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Functional implications of age-related atrophy of the corpus callosum

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ABSTRACT

The corpus callosum plays a critical role in inter-hemispheric communication by coordinating the transfer of sensory, motor, cognitive, and emotional information between the two hemispheres. However, as part of the normal aging process, the corpus callosum undergoes significant structural changes, including reductions in both its size and microstructural integrity. These age-related alterations can profoundly impact the brain's ability to coordinate functions across hemispheres, leading to a decline in various aspects of sensory processing, motor coordination, cognitive functioning, and emotional regulation. This review aims to synthesize current research on age-related changes in the corpus callosum, examining the regional differences in atrophy, its underlying causes, and its functional implications. By exploring these aspects, we seek to emphasize the clinical significance of corpus callosum degeneration and its impact on the quality of life in older adults, as well as the potential for early detection and targeted interventions to preserve brain health during aging. Finally, the review calls for further research into the mechanisms underlying corpus callosum atrophy and its broader implications for aging.

1. Introduction

In recent decades, the number of individuals living to an advanced age has surged significantly, and this trend is expected to persist in the coming years. As reported by the United Nations (2022), the proportion of people aged 65 and older is growing at a faster pace than the younger population. The global percentage of those aged 65 and above is projected to increase from 10 % in 2022–16 % by 2050. The rapid expansion of the aging population presents significant societal challenges, particularly in ensuring that older adults remain self-sufficient and continue to function in a world where technological advancements predominantly cater to younger generations. This task is especially daunting, as healthy aging is often accompanied by a gradual decline in various cognitive domains. This decline in cognitive function is generally linked to the reduction in both gray and white matter volume, especially in the brain's anterior regions (Murman, 2015). A study by Ziegler et al. (2010) even suggests that age-related cognitive decline may be more strongly associated with a decrease in white matter volume than gray matter. This implies that the axons responsible for transmitting information between neurons (i.e., the white matter) might be a primary contributor to cognitive decline, rather than the neuron nucleus itself. As the brain's largest white matter structure, and a critical component for inter-hemispheric communication, the corpus callosum (CC) is not immune to degeneration.

This review paper explores age-related changes in the CC, emphasizing its importance in brain aging. We begin by outlining the structure and function of the CC and its role in inter-hemispheric communication. Next, we discuss the structural changes the CC undergoes during normal aging and the implications these changes have on various levels of brain processing, from the inter-hemispheric transfer of information to more complex cognitive tasks. The paper then examines the clinical significance of age-related CC atrophy, its impact on the quality of life in older adults, and the potential for early detection and targeted interventions to preserve brain health during aging. Finally, we identify key questions and areas where future research is needed to enhance our understanding of the mechanisms driving CC atrophy and its broader implications for aging.

2. Corpus callosum

2.1. Structure

The CC is the largest inter-hemispheric commissure, and largest white matter structure in the human brain, consisting of approximately 200 million myelinated nerve fibers (Aboitiz et al., 1992; van der Knapp & van der Ham, 2011). It spans the midline of the brain, forming a bridge that links the left and right hemispheres. The CC interconnecting fibers mainly project to homotopic cortical areas (e.g., frontal lobe to

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frontal lobe, etc.), enabling the two hemispheres to communicate and coordinate their functions (Banich, 1995; Bloom and Hynd, 2005). Some fibers also project to heterotopic regions (e.g., occipital lobe to parietal lobe, etc.) (Rakic and Yakovlev, 1968). This large structure is typically subdivided into five distinct subregions (Fig. 1), though there are no defined anatomical borders between areas (Goldstein et al., 2023). The most anterior part of the CC is called the Rostrum. It is a thin, curved structure, that is located beneath the frontal lobes. Located just behind the Rostrum, the Genu is a bend in the CC that arches anteriorly. The Body (or Trunk) is the longest section and central part of the CC. The Splenium is the posterior end of the CC and is thicker than the other regions. Finally, the Isthmus is a smaller, narrow segment located between the Body and the Splenium. Axons in the anterior region of the corpus callosum link the frontal cortices, whereas axons in the posterior corpus callosum connect the parietal, temporal, and occipital cortices (Schmahmann and Pandya, 2006). Those CC regions also differ in fiber composition with smaller, thinner and lightly myelinated axons present in the anterior part of the CC, such as the rostrum, genu and anterior body, and thicker and stronger myelinated axons in the posterior body, isthmus and splenium (Aboitiz et al., 1992).

