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ORIGINAL ARTICLE

High resilience of human cerebellum in Alzheimer's disease: reciprocal coupling of cellular anabolic and catabolic fluxes enable intensive neuroprotection

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Abstract

We elucidate that the cerebellum displays striking resilience to neurodegenerative changes under aging or Alzheimer's disease (AD). We identify the neurobiological factors that underlie the natural neuroprotective characteristic of cerebellum, thereby obtaining innovative therapeutic directions that may duplicate this naturalistic neurorestorative response. We investigated the mass spectrometry/liquid chromatography-based proteomics profile from AD tissue: sparely affected cerebellum and highly affected hippocampus/cingulate/entorhinal cortex. We found 83 upregulated and 37 downregulated cerebellar genes. Top five upregulated genes were *GAP43* (hub-gene), *APLP1, NCAM1, THY1, SNCB;* these encode for neurorestorative processes, as axonal, dendritic, and myelination growth. Contrastingly, the top five downregulated genes were *NDUFS8* (hub-gene), *NDUFA9, NDUFU2, NDUFA12, NDUFV1*. These encode for NADH-dehydrogenase subunit in mitochondria; their increased expression relates to mitochondrial-based ROS stress-based apoptosis; hence, their downregulation reduces apoptosis, reinforcing neural survival. Indeed, cerebellum displays unique neuroprotection, by coupling of two reciprocal cytometabolic fluxes: (1) hyperactivation of neural anabolic processing, as neuronal growth, and (2) hypoactivation of neural catabolic processing, as mitochondrial caspase-induced neural degradation. Hence, for inducing the endogenous neuroprotective response, one needs to pharmacologically modulate both these cytometabolic processes: (i) agonism of neural synaptotropic anabolic pathway, coupled to (ii) antagonism of mitochondrial catabolic neurotoxic pathway. We also observed that synaptic efficiency-encoding genes constitute majority (70%) of upregulated cerebellar genes. We noted the unexpected observations, namely that (a) the neuron is the most pivotal factor for the restorative response than any type of glial or other cells, (b) with respect to the neuron, the synaptogenesis process is much more critical than the neurogenesis process, and (c) collaterally, the hypomodulation of the mitochondrial NADHD ubiquinone activity is the key factor. A unique significance is that a naturally occurring neurorestorative response may be therapeutically harnessed in neurons, minimizing off-target effects that are often hazardous disadvantages of conventional dementia therapeutics.

Keywords Dementia · Hippocampus · Mitochondria · Neurodegeneration · Neurorestoration · Synaptogenesis

Introduction

The brain is one of the most complex and sophisticated structure of human body, and it controls our thoughts, emotions and actions. Over millions of years, the brain has evolved, and has undergone some dramatic changes. The primordial brain is made up of clusters of cells, at the front of an organism near the mouth, so that the organism could track or see its food. These cells process information from the sensory organs of the body. Humans have the greatest brain volume in terms of the body size of any living organism (Hofman 2014). The brain of vertebrates has grown in size and sophistication as evolutionary progression occurred

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(Barton and Venditti 2014). The different parts of the brain have evolved into specialized structures and functions. For instance, the cerebellum (CB) is a major structure engaged in movement and coordination (Koziol et al. 2014), whereas the cerebral cortex is a main entity involved in learning and memory (Bear 1996). As we age, various changes in the human brain can be observed including decline in cognitive function, memory, and motor coordination. While the aging process produces certain changes in the brain, the neurodegenerative disorders can also induce additional changes in the brain.

However, it is known that the CB is much less affected in aging as well as in neurological disorders like Alzheimer's disease or Parkinson's disease (Xu et al. 2019). The CB is a most significant sensorimotor structure in the ventral portion of the brain, with extensive connections to the brainstem, cerebral hemispheres, and spinal cord; the CB not only maintains balance and posture but is also involved in a wide range of cognitive functions (Gao et al. 2020). Actually, the CB is also involved in complicated behavioral sequences, such as those involved in manual manufacturing and in using tools (Hofman 2014). CB's size is small compared to the cerebral hemispheres; however, in humans, the CB contains four times more neurons than the cerebrum (Barton and Venditti 2014). The latter study, based on an evolutionary approach to the CB, revealed that it expanded at a considerably faster relative rate than the expansion of cerebral neocortex during the last 5 million years as the great ape hominins evolved that led finally to the emergence of modern humans (*Homo sapiens*); this study indicates that the CB was far more a critical component of brain evolution than the neocortex in the later state of the evolution of the *Homo* genus. Hence, it may be of considerable significance that one should investigate the CB, as it is mainly associated with tool using/tool making or technical intelligence, in contrast to the cerebral neocortex, generally associated with social intelligence.

An important aspect is to study the change of cerebellum with aging. Aging-induced neurodegenerative impairments affect nearly 100 million people globally, without there being highly effective neuroprotective treatment for the vast impaired populace. A meaningful way to approach this problem is to investigate how brain regions show different susceptibility/resistance to neurodegenerative changes during aging. This may indicate differential factors that may predispose to, or protect from, aging-induced neurodegeneration, with possible therapeutic implications. Thus, we selected the cerebellum as the region of interest for our study, the CB being well segregated from the cerebral hemispheres. The cerebral hemispheres are primarily affected in the progression of Alzheimer's disease, AD (Xu et al. 2019), thereby ushering in progressive dementia. AD pathogenesis is induced by the accumulation of beta-amyloid (Aβ) peptide and microtubule-associated protein tau, which is hyperphosphorylated and undergoes oxidative changes to form plaques and tangles.

A well-known investigation (Klunck et al. 2004) using radiolabeled thioflavin T showed that the cerebellum has negligible or little amyloid deposition both in controls and AD, nevertheless amyloid deposition is high in cerebral neocortex of AD patients, yet there is some modest deposition of amyloid in neocortex of control normal subjects. Moreover, this study was well validated by another one, using computed emission tomography, which revealed that (i) in normal subjects: there is hardly any amyloid deposition in CB as compared to cerebral cortex, and (ii) in AD patients: there is very significantly less amyloid beta deposition in CB as compared to cerebral cortex (Murphy and Levine 2010).

In another investigation, which was a post-mortem brain tissue analysis, six functionally distinct regions of the autopsied human brain were assessed: five cerebral regions, and one extra-cerebral region (cerebellum), the five cerebral regions being the hippocampus (HP), entorhinal cortex (ENT), cingulate gyrus (CG), sensory cortex (SCx), and the motor cortex (MCx) (Xu et al. 2019). Their evaluation showed that all the five cerebral regions were impacted by AD: the limbic region was highly affected (hippocampus, entorhinal cortex and cingulate gyrus), and the isocortical region was moderately affected (sensory cortex and motor cortex); on the other hand, the cerebellum displayed a strikingly protective response. To underscore, CB shows neuroprotective behavior, and as per the Thal phases, the cerebellum does not show any appreciable amyloid deposition as AD progresses, only in the last phase (Thal phase 5) does the CB show amyloid deposit (Thal et al. 2002). To illustrate, CB region is typically used as a control area containing negligible amyloid in imaging investigations of the AD brain (Van Berckel et al. 2013).

The aim of our present study is to determine the factors of the neuroprotective behavior of the cerebellum. In addition, we seek to understand how the cerebellum's differentially expressed genes (DEGs) function to ameliorate the effect of neurodegenerative changes. Therefore, we utilize integrative network biology and biomolecular pathways to analyze the differentially expressed genes of the cerebellum. To have a translational perspective, we further perform analysis using networking approach that elucidated possible leads, targets, and pathways for therapeutic intervention. We may highlight that recently network pharmacological approach is getting introduced for probing neurodegenerative diseases (Ramakishna et al. 2024). According to our networking analyses in this report, we find that the cerebellum has synaptotropic genes that retard the effect of neurodegenerative processes, whereas the cerebral

areas highly affected by neurodegenerative processes (HIP, ENT and CG) have low-level functionality of these neuroprotective genes. We also conducted enrichment analysis on the genes shared by CB and those three highly affected regions of AD. Our observation was that the behavior of these gene elements in the cerebellum was radically different from how these gene elements behaved in those cerebral regions.

Furthermore, our investigation indicated that the cerebellar region, when compared to the cerebral regions, has an entirely divergent profile of susceptibility/resistance to neurodegenerative changes in aging. By performing genomic analysis of the cerebellar region, we demarcated the putative factors responsible and, thereby, possible target leads, and we used these findings to home onto the potential novel therapeutic approach. The schema of our study is illustrated in Fig. 1a.

