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REVIEW

Cognitive Impairment in Idiopathic Normal Pressure Hydrocephalus

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Abstract Idiopathic normal pressure hydrocephalus (iNPH) is a significant cause of the severe cognitive decline in the elderly population. There is no cure for iNPH, but cognitive symptoms can be partially alleviated through cerebrospinal fluid (CSF) diversion. In the early stages of iNPH, cognitive deficits occur primarily in the executive functions and working memory supported by frontostriatal circuits. As the disease progresses, cognition declines continuously and globally, leading to poor quality of life and daily functioning. In this review, we present recent advances in understanding the neurobiological mechanisms of cognitive impairment in iNPH, focusing on (1) abnormal CSF dynamics, (2) dysfunction of frontostriatal and entorhinal-hippocampal circuits and the default mode network, (3) abnormal neuromodulation, and (4) the presence of amyloid-β and tau pathologies.

Keywords Idiopathic normal pressure hydrocephalus · Cognitive impairment · Cerebrospinal fluid dynamics · Frontostriatal circuits · Entorhinal-hippocampal circuits · Neuromodulation · Amyloid-β pathology · Tau pathology

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Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a syndrome characterized by a clinical triad of progressive gait disturbance, cognitive impairment, and urinary incontinence in the context of relative ventricular enlargement and a normal cerebrospinal fluid (CSF) pressure (70–200 mm H_2O) [1–4]. There is no consensus on essential criteria for diagnosing iNPH. The most widely used diagnostic criteria are the Japanese guidelines [2, 5] and the American-European guidelines [3, 6].

iNPH often occurs in the elderly population [7]. In Japan, the prevalence in people >65 years old is ~2.9% following the Japanese guidelines [8, 9] and ~1.4% following the American-European guidelines [10]. In Northern Europe, the prevalence is 0.1%–3.7% in people >65 years following the American-European guidelines [11, 12]. In the United States, the prevalence is 0.2% in people >60 years following the International Classification of Diseases code (ICD-9-CM 331.5 and ICD-10-CM G91.2) [13]. The prevalence of iNPH increases markedly with age. The prevalence in people >80 years is 1.4%–3.8% following the Japanese guidelines [12, 14] and 0.1%–8.9% following the American-European guidelines [11, 12, 15]. Table 1 summarizes recent findings on the prevalence of iNPH. However, there is a lack of statistics from the Chinese population.

Inconsistent prevalence is a consequence of different diagnostic criteria, which may lead to misdiagnosis and underdiagnosis of iNPH. Different diagnostic criteria may also impact clinical practice (e.g., inappropriate treatment and management of patients) [12, 16] and basic research (e.g., inconsistent findings on cognitive impairment).

NPH is a significant cause of the severe cognitive decline in the elderly population, accounting for 1.0%–

Table 1 Recent findings on the prevalence of probable iNPH.

Country (year)	Sample size (*n*)	Age range (years)	Prevalence (%)	Reference
Following Japanese guidelines				
Japan (2008)	170	≥65	2.9	[9]
Japan (2009)	790	61 & 70–72	0.5	[17]
Japan (2014)	271	70	0.4	[14]
	211	80	1.4	
Japan (2016)	607	≥65	2.8	[8]
Japan (2017)	2012 population	≥60	0.03	[18]
Sweden (2019)	515	65–79	0.8	[12]
	158	≥80	3.8	
Following American-European guidelines				
Norway (2008)	34,775	≥65	0.1	[11]
	14,860	70–79	0.2	
	10,718	≥80	0.1	
Japan (2009)	497	≥65	1.4	[10]
Sweden (2014)	834	70–79	0.2	[15]
	404	≥80	5.9	
Sweden (2019)	515	65–79	2.1	[12]
	158	≥80	8.9	
Following International Classification of Diseases [a]				
United States (2021)	2008–2017 populations	≥60	0.2	[13]
Unknown diagnostic criteria				
San Marino (1989) [b]	369	≥65	0.5	[19]

[a]ICD-9-CM 331.5 and ICD-10-CM G91.2.

[b]This study was conducted before the publication of the first diagnostic guidelines.

