiūtė, and Fulcher 2019). To date, potential associations between MSN and specific transcriptional expression patterns have been observed in a variety of psychiatric disorders, including schizophrenia (Morgan et al. 2019), major depressive disorder (Li et al. 2021), and autism (Romero-Garcia et al. 2019). Therefore, whether MSN in subtypes of ID is associated with regional gene expression patterns needs to be further explored, which will help to understand the underlying pathogenesis and develop new therapeutic targets for different subtypes of ID.

Based on the above background, we investigated the association between molecular mechanisms and structural alterations in different ID subtypes. First, we used the HYDRA to identify subtypes based on MSN features. We used various tests to assess the differences among subtypes better and identify the subtypes' different clinical and psycho-behavioral characteristics. In addition, for each subtype, we investigated the relationship between changes in ID-related regions in the MSN and the expression patterns of corresponding genes using AHBA data to identify ID-related genes. Finally, we used enrichment analysis to annotate the identified ID-related gene sets functionally. In summary, our findings contribute to a better understanding of ID subtypes, highlight the need to delineate ID subtypes, and reveal complex links between structural changes in the MSN and specific transcriptional expression patterns.

2 | Methods and Materials

2.1 | Participants

This study included 144 patients with ID and 124 healthy controls (HC). The patients were recruited from and diagnosed with ID by the sleep psychology department in three hospitals in Chongqing. In contrast, the HC were recruited from the local community through electronic advertising. The IDs were diagnosed by professional psychiatrists using the Structured Clinical Interview based on DSM-V. The inclusion criteria for ID patients are as follows: (1) Pittsburg sleep quality index (PSQI) > 7 and insomnia severity index (ISI) > 10; (2) the sleep disturbance occurred at least 1 year; (3) do not have other acquired psychiatric and physiological diseases or any other sleep disorders; (4) no medication used within the past week; and (5) no history of claustrophobia or the presence of metal implants, that is meeting the objective conditions for magnetic resonance imaging. The inclusion criteria of HCs were as follows: (1) PSQI ≤ 7 and ISI ≤ 10; (2) no history of shift work and sleep complaints; (3) no other psychiatric history or brain injury; and (4) no history of claustrophobia or the presence of metal implants. It is important to note that in this study, a PSQI cutoff value of 7 was set because the participants in our study were from China, and previous research by Chinese scholars on the PSQI indicates that a cutoff score of 7 with a sensitivity and specificity of 98.3% and 90.2% for evaluating patients and normal individuals respectively (Kappa = 0.89, $p < 0.01$) (Liu and Tang 1996), and an ISI cutoff value of 10 was used because that in community samples, a cutoff

score of 10 is typically recommended due to its high sensitivity (86.1%) and specificity (87.7%) (Morin et al. 2011). All participants signed the informed consent form to confirm their participation and complete knowledge of the present study protocol, and they were compensated in cash. The Faculty of Psychology, Southwest University's ethical review committee approved the study (H21070), and all procedures followed the Declaration of Helsinki. The workflow of the present study is shown in Figure 1.

2.2 | Imaging Data Acquisition and Processing

Imaging data for HC were collected from the Southwest University using a 3.0 Tesla Siemens Prisma MRI Scanner (MAGNETOM Prisma 3T, Siemens Medical Solutions, Germany). The high-resolution T1-weighted structural images were acquired using the 3D-SPGR sequence with the following parameters: TR/TE = 2530/2.98 ms, FOV = 256 × 256 mm^2, voxel size = 0.5 × 0.5 × 1 mm^3, flip angle = 7°, acquisition matrix = 512 × 512, thickness/gap = 1/0 mm, slices = 192, phase enc. dir = A>>P. Imaging data for ID were collected from the Youlian Medical Imaging Diagnosis Center in Chongqing using a 3.0T GE SIGNA Pioneer MRI Scanner. The high-resolution T1-weighted structural images were acquired using the 3D-SPGR sequence with the same parameters as in the Southwest University.

The T1-weighted images were preprocessed in surface-based space using FreeSurfer (v6.0, http://surfer.nmr.mgh.harvard.edu/) through standardized processing pipelines (Fischl 2012). Specifically, the preprocessing step involved skull stripping, segmentation of brain tissue, separation of hemispheres and subcortical structures, and construction of the gray/white interfaces and the pial surfaces. Before processing, all T1-weighted images were visually inspected for quality.

2.3 | Construction of MSN

The cortical surfaces were divided into 308 spatially adjacent regions by segmenting 68 cortical regions in the D-K atlas (Seidlitz et al. 2018). Then, the parcellated D-K atlas was transformed into each participant's surface. Five features of each region, including surface area, cortical thickness, gray matter volume, Gaussian curvature, and mean curvature, were derived from T1w imaging. Each morphometric feature vector underwent z-normalization across the areas in each subject to accommodate variations in value distributions among features. Subsequently, Pearson's correlation analysis was conducted on morphometric feature vectors to establish pairwise correlations between cortical regions, generating a 308 × 308 connection matrix for each participant without applying any threshold. The average weighted correlation coefficient between a special area and all other areas (i.e., the corresponding column in the connection matrix) was calculated to evaluate the MSN strength and quantify the region's connectivity strength, named regional MSN strength (RMS).

2.4 | Subtyping ID With HYDRA

The HYDRA was used to cluster ID into different subtypes, where RMS was set as input features. The HYDRA analyses'