2.2. Function

The primary function of the CC is to enable communication between the left and right cerebral hemispheres. Early research involving patients who have undergone surgery to sever the callosal fibers to control seizures due to intractable epilepsy has evidenced the role of the CC in inter-hemispheric communication. Surgical severing of the CC, known as a corpus callosotomy, can lead to split-brain syndrome, where the two hemispheres can no longer communicate effectively (Bloom and Hynd, 2005; Sperry, 1982; Van Wagenen and Herren, 1940). Patients with split-brain syndrome may exhibit unusual behaviors, associated with deficits of inter-hemispheric communication (Fabri et al., 2001; Yamauchi et al., 1997). For example, Gazzaniga (1967) demonstrated split-brain patients were unable to name stimuli presented to their left visual field (processed in the right hemisphere) as information could not be successfully transferred to the language dominant left hemisphere via

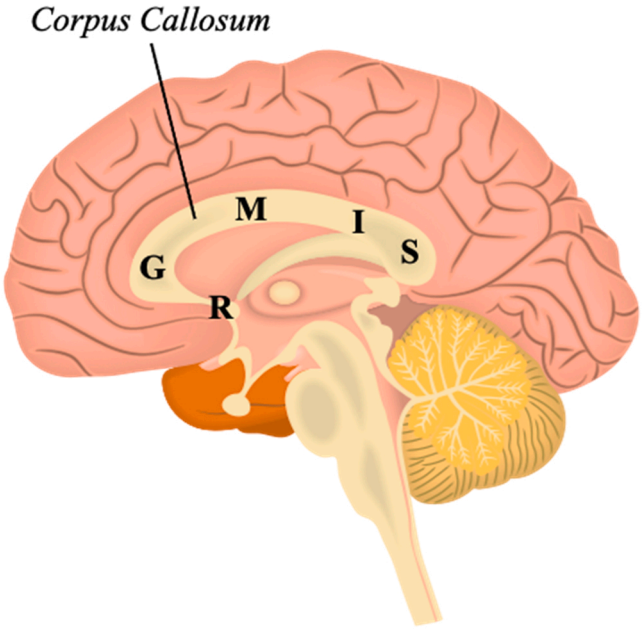

Fig. 1. Illustration of the mid-sagittal plane of the brain indicating the anatomical subdivisions of the CC: **R** = Rostrum, **G** = Genu, **M** = Midbody, **I** = Isthmus, **S** = Splenium. Adapted from TogoTV (© 2016 DBCLS TogoTV, CC-BY-4.0 https://creativecommons.org/licenses/by/4.0/).

callosal tracts.

However, the CC does much more than simply transfer information between hemispheres. It also plays a crucial role in both coordinating and segregating functions of the two hemispheres, helping them work in tandem without interfering with each other. This modulation supports hemispheric specialization, allowing each hemisphere to focus on its specialized tasks (e.g., language in the left hemisphere, spatial processing in the right) while also allowing for integrated functions when necessary. Studies show that this balance between cooperation and competition between hemispheres depends on the CC's ability to regulate excitatory and inhibitory signals (Banich, 2003; Innocenti et al., 2022; van der Knaap and van der Ham, 2011). Inhibitory and excitatory activities of callosal fibers describe two types of neural signaling. Excitatory callosal fibers transmit signals that increase neuronal firing in the opposite hemisphere. These excitatory actions are mediated through glutamatergic (glutamate-releasing) neurons, which are common in long-range cortical projections, including those in the CC. When an excitatory signal reaches its target in the opposite hemisphere, it induces action potentials, leading to synchronized activity between similar cortical areas. Excitatory callosal activity allows for inter-hemispheric transfer and communication. Inhibitory callosal fibers, in contrast, work by suppressing neural activity in target regions in the opposite hemisphere. This inhibition is typically mediated by GABAergic (GABA-releasing) interneurons, which either directly or indirectly reduce neuronal activity. Inhibition through callosal fibers helps the brain prevent competing signals from different hemispheres.