6.0% of dementia [20]. About 80.0%–98.5% of patients with iNPH have a disturbance of cognition in different domains, including executive functions, working memory, memory, visuospatial functions, language, and attention [21–24]. In a sample of 64 patients with iNPH, Picascia *et al.* found that 42.2% exhibited a global cognitive decline, and only 17.2% showed deficits in a single cognitive domain [25]. Moreover, 23.4% of patients with iNPH show deficits in executive functions and working memory supported by frontostriatal circuits [25]. Cognitive impairment could be the initial symptom or even the only clinical manifestation in some cases [18]. In this review, we summarize recent advances in the neurobiology of cognitive impairment in iNPH.

Although there is no cure for iNPH, in many cases, most symptoms (including cognitive impairment) can be significantly alleviated through CSF diversion [1, 24, 26, 27]. Various CSF diversion strategies have been developed for treating iNPH, including a ventriculoperitoneal (VP), lumboperitoneal, ventriculoatrial, or ventriculopleural shunt, and endoscopic third ventriculostomy. There is no consensus on the best surgical therapy for treating iNPH. In the United States, the most common surgical procedure is the VP shunt (72.0%), among which 90.7% are open VP shunts, and 9.3% are laparoscopic VP shunts [13]. In Japan, the lumboperitoneal shunt is the first choice (55.1%), followed by the VP shunt (43.2%) [18]. Before surgery, a high-volume lumbar puncture (i.e., CSF tap test) is often used to identify patients suitable for shunting [28, 29]. The therapeutic effects of CSF diversion can last 2–5 years, especially for iNPH patients below 80 years [30–34]. However, an additional year of iNPH lowers the likelihood of response to CSF diversion by 13% [35].

Cognitive Impairment in iNPH

At the early stages of iNPH, cognitive deficits are primarily observed in executive functions and working memory supported by frontostriatal circuits. As the disease progresses, cognition declines continuously, and cognitive deficits occur in multiple domains, leading to daily-life difficulties and great financial burdens. Early shunting has the potential to improve cognition in patients with iNPH. Table 2 summarizes recent findings on cognitive domains and cognitive effects of CSF diversion.

Table 2 Cognitive domains, clinical assessments, and effects of CSF diversion in iNPH.

Cognitive domains	Clinical assessments	Compared to healthy adults	Effects of CSF diversion
Global cognition			
Global cognition	Mini-Mental State Examination (score)	Impaired [25, 36–41]	Improved [42, 43]
Executive Functions			
Inhibition	Stroop color-word test (error rate)	Impaired [39, 44, 45]	Improved (time) [46]
Shifting	Intra-dimensional/extra-dimensional test (score)	Impaired [42]	Not significant [42]
	Trail-making test – B (completion time)	Impaired [36, 38]	Improved [47, 48]
			Not significant [43, 49]
Updating	Digit span backward test (score)	Impaired [39, 44, 45]	Improved [43, 51]
		Not significant [50]	Not significant [49]
Working memory			
Visuospatial working memory	Corsi block-tapping test (score)	Impaired [25, 37, 52]	None
Verbal working memory	Symbol digit modalities test (score)	Impaired [50, 53]	Improved [38]
Long-term memory			
Memory and learning	Rey Auditory Verbal Learning Test – delay recall (score)	Impaired [25, 44, 52]	Improved [36, 46, 48, 54]
			Not significant [49]
	Rey Complex Figure Test – delay recall (score)	Impaired [39, 55]	Improved [48, 56]
		Not significant [54]	Not significant [47]
Visuospatial functions			
Simple figure discrimination	Visual discrimination of simple figures (score)	Not significant [37]	Not significant [37]
Complex figure discrimination	Rey Complex Figure Test (score)	Impaired [37, 39]	Improved [48, 56]
			Not significant [47, 48]
Language			
Naming	Boston Naming Test (score)	Not significant [37, 54]	Improved [43, 51]
			Not significant [57]
Verbal fluency	Phonemic fluency test (score)	Impaired [37, 44, 45, 50, 52]	Improved [43, 51, 58] [a]
			Not significant [49]
	Semantic fluency test (score)	Impaired [37, 50, 52]	Improved [59]
			Not significant [43, 49, 51, 60]
Attention			
Attention	Trail-making test – A (completion time)	Impaired [36, 37]	Improved [43, 49, 61]
		Not significant [47]	Not significant [62, 63]

[a]Ref. 58 includes both patients with iNPH and patients with secondary NPH.