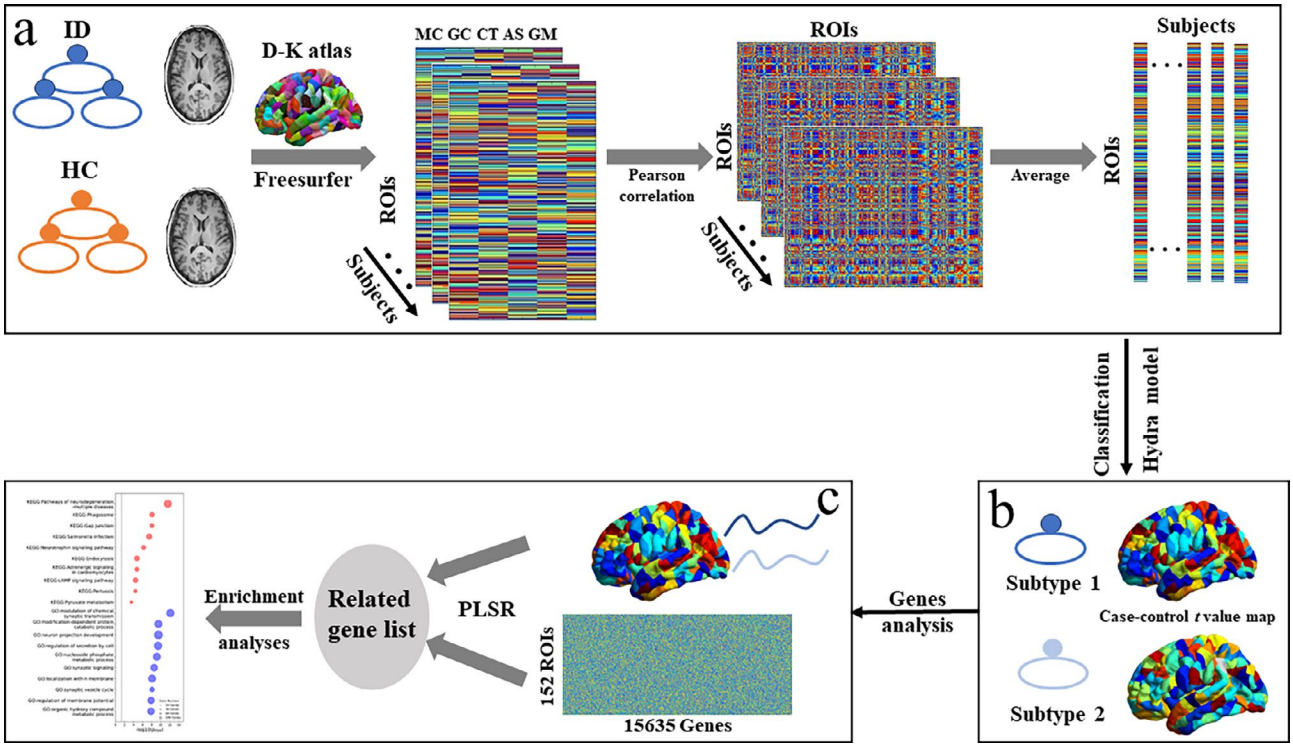

FIGURE 1 | The workflow of the present study. (a) Morphometric similarity network (MSN) construction. (b) Using HYDRA model to classify ID subtypes. (c) Association analysis with brain gene expression. SA, surface area; CT, cortical thickness; GM, gray matter volume; GC, Gaussian curvature; MC, mean curvature; PLSR, partial least squares regression.

parameters were as follows: 50 iterations between estimating hyperplanes and cluster estimation, 20 clustering consensus steps, 0.25 regularization parameter, 10-fold cross-validation, and age and sex were included as covariates. In addition, the adjusted rand index (ARI) was used to quantify the similarity between clustering results in the 10-fold cross-validation by considering the clustering stability between each cross-validation (Chand et al. 2020). Furthermore, to confirm the reliability of subtyping, we validated the subtyping results by using permutation tests with 50 permutations (Nichols and Holmes 2002).

2.5 | Objective Clinical Characteristics and Psycho-Behavioral for Subtypes

2.5.1 | All-Night Sleep Electroencephalography

UMindSleep (EEGSmart Technology Co. Ltd., Shenzhen, China) is a wearable forehead sleep recorder that monitors sleep. Although only with limited EEG channels, it is highly consistent with PSG (polysomnography) in recording sleep-related parameters (Chen et al. 2023). We used the device to capture the patient's sleep EEG throughout the night and then derived the following measures using the device's built-in automated algorithm, including sleep latency, total sleep duration (calculated by the duration from the start of the entry into the any stable Sleep Stage until the complete awakening in the morning, so the wake duration during sleep is included), duration of non-rapid eye movement sleep stage 1 and 2, duration of non-rapid eye movement sleep stage 3, the number of cycles of rapid eye movement sleep stage and the duration of rapid eye movement sleep stage, and wake duration.

2.5.2 | Cognitive Testing

Executive function (EF) is a core cognitive function in humans, and response inhibition is central to EF (Diamond 2013); therefore, the Go/Nogo task (GNT) was chosen in this study to assess patients' cognitive functions. GNT was compiled using the jsPsych framework in JavaScript. The jsPsych is an open-source library for creating psychology experiments that offer a wealth of features and flexibility (de Leeuw 2015). We used its version 6.0.4 to design and run the tasks. The task contained 210 trials; the first 10 were practice, and the remaining 200 were test trials. Patients were required to press the space key when a blue box was displayed (Go trial) and not to press the key when an orange box was displayed (Nogo trial), with a ratio of 9 Go trials to 1 Nogo trial. The stimuli (blue or orange boxes) were presented for 750 ms in each trial. Participants must choose whether to respond according to the stimuli' color. They would move on to the next trial once the participants had pressed the space key or the presentation duration has exceeded 750 ms. Feedback was given on practice trials but not on test trials. The dependent measures including: the accuracy of Go trials (Go ACC), of Nogo trials (NoGo ACC), and difference score (Go trial ACC minus Nogo trial error rate).

As not all participants had an all-night sleep EEG and GNG tasks, the above analyses only included participants who had the corresponding data captured. When demographic variables (sex and age) were not significantly different between groups, a two-sample *t*-test was performed. Otherwise, an analysis of covariance (ANCOVA) was used.

2.6 | Case–Control Analysis of MSN Strength for ID Subtypes

The linear regression model was used to examine the ID subtypes and HC differences, where the MSN strength was set as the dependent variable and age and sex were set as covariates. The following formula was used: $MSN_i = \text{intercept} + \beta 1 \times \text{age} + \beta 2 \times \text{sex}$ (MSN_i: MSN values of each region). Then, two-sided *t*-tests (contrast = subtyping ID-HC) were performed. Significance was set at $p < 0.05$ with FDR correction for multiple comparisons across 308 regions.

2.7 | Estimation of Regional Gene Expressions

The brain gene expression data were obtained from the AHBA (http://human.brain-map.org). The dataset includes gene expression measures from 3702 brain tissue samples obtained using probes (Hawrylycz et al. 2012). The detailed information can be found in Table S1. We used the Abagen toolbox (https://github. com/rmark ello/abagen) to preprocess the AHBA dataset and followed the standard protocols (Markello et al. 2021). Specifically, the following steps were performed: (1) Probe-to-gene annotations, (2) excluding low-intensity probes with expression below the background noise in over 50% of samples, (3) selecting probes with the highest homogeneities of regional variation for genes targeted by multiple probes, (4) assigning the samples to the D-K atlas within 2 mm Euclidean distance, and (5) normalizing gene expression across tissue samples using a scaled robust sigmoid function. The analysis focused solely on the left hemisphere due to the inclusion of only two right-hemisphere data donors in the AHBA dataset. Therefore, we ultimately obtained a gene expression matrix (152 regions × 15,635 gene expression levels).