The balance of excitatory and inhibitory effects in these fibers significantly influences sensory and motor processing. Excitatory signals from callosal fibers enhance sensory integration by synchronizing activity between the two hemispheres. For example, the CC helps integrate visual information from both hemispheres, which is crucial for depth perception and a unified visual field (Schulte and Müller-Oehring, 2010). The CC also facilitates the integration of auditory information from both ears, which is important for understanding complex auditory environments (Hausmann et al., 2005). Similarly, sensory information related to touch, pressure, pain, and temperature is shared across hemispheres, aiding in coordinated motor responses and spatial awareness (Musiek, 1986). This is particularly important for tasks that require bilateral coordination and precise coordinated movements such as walking, typing or playing a musical instrument, where sensory information about balance and proprioception must be synchronized between both sides of the body (Takeuchi et al., 2012; Wahl and Ziemann, 2008). Inhibitory signals from callosal fibers, on the other hand, reduce conflicting or redundant sensory inputs across hemispheres, allowing each hemisphere to focus on unique sensory information. This is crucial in tasks requiring precision, like tactile discrimination and auditory localization, where inhibition refines sensory signals (Bloom and Hynd, 2005). By suppressing excessive excitatory activity, callosal inhibition prevents sensory overload, facilitating smooth, controlled perception in environments with multiple stimuli (Carson, 2020). In motor tasks, callosal inhibition helps one hemisphere suppress motor cortex activity in the opposite hemisphere, thus preventing competing movements and allowing precise unilateral movements. This transcallosal inhibition is essential for activities like reaching or grasping, where only one hand or limb should be active (Meyer et al., 1998).

The excitatory and inhibitory activities of callosal fibers are also fundamental in shaping cognitive processing. For instance, CC thickness has been shown to be associated with increased processing speed (Penke et al., 2010), problem solving abilities (van Eimeren et al., 2008) and even intelligence (Hutchinson et al., 2009). Excitatory callosal activity allows the integration of sensory inputs and cognitive processing across hemispheres. This integration is vital for tasks that involve spatial reasoning, memory, language, and problem-solving, as these functions often require the combined efforts of both hemispheres. Inhibitory callosal activity is essential for efficient cognitive processing by reducing inter-hemispheric interference and enhancing hemispheric

specialization for tasks like language and visuospatial reasoning (Clarke and Zaidel, 1994).

Finally, the excitatory and inhibitory activities of callosal fibers may play a role in emotional regulation by balancing inter-hemispheric communication, modulating affective responses, and enabling specific emotional processing. It has been suggested that the CC is not essential to understand and process basic emotions, however it is necessary to support the processing of more complex emotions, particularly in the context of social interactions (Anderson et al., 2017). Studies have evidenced an association between reduced callosal integrity and alexithymia - the inability to recognize or describe one's own emotions (Seyedmirzaei et al., 2022). Evidence from split-brain patients also suggests a role of the CC in interpreting and communicating emotions (TenHouten et al., 1985a, 1985b). Callosal excitation may support emotional regulation by facilitating communication between bilateral areas involved in emotional regulation, such as the prefrontal cortex and the limbic system. Callosal inhibition may also affect emotional regulation by maintaining a balance between hemispheric emotional responses, especially in processing affective states like anger and fear. Schutter and Harmon-Jones (2013), for instance, found that callosal fibers play a role in modulating aggression and anger responses by inhibiting emotional overactivation across hemispheres. However, findings are currently inconsistent (van der Velde et al., 2014) with further study required to substantiate conclusions linking CC integrity to emotional experiences.

In conclusion, the CC contributes to brain function far beyond simple inter-hemispheric information transfer. It plays a multifaceted role in coordinating hemispheric specialization, sensory and motor integration, and possibly emotional regulation. Its role is essential for ensuring balanced brain activity, preventing inter-hemispheric conflict, and supporting complex cognitive processes.

3. Age-related changes in the corpus callosum

Aging is known to induce structural changes in the brain, including the CC. Both post-mortem and neuroimaging studies have consistently shown age-related atrophy of the CC (e.g., Danielsen et al., 2020; Davis et al., 2009; Delvenne et al., 2021; Fling et al., 2011a; Hou and Pakkenberg, 2012; McLaughlin et al., 2007; Michielse et al., 2010; Ota et al., 2006; Salat et al., 2005; Sullivan et al., 2010). Atrophy refers to the progressive loss or degeneration of tissue, which affects the structure and integrity of the CC at both, macrostructural (volume and shape) and microstructural (cellular integrity) levels.