Global cognitive decline

In iNPH, 48.6% of patients exhibit a global cognitive decline, with a mean Mini-Mental State Examination (MMSE) score of 16.6/30 (range, 6–23) [36]. The MMSE score of patients with iNPH is comparable with age- and education-matched patients with Alzheimer's disease (AD) but significantly lower than matched healthy adults [25, 37–41]. Patients with iNPH also perform worse than healthy adults in complex cognitive tasks that heavily rely on multiple cognitive domains (e.g., Raven's Colored Matrices) [25, 39, 52].

CSF diversion tends to benefit iNPH patients with more severe cognitive impairment but a shorter symptom duration. Iddon *et al.* found that iNPH patients with a baseline MMSE score <24 showed a significant score increase (15.4 on average) after VP shunting, but those with a baseline MMSE score >24 did not [42]. Solana *et al.* found a relationship between postoperative cognitive outcomes and preoperative cognitive status: a higher preoperative MMSE score was associated with

postoperative improvement in executive functions and memory; a lower preoperative MMSE score was associated with postoperative improvement in working memory and language [36].

Executive functions

Executive functions refer to a series of top-down cognitive processes needed for goal-directed behaviors, including inhibition of prepotent responses (inhibition), mental set shifting (shifting), and information updating and monitoring (updating). Inhibition and shifting abilities could be impaired even in the early stages of iNPH [64].

Inhibition is often assessed with a color-word Stroop test. Participants are asked to name the ink color of a word quickly and accurately regardless of the meaning of the word. When the word's color is incongruent with its meaning (e.g., GREEN written in red), participants have to suppress the prepotent tendency to name the word. Conversely, no inhibition is needed when the word's color is congruent with its meaning (e.g., RED written in red). It is consistently reported that patients with iNPH make more errors than healthy adults and patients with AD in the incongruent condition [39, 44, 45], even though patients with iNPH perform as well as healthy adults in the congruent condition [47]. Other assessments of inhibition have revealed similar results [45]. CSF diversion may have therapeutic effects on inhibition. For example, Hellström *et al.* reported that 82.0%–91.0% of patients with iNPH take a significantly shorter time to complete the Stroop test three months after VP shunting [46]. Similarly, Duinkerke *et al.* reported a one-standard-deviation decrease in the Stroop completion time in 60.0% of patients six months after VP shunting, even though there was no significant change at the group level due to inter-individual variability [47].

The shifting ability can be assessed using the intra-dimensional/extra-dimensional (ID/ED) test and trail-making test-B (TMT-B). In the ID/ED test, participants need to learn multiple rules and frequently shift between them. Iddon *et al.* found that patients with iNPH made more errors than healthy adults in the ID/ED test, even though the patients scored >24 in the MMSE [42]. Moreover, 83.3% of the patients failed to learn a new rule or ignored a previously learned rule [42]. However, the researchers did not find a therapeutic effect of VP shunting on the ID/ED test performance [42]. In the TMT-B, participants need to alternately connect a sequence of 25 numbers and letters (e.g., 1-A-2-B-3-C). Katzen *et al.* found that patients with iNPH took a longer time to complete the TMT-B than healthy adults [38]. Solana *et al.* reported that 99.3% of patients with iNPH showed a TMT-B completion time 1.5 standard deviations longer than that of healthy adults [36]. A prospective study by Engle *et al.* suggested that the TMT-B impairment may even occur before the presence of characteristic imaging features (e.g., ventricle enlargement and a small callosal angle) and clinical symptoms of iNPH (e.g., slowed gait) [64]. After CSF diversion, the TMT-B completion time was significantly shortened in some studies [47, 48] but not in others [43, 49].

The updating ability can be quantified with a digit span backward test, in which participants need to remember a sequence of random numbers and recall them in reverse order. Some studies reported a lower backward span in patients with iNPH than in healthy adults and patients with AD [39, 44, 45] but other studies did not [50]. CSF diversion has mixed effects on updating [43, 49, 51]. The meta-analysis by Peterson *et al.* suggested that the shunting-induced improvement in the digit span backward test is not robust [58].

Working memory

Working memory allows us to temporarily hold and actively manipulate information that no longer exists in the environment. Two types of working memory have been investigated in iNPH: visuospatial working memory (e.g., the Corsi block-tapping test) and verbal working memory (e.g., the symbol digit modalities test). Both visuospatial and verbal working memory seem to be impaired in iNPH.