2.8 | The Relationship Between MSN Strength and Transcriptome

Partial least squares (PLS) regression (Abdi and Williams 2013) was used to examine the relationships between the gene expression (predictor variables) and regional MSN changes, that is, the *t*-value maps (comparison between a subtype of ID and HC) from 152 cortical regions (response variables). The first PLS component (PLS1) was the linear combination of gene expression exhibiting the strongest association with *t*-value maps. We examined if the covariance between transcriptomic scores and *t*-statistic maps in the PLS1 component exceeded chance expectations by using a permutation test with 5000 iterations. Then, to obtain a significant list of gene sets, bootstrapping (with 10,000 bootstrap samples) was used to examine the variability of each gene's PLS1. The *Z* values were calculated as the ratio of each region's expression weight to its bootstrap standard error, and all genes were ranked according to their contributions to PLS1 (Morgan et al. 2019). Finally, the significant genes were defined

as PLS1+ genes ($Z > 5$) and PLS1− genes ($Z < -5$) according to their PLS1 weight values. The above procedure was conducted separately in each ID subtype.

2.9 | Differential Gene Expression Analysis in Major Psychiatric Disorders

Next, we examined potential associations between the transcriptional correlates of PLS1-weight values and differential gene expression (DGE) values for various psychiatric disorders. Gandal reported the DGE values of dysregulated gene list related to four major psychiatric disorders: major depressive disorder (MDD), autism spectrum disorder (ASD), bipolar disorder (BD), and schizophrenia (SCZ) (Gandal et al. 2018) (Table S2). The Spearman's correlation analysis was used to determine relationships between PLS1− gene weights and DGE values of up or downregulated genes. A significant level was set as $p < 0.05$ with FDR correction.

2.10 | Enrichment Analysis

We next performed functional annotation of PLS1+ ($Z > 5$) and PLS1− ($Z < -5$) genes using Metascape (Zhou et al. 2019) (https://metascape.org/gp/index.html#/main/step1/) for well understanding their biological functions, including biological process (BP) of gene ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. The 0.05 corrected by the FDR was set as the threshold for significance.

3 | Results

3.1 | Demographic and Clinical Characteristics and Two ID Subtypes

The demographic and clinical analysis found no significant difference in sex and age between HC and ID. However, the PSQI and ISI scores of the ID were significantly higher than the HC (Table 1). The subtype analysis of HYDRA found that the number of subtypes of 2 had the highest reproducibility (ARI = 0.762), and other numbers of subtypes (3–6) all yield lower ARI values than 2 (Figure S1). In addition, the permutation test results showed that the AIRs of all subtypes numbers (2–6) were significantly higher than from the null distribution ($P_{FDR} < 0.001$), as shown in Table S3 and Figure S2. Therefore, 80 patients with ID were assigned to subtype 1, and 64 were assigned to subtype 2.

3.2 | Demographic, Clinical Characteristics, and Psycho-Behavioural Differences for Subtypes

The results showed no significant difference in sex, age, the total score of PSQI and ISI, and six sub-dimensions of PSQI (including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, and use of sleep medicines) between the two subtypes. However, subtype 1 reported more complaints about daytime functioning than subtype 2 (Table 2). The ANCOVA (age was set as covariate) of data on objective sleep parameters in some patients (subtype 1: $n = 54$, 15 male, mean age = 38.91, SD = 12.97; subtype 2: $n = 47$, 17 male, mean age = 45.02, SD = 13.99) showed that the total sleep duration was significantly shorter in subtype 1 than in subtype 2 ($p = 0.02$). However, there were no significant differences in other objective sleep parameters (Figure 2a and Table S4). Two-sample *t*-tests on the GNG task showed that subtype 1 ($n = 50$, 13 male, mean age = 39.68, SD = 12.49) performed significantly worse than subtype 2 ($n = 38$, 9 male, mean age = 44.27, SD = 14.93) on the measures of NoGo ACC ($p = 0.05$) and difference score ($p = 0.03$), as shown in Figure 2b and Table S5.

TABLE 1 | Demographic and clinical characteristics of participants.

	HC ($N = 124$)	ID ($N = 144$)	*p*
Male, no. (%)	60 (48%)	65 (45%)	0.20[a]
Age, mean (SD)	39.85 (15.30)	41.89 (14.12)	0.26[b]
PSQI, mean (SD)	3.90 (2.43)	12.26 (2.91)	< 0.001[b]
ISI, mean (SD)	4.00 (2.94)	17.82 (4.55)	< 0.001[b]

Abbreviations: HC, healthy control; ID, insomnia disorder; ISI, insomnia severity index; PSQI, pittsburg sleep quality index.
[a]χ^2 *t*-test.
[b]Two-tailed two-sample *t*-test.

3.3 | Subtyping ID-Related Changes in MSN Strength

Overall, high MSN strength was observed in the temporal and frontal lobes, and low MSN strength was observed in the somatosensory and occipital cortices (Figure 3a). Both subtypes showed significant differences in MSN strength in specific cortical regions with some overlap (e.g., significant decreases in the temporal lobe and significant increases in the occipital lobe) compared to HC but also showed some differences, with subtype 1 showing decreased MSN strength over a wide range of medial frontal lobe regions but subtype 2 did not (Figures 3b,c and S3 and Table S6). Then, we examined the relationship between the MSN strength of HC and the case–control *t*-map for two subtypes. Both subtypes showed negative and spatial correlation (subtype 1: $r_{(308)} = -0.81$, $p_{spin} < 0.001$; subtype 2: $r_{(308)} = -0.74$, $p_{spin} < 0.001$). In addition, 48% of the positive MSN strength in HC and the negative *t*-values in subtype 1 were in decoupling, which is 47% in subtype 2, and 34% of the negative MSN strength in HC and positive *t*-values in subtype 1 exhibited dedifferentiation, which is 32% in subtype 2 (Figure 3d).

3.4 | Transcriptional Patterns Related to Regional Changes in MSN Strength for Subtypes

We identified MSN change-related genes for two subtypes by PLS regression. The PLS1 of two subtypes effectively explained 34% and 42% of the variations in the MSN strength changes, respectively ($p_{perm} < 0.001$). Furthermore, the PLS1 scores showed a significant correlation with the case–control *t*-value maps in MSN strength for subtype 1 ($r_s = 0.54$, $p_{spin} < 0.001$) and subtype 2 ($r_s = 0.60$, $p_{spin} < 0.001$) (Figure 4). Then, for subtype 1, we identified 1172 PLS1+ genes ($Z > 5$) and 1628 PLS1− genes ($Z < -5$)

TABLE 2 | Demographic and clinical characteristics of participants in each insomnia subtype.