3.1. Macrostructural and microstructural changes

Macrostructural atrophy in the CC appears as a reduction in its volume and thickness during normal aging, and this shrinkage is typically detectable with imaging methods like MRI (e.g., Danielsen et al., 2020; Fling et al., 2011a). Although the entire brain experiences age-related reductions in size, the CC shows a disproportionately high rate of shrinkage compared to other brain regions (Danielsen et al., 2020), making it one of the structures most impacted by normal aging. In contrast, microstructural atrophy involves alterations in the cellular composition and integrity of CC tissue. These microstructural changes can be assessed using MRI-based diffusion techniques, such as diffusion tensor imaging (DTI). Over the last three decades, DTI has become a cornerstone in neuroscientific studies (Assaf and Pasternak, 2008). DTI visualizes and measures the diffusion of water molecules in the brain's white matter, offering unique insights into the microstructural integrity and organization of white matter tracts (Basser and Pierpaoli, 2011; Beaulieu and Allen, 1994; Le Bihan et al., 2001). Various parameters can be extracted from DTI to assess the CC (Tournier et al., 2011), with Fractional Anisotropy (FA) being the most used. FA indicates the degree of anisotropy in water diffusion; high FA values indicate highly directional (anisotropic) diffusion, typical of healthy, organized white matter tracts, while low FA values suggest more isotropic diffusion, which can indicate white matter damage or less organized tracts (Basser and Pierpaoli, 2011). Mean Diffusivity (MD) is another DTI metric that describes the overall diffusion within a voxel; elevated MD can signal tissue damage, including axonal loss or demyelination (Seehaus et al., 2015). Radial Diffusivity (RD) measures diffusion perpendicular to the main diffusion pathway; increases in RD are typically associated with demyelination or changes in the myelin sheath (Wei et al., 2013). Axial Diffusivity (AD) quantifies diffusion along the main diffusion direction; a decrease in AD can indicate axonal damage or degeneration (also known as 'Wallerian degeneration') (Song et al., 2002). So, higher values of FA and AD indicate greater white matter integrity, while higher values of MD and RD suggest lower integrity. Therefore, DTI metrics provide comprehensive information about the microstructural properties of brain tissues, particularly the white matter of the CC.

The interplay between microstructural and macrostructural atrophy in the CC represents a dynamic process in which cellular degradation leads to visible structural shrinkage, and this shrinkage, in turn, exacerbates cellular breakdown. Myelin and axonal degeneration reduce white matter integrity, which over time becomes evident as observable volume loss and thinning. Concurrently, as macrostructural atrophy advances, the remaining axons may face increased metabolic strain, accelerating further microstructural deterioration. For example, Vos et al. (2011) demonstrated that common diffusion metrics, such as FA and MD, are influenced by fiber thickness, highlighting how macrostructural characteristics modulate microstructural degeneration. This cyclical process can create a feedback loop, amplifying both micro- and macrostructural loss over time.

3.2. Regional differences in age-related corpus callosum atrophy

Research indicates that the age-related atrophy is not uniform across all regions of the CC. The anterior part, including the genu, shows more significant atrophy compared to the posterior part, such as the splenium (Bennett et al., 2010; Davis et al., 2009; Fan et al., 2019; Hasan et al., 2009; Hou and Pakkenberg, 2012; Inano et al., 2011; Lebel et al., 2012; Liu et al., 2021; Madden et al., 2004; Ota et al., 2006; Ouyang et al., 2021; Pfefferbaum et al., 2005; Pietrasik et al., 2020; Salat et al., 2005; Sullivan et al., 2006, or for a review see Madden et al., 2009). For example, Ota and colleagues (2006) found that age negatively correlated with FA values, but positively correlated with MD values, in the genu, but not in the splenium. This suggests an antero-posterior deterioration gradient of aging (Head et al., 2004). Typically, decreases in FA and (to a lesser extent) AD, along with increases in MD and RD, are most pronounced in anterior CC regions and least severe in posterior regions. As the anterior CC regions reach maturation at a later point in development than the posterior regions (Lebel et al., 2010), this gradient likely mirrors the developmental pattern of CC subregions, known as the "last in, first out" principle (Brickman et al., 2012; Raz and Kennedy, 2009).