Materials and methods

Procedure

We analyzed collateral available human brain proteomics profile from liquid chromatography/mass spectrometry assay. It may be mentioned that we took recourse to the platform of Xu et al. (2019). In that investigation, mass spectrometry was used to record protein expression changes from human post-mortem brains, in five cerebral regions [hippocampus (HP), entorhinal cortex (ENT), cingulate gyrus (CG), sensory cortex (SCx), and motor cortex (MCx)] and one extra-cerebral region (cerebellum, CB) (Fig. 1b). That study did brain autopsy on 11 AD patients, and 9 control subjects of similar age and gender distribution (the controls did not have any neurological disorder), and therein an isobaric tagging approach determined relative protein expression followed by two-dimensional liquid chromatography and mass spectrometry (details in Supplementary Material S1 for the procedure). Our acquisition of all of their raw mass spectral data was performed via the PRIDE platform (Supplementary Fig. S1) [further details at: www.manchester.ac.uk/dementia-proteomes-project]. The ages of the subjects lie in 2 decade ranges: AD subjects, 60–79 years (M = 5, F = 6); controls, 61–78 years (M = 5, F = 4).

Differentially expressed genes of CB

We filtered out 120 differentially expressed genes (DEGs) exclusively in CB. All the DEGs were filtered using the criteria of fold change ($-1.05 < \log_2 fc > 1.05$) and p value < 0.05. Thereby we identified 83 upregulated and 37 downregulated genes out of the 120 cerebellar genes.

Common genes between the cerebellum and the cerebrum (HIP, ENT, and CG)

For a comparison study, we looked for differentially expressed genes common in the cerebellum and the cerebrum (hippocampus, entorhinal cortex, and cingulate gyrus). We have found five common genes, three of them shared by CB and HIP and one shared by CB and ENT, and another by CB and CG (Fig. 2).

Identification of hub genes and subnetwork analysis

We used two platforms, the Search Tool for the Retrieval of Interacting Genes (STRING v11.0) (Doncheva et al. 2019) and the Cytoscape v3.7.1 procedure (Shannon et al. 2003), to create the protein–protein interaction (PPI) networks. The modules of the PPI network were processed using the Cytoscape plugin Molecular Complex Detection (MCODE) analysis (Su et al. 2014) with a degree cut-off of 2, a node score cut-off of 0.2, a k-core of 2, and a maximum depth of 100. CytoHubba method (Chin et al. 2014) was used to find the hub genes. The top ten nodes were chosen as noteworthy hub genes. This analysis was performed on the aforesaid 83 upregulated and 37 downregulated genes, and we constructed the protein–protein interaction network for the top 10 upregulated hub genes and the top 10 downregulated hub genes.

Pathway enrichment analysis

We then performed the pathway enrichment analysis by utilizing the ClueGo methodology (Bindea et al. 2009) v2.5.5 platform from Cytoscape to detect the significant DEGs. The ClueGO procedure integrates Gene Ontology terms (GO) (Ashburner et al. 2000) and KEGG/BioCarta pathway processing (Kanehisa et al. 2002) pathways and creates a functionally organized GO/pathway term network. This operation can analyze one list or compare two lists of genes and comprehensively visualize the functionally grouped terms. The ClueGo analysis builts and compares the networks of functionally linked GO terms using kappa statistics, which in this analysis was put to a value > 0.4. This analysis was performed on the abovementioned 83 upregulated and 37 downregulated genes. Furthermore, we performed the same steps to analyze the five common genes of Fig. 2.

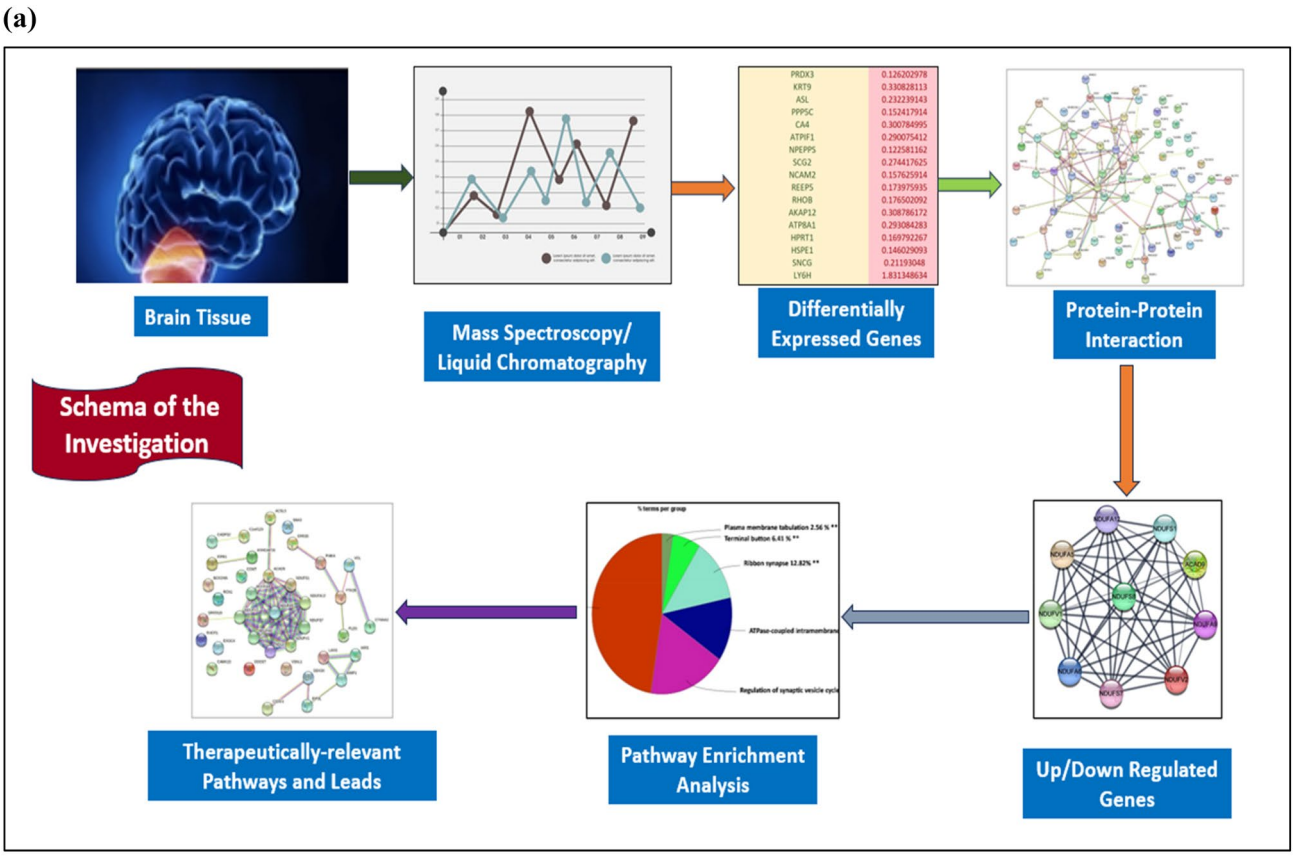

Fig. 1 **a** The schema of the investigation undertaken. The flow chart shows the serial stages of the study, namely accession to the brain tissue for analysis, mass spectroscopy/liquid chromatography-based protein estimation, identification of differentially expressed gene gamut, mapping of the protein–protein interaction and its network biology-based assessment, upregulation and downregulation profiling and evaluation, pathway enrichment analysis with biological process delineation, and finally obtaining pharmacological targets and therapeutic leads. **b** Anatomical sites of tissue analysis. The first panel represents the lateral surface, while the second panel shows the medial surface of the human brain. The front of the head is on the left side for both panels, while the dorsal and ventral aspects of the brain are in the upper and lower directions respectively. *Cerebral region*: five sites: (A) motor cortex, (B) sensory cortex, (C) hippocampus (located at depth), (D) cingulate, and (E) entorhinal cortex; *extra-cerebral region*: (F) cerebellum