	Subtype 1 ($N=80$)	Subtype 2 ($N=64$)	p
Male, no. (%)	35 (44%)	30 (47%)	0.20[a]
Age, mean (SD)	39.8 (12.66)	43.88 (14.10)	0.07[b]
ISI, mean (SD)	18.26 (3.94)	17.27 (5.19)	0.19[b]
PSQI, mean (SD)	12.31 (2.86)	12.20 (2.99)	0.82[b]
PSQISQ, mean (SD), range	2.75 (0.49)	2.61 (0.58)	0.32[b]
PSQILATEN, mean (SD), range	2.29 (0.75)	2.30 (0.77)	0.82[b]
PSQIDURAT, mean (SD), range	1.40 (1.21)	1.63 (1.23)	0.46[b]
PSQISE, mean (SD), range	0.44 (0.99)	0.27 (0.65)	0.72[b]
PSQIDISTB, mean (SD), range	1.78 (0.64)	1.77 (0.58)	0.90[b]
PSQIUOSM, mean (SD), range	1.05 (1.31)	1.25 (1.38)	0.80[b]
PSQIDF, mean (SD), range	2.63 (0.72)	2.39 (0.75)	0.05[b]

Abbreviations: HC, healthy control; ISI, insomnia severity index; PISQ, PSQI sleep quality; PSQI, pittsburg sleep quality index; PSQIDF, PSQI daytime functioning; PSQIDISTB, PSQI sleep disturbance; PSQIDURAT, PSQI sleep duration; PSQILATEN, PSQI sleep latency; PSQISE, PSQI sleep efficiency; PSQIUOSM, PSQI use of sleep medicines; TIV, total intracranial volume.
[a]χ^2 t-test.
[b]Two-tailed two-sample t-test.

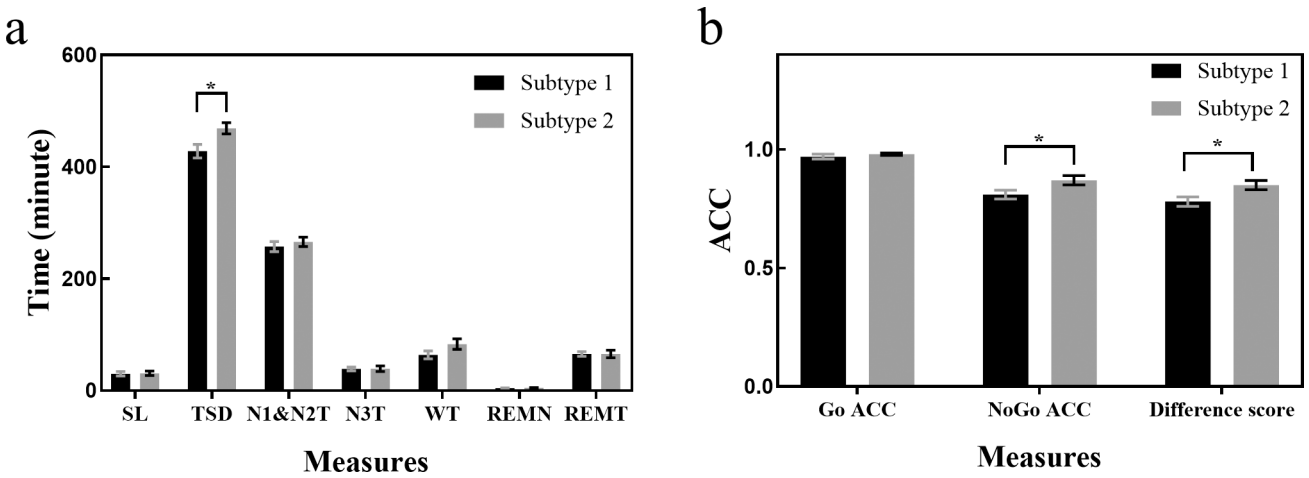

FIGURE 2 | Differences in objective sleep parameters and Go/NoGo task performance between the two subtypes. (a) The total sleep duration (TSD) was significantly shorter in subtype 1 than in subtype 2, but no significant differences in other objective sleep parameters. (b) Subtype 1 performed significantly worse than subtype 2 on the measures of NoGo ACC and difference score. SL, sleep latency; TST, total sleep duration; N1 & N2T, time of non-rapid eye movement sleep stage 1 and 2; N3T, time of non-rapid eye movement sleep stage 3; WT, wake time; REMN, number of cycles of rapid eye movement sleep stage; REMT, time of rapid eye movement sleep stage; Go ACC, the accuracy of Go trial; NoGo ACC, the accuracy of NoGo trial; difference scores, Go trial ACC minus Nogo trial error rate. *$p<0.05$.

(Table S7). For subtype 2, we identified 1724 PLS1+ genes ($Z>5$) and 2092 PLS1- genes ($Z<-5$) (Table S8).

3.5 | Potential Relationship Between ID-Related Changes in MSN Strength and Transcriptional Dysregulation of Other Mental Disorders

For subtype 1, we first identified the overlapping genes for other psychiatric disorders with PLS1 genes (124 genes for ASD, 73 genes for BD, 40 genes for MDD, and 126 genes for SCZ, Table S9). Then, we found PLS1 gene weights positively correlated with ASD ($r_s=0.25$, $p_{perm}=0.02$) and negatively correlated with MDD ($r_s=-0.36$, $p_{perm}=0.05$). However, no significant correlation was found with BD ($r_s=0.20$, $p_{perm}=0.11$) and SCZ ($r_s=0.14$, $p_{perm}=0.11$). For subtype 2, we identified the overlapping genes for other psychiatric disorders with PLS1 genes (153 genes for ASD, 93 genes for BD, 48 genes for MDD, and 154 genes for SCZ, Table S10). In contrast, for subtype 2, PLS1 gene weights were only positively correlated with ASD ($r_s=0.27$, $p_{perm}=0.003$) but not significantly correlated with other psychiatric disorders (Figure 5). These results indicated that the two subtypes have similar but also distinct gene expression patterns of psychiatric disorders.