3.3. Causes of age-related corpus callosum atrophy

The atrophy of the CC in aging is caused by a combination of factors that contribute to the degeneration of brain tissue and the decline in neural connectivity. One of the most significant contributors is neuronal and synaptic loss. Aging leads to the progressive death of neurons, including those forming the white matter tracts of the CC, reducing its structural integrity (Morrison and Hof, 1997). The number of synapses also decreases with age, affecting communication pathways within the CC and between hemispheres (Peters et al., 2008). Alongside neuronal and synaptic loss, nerve fibers in the aging CC may become less myelinated, leading to reduced speed and efficiency of inter-hemispheric communication (Bartzokis, 2004). Vascular factors may also contribute to CC atrophy. Aging is associated with decreased cerebral blood flow, which can be worsened by conditions like

hypertension, atherosclerosis, or microvascular disease (Mokhber et al., 2021). This can impair the delivery of oxygen and nutrients to the CC, causing tissue damage and atrophy. In addition, chronic inflammation and oxidative stress can directly damage neurons and synapses, furthering the process of CC atrophy (Finkel and Holbrook, 2000). Furthermore, the process of neuronal and synaptic degeneration in the CC can be accelerated by neurodegenerative diseases, such as Alzheimer's and Parkinson's disease (Frederiksen et al., 2011b; Goldman et al., 2017; Vermersch et al., 1994; Zhu et al., 2014), as well as lifestyle and environmental factors like lack of physical activity (Pani et al., 2022), poor diet (Lau et al., 2005), and chronic stress (Villarreal et al., 2004).

4. Age-related changes in inter-hemispheric communication

The degeneration of the CC in normal aging has significant effects on how the brain's hemispheres communicate. Studies of functional connectivity, which measure the synchronization of activity between corresponding regions in both hemispheres, have shown that increased age is associated with reduced inter-hemispheric functional connectivity (Chen et al., 2019; Lewis et al., 2022; Zhao et al., 2020). At the functional level, reduction in connectivity affects various levels of brain processing, from the inter-hemispheric transfer of sensory information to more complex cognitive tasks.

4.1. Sensory processing

As the CC undergoes atrophy with age, its efficiency in transferring sensory information between hemispheres is compromised, resulting in slower sensory integration. This effect has been well-documented in the literature, demonstrating a link between callosal connectivity and prolonged inter-hemispheric transfer time (IHTT). Such findings have been observed in various populations with CC atrophy, including split-brain and acallosal patients (Corballis, 1998; Iacoboni et al., 2000; Marzi et al., 1991; Mooshagian et al., 2009; Paul et al., 2007; Reuter-Lorenz et al., 1995; Roser and Corballis, 2002), as well as patients with multiple sclerosis (Warlop et al., 2008), schizophrenia (Schrift et al., 1986; Woodruff et al., 1997), alcoholism (Hutner and Oscar-Berman, 1996; Schulte et al., 2004, 2005, 2008), and autism (Keary et al., 2009).

IHTT is commonly measured using the Poffenberger paradigm (Poffenberger, 1912), where participants respond with either their left or right hand to visual stimuli presented randomly to the left or right visual field. The primary measure is the crossed-uncrossed difference (CUD), which is the difference in reaction times (RTs) between inter-hemispheric (crossed) and intra-hemispheric (uncrossed) responses. Typically, contralateral responses take approximately 3 ms longer due to the need for information to travel between hemispheres via the CC (Nowicka and Tacikowski, 2011). This delay provides an estimate of visuomotor information IHTT. IHTT can also be assessed by the time lag between ipsilateral and contralateral event-related potentials (ERPs) evoked by the stimuli (Saron and Davidson, 1989). Numerous studies have reported increased IHTT in older adults compared to younger adults (Bellis and Wilber, 2001; Curran et al., 2001; Davis et al., 2012; Jeeves and Moes, 1996; Reuter-Lorenz and Stanczak, 2000; Riedel et al., 2022; Schulte et al., 2004). It's worth noting that not all studies have identified an age-related increase in IHTT (e.g., Scally et al., 2018; Schulte et al., 2013). These discrepancies may be due to variations in experimental design, such as differences in stimulus size, trial numbers, duration, or stimulus eccentricity. However, the overall trend of increased IHTT with age in most studies indicates that the transfer of visual and visuomotor information between hemispheres tends to slow with aging.