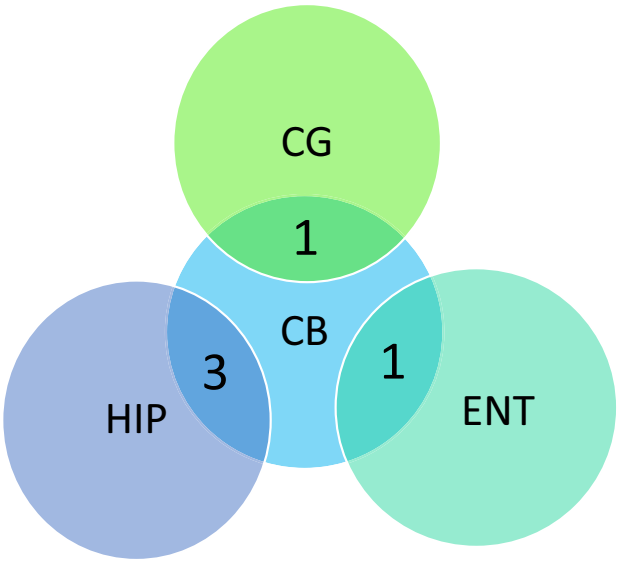

Fig. 2 Venn diagram showing the common genes shared by the cerebellum with the cerebral regions (hippocampus, cingulate gyrus and entorhinal cortex). The following abbreviations are used: CB—cerebellum, CG—cingulate gyrus, HIP—hippocampus, and ENT—entorhinal cortex. CB and HIP has three common genes, while the pair CB and CG and the pair CB and ENT share one common gene each

Results

Differentially expressed genes (DEGS) of the cerebellum

In this present study, we found 120 differentially expressed genes (DEGs) in cerebellum, which were filtered out using the criteria of fold change ($-1.05 < \log_2 fc > 1.05$) and p value < 0.05. Out of these 120 identified DEGs in CB, we delineated that 83 were upregulated genes, and 37 were downregulated genes. The lists of these two gene sets are enumerated in Supplementary Tables S1 and Table S2.

Protein–protein interaction (PPI) network

As mentioned earlier, using the STRING procedure, a PPI network comprising differentially expressed genes of 83 upregulated genes and 37 downregulated genes was separately constructed (Fig. 3a, b). This PPI network of DEGs was further utilized to identify the most influential genes and delineate their respective roles in the neuroprotection of CB in Alzheimer's disease.

Gene ontology analysis

The string network obtained from the previous step was utilized further to perform the functional analysis of DEGs of the cerebellum using the ClueGo module of the Cytoscape platform, for the upregulated genes (83) and the downregulated genes (37). A functionally categorized network of enriched categories was thereby formulated, using altered kappa statistics (> 0.4 in this analysis), The ClueGo output was constructed, and the networks were compared regarding the functionally connected GO terms. Thence, the Cytoscape 2.8.3 procedure has been used for visualization. The pathway enrichment analysis of upregulated genes is shown in Fig. 4a. The illustration shows that these genes are involved in numerous neurorestorative processes, as dendrite morphogenesis, synaptic vesicle recycling, neuron recognition, neural projection regeneration, neuronal synaptic plasticity, regulation of filopodium, etc.

The differential gene expression observed across the cerebellum likely represents a collective effect of both neurons and glial cells, which work together to maintain cerebellar resilience. For instance, glial cells are known to support structural binding function and modulate vascular/lymphatic flow, while neurons contribute directly to synaptic plasticity and neurorestoration. We can make a first-level assessment of the relative levels of the neuronal and glial factors in the cerebellar protective processes. From Fig. 4a of the pathway enrichment analysis of the neuroprotective genes, we can calculate the neuron's contribution by adding the percentage values given in that figure related to neuron or neuron components, namely the items of Fig. 4a as synaptic vesicle, dendrite morphogenesis, neuronal projection, synaptic plasticity and neuron regulation, which thereby totals to 31.6%. Likewise, from Fig. 4a, the glial contribution (as gliovascular endothelial activity, and heterotypic adhesion primarily induced by glia) totals to 10.4%. These two summative values are shown in Fig. 4b. In other words, the contribution of the neuronal factors strongly dominates and is three times that of the contribution of the glial factors.

Now we deal with the downregulated genes and Fig. 5a displays the pathway enrichment analysis. This diagram shows the vast majority of the downregulated genes are involved in a biological process to form NADH dehydrogenase (ubiquinone), i.e., respiratory complex 1 or mitochondrial complex I enzyme. The rest of the downregulated genes are involved in assembly of NADH dehydrogenase. It may be mentioned that this enzyme is the first large protein complex of respiratory chain and acts in the mitochondrial membrane, initiating the catabolic oxidative process, reactive oxygen species, and cellular oxidative stress (Murphy 2009), thus downregulation can inhibit the catabolic process in neurons, and facilitate neuronal survival in CB. Indeed, it is known that the drug metformin has neuroprotective characteristics against AD (Koenig et al. 2017), and acts by inhibiting the aforesaid enzyme NADH dehydrogenase (ubiquinone), i.e., respiratory complex 1 (Viollet et al. 2012). As a collateral

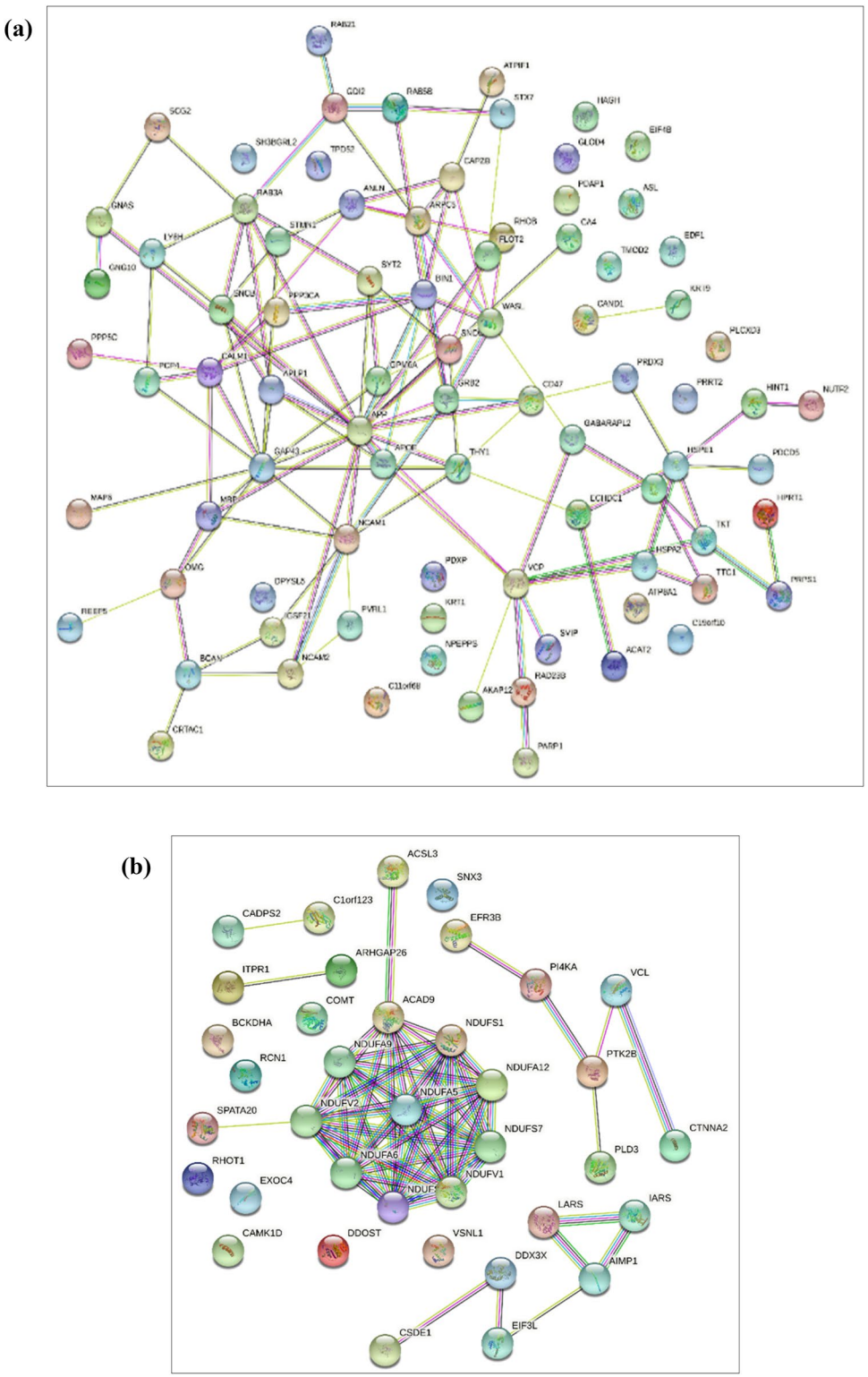

Fig. 3 This diagram shows the entire network of differentially expressed genes. **a** There are 83 genes in the network of upregulated genes; **b** here there are 37 genes present in the network of downregulated genes. Proteins are represented by the nodes, and physical and functional relationships are shown by the edges. With a medium confidence level ($\kappa > 0.4$), this network is constructed using STRING methodology, where interaction is represented by the color of the edges. Protein clustering in dense sub-networks indicates groupings that are functionally related and may be involved in important biological processes.

substantiation, investigators have earlier undertaken a system approach-based investigation of the neuroprotective aspect of metformin (Bhattacharjee and Roy 2023), whose validatory clinical trial analysis has also been performed separately (Bhattacharjee and Roy 2024).