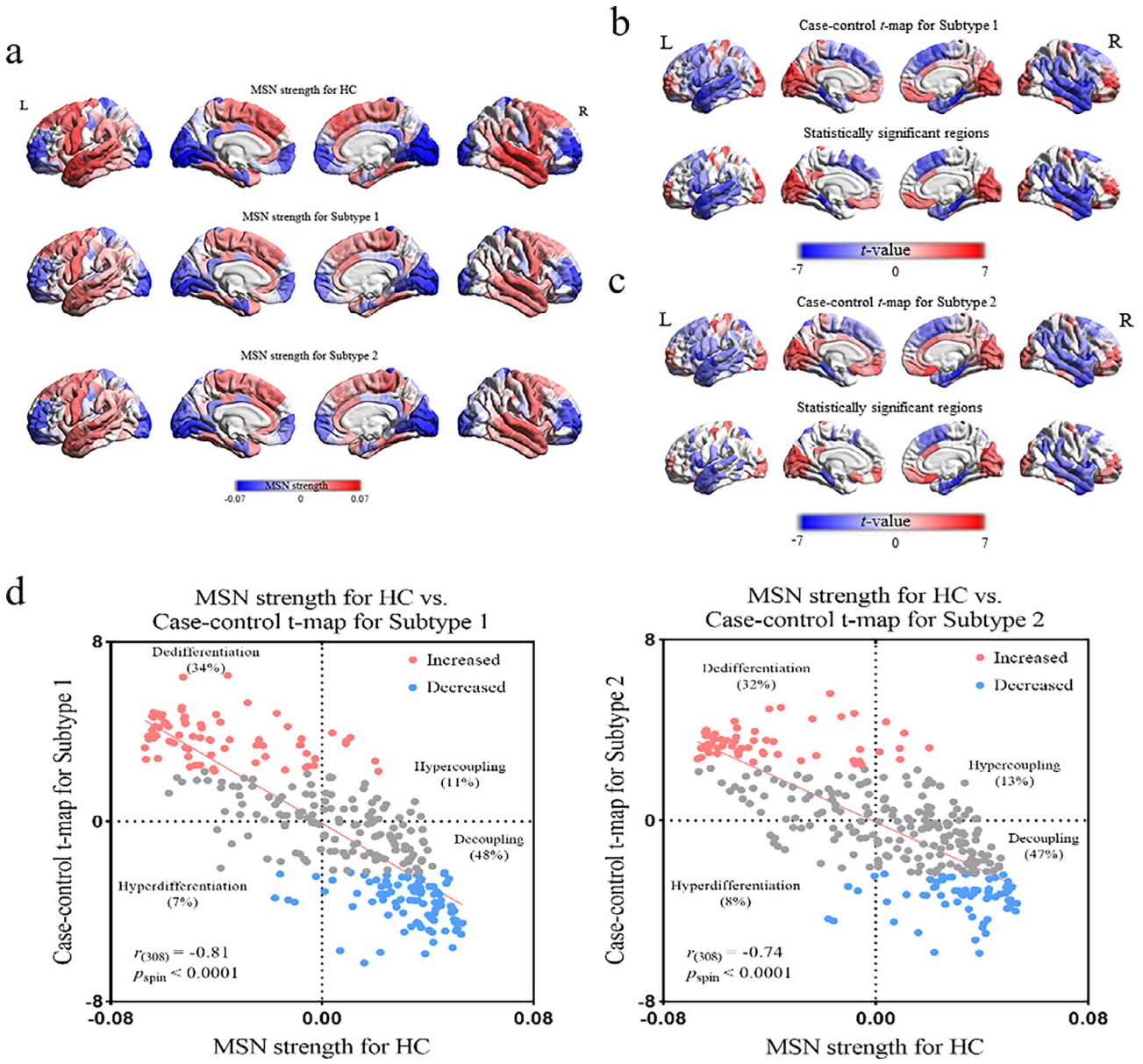

FIGURE 3 | The regional changes in MSN strength for two ID subtypes. (a) The MSN strength of ID subtypes and HC. (b) Case–control comparison of MSN strength for subtype 1. (c) Case–control comparison of MSN strength for subtype 2. (d) Scatterplot of the control MSN strength and case–control *t*-map for subtype 1 and 2.

3.6 | Enrichment Results

The GO and KEGG enrichment analyses of genes correlated with regional changes in MSN indicated some overlap in the biological processes of the two subtypes, but they were also very different. For GO enrichment analyses of PLS1+ genes, both subtypes were significantly enriched for many metabolic processes (e.g., mRNA metabolic process, DNA metabolic process, and ncRNA metabolic process), chromatin organization, response to hormone, and head development. However, only subtype 1 showed a significant enrichment for early embryogenesis processes (e.g., embryonic morphogenesis, microtubule organizing center organization, and regulation of cilium assembly), and only subtype 2 showed a significant enrichment for response to steroid hormone. KEGG enrichment analyses of PLS1+ genes found that both subtypes were significantly enriched for MAPK signaling pathway, Herpes simplex virus 1 infection, and taste transduction. Meanwhile, only subtype 1 was enriched for Circadian rhythm. In contrast, subtype 2 showed enrichment for many pathways of cancer (e.g., pathways in cancer and transcriptional misregulation in cancer).

For GO enrichment analyses of PLS1− genes, both subtypes were significantly enriched in synaptic signaling-related functions (e.g., modulation of chemical synaptic transmission, synaptic signaling, regulation of secretion by cell, and regulation of membrane potential) and neuron projection development. Whereas metabolically, the two subtypes exhibited different biological processes (subtype 1 showed enrichment for nucleoside phosphate metabolic process and organic hydroxy compound metabolic process, but subtype 2 for generation of precursor metabolites and energy and carbohydrate derivative biosynthetic process). For KEGG enrichment analyses of PLS1− genes, it was