The age-related decline in inter-hemispheric transfer of sensory information is not confined to visual and visuomotor information. Similar declines have been observed across various modalities. For example, Piccirilli et al. (2020) examined how aging affects the efficiency of inter-hemispheric transfer of tactile information. They used a fingertip cross-localization task in which participants responded to a tactile stimulus applied to one hand by using either the same (ipsilateral) hand (uncrossed condition) or the opposite (contralateral) hand (crossed condition). Results indicated that performance in the crossed condition significantly declines around the seventh decade of life, with the most rapid decline occurring in the subsequent decades. There is also substantial evidence that inter-hemispheric transfer of auditory information deteriorates with age. Studies using the dichotic listening paradigm, in which different auditory stimuli are presented simultaneously to each ear, have shown an increase in laterality preferences in older adults: a left-ear preference for stimulus localization and a right-ear preference for stimulus recall become more pronounced with age (Gootjes et al., 2004; Westerhausen et al., 2015). Age-related performance decline is most notable for the ear ipsilateral to the hemisphere dominant for the specific function, indicating a reduction in inter-hemispheric transfer efficiency. Furthermore, the relationship between age-related CC degeneration and auditory inter-hemispheric integration is supported by findings from Dias et al. (2020), who demonstrated that higher FA in callosal tracts connecting the left and right prefrontal and posterior parietal cortices correlates with improved segregation and identification of spatially cued speech.

4.2. Motor functioning

Bilateral motor coordination, essential for mobility, balance, proprioception, and precise bimanual skills, relies on effective inter-hemispheric sensory integration (Delhaye et al., 2018; Fabri et al., 2014; Goldstein et al., 2023; Richmond et al., 2022; Tuthill and Azim, 2018). Given the established evidence that age-related CC atrophy disrupts inter-hemispheric sensory integration, many studies have explored the associations between age-related CC degeneration and complex motor abilities. Poorer performance on tests of proprioception, gait, frailty, and balance function has been found to be correlated with CC degeneration (Bhadelia et al., 2009; Brodoefel et al., 2013; Gutiérrez-Zúñiga et al., 2023; Massa et al., 2019; Tian et al., 2020; Van Impe et al., 2012), supporting the notion that CC atrophy can lead to difficulties in coordinating movements and maintaining postural stability. For instance, Gutiérrez-Zúñiga and colleagues (2023) explored cross-sectional associations between brain regions using MRI technology and self-reported frailty index scores among 523 community-dwelling adults aged 50 years and older. Analysis of white matter integrity revealed that the CC, particularly the genu connecting to frontal brain regions, had higher associations with frailty scores among subjects.

As part of healthy aging, the ability to execute bimanual tasks requiring precise coordinated movement also declines (Bernard and Seidler, 2012). Bimanual movements rely on visual and proprioceptive feedback alongside information exchange between both cerebral hemispheres via the CC to execute precise actions (Gerloff and Andres, 2002; Gooijers and Swinnen, 2014). Research has found negative correlations between the integrity of the CC and bimanual motor tasks in older adults (Fling et al., 2012; Richmond and Fling, 2019; Serbruyns et al., 2015; Sullivan et al., 2001), confirming that the structural integrity of callosal fibers is crucial in moderating older adults' ability to perform complex motor movements, including skilled fine motor abilities.

While inter-hemispheric interactions rely on a balance of excitatory and inhibitory processes, research shows that connections between sensorimotor cortical regions are predominantly inhibitory (De Gennaro et al., 2004; Lenzi et al., 2007). This inhibition supports independent control of each hand, as needed for tasks like cutting food. However, studies using Transcranial Magnetic Stimulation (TMS) indicate that mutual inhibition between motor cortices diminishes with age, shifting the balance toward greater excitatory interactions (Davidson and Tremblay, 2013; Coppi et al., 2014; Fling and Seidler, 2012; Fling et al., 2011b). As a result, older adults experience reduced inhibitory control, leading to "motor overflow," where unintentional movements may

occur. This reduction in inhibition may contribute to motor control difficulties in aging, particularly for tasks requiring unilateral hand movements without interference from the other hand, which could help explain age-related challenges in tasks demanding precise motor coordination.