Regarding cerebellar neuroprotection, we can have an assessment of the relative significance of the two modes of the downregulation process from Fig. 5a which shows that there are only two modes, NADH dehydrogenase (ubiquinone) activity and NADH dehydrogenase complex

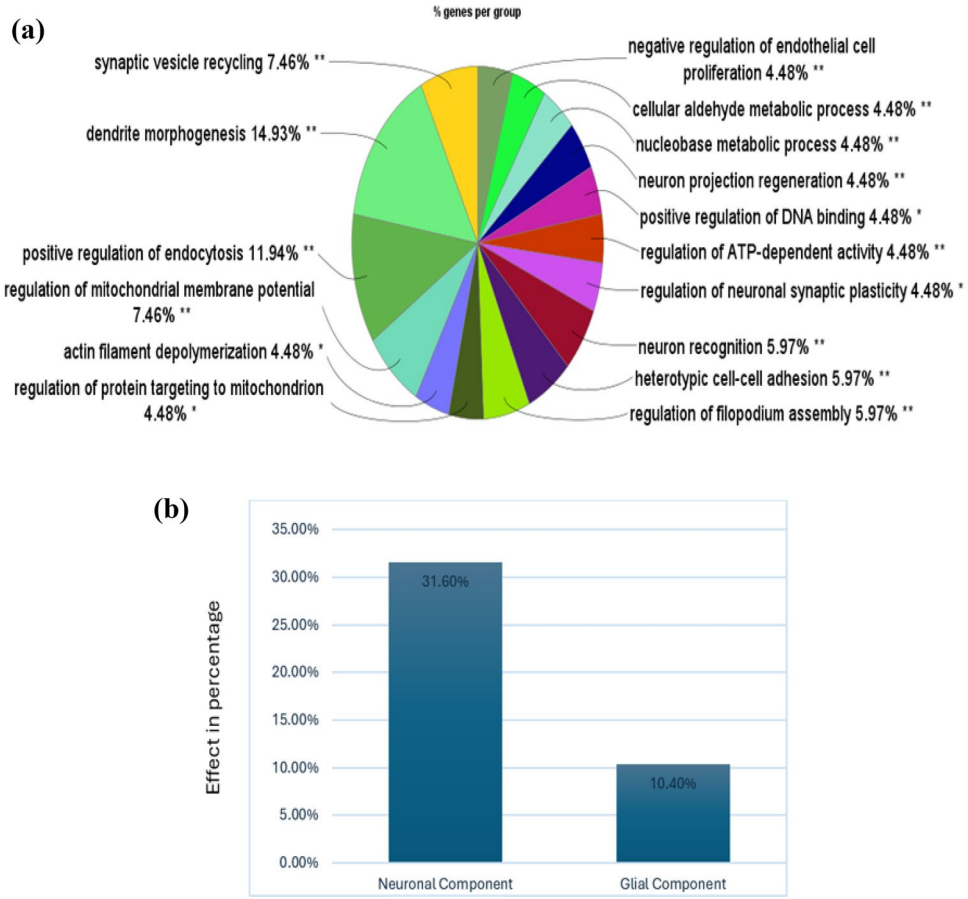

Fig. 4 **a** Pathway enrichment analysis of the 83 upregulated genes in the cerebellum. The different colors show the different biological processes in which these genes are involved, and indicate that the various functionalities of the upregulated genes enable the neuronal growth and protection in the cerebellum. **b** Regarding the cerebellar neuroprotection behavior with respect to the upregulated genes, the contribution of the neuronal factors strongly dominates and is three times that of the contribution of the glial factors

assembly. To illustrate, from that diagram, we note that the readouts for the NADH dehydrogenase (ubiquinone) activity and NADH dehydrogenase complex assembly are, respectively, 86% and 14%. Indeed, the main role of NADHD (ubiquinone) activity is in the electron transport chain, enabling the transfer of electron from NADH to quinone, while, in contrast, NADHD complex assembly is the process where the different subunits of NADHD consolidate together to form a structural complex for energy production electron transport (Lodish et al. 2018). From the percentage values mentioned, we note that the contribution of mitochondrial NADHD (ubiquinone) activity is about six times of that of mitochondrial NADHD complex assembly. We clarify this in Fig. 5b where we have normalized the contribution of NADHD complex assembly to unity. This can be of appreciable translational implication as delineated later.

Identification of the hub genes

The modules of the PPI network were screened using the Cytoscape plugin MCODE (Su et al. 2014) with a degree cut-off of 2, a node score cut-off of 0.2, a k-core of 2, and a maximum depth of 100. The hub genes were located using the CytoHubba module (Chin et al. 2014). The top ten upregulated hub genes and top ten downregulated hub genes have been illustrated in Figs. 6 and 7, respectively. The description and function of these upregulated and downregulated hub genes have been represented in Tables 1 and 2, respectively.

Analysis of genes shared by the cerebellum and the cerebri (three regions ENT, CG, and HIP)

The cerebral regions (cingulate gyrus, hippocampus, and entorhinal cortex) are considerably affected regions during the progression of Alzheimer's disease (Braak and Braak 1991). Therefore, we selected the genes shared by our region of interest (i.e., cerebellum) and those three heavily affected regions of the cerebri. We filtered the genes from the earlier mentioned repository (www.manchester.ac.uk/dementia-proteomes-project). Accordingly, we found five common genes (Fig. 2), and these are elucidated as follows.

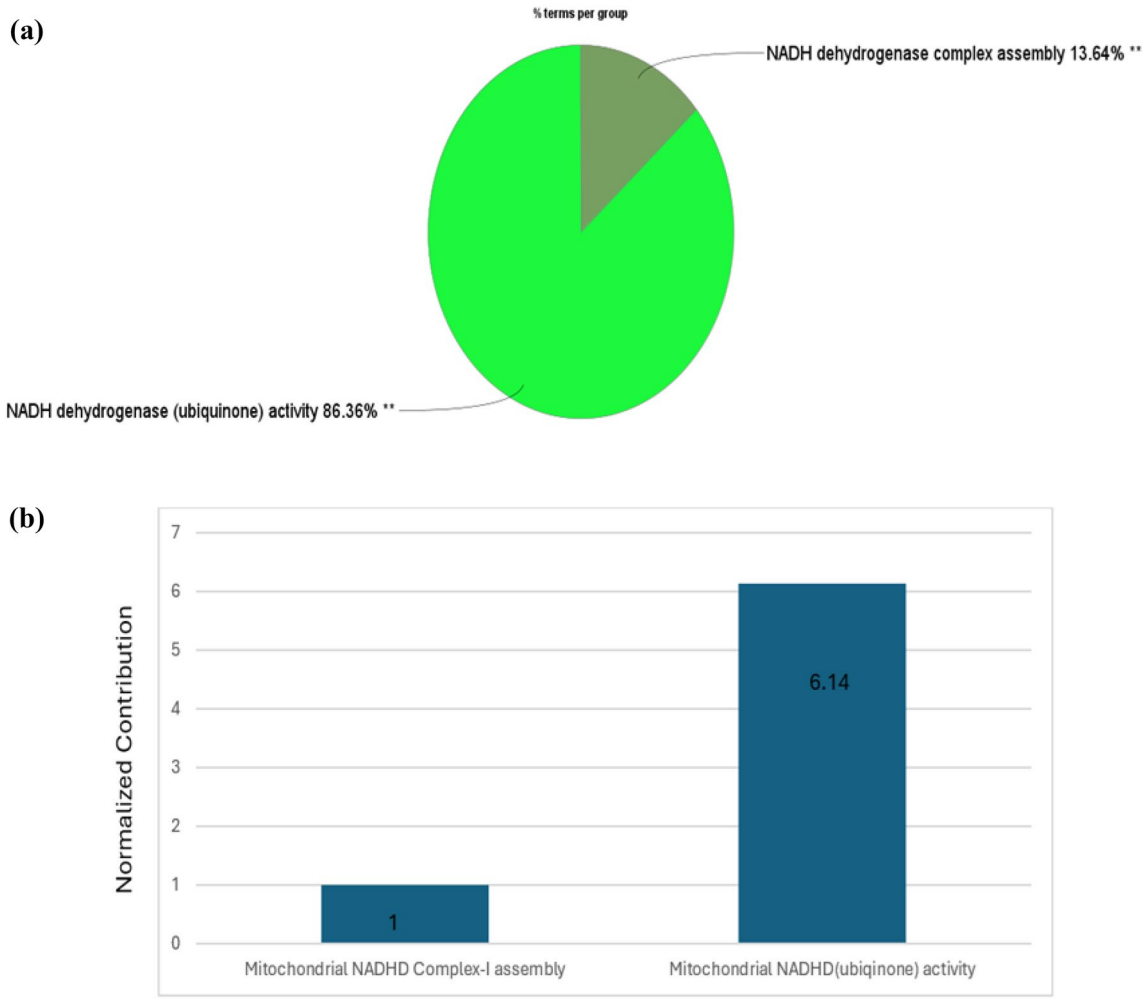

Fig. 5 **a** Pathway enrichment analysis of the 37 downregulated genes of the cerebellum. The vast majority genes are involved in the activity of NADH dehydrogenase (ubiquinone). Downregulation of these genes may induce neuroprotection by diminishing cellular oxidative stress (see text). **b** With respect to the neuroprotection contribution of the downregulated genes, the effect of the mitochondrial NADHD (ubiquinone) activity is about six times that of mitochondrial NADHD complex assembly