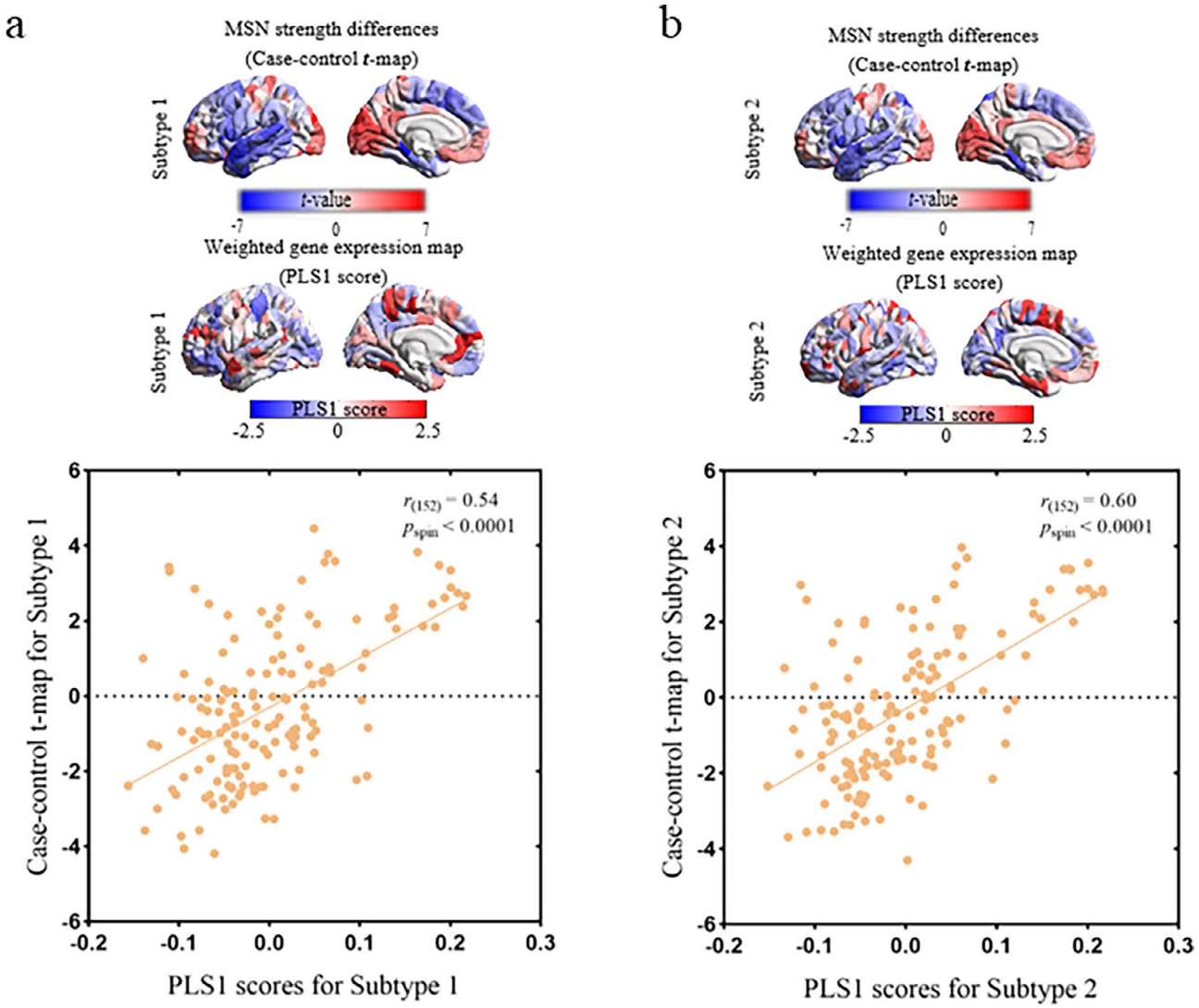

FIGURE 4 | Transcriptional expression patterns related to differences in MSN strength. (a) In subtype 1, the distribution of differences in MSN strength and PLS1 scores in the left hemisphere, and spatial correlation between PLS1 scores and the case–control *t*-value maps of MSN strength. (b) In subtype 2, the distribution of differences in MSN strength and PLS1 scores in the left hemisphere, and spatial correlation between PLS1 scores and the case–control *t*-value maps of MSN strength.

found that both subtypes were significantly enriched in synaptic signaling-related functions (e.g., phagosome, gap junction, and endocytosis) and pathways of neurodegeneration—multiple diseases. However, there are differences between the two subtypes in terms of specific signaling types (subtype 1 showed enrichment for Neurotrophins signaling pathway, adrenergic signaling in cardiomyocytes, cAMP signaling pathway, and pyruvate metabolism but subtype 2 for retrograde endocannabinoid signaling and oxytocin signaling pathway) (Figure 6).

4 | Discussion

The present study investigated the neuroanatomical subtypes of patients with ID using MSN macrostructural changes. Furthermore, it combined a wide range of clinical behavioral measures and transcriptomic insights into the characteristics of the subtypes. By performing the HYDRA algorithm, we identified two different MSN-based ID subtypes, each exhibiting significantly different MSN changes than HC. Clinical and behavioral performance analysis found that subtype 1 had shorter objective sleep duration than subtype 2, and performance on response inhibition tasks was significantly worse than that of subtype 2. Further analysis of the association with the transcriptome revealed that MSN-related changes in subtypes 1 and 2 were linked to brain gene expression. However, in specific biological processes, subtype 1 was involved in multiple pathways that regulate sleep, whereas subtype 2 was not. In addition, the PLS1-weighted genes of subtype 1 were associated with DGEs from ASD and MDD. In contrast, subtype 2 was associated only with ASD. These findings support the existence of neuroanatomical subtypes of ID and explore multiple aspects of clinical behavioral, neuroimaging, and transcriptomic characteristics for distinct subtypes, contributing to a comprehensive understanding of ID subtypes.

We identified two subtypes by HYDRA, and subtype 1 reported more complaints about daytime functioning compared to

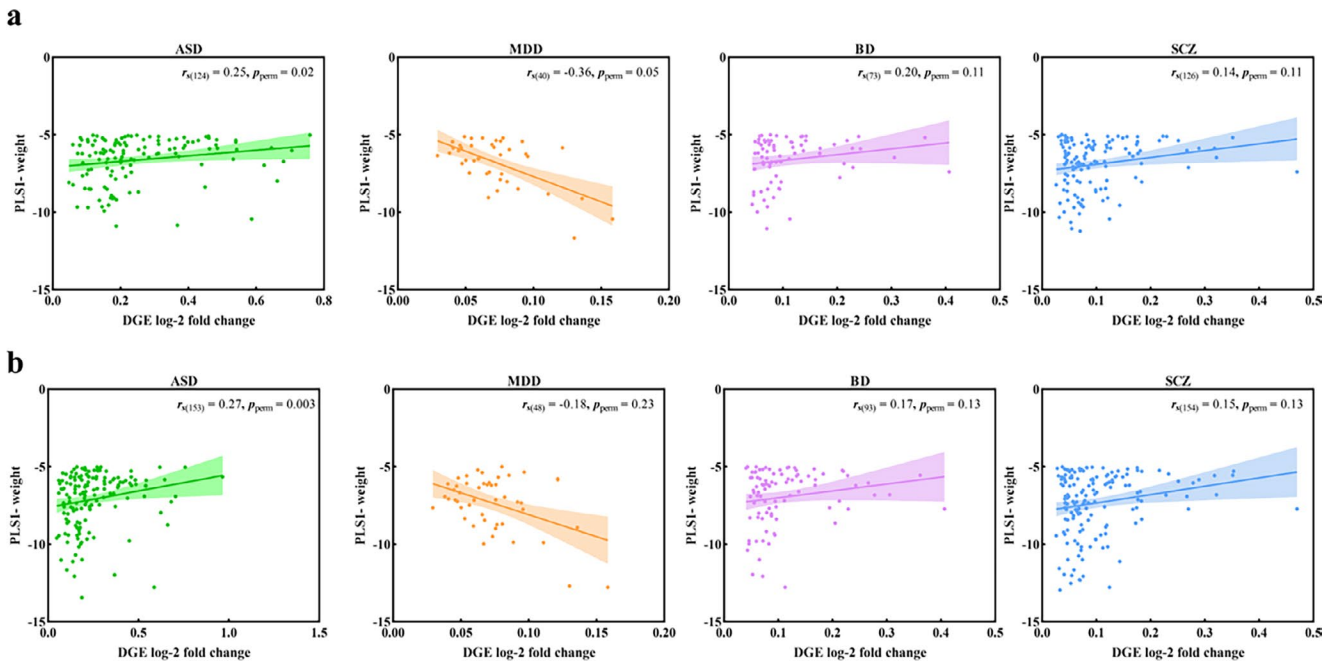

FIGURE 5 | The correlations of the PLS1 weighted gene expression of changes in MSN strength with differential gene expression (DGE) values in other psychiatric disorders. (a) The results of subtype 1. (b) The results of subtype 2. MDD, major depressive disorder; ASD, autism spectrum disorder; BD, bipolar disorder; SCZ, schizophrenia.