4.3. Cognitive functioning

Inter-hemispheric communication is generally essential for most cognitive tasks. Efficient inter-hemispheric communication ensures that both hemispheres can collaborate, integrating their specialized functions to support complex cognitive tasks (Banich, 2004; Bloom and Hynd, 2005; Gazzaniga, 2000; Hinkley et al., 2012). As the integrity of the CC deteriorates in aging, inter-hemispheric functional connectivity is reduced (Chen et al., 2019; Lewis et al., 2022; Zhao et al., 2020), impacting cognitive task performance (Frederiksen et al., 2011a; Jokinen et al., 2007; Raghavan et al., 2021; Ryberg et al., 2011). Indeed, literature has well documented significant associations between age-related CC atrophy and performance in various cognitive tasks, including processing speed (Fling et al., 2011a; Jokinen et al., 2007; Kennedy and Raz, 2009; Penke et al., 2010; Sullivan et al., 2010), executive functioning (Di Paola et al., 2011), working memory (Delvenne, 2024; Fan et al., 2019; Fling et al., 2011a; Kennedy and Raz, 2009; Zahr et al., 2009), problem-solving (Danielsen et al., 2020; Zahr et al., 2009), and overall memory (Frederiksen et al., 2011a; Persson et al., 2006). For example, to evaluate older adults' ability to transfer visual memory traces across hemispheres, Delvenne (2024) employed a divided-field one-back task where visual stimuli were presented in either the left or right hemifield. Given the contralateral organization of visual memories (Delvenne, 2012; Delvenne et al., 2011; Gratton et al., 1997), accurately matching bilateral stimuli requires communication between the hemispheres. The findings of Delvenne (2024)'s study demonstrated a significant decline in visual memory performance among older adults when matching stimuli were presented in opposite hemifields compared to the same hemifield, suggesting a disruption in inter-hemispheric communication. In some situations, the impact of CC degeneration can be beneficial, especially when normal inter-hemispheric communication causes interference. For example, in a divided-field Stroop task where the target and distractor are spatially separated and presented either within a single hemifield or in different hemifields, Delvenne and Castronovo (2018) found a significant reduction in inter-hemispheric interference in older adults compared to intra-hemispheric interference. This suggests that a fully developed and healthy CC naturally facilitates information exchange between hemispheres, which can sometimes negatively affect task performance (Qin et al., 2016). In older adults, callosal thinning may reduce inter-hemispheric interference, allowing the two hemispheres to process information more independently. It is important to note that the direct impact of callosal degeneration on cognitive task performance has not been consistently established in past studies. Future research is needed to clarify how age-related CC atrophy specifically influences cognitive functions.

Interestingly, despite age-related degeneration of the CC, older adults often recruit more bilateral neural resources to accomplish cognitive tasks (Cabeza et al., 2002; Reuter-Lorenz and Cappell, 2008). This is evident as they often engage both brain hemispheres for tasks that typically involve unilateral processing in younger adults (Reuter-Lorenz and Lustig, 2005; Seidler et al., 2010). Several models have been proposed to explain the increased bilateral recruitment seen in older adults. The leading model, *HAROLD* (Hemispheric Asymmetry Reduction in Older Adults), introduced by Cabeza (2002), posits that older adults show reduced lateralization in brain activity, particularly in the prefrontal cortex. Other variances of this model have been proposed, such as the *CRUNCH model* (Compensation-Related Utilization of Neural Circuits Hypothesis), described by Reuter-Lorenz and Cappell (2008), which suggests that older adults initially compensate by engaging additional neural resources within a hemisphere but then recruit contralateral areas as task demands increase; The *STAC model* (Scaffolding Theory of Aging and Cognition), proposed by Park and Reuter-Lorenz (2009), proposes that aging brains recruit additional networks, or "scaffolds", to maintain cognitive performance, leading to increased bilateral activation; The *PASA model* (Posterior-Anterior Shift in Aging), introduced by Davis et al. (2008), explains a shift in activation from posterior to anterior brain regions with age, often accompanied by increased bilateral recruitment.

There is ongoing debate over the role of this reduction in asymmetry and increase in bilateral activation. One perspective is the *compensation hypothesis* (Cabeza et al., 1997), which proposes that bilateral recruitment helps counteract cognitive decline in aging brains, as bilateral activation is often linked to better cognitive performance (Reuter-Lorenz et al., 2000). An alternative view, the *dedifferentiation hypothesis* (Li and Lindenberger, 1999), suggests that bilateral recruitment reflects a reduced capacity to engage specialized neural processes, consistent with findings that correlations between among different cognitive measures, and between cognitive and sensory measures, increase with age.