(i) *Cerebellum and hippocampus:* Three common genes as Complexin1 (CPLX1), Syndapin I (PACSINI), and Transmembrane protein 30 A (TMEM30A).
(ii) *Cerebellum and cingulate gyrus:* One common gene as CaM Kinase-Like Vesicle-Associated Protein (calmodulin-dependent protein kinase).
(iii) *Cerebellum and entorhinal cortex:* One common gene as Transgelin-3 (TAGLN3).

Interestingly, all the five genes are upregulated in the cerebellum, but downregulated in the corresponding cerebral regions (hippocampus, cingulate gyrus, and entorhinal cortex). Finally, the pathway enrichment analysis on these genes was performed (Fig. 8a). This illustration shows the functionality of the processes involved, such as synaptic vesicle cycle, synaptic vesicle regulation, ribbon synapse activity, Axonal terminal button, synaptic function, plasma membrane tabulation (cytoneme/axonal filopodium formation), ATPase transmembrane lipid transportation (e.g., ion channel transport). Indeed, the synaptotropic-synaprogenesis aspects account for the majority (~ 70%) of the biological processes in Fig. 8a. In other words, from the perspective of neuroprotection, these processes are involved in proper synaptic activity, and upregulation of these operations in the cerebellum contribute to its neuroprotective behavior, and these synaptotropic-synaptogenesis functions are considerably downregulated in the cerebral hemispheres (the highly affected regions of the hippocampus, cingulate gyrus, and entorhinal cortex). In contrast, we did not find significant biological process pertaining to neurogenesis as mapped in Fig. 8a. The considerable presence of synaptogenesis aspect in cerebellum, without presence of neurogenesis aspect was unexpected and paradoxical, as our findings indicate that cerebellar neuroprotection is highly contingent on

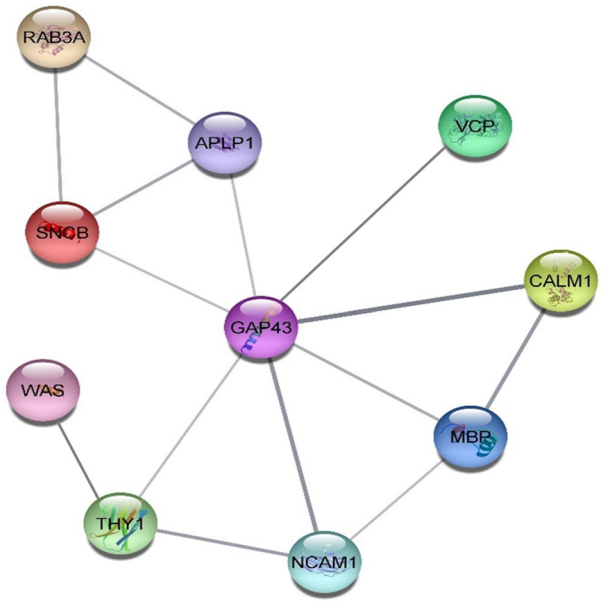

Fig. 6 Construction of the protein–protein interaction network of the top ten hub genes upregulated in the cerebellum. The links demarcate the protein–protein interaction (PPI) network of the top ten upregulated hub genes in the cerebellum. The network shows Growth Associated Protein 43 (GAP43) as a central hub, interacting with proteins involved in synaptic plasticity, neuronal signaling, and myelination. GAP43 is essential for axonal growth, regeneration, and synaptic remodeling. Key interactors include Synuclein beta (SNCB) and amyloid beta precursor-like protein 1 (APLP1), which regulate synaptic vesicle trafficking and neuronal adhesion. Calmodulin 1 (CALM1) serves a calcium sensor in neuronal signaling, while Myelin Basic Protein (MBP) is crucial for myelination. Neural cell adhesion molecule 1 (NCAM1) and Thy-1 Cell Surface Antigen (THY1) actuate the synaptic organization and neuroprotection, whereas valosin-containing protein (VCP) and Wiskott-Aldrich syndrome protein (WAS) regulate protein homeostasis and cytoskeletal remodeling. This interaction network highlights the role of these upregulated genes in maintaining the cerebellar function, enhancing synaptic connectivity, and promoting neuroprotection, potentially supporting adaptive plasticity and resilience in the aging cerebellum\

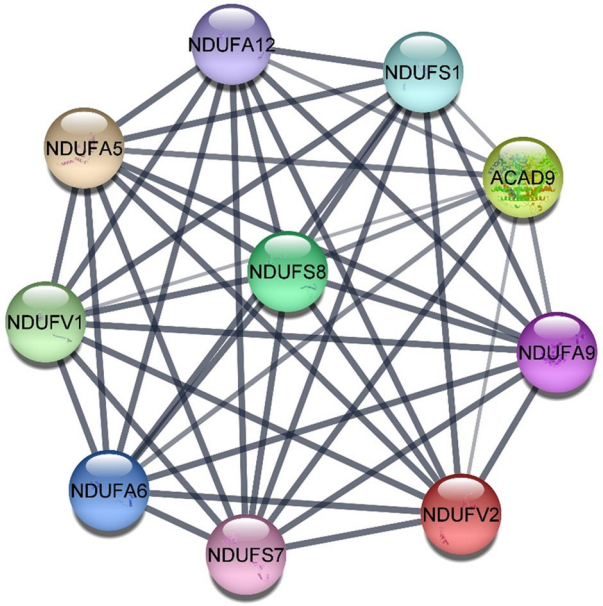

Fig. 7 Construction of the protein–protein interaction network of the top ten downregulated hub genes in the cerebellum. The network comprises key mitochondrial respiratory chain components, primarily NADH: ubiquinone oxidoreductase (complex I) subunits. Downregulation of these genes contributes to reduced reactive oxygen species (ROS) production, potentially minimizing oxidative stress and promoting neuronal survival and neurorestoration in the aging cerebellum

synaptogenesis process, but not on neurogenesis process, this is much counterintuitive to the present perspective of regenerative neurology, which posits that the neurogenesis process (So and Xu 2015) is the significant determinant of neurorestoration. Thus, our observations indicate that for neuroprotection therapeutics, one should give considerable emphasis to the development of synaptogenesis-oriented intervention, rather than the customary stress on neurogenesis-based inputs.

We observe from Fig. 8a that the readout or factor weight of synaptotropic processes—such as the sectors of synaptic vesicle cycling and its regulation, terminal synaptic button and ribbon synapse activities—total to 55.2%. On the other hand, from that diagram, we noted that the corresponding factor weight for the axonotopic/neurotropic activity and the other sectors total to 15.4%, such as plasma membrane tabulation/cytoneme axonal migration formation and ATPase-coupled intramembrane lipid transportation. We illustrate these two values in Fig. 8b, from which we find that that the significance of the synaptic processes (as synaptotropic/synaptogenesis behavior) is about four times that of non-synaptic neural processes (e.g., axonotropic/neurogenesis behavior).