In the Corsi block-tapping test, participants need to remember and recall nine spatial locations. It is consistently reported that patients with iNPH remember fewer spatial locations than healthy adults and patients with AD or Parkinson's disease (PD) [25, 37, 52]. In the symbol digit modalities test, participants need to remember nine pairs of numbers and abstract geometric figures. Patients with iNPH often score lower than healthy adults and patients with AD [50, 53]. Other assessments of verbal working memory have revealed similar results [25, 39, 45, 52].

Verbal working memory might be normalized after CSF diversion. For example, Katzen *et al.* found that, at six months after VP shunting, patients with iNPH performed significantly better than themselves at baseline and similarly to healthy adults [38]. However, contradictory results exist [43, 46, 49, 51]. For example, Hellström *et al.* reported no group-level improvement in the digit span forward test in patients with iNPH three months after VP shunting [46]. Only 26.0% of the patients showed an increased digit forward span [46]. The impact of CSF diversion on visuospatial working memory has not been systematically investigated.

Long-term memory

The ability to store words and figures and retrieve them from long-term memory can be assessed with the Rey Auditory Verbal Learning Test and Rey Complex Figure Test. Several studies consistently reported that after a 30-min delay, patients with iNPH recall fewer correct words and make more errors than healthy adults and patients with PD in the two tests [25, 39, 44, 52, 55] (but see [54] for a negative result). Other memory assessments have revealed similar results [39, 50, 52, 55]. In addition, iNPH patients whose initial symptoms are cognitive impairment tend to have worse long-term memory than those whose initial symptoms are slowed gait [36].

Several studies have shown the therapeutic effects of CSF diversion on long-term memory [43, 46, 48, 54] (but see [59] for a negative result). For example, Duinkerke *et al.* found that 50.0% of patients with iNPH show a one-standard-deviation score increase in the Rey Auditory Verbal Learning Test delayed recall, and 38.0% show a similar increase in the Rey Complex Figure Test delayed recall at 6–12 months after VP shunting [47].

Visuospatial functions

Visuospatial functions include discriminating visually simple (e.g., a single form) and complex figures (e.g., multiple figures with different colors and forms). iNPH may lead to impairment in discriminating complex but not simple figures. For example, Saito *et al.* systematically investigated visuospatial functions in patients with iNPH [37] and found that they made more errors than healthy adults and patients with AD when discriminating rotated and flipped graphics or complex figures with different colors and forms, but not when discriminating the length and size of a single form [37]. Similarly, other studies have reported that patients with iNPH make more errors than healthy adults when asked to replicate a Rey complex figure but not when asked to copy a simple cube [39, 53]. The impact of CSF diversion is more robust in visuospatial tests with complex visual figures [36, 43, 49].

Language

Basic language skills such as naming seem well preserved in patients with iNPH and do not change after CSF diversion [37, 54]. However, iNPH-related deficits are consistently reported when executive functions are required for completing language tests. For example, in phonemic fluency tests, patients with iNPH generate fewer correct and non-repetitive words than healthy adults and patients with AD or PD [37, 44, 45, 50, 52]. In semantic fluency tests, patients with iNPH perform worse than healthy adults but similarly to patients with AD or PD [37, 50, 52].

The meta-analysis by Peterson *et al.* suggested a significant and robust impact of CSF diversion on phonemic verbal fluency [58]. However, Peterson *et al.* did not separate patients with iNPH from those with secondary NPH. Unlike iNPH, secondary NPH is caused by injuries or diseases that interfere with CSF absorption and is associated with moderate elevation of CSF pressure. In general, there is little evidence that semantic or phonemic verbal fluency are significantly improved after CSF diversion [43, 50, 51].

Attention

Attention is the ability to selectively process relevant information and inhibit irrelevant information in the environment. Attention is often assessed with the trail-making test – A (TMT-A), in which participants are asked to quickly and accurately connect 25 numbers that are randomly distributed on a page. Saito *et al.* found that patients with iNPH take longer to complete the TMT-A than healthy adults and patients with AD [37]. Similarly, Solana *et al.* found that in a sample of 173 patients with iNPH, 97.1% showed a completion time 1.5 standard deviations longer than healthy adults [36]. However, contradictory findings exist. For example, Duinkerke *et al.* found no difference between patients with iNPH and healthy adults in the TMT-A completion time [47]. Attention can be significantly improved 6–12 months after CSF diversion [43, 49, 61], but not necessarily 3 months post-operation [62, 63].