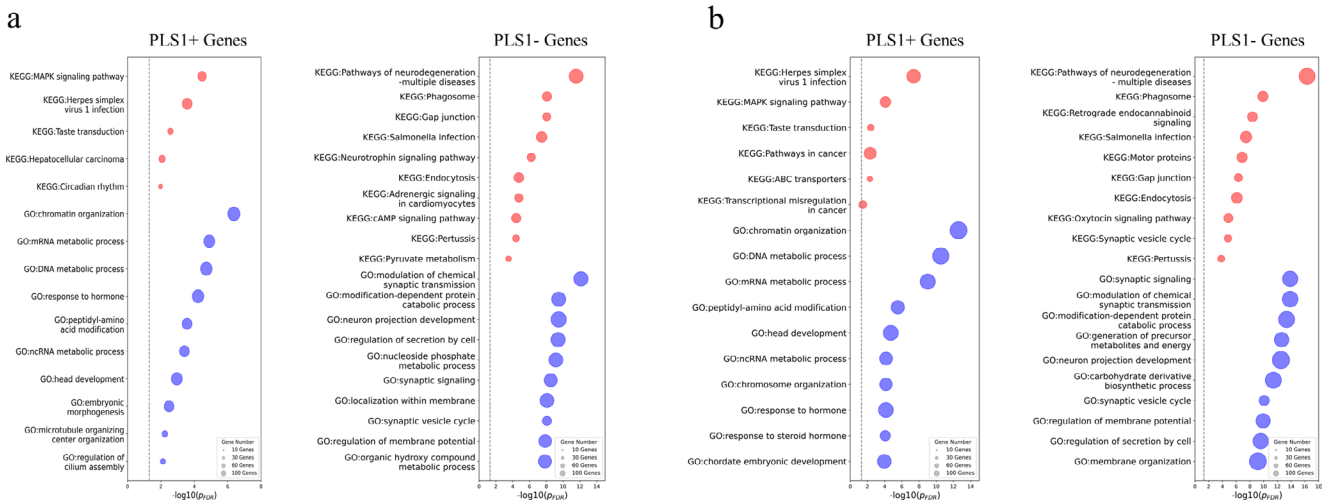

FIGURE 6 | Top 10 enrichment pathways from the enrichment analysis for the gene ontology (GO) biological processes and Kyoto encyclopedia of genes and genomes (KEGG) pathways for PLS1 weighted genes related to regional changes in MSN of subtype 1 (a) and subtype 2 (b). P_{FDR}, adjusted p value after FDR multiple testing corrections. Node size is proportional to the number of input genes included in that term.

subtype 2, which is similar to a previous study (Zhang, Sun, Li, Fan, et al. 2023). Moreover, the present study further complements the objective measures, and we found that subtype 1 had shorter objective sleep duration and performed worse on GNT tasks than subtype 2. These findings suggested a clear difference between the two subtypes in sleep-related parameters and cognitive functioning. Insomnia with objective short sleep duration (ISSD) is a severe biological subtype (Fernandez-Mendoza 2017). Some research, including several meta-analyses (Ballesio et al. 2019; Ren and Jiang 2023; Wardle-Pinkston, Slavish, and Taylor 2019) and empirical research (Fernandez-Mendoza et al. 2021; Olaithe et al. 2021), has found that objective sleep duration appears to be an essential factor in determining whether cognitive functioning is impaired in ID. Therefore, we suggest that the subtype 1 we obtained is likely similar to the ISSD. Subtype 2 is similar to insomnia with normal objective sleep duration (INSD), characterized by complaints of sleep difficulties but with normal objective sleep duration. However, it should be noted that previous studies focusing on ISSD and INSD have used an objective sleep duration of 6 or 6.5 h as a criterion for division.

In contrast, in the present study, we found that it may be more reasonable to divide it by 7 h (the average TSD of subtype 1 was roughly 7 h, whereas subtype 2 was significantly higher than 7 h). Furthermore, although the ICSD-3 no longer distinguishes between different ID subtypes, it collectively refers to them as chronic insomnia (Kay, Buysse, and Levenson (2015); Sateia 2014). However, based on the results of this study, we suggest that the presence of insomnia subtypes must be considered, especially subtypes divided by objective sleep duration, as this can result in differences not only in neuroanatomy but also in objective clinical behavior.

We found that the two subtypes were not completely separated regarding MSN pattern changes. Both subtypes showed a significantly decreased MSN strength in the temporal cortex and a significantly increased MSN strength in the occipital lobe compared to HC. However, in the frontal cortex (especially dorsolateral and medial regions), only subtype 1 exhibited a widespread decreased MSN strength, whereas subtype 2 did not. These findings may indicate that the two subtypes share some commonalities (e.g., complaints about sleep problems and hyperarousal) and show some differences (e.g., dysregulation of cortical inhibition). For example, it has been found that decreased GMVs in the temporal cortex affect the patient's ability to process external auditory information during sleep and lead to hyperarousal (Joo et al. 2013). Morphological measures of the temporal lobe have also been found to be associated with subjective reports of sleep quality (Wang et al. 2021). The decreased MSN strength in frontal regions only observed in subtype 1 may represent a dysfunction of their cortical inhibition, thus affecting homeostatic sleep processes and cognitive abilities. Decreased GMVs in frontal regions of ID and further contributing to cortical hyperarousal has become a consensus among researchers (Altena et al. 2008; Joo et al. 2013; O'Byrne et al. 2014; Spiegelhalder et al. 2013). More importantly, the prefrontal lobes (including frontal regions) are thought to be associated with attention and higher executive functions (Zhang et al. 2022). A recent study of patients with subclinical insomnia has identified frontal GMVs and their associated functional connectivity as a neural mechanism that responds to impaired response inhibition (Zhang, Sun, Li, Yang, et al. 2023). Thus, the unique MSN pattern in the frontal regions of subtype 1 may be an important contributor to its short objective sleep duration and impaired cognitive function.