Discussion

In the present study, we examined 120 differentially expressed cerebellar genes, whereby we found 83 upregulated and 37 downregulated genes. Then we performed the Gene Ontology analysis in which the functionally categorized network of enriched categories was created for the upregulated (83) and downregulated (37) genes. Further, we discovered the hub genes and their roles in CB during the progression of Alzheimer's disease. In addition, we were seeking to understand more about the behavior of the genes that were shared by CB, HIP, ENT, and CG. To

Table 1 Top ten upregulated hub genes identified in the cerebellum

Gene symbol	Swiss Port Id	Gene description	Function
APLP1	P20336	Amyloid beta precursor-like protein 1	Regulatory role in nuclear translocation of APP family
GAP43	P17677	Axonal membrane protein	Enhances neuronal growth and regeneration
NCAM1	P13591	Neural cell adhesion molecule-1	Mediates cell adhesion, guidance and differentiation during neuronal growth
THY1	P04216	Membrane glycoprotein	Cell communication and cell adhesion
SNCB	P51693	Synuclein beta	Protect neuronal cells
RAB3A	O00401C	Member RAS oncogene family	Enables GTPase activity and myosin V binding activity
VCP	P55072	Transitional endoplasmic reticulum	Provides instruction for making the enzyme valosin-containing protein
CALM1	P02686	Calmodulin 1	Regulates and modulates ion channel
WASP	P62158	Wiskott–Aldrich syndrome protein	Regulates actin dynamics for phagocytic cup formation
MBP	P02686	Myelin membrane encephalitogenic protein	Regulates myelination

Table 2 Top ten downregulated hub genes identified in the cerebellum

Gene Symbol	Swiss Prot Id	Gene description	Function
NDUFS8	P04216	NADH dehydrogenase Fe-S protein 8	All these genes encode the subunits of NADH dehydrogenase (ubiquinone) complex, which is located in the mitochondrial inner membrane and is the largest complex of the electron transport chain
NDUFA9	P13591	NADH dehydrogenase alpha subcomplex subunit 9	
NDUFV2	P55072	NADH dehydrogenase flavoprotein 2	
NDUFA12	Q16143	NADH dehydrogenase alpha subcomplex subunit 12	
NDUFV1	P51693	NADH dehydrogenase flavoprotein 1	
NDUFA5	P20336	NADH dehydrogenase alpha subcomplex subunit 5	
NDUFS7	O00401C	NADH dehydrogenase (ubiquinone) Fe-S	
ACAD9	P62158	Acyl-CoA dehydrogenase family member 9 [associates with NDUFAF1, an assembly factor of NADH dehydrogenase (ubiquinone)]	
NDUFS1	P02686	NADH dehydrogenase Fe-S protein 1	
NDUFA6	P17677	NADH dehydrogenase alpha subcomplex, 6	

do this, we identified five genes that the HIP, ENT, CG, and CB, all shared. These genes had contrasting effects in CB as compared to the areas that had been most adversely affected during the progression of Alzheimer's disease, i.e., HIP, ENT, and CG.

Upregulated genes provide neuroprotection to the cerebellum

We identified the top ten upregulated genes ranked by the maximal clique centrality (MCC) method in CytoHubba. The observations on our findings are delineated below, ordered as per the rankings (Table 1), from the first to the tenth ranged gene:

i. *APLP1:* The first gene that we demarcated was the gene that codes for amyloid beta precursor-like protein 1 (APLP1), which is involved in postsynaptic function and controls neurite outgrowth by binding to heparin and collagen found in the extracellular matrix (Schilling et al. 2017).
ii. *GAP43:* The second rank gene we identified was axonal membrane protein (GAP43, Neuromodulin), a protein associated with nerve growth, whereas the preservation or increase in GAP43 raises the possibility that surviving neurons may initiate axon growth by upregulating GAP43 to make up for the lost connections, the reduction in GAP43 immuno-reactivity certainly reflects a significant loss of neurons. (Chung et al. 2020).
iii. *NCAM: The third gene* encodes for neural cell adhesion molecule (NCAM). This gene plays important roles in synaptic plasticity, axonal/dendritic growth, and normal brain development. (Gnanapavan et al. 2013)

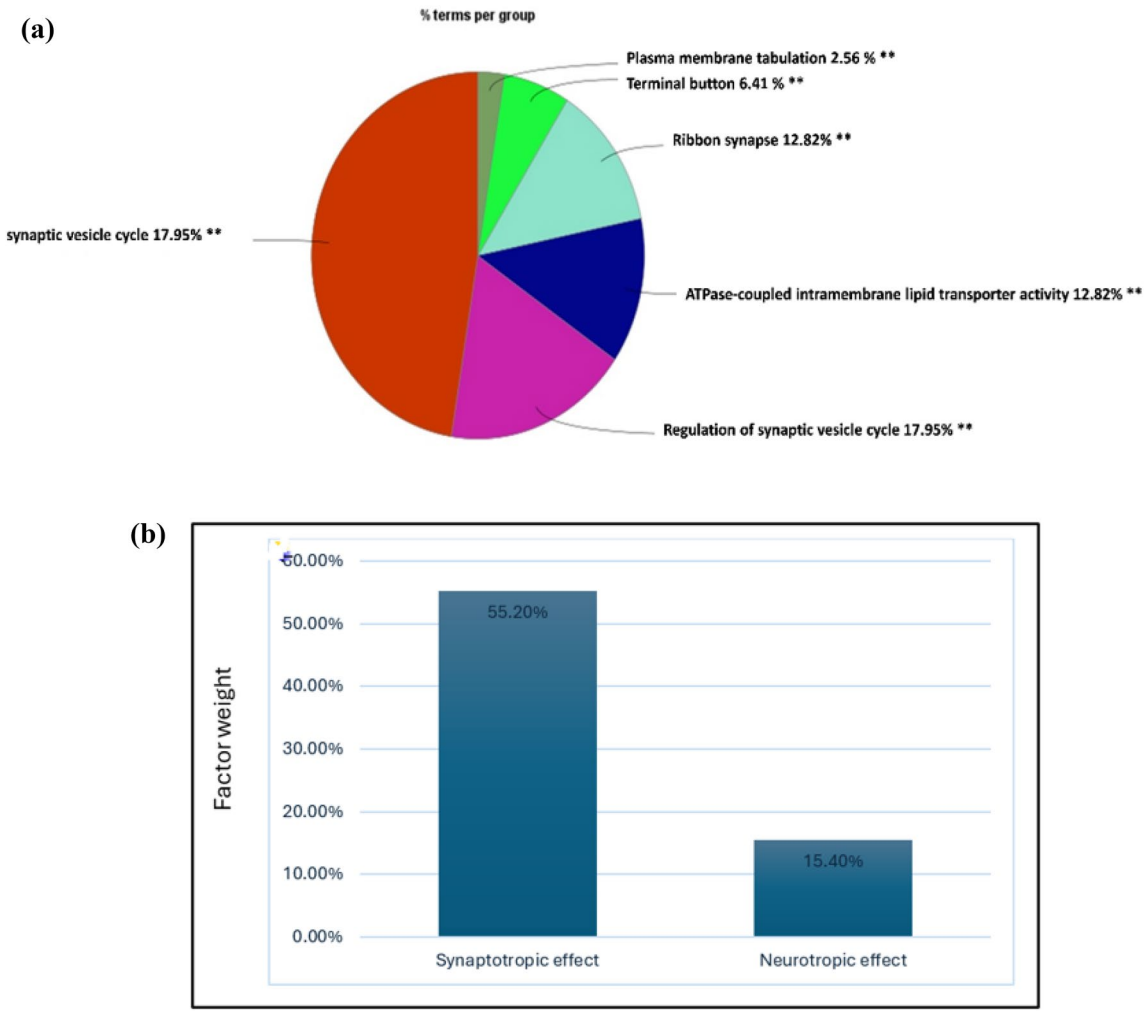

Fig. 8 **a** Pathway enrichment analysis of the five genes that were common in cerebellum and cerebri (highly affected regions). These genes were downregulated in cerebral hemisphere regions but upregulated in cerebellum and the genes are associated with synaptotropic and synaptogenesis-related processes as enumerated in the diagram. **b** The contribution of the synaptic processes (as synaptotropic/synaptogenesis behavior) is about four times that of non-synaptic neural processes (e.g., axonotropic/neurogenesis behavior)

iv. *THY1:* We identified the fourth gene, membrane glycoprotein (THY1), which is associated with nerve growth and plays a role in axonal and dendritic filopodia induction (Hu et al. 2022).
v. *SNCB: The fifth gene* which we identified is beta-synuclein which secures the neurons from the toxic effects of alpha-synuclein in neurological disorders (Hashimoto et al. 2004). A non-amyloid part of senile plaques linked to Alzheimer's disease is synuclein beta (SNCB). It controls SNCA aggregation, defends neurons from staurosporine and 6-hydroxy dopamine (6OHDA)-stimulated caspase activation, and helps restore SNCA's anti-apoptotic function that was destroyed as a result of 6OHDA (Sim et al. 2006).
vi. *RAB3A: The sixth gene* is a member of the RAS oncogene family (RAB3A). By regulating a late stage of synaptic vesicle fusion, it assists in exocytosis. It is known that regulating membrane flow at the nerve terminal may contribute to neurotransmitter release and in enhancing amyloid clearance (Krishna et al. 2020).
vii. *VCP:* This gene encoding valosin-containing protein (VCP) is involved in the creation of the transitional endoplasmic reticulum (Ralston and Albagha 2018).
viii. CALM1: This denotes calcium binding, calmodulin 1 (CALM1) mediates the regulation of numerous enzymes, ion channels, and other proteins. It also favorably controls neuronal ion channel activity, such as the calcium-activated potassium ion channel activity of KCNN2 (Barrera-Chimal and Jaisser 2020).