Relationship between cognitive and movement impairment

Cognitive impairment in iNPH is often accompanied by movement impairment (e.g., gait disturbance). iNPH patients who take a longer time or more steps to walk 10 meters score lower in the Frontal Assessment Battery, verbal fluency, and serial subtraction tests [65]. However, global cognitive decline in iNPH cannot be simply attributed to movement impairment. Patients' performance in 10-meter walk tests (e.g., completion time, number of steps, and gait velocity) does not correlate with MMSE scores [39, 65]. It is unclear whether cognitive improvement is related to movement improvement after CSF diversion.

Neurobiology of cognitive impairment in iNPH

Cognitive impairment in iNPH has been linked to abnormal CSF dynamics, dysfunction of frontostriatal and entorhinal-hippocampal circuits, abnormal neuromodulation, and

the presence of amyloid-β (Aβ) and tau pathologies. However, the exact neurobiological mechanisms of cognitive impairment remain unclear.

Abnormal CSF dynamics

Abnormal CSF dynamics is the key pathogenesis of iNPH. In healthy brains, CSF is produced by the choroid plexus. It flows continuously in the ventricles, around the brain and spinal cord, to support the exchange of nutrition and metabolic waste. It is then reabsorbed by the bloodstream and completes its circulation. In iNPH, increased intracranial pressure may reflect an imbalance between CSF production and reabsorption. Moreover, the enlarged CSF space may reduce the CSF turnover rate and compromise the glymphatic (glial-lymphatic) system, which plays a role in clearing excessive brain fluids and metabolic waste (e.g., toxic Aβ) [66−68]. However, only a few studies have directly linked abnormal CSF dynamics with cognitive impairment in iNPH.

Intracranial pressure amplitude

Increased intracranial pressure has adverse effects on cognition, probably by reducing cerebral blood flow and oxygen metabolism or altering protein synthesis in neurons and glia [66]. Intracranial pressure signals have steady and pulsatile components. Mean intracranial pressure refers to the mean amplitude of steady components. Intracranial pressure amplitude refers to the amplitude difference between systolic and diastolic pressures. However, very few studies have directly investigated the relationship between intracranial pressure and cognition in iNPH.

It has been consistently reported that iNPH patients who respond to VP shunting have higher intracranial pressure amplitudes, but not a higher mean intracranial pressure, than patients who do not respond to shunt surgery [69, 70]. In particular, the shunt responders with higher intracranial pressure amplitudes have better cognitive outcomes than the non-responders with lower intracranial pressure amplitudes [71]. Moreover, iNPH patients who show frontal cortical Aβ pathology (with or without hyperphosphorylated tau) have higher intracranial pressure amplitudes than those with neither Aβ nor tau pathology [72].

Glymphatic circulation

Magnetic resonance imaging (MRI) studies using the CSF tracer gadobutrol have shown that patients with iNPH have delayed glymphatic clearance in the basal ganglia, hippocampus, and limbic system than controls in a time window of 24–48 h [73−75]. Consistently, a recent diffusion tensor imaging study measured the water diffusivity along the direction of parenchymal vessels of the deep white matter and found lower glymphatic system activity in patients with iNPH than healthy controls and patients not diagnosed with iNPH [76]. However, there is no direct evidence linking the glymphatic system and cognition in iNPH.

Dysfunction of neural circuits

Dysfunction of neural circuits and networks may also play a crucial role in cognitive impairment in iNPH. Previous studies have linked the global cognitive decline of iNPH with dysfunction of the frontostriatal and entorhinal-hippocampal circuits, and the shunting-induced reversal of cognitive symptoms with frontal and parietal functions.