We found that both subtypes exhibited spatially positive correlations between MSN pattern changes and transcriptome in correlation analyses with the transcriptome. This suggests a link between gene expression and macrostructural changes. In association analyses with other major psychiatric disorders, the two subtypes showed significantly different results. In subtype 1, the PLS1 weights were significantly positively correlated with ASD-related and MDD-related DGE values. However, the PLS1 weights of subtype 2 were only significantly positively correlated with ASD-related DGE values. This suggests that the genetic commonality of the two subtypes with different psychiatric disorders is different, especially for MDD. The shared genetic commonality may be the main reason linking subtype 1 to MDD. A previous study found that sleep duration (this is a characteristic of subtype 1, not subtype 2) could predict the course of depressive disorders, but subjectively reported severity of insomnia could not (van Mill et al. 2014).

Furthermore, it is interesting that we did not find an association between the PLS1 weights of two subtypes with SCZ-related and BD-related DGE values. At first glance, this seems to be significantly strange and counterintuitive because insomnia is often one of the outward symptoms of SCZ and BD. However, this may indicate that the link between ID and these two diseases is not expected at the genetic level. Current studies using Mendelian randomization methods to explore the links between ID and other psychiatric disorders have also failed to reach consistent conclusions. For example, Gao et al. (2019) only found significant associations between ID BD and ASD but not with MDD, SCZ, and ADHD (Gao et al. 2019). Whereas in another study, a significant relationship was observed between ID and all five psychiatric disorders (Sun et al. 2022). At the same time, given that this study focuses on analyzing brain structural changes, different results may be obtained when focusing on brain functional changes.

The enrichment analyses provided insights into the transcriptional signatures concerning the MSN strength changes for two subtypes. In subtype 1, we observed that PLS1-weighted genes were significantly enriched in various pathways associated with sleep regulation and the sleep–wake cycle. For example, PLS1+ genes were enriched in the Circadian rhythm of KEGG, which may explain why subtype 1 exhibits shorter objective sleep duration. The PLS1− genes were enriched in organic hydroxy compound metabolic process ontological term. The 5-hydroxytryptophan (5-HTP) is an organic hydroxyl compound metabolite of tryptophan. 5-HTP is converted in the body to serotonin. This neurotransmitter is widely believed to regulate sleep–wake behavior (Monti 2011). In addition, a recent study found that serotonin plays a vital role in individual response inhibition behavior (Cui et al. 2023). This may explain why subtype 1 has a worse response inhibition function. In subtype 2, the PLS1-weighted genes were enriched in some emotion perception and regulation pathways. For instance, PLS1− genes were enriched in retrograde endocannabinoid signaling and oxytocin signaling pathways. Oxytocin is a pituitary neuropeptide produced by neurons in the paraventricular nucleus and supraoptic nucleus of the hypothalamus that modulates anxious behavior (Moaddab and Dabrowska 2017; Tai and Lau 2021). Similarly, endogenous cannabinoids, critical communication systems that coordinate the regulation of signals in the body, which bind to specific receptors (THC) in the hippocampus, play a vital role in the formation of mood and regulate anxiety and depression (Chevalier et al. 2020; Gerhardt et al. 2022). Disturbances in these pathways may explain why subtype 2 has normal objective sleep duration but subjectively complains of poor sleep—they are overly anxious and harbor poor emotional attitudes toward their sleep.

There are still several limitations that need to be acknowledged. First, although we tested the stability of the subtype classification results using a permutation test, the sample size was still relatively limited. Therefore, larger sample sizes and complementary independent validation datasets are needed in future studies. Second, the present study included objective measures for assessing clinical behavioral traits, but they are still relatively limited. Therefore, future studies could supplement PSG data (e.g., micro-sleep measures such as the EEG power spectrum of some specific sleep stages), more comprehensive cognitive-behavioral test (e.g., attention or work memory tests) and mood-related tests (e.g., emotional recognition or regulation) to

assess the different subtypes' characteristics comprehensively. Meanwhile, the healthy control also lacks many objective behavioral measures, which limits our analysis. Furthermore, while we observed distinct MSN strength changes in regions like the frontal cortex between subtype 1 and subtype 2, and their associations with behavioral traits, it remains unclear whether these brain structural changes directly lead to behavioral changes. Existing literature suggests that the relationship between neuroimaging changes and behavior is often complex and influenced by multiple factors (Marques, Kay, and da Silva 2022). Therefore, while our study provides valuable evidence linking brain structure and behavioral changes, neuroimaging data alone cannot fully explain the neurobiological mechanisms underlying ID subtypes. Future research should combine neuroimaging, behavioral, and genomic data to more precisely characterize the subtype features in ID patients. In addition, the brain structure imaging data of the healthy control and patients are collected by different MRI scanners, and whether this will affect the study results still needs further consideration. Finally, as only two donors have the right hemisphere in AHBA data, our analysis only focused on the left hemisphere. Therefore, the obtained transcriptome–MSN changes relationships in two subtypes do not represent the condition of the whole brain.

5 | Conclusion

We identified two distinct subtypes of ID. Subtype 1 is characterized by objective short sleep, impaired cognitive function, and complex relationships with DGEs of ASD and MDD. In contrast, subtype 2 has normal objective sleep duration but subjectively reports poor sleep and is only related to the DGE of ASD. In addition, the pathogenesis of subtype 1 may be related to genes that regulate sleep rhythms and sleep–wake cycles. In contrast, subtype 2 is more due to adverse emotion perception and regulation (e.g., excessive worry and wrong opinions about sleep problems). Overall, this study provides new insights into the neuroanatomical subtypes of ID, elucidating the complex relationships between structural and molecular aspects of the relevant subtypes. In addition, these findings highlight the need to classify ID subtypes and develop precise intervention protocols corresponding to different subtypes.

Author Contributions

X.L. led the project. X.L. and H.B.Z. involved in study concept and the design of the study. H.B.Z. was responsible for the analysis of the transcription and behavioral data. H.B.Z., H.N.S., and J.Q.L. processed the image data. H.B.Z. wrote the draft of the manuscript. X.L. made valuable corrections to the contents of the manuscript. All authors approved the final version of the paper for submission.

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Ethics Statement

The ethical review committee of the Faculty of Psychology, Southwest University approved the present study (H21070), and all experimental operations were conducted in accordance with the approved guidelines.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The raw data are not publicly available due to ethical issues. The other processed data and code that support the findings of this study are available on request from the corresponding author upon reasonable request, after consideration by the local ethics committee.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.