ix. *WASP: The ninth gene* we found out was Wiskott–Aldrich syndrome protein (WASP), which controls actin polymerization by enhancing the actin-nucleating activity of the Arp2/3 complex. Through its control of actin polymerization, WASP also controls mitosis and cytokinesis; also, it plays a role in dendrite spine morphogenesis (Marchand et al. 2001).
x. *MBP: The tenth ranked gene* which we identified is myelin membrane encephalitogenic protein (MBP); the conventional MBP isoform family (isoforms 4-isoform 14) is recognized to play a significant role in the remyelination of denuded axons, e.g. in multiple sclerosis (Suter and Martini 2005).

Thus, we find that upregulation of the genes would enhance neuronal function across all the numerous constituent cytological domains of the neuron, namely:

(a) Dendrite, synapse, axon, myelin
(b) Neural growth, neurotransmitter release, intracellular transport
(c) Protection against damaging effects of toxic protein entities
(d) Degradation of these neurotoxic entities

To paraphrase, our overall finding is that the aforementioned hub genes preserve the neurons in cerebellum, hence the upregulation of these genes in CB enhances the neurorestorative effect; therefore, the cerebellum remains protected even in the presence of Alzheimer's disease.

Genes involved in neurodegeneration are downregulated in cerebellum

All the ten hub genes which are downregulated in CB (Table 2) are a subunit of NADH dehydrogenase (ubiquinone) complex, situated in the mitochondrial inner membrane, which is the largest complex of the electron transport chain. Hyperexpression of these genes disrupt the mitochondrial electron transport chain, which generates a high level of reactive oxygen species (ROS), thereby inducing apoptosis, through the cleavage of specific caspase substrates in the cell, the permeabilization of the mitochondrial outer membrane and the release of cytochrome C (CytC) facilitate caspase activation and the generation of apoptosis, leading to neuronal death. These permeabilized mitochondria themselves are one of the first targets of activated caspases, which impairs electron transport and results in the loss of mitochondrial transmembrane potential, a diminution in ATP levels and increase of reactive oxygen species (ROS), with a loss of mitochondrial structural integrity (St-Jean et al. 2004). Actually, it is known that such a perspective may furnish pharmacological targets for decreasing oxidative stress as an interventional modality for Alzheimer's disease (Tripathi et al. 2024). Hence, downregulation of these genes will decrease the mitochondria-based cell damage, and thus enhance neuroprotection and neuronal survival in the cerebellum.

As an illustration, to elucidate further the downregulation process, we shall now give specifics of a couple of the downregulated genes, say *NDUFS1* and *ACAD9*. For instance, NDUFS1 is a 75 kDa respiratory complex I subunit, a crucial caspase substrate in the mitochondria (Sharma et al. 2009). It is known that impairment of mitochondrial function during apoptosis is mediated by caspase-induced cleavage of this 75 KDa entity NDUFS1 (Ricci et al. 2004). Thus, lower expression or diminution of NDUFS1 would decrease the apoptosis process. In other words, NDUFS1 downregulation would increase neuronal survival. Now, we consider the ACAD9 gene. It transpires that ACAD9 binds to NDUFAF1, an assembly factor of NADH dehydrogenase [ubiquinone] (Voet et al. 2016), and that a mutational underexpression or loss of function of ACAD9 can induce neurodegenerative pathology as leukodystrophy and encephalopathy (Robinson 1998). To sum up, we note that the downregulation of the genes in Table 2 enhances neuronal longevity and diminishes neuronal degradation in the cerebellum.

Complimentary symbiosis of upregulated and downregulated genes for cerebellar neuroprotection

One of our findings regarding the spectrum of the upregulated genes is that higher expression of these genes enables protective effects on the neuronal cell, across the diverse cytological domains of the neuronal cell somatic entity, as axon, dendrite, synapse, myelin, etc. On the hand, regarding the gamut of downregulated genes, we have arrived at an unexpected finding, namely that all the downregulated genes act only by a sole cytological domain, the mitochondrion. Furthermore, from a developmental perspective, it is known that the initial etiopathogenesis of neurodegenerative condition as Alzheimer's disease is mitochondrial damage, namely impaired mitophagy in the entorhinal cortex (Kobro-Flatmoen et al. 2021). Indeed, the focal significance of mitochondrial dysfunction in pathogenesis of Alzheimer's disease is now known (Rai et al. 2020). Thus, for considering neurorestoration, we need to consider that neuroprotective modulation occurs via two dual functional aspects of the neuron cell, namely (i) the mitochondrion entity (catabolic constituent of the cytometabolic flux), and (ii) neuron cell somatic entity (anabolic constituent of the cytometabolic flux) (Fig. 9). It may be mentioned that this duality of cell

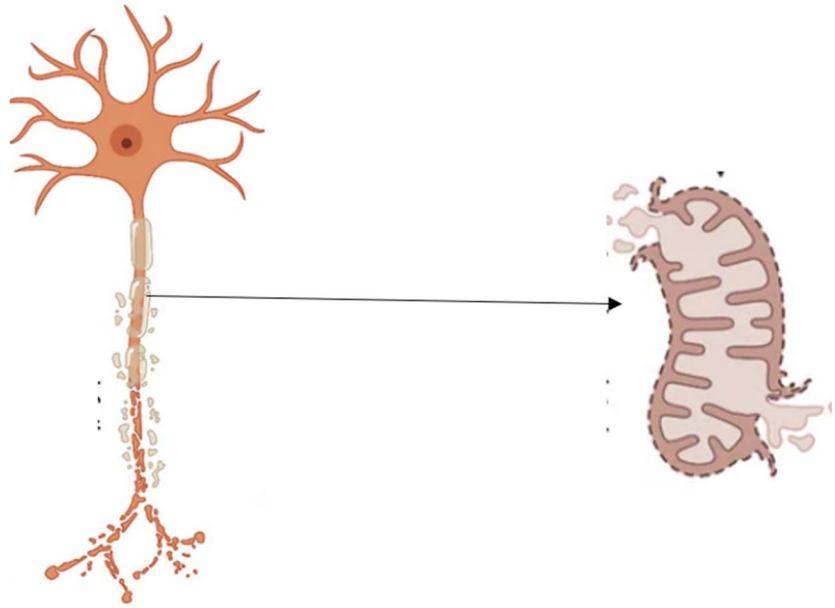

Fig. 9 The two complimentary symbiotic modes of neuroprotection: **a** upregulated genes enable maintenance of the neural cell somatic domain; these genes support synaptogenesis, neuronal plasticity, and axonal stability, essential for cerebellar function and resilience. **b** Downregulated genes enable the preservation of the mitochondria stability. This downregulation can play a role in minimizing excessive ROS (reactive oxygen species) production and in maintaining optimal energy utilization, which are crucial for sustaining neuronal health. Together, these two complimentary mechanisms may provide a neuroprotective advantage, thereby facilitating the cerebellum to maintain functionality despite advanced aging

soma and mitochondrion is well observed in developmental biological process, whereby it is known that both the cell soma and the mitochondrion act as autonomous cytological domains, each with its own distinct independent genetic and replication systems.

Indeed, cell physiological evidence has substantiated that these two individualistic domains (cell soma and mitochondrion) have been autonomous for long, indeed these two cytological domains in cells evolutionarily originated, respectively, from two separate constituent prokaryotes, an archaebacterium and a protobacterium, both of which fused with each other symbiotically by endosymbiosis, forming the eukaryotic cell with cell soma and mitochondrion (Latorre and Moya 2013). To summarize, we observe the significance of considering the functionality of both the mitochondrion and cell soma for cellular maintenance, and hence the importance of enabling neuroprotection by symbiotic protection of both the cell somatic dynamics and the mitochondrial dynamics. Enabling these two dynamics is what is precisely actuated, respectively, by our upregulated genes and downregulated genes.