Frontostriatal circuits

Executive dysfunction and working memory deficits in neurodegenerative diseases have been linked to dysfunction of the frontostriatal circuits [77−79]. Functioning of the frontostriatal circuits requires a perfect balance between the direct (excitatory) and indirect (inhibitory) pathways, both of which connect the frontal cortex with the striatum. In the direct pathway, the striatum inhibits the globus pallidus internus (GPi)/substantia nigra pars reticulata (SNr) and excites the thalamus, exciting the activity of cortical neurons. In the indirect pathway, the striatum inhibits the globus pallidus externa (GPe), which excites the GPi/SNr and inhibits the thalamus, suppressing the activity of cortical neurons. However, relationships between cognitive impairment and dysfunction of the frontostriatal circuits have not been systematically investigated. Previous studies addressed the issue indirectly, focusing on altered frontal neural oscillations and reduced striatal grey matter.

Prefrontal cortical alpha oscillations (8–13 Hz) are correlated with executive functions in iNPH. In patients with iNPH, Aoki *et al.* measured resting-state cortical oscillations in the scalp electroencephalogram (EEG) and assessed cognition with a comprehensive battery of neuropsychological tests [80]. In iNPH patients who responded to shunt surgery, the normalized power variance of medial frontal alpha oscillations decreased significantly after CSF tapping [80]. Conversely, in iNPH patients who did not respond to shunt surgery, the normalized power variance of right dorsolateral prefrontal alpha oscillations increased significantly after CSF tapping [80]. Across responders and non-responders, the change in the normalized alpha power variance over the right dorsolateral prefrontal cortex is associated with performance change in an executive control task that emphasizes the suppression of overlearned behavior [80].

Loss of striatal grey matter may correlate with cognitive functions in multiple domains in iNPH. In a recent MRI study, Peterson *et al.* measured the volume of subcortical grey matter and assessed global cognition, verbal fluency, and verbal learning and memory in patients with NPH (85.7% had iNPH) [59]. The grey matter volumes of the caudate nucleus, putamen, nucleus accumbens, and globus pallidus were significantly smaller in patients with NPH than in healthy adults [59]. NPH patients with a smaller caudate nucleus had worse global cognition, verbal fluency, and verbal memory, and those with a smaller nucleus accumbens had worse verbal memory [59]. However, the grey matter volumes of the caudate nucleus and nucleus accumbens did not change after CSF diversion, even though verbal fluency, verbal learning, and memory were significantly improved [59].

Entorhinal-hippocampal circuits

The entorhinal cortex projects to the hippocampus through two excitatory pathways: the trisynaptic and monosynaptic pathways [81, 82]. The trisynaptic pathway originates from stellate cells in the second layer of the entorhinal cortex and projects to the dentate gyrus, CA3, and CA1 of the hippocampus. This pathway is associated with the rapid acquisition of new memories for places and events in a novel environment [83]. The monosynaptic pathway originates from pyramidal cells in the third layer of the entorhinal cortex and projects to CA1. This pathway is associated with slow incremental spatial learning in a familiar environment [83].

Entorhinal and hippocampal atrophy are correlated with global cognitive decline. In a recent MRI study, Eide *et al.* found that patients with iNPH have a thinner entorhinal cortex than patients with CSF leaks (controls), in addition to a larger Evans' index (a classic radiological marker of iNPH) [74]. In patients with iNPH, a thinner entorhinal cortex and smaller hippocampus are associated with worse global cognition [74, 84]. However, it is unclear whether there is a relationship between entorhinal-hippocampal dysfunction and memory loss in iNPH.

Default mode network (DMN)

The DMN is a system of functionally-connected brain regions displayed in resting-state functional MRI. It comprises the medial prefrontal cortex, posterior cingulate cortex, and precuneus. The DMN is often activated when a person does not focus on the outside world (e.g., day-dreaming) and is deactivated when a person concentrates on cognitively demanding tasks.

Recent resting-state functional MRI studies have linked altered DMN connectivity with cognitive deficits in iNPH. Functional connectivity within the DMN is weaker in patients with iNPH than in healthy adults [85, 86]. In particular, reduced functional connectivity of the precuneus and whole DMN is associated with executive dysfunction and poor verbal memory [85, 86]. Compared to patients with preserved DMN connectivity, iNPH patients with reduced DMN connectivity show worse verbal memory at baseline and slight improvement after VP shunting [86]. Moreover, temporal dynamic interactions between the DMN and other resting-state networks are also abnormal in patients with iNPH. The co-activation pattern between the DMN and the dorsal attention, ventral attention, and salience networks is weaker [50]. In contrast, the co-activation pattern between the DMN and the executive control network is more robust in patients with iNPH than healthy adults [50].