Collectively, these models illustrate the impact of aging on hemispheric interactions, often increasing the need for bilateral recruitment. Although this recruitment may compensate for cognitive decline, it could also reflect dedifferentiation due to difficulties in accessing specialized neural processes. Importantly, an increase in bilateral recruitment may seem at odds with age-related atrophy of the CC and reduced inter-hemispheric communication. One possibility is that reduced lateralization and increased bilateral activation may result from a decrease in inter-hemispheric inhibition as the CC deteriorates with age. Further research is needed to clarify the relationship between increased bilateral recruitment and CC atrophy in older adults.

4.4. Emotional and social implications

The CC may also disrupt the inter-hemispheric transfer of information from bilateral areas involved in emotional regulation, leading to difficulties in regulating and interpreting emotions. The link found between callosal integrity and alexithymia (Paul et al., 2021; Seyedmirzaei et al., 2022; TenHouten et al., 1985a, 1985b) may potentially explain the decline in emotional awareness, defined as the ability to recognize and make sense of emotions, often observed in late adulthood (Feiguine et al., 1982; Mattila et al., 2006; Orlando et al., 2023; Skumlien et al., 2018). For example, Orlando and colleagues (2023) demonstrated that emotional recognition performance is positively correlated with preserved white matter integrity in the mid-cingulate CC region in older adults. However, it should be noted that correlation studies cannot establish causal relationships. The observed reduction of emotional awareness and callosal connectivity found in Orlando et al. (2023)'s study may reflect parallel instead of inter-dependent processes. For instance, Skumlien and colleagues (2018) found that decrease aspects of emotional awareness are correlated with reduced midsagittal callosal size and decreased integrity of the anterior region of the CC in older adults. However, their formal mediation analysis could not demonstrate that age-related decline in emotional awareness is directly mediated by the CC.

The disruption in the ability to recognize and make sense of emotions in old age may possibly result in increased irritability, anxiety, mood swings, and depression. Indeed, late-onset depression has been linked to both white matter changes (Herrmann et al., 2008), including CC atrophy (Ballmaier et al., 2008; Cyprien et al., 2014; Touron et al., 2022), and abnormal inter-hemispheric information transfer (Yuan et al., 2010). This suggests that CC degeneration may be contributing to depression in old age. In support for this, Cyprien and colleagues (2014) conducted a longitudinal neuroimaging study to assess the relationship between age-related CC changes and late-onset depression. Analysis revealed that a smaller CC size in anterior, mid, and posterior regions is a predictive factor of late-onset depression in older women.

The Impact of age-related CC atrophy on emotions and mood can

lead to challenges in social interactions and potentially contribute to social withdrawal. The reduced engagement in social activities may further impact mood and emotional well-being. Evidence linking CC size and social engagement in older adults has indeed been found in the literature (James et al., 2012), although the causality of such relationship still must be determined. On the one hand, CC atrophy may cause older adults to become less socially engaged as they become more emotionally sensitive due to changes in function. On the other hand, CC atrophy may be exacerbated by a lack of social engagement. Indeed, participation in meaningful social activity has been associated with preserved cognitive health and lower rates of cognitive decline among older adults (Ertel et al., 2008; James et al., 2011; Piolatto et al., 2022). It has also been linked to both greater microstructural integrity of both grey (Felix et al., 2021) and white matter, particularly in the anterior CC (Molesworth et al., 2015). It is therefore plausible to assume that social engagement may somewhat slow down CC atrophy.

5. Clinical Significance

It has become clear that the CC exhibits degeneration as part of the normal aging process and can have several functional consequences. The combined effects of sensory, motor, cognitive decline, and potentially emotional and social complications, due to CC atrophy can significantly affect daily living activities. Older adults may experience increased difficulty in performing routine tasks, thereby reducing independence and quality of life. Firstly, impaired inter-hemispheric transfer of sensory information (e.g., Riedel et al., 2022) can affect the ability to integrate sensory inputs, leading to issues such as difficulty in processing visual and auditory information simultaneously. This can impact activities like driving, where quick responses to visual and auditory cues are crucial. Secondly, reduced connectivity may also affect the sense of body position and movement, impacting balance and coordination (e.g., Tian et al., 2020). This can affect walking, climbing stairs, or engaging in physical activities. This can also lead to a higher risk of falls, which is known to be the most common type of accidents in people 65 years of age and older (Akyol, 2007; Osoba