Comparison study

Interestingly, the five genes that we identified as common in cerebellar and cerebral compartments had contrasting expressions in the two compartments (Fig. 8a). All the five genes were upregulated in the cerebellum (CB), but downregulated in the cerebrum [hippocampus (HIP), entorhinal cortex (EC), and cingulate gyrus (CG)]. To illustrate, the genes CPLX1 (Complexin1), PACSIN1 (Syndapin I) and TMEM30A (Transmembrane protein 30 A) were all upregulated in CB, but downregulated in HIP. To wit, CPLX1 (Complexin1) is a cytosolic protein that regulates synaptic vesicle exocytosis (Südhof and Rizo 2011), so this gene's downregulation may critically impair neural information transmission and thus lead to neuronal disruption; thus, HIP is well affected in Alzheimer's disease, while CB is spared. The other gene shared between CB and HIP, i.e., PACSIN1 has a crucial role in controlling microtubule dynamics and inducing axonal plasticity (Sakakibara et al. 2013); as this gene's activity is decreased in HIP, axons are not able to display plasticity or adaptation to the altered environment, but the gene activity is enhanced in CB where the plasticity and adaptation are, thus, maintained. Finally, the third gene

common between CB and HIP is TMEM30a. It may be mentioned that the neuronal senescence and cerebellar ataxia can be effects of TMEM30a hypofunctionality (Yang et al. 2018). Downregulation of these genes may be a key factor for the substantial neurodegenerative changes in the hippocampus; in contrast, these genes are upregulated in the CB, and act as neuroprotective entities.

Now we consider the other genes shared by CB with the other two cerebral regions, ENT and CG. Hence, we attend to the genes CAMKV and TAGLN3 which are downregulated, respectively, in the cingulate gyrus and entorhinal cortex, but both these genes are upregulated in CB. We may note that these genes support axonal/dendritic development and branching as well as synaptic plasticity maintenance (DeFelipe et al. 2010). Thus, cerebellar upregulation of these genes during neurodegenerative conditions may preserve the neural functionality in the cerebellum. Indeed, all the five genes are crucial in ensuring the neuron's normal electrical functioning, such as excitatory summation potential (Südhof and Rizo 2011). Thus, we observe that selective upregulation of these genes only in the cerebellum, in contrast to their downregulation in the cerebrum, does indicate that the cerebellum maintains neuroprotective behavior despite neurodegenerative insult.

We may utilize the findings of the above comparison study of this subsection to furnish additional substantiation in support of our main formulation that in cerebellum, there is upregulation of neurotropic/neuroprotective processes, coupled to downregulation of neurotoxic processes. This extra corroboration comes from the nested study within our main study in the paper. In the main study (Table 1), we compared the neuroprotective region (cerebellum) with a gamut of neurodegenerative regions, namely modestly affected neurodegenerative region (as motor cortex), medium affected neurodegenerative region (as sensory cortex), and highly affected neurodegenerative region (as hippocampus, entorhinal cortex, cingulate). In the nested study (Fig. 8), we took a comprehensive gradient, and compared the neuroprotective region (cerebellum) with the highly neurodegenerative region (as hippocampus, entorhinal cortex, cingulate). We found a close concurrence between our main study and our nested study. In our main study, the cerebellar neuroprotective processes were based on "Discussion":

(a) Positive regulation of dendritic, axonal and synaptic processes
(b) Neuroplasticity, ionic action potential and vesicle transport operations

Likewise, in our nested study analysis (Fig. 8), we also found that cerebellar neuroprotection was ensured by the same processes as in the earlier main study. It may be highlighted that nested investigations are often incisive collateral validation of the main investigation (Rick Turner 2013). Thus, we see that our nested study closely corresponds to the main study, thus providing collateral substantiation to our principal investigation.

Overall observations of the study

We now sum up our main observations regarding cerebellum's resilience and neuroprotection process as arrived at in this investigation:

(a) Upregulation of neural soma-based tropic process, as increasing of neuritic, dendritic, axonal, and myelinated growth ("Discussion" section, its first sub-heading)
(b) Downregulation of neural mitochondria-based neurotoxic processes, i.e., decreasing of NADH-activated mitochondrial ROS toxicity (Fig. 5).
(c) The hub driver gene of the upregulation process is GAP-43 which enables axonal migration and neuronal progression (Fig. 6).
(d) The hub driver gene of the downregulation process is NADH dehydrogenase-Fe-S8, whose downregulation facilitates the diminution of electron transport chain impairment, increasing the neural survival (Fig. 7).
(e) The downregulated proteins show that only a single entity (attenuation of mitochondrial oxidative stress) is responsible for all the pivotal downregulation dynamics, resulting in decreasing caspase-mediated apoptosis and enhancing the neural endurance (Fig. 5).
(f) Coupling of anabolic and catabolic processes increases the neuroprotection and decreases the neurotoxicity (see "Result" section).
(g) Synaptotropic factors are more efficient than neurotropic factors for neurorestoration, hence therapeutic strategies should be more focused on synaptogenesis than neurogenesis, which is in contrast to customary practice (this finding is of considerable relevance for clinical long-term translation) (Fig. 8b).

Targets for therapeutic intervention

In this study, we have identified the top upregulated and downregulated hub genes and their role in providing the neuroprotection in the CB. The associated pathways and targets may furnish therapeutic leads for putative pharmacological agents that can mimic the functions and expression of the hub genes, so that if the candidate drugs are probed for intervention, then the resultant drug molecules may also be utilized for possible neurorestoration protocols.

One may underscore that recently pharmacoinformatics and virtual screening procedures are being developed to identify novel candidate molecules with a focus to neuroprotection (Srivastava et al. 2019). Indeed, the cerebellum, across the long human life span, may enables its neuroprotection by our aforesaid pathways without inducing any toxicity nor any off-target effects on the individual. Our approach could be of considerable potentiality for clinical neuroscience, since conventional dementia intervention has often hazardous side effects, which may be bypassed by the approach delineated here.

Translational leads

From our earlier quantitative findings (Figs. 4b, 5b, 8b), we can possibly formulate a potential comprehensive clinical approach to pharmacologically enhanced neuroprotection. The aforesaid figures respectively highlight the following observations:

(i) Upregulation aspect: Among the numerous cells in the nervous system (e.g., astrocytes, oligodendrocytes, neurons, microglia, endothelial cells and meningeal cells), only one type of cell, namely the neuron, is the major focal factor for the neuroprotective effect (Fig. 4b).
(ii) Downregulation aspect: Among the plethora of attenuated entities found (Fig. 3b), the inhibition of only one factor (namely, antagonism of mitochondrial NADHD ubiquinone activity) provides the vast major contribution to neurorestoration (Fig. 5b.
(iii) From the neuron cell perspective [item (i) above], only the synaptotropic/synaptogenesis contribution (instead of the axonotropic/neurogenesis contribution) is the major extensive component of the neuron factor that needs to be considered (Fig. 8b).

Thus, we note that among the plethora of multifarious confounding neurological pharma agents available, two elementary and affordable approaches could be taken up for clinical translation, i.e., utilization of (1) a synaptotropic/synaptogenesis drug, whether candidate small molecules, or reprofiled agents; (2) hypomodulator of NADHD ubiquinone activity, both investigative drugs or repositioned pharmaceuticals being available.

Conclusion

Using integrative network biology analysis, we investigated the alteration of gene expression profile of cerebellum when contrasted with the cerebral regions, and probed the change in this profile alteration in two situations: healthy normal and neurodegenerative condition as Alzheimer's disease. Our investigation revealed that cerebellum has higher expression of synaptotropic genes (compared to cerebral regions), and the higher expression of these genes can protect the cerebellum during dementia or Alzheimer's disease. In this study, we also observed that neuroprotective genes are downregulated in other regions of the brain as cerebral hemispheres, thus actuating neurodegenerative transition in the latter brain regions. The relevant genes may furnish therapeutic leads from the pathways and targets that can have the incisive potentiality to induce neuroprotection and neurorestoration.

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Author contributions Conceptualization: BB, BK, AB, PR; methodology: BB, BK, AB; formal analysis and investigation: BB, BK, AB, PR; writing—original draft preparation: BB, PR; writing—review and editing: BB, BK, AB, PR; resources: PR, SS; supervision: PR, SS.

Data availability All the data are included in this manuscript. For further clarifications, please communicate with the corresponding author PKR at Dept. of Life Sciences, Shiv Nadar University, Dadri 201314, India.

Declarations

Conflict of interest The authors declare that there is no conflict of interest.

Research involving human participants and/or animals The work performed in the manuscript does not involve any human participants or animal preparations.

Informed consent Not applicable.

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