Parietal cortex

Very few studies have investigated the role of parietal dysfunction in iNPH-related cognitive impairment. In a recent positron emission tomography (PET) study, Chiaravalloti *et al.* reported that glucose consumption in the left parietal and frontal lobes increases significantly in patients with iNPH after VP shunting [87]. The glucose consumption increase in the left parietal lobe is associated with improved global cognition and frontal executive functions [87].

White matter integrity

White matter tracts mediate the transfer of information within and between distributed neural networks. Hydrocephalus in the ventricle may damage periventricular white matter tracts and potentially cause cognitive deficits in iNPH.

The structural integrity of the bilateral periventricular white matter is reduced in iNPH. Using diffusional kurtosis imaging, Kamiya *et al.* found decreased fractional anisotropy in the corpus callosum and frontoparietal subcortical white matter and decreased mean kurtosis in the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior and superior corona radiata, and frontoparietal subcortical white matter in patients with iNPH [88]. Moreover, reduced fractional anisotropy and mean kurtosis in the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, anterior and superior corona radiata, and frontoparietal subcortic white matter tracts was associated with global cognitive decline and executive dysfunction in iNPH [88]. Consistent with this, Mataró *et al.* also found a smaller corpus callosum in patients with iNPH [43]. However, a postoperative size increase in the corpus

callosum was not accompanied by significant cognitive improvement [43].

Abnormal neuromodulation

In PD and other neurodegenerative diseases, cognitive deficits have been linked with dopaminergic, noradrenergic, and cholinergic abnormalities in the central nervous system. However, in iNPH, direct evidence for the neuromodulation of cognition is limited.

Striatal dopamine may play a role in cognition in iNPH. In an early PET study, Ouchi *et al.* found a significant reduction in the postsynaptic D2 receptor binding but not in the presynaptic dopamine transporter binding in the dorsal and ventral striatum of patients with iNPH [89]. Nakayama and colleagues further investigated the effect of VP shunting on the striatal D2 receptor binding [90], and found a significant shunting-induced increase in the postsynaptic D2 receptor binding in the bilateral nucleus accumbens, bilateral dorsal putamen, and left ventral putamen [90]. In particular, the left nucleus accumbens increase was associated with improvement in emotion recognition, and the total striatal increase was associated with improvement in global cognition [90].

In kaolin-induced hydrocephalic rats, Egawa *et al.* found a relationship between hippocampal acetylcholine and noradrenaline and spatial memory deficits [91]. In particular, the cholinergic content in the dorsal and ventral hippocampus was significantly reduced in hydrocephalic rats that could not solve a standard spatial memory maze test [91]. In addition, the noradrenergic content in the ventral hippocampus was reduced considerably in hydrocephalic rats that could not solve a spatial memory maze test with delayed response [91]. Using the short-latency afferent inhibition (SAI) of transcranial magnetic stimulation, Nardone *et al.* examined the functioning of cholinergic pathways in the motor cortex of human patients [92]. The SAI index was significantly lower in patients with iNPH than in healthy adults [92]. In iNPH, the SAI index correlated with global cognition, executive functions, working memory, and verbal learning and memory [92].

Presence of Aβ and tau pathologies

Cerebral Aβ and tau pathologies are often seen in iNPH [93]. However, the role of toxic Aβ and tau protein accumulation in iNPH is still inconclusive. The presence of these pathologies might suggest the comorbidity of neurodegeneration (e.g., AD). However, several studies have shown that iNPH patients with moderate to severe densities of Aβ plaques and neurofibrillary tangles have more severe cognitive impairment and less cognitive improvement than those with no pathology [94–96], suggesting that Aβ and tau pathologies contribute to the cognitive impairment in iNPH.

Aβ is a series of protein peptides formed in the proteolytic processing of amyloid precursor protein by β- and γ-secretases. In the healthy brain, Aβ proteins are typically broken down and eliminated. In neurodegenerative diseases; however, Aβ proteins aggregate into insoluble Aβ plaques that are neurotoxic. Tau proteins are a family of neuronal proteins involved in the stabilization of microtubule formation and maintenance. Tau pathology is characterized by the abnormal accumulation of hyperphosphorylated tau proteins into neurofibrillary tangles.

Early autopsy studies showed the co-occurrence of cognitive impairment, Aβ pathology, and vascular lesions in iNPH [93]. Leinonen *et al.* followed up seven iNPH patients with cognitive impairment until death and conducted a comprehensive neuropathological examination. All patients showed Aβ pathology. In addition, four patients showed infarctions in the hippocampus and occipital cortex. However, the researchers did not find a relationship between neuropathological or vascular lesion measures and cognitive measures in the patients.

The severity of cerebral Aβ and tau pathologies can be measured *in vivo* using PET with specific radiolabeled compounds. In a PET study, Hiraoka *et al.* found that half of the patients with iNPH showed an amyloid deposition level as high as patients with AD, while the other half showed an amyloid deposition level similar to healthy adults [97]. However, the two subgroups did not differ in global cognition or executive functions [97].

Alternatively, the severity of cerebral Aβ and tau pathologies can be monitored with CSF biomarkers. In an earlier study, Arai and colleagues investigated the CSF levels of phosphorylated tau proteins in patients with iNPH [98]. They found that, after lumboperitoneal shunting, global cognition was improved early and maintained after three years in iNPH patients with low phosphorylated tau levels [98]. In contrast, in the patients with high phosphorylated tau levels, global cognition did not improve after CSF diversion and declined further in the following three years [98]. In a recent study, Arai and colleagues further investigated the CSF levels of toxic Aβ oligomers in patients with iNPH, AD, PD, or progressive supranuclear palsy [99]. They found that patients with iNPH showed a CSF Aβ oligomer level similar to that of patients with AD and higher than those of patients with PD or progressive supranuclear palsy and healthy adults [99]. At the group level, the CSF Aβ oligomer level significantly decreased one year after lumboperitoneal shunting [99]. But individual patients varied in their responses to the shunt surgery. iNPH patients with an Aβ oligomer decrease showed better cognitive outcomes: they had better executive functions one year after the shunt surgery and better preserved global

cognition three years after the surgery, as compared to the patients with an Aβ oligomer increase [99].

Cerebral Aβ and tau pathologies may interact. For example, Arai and colleagues reported that iNPH patients who received better cognitive outcomes two years after lumboperitoneal shunting had lower $A\beta_{1\text{-}38}/A\beta_{1\text{-}42}$ ratios and lower phosphorylated tau levels at baseline [100]. In addition, the $A\beta_{1\text{-}38}/A\beta_{1\text{-}42}$ ratio of iNPH patients with improved cognition increased during recovery, which may reflect enhanced synthesis of $A\beta_{1\text{-}38}$ (a negative regulator of $A\beta_{1\text{-}42}$) [100–102]. In another study, the same research team measured the CSF levels of phosphorylated tau and $A\beta_{1\text{-}42}$ toxic conformers in patients with iNPH [103]. They separated the patients with low phosphorylated tau levels from those with high phosphorylated tau levels. One year after CSF diversion, the low phosphorylated tau group showed better cognitive outcomes than the high phosphorylated tau group [103]. They then divided the low phosphorylated tau group into two subgroups according to individual patients' preoperative CSF $A\beta_{1\text{-}42}$ toxic conformer ratios (i.e., the concentration of $A\beta_{42}$ toxic conformer divided by the total concentration of $A\beta_{42}$). Like Kawamura *et al.* [99], Arai and colleagues found that iNPH patients with decreased $A\beta_{1\text{-}42}$ toxic conformer ratios received better cognitive outcomes than those with increased $A\beta_{1\text{-}42}$ toxic conformer ratios [103].

Conclusions

iNPH is a significant cause of the severe cognitive decline in the elderly population. At the early stages of iNPH, cognitive deficits occur primarily in executive functions and working memory supported by frontostriatal circuits. As the disease progresses, cognition declines continuously and globally, leading to poor quality of life and daily functioning. iNPH-related cognitive impairment has been linked with abnormal CSF dynamics, dysfunction of frontostriatal and entorhinal-hippocampal circuits, abnormal neuromodulation, and the presence of Aβ and tau pathologies. However, the exact neurobiology is still unclear. Further studies are needed to better understand the neural and neuropathological mechanisms underlying the development and progression of cognitive impairments in iNPH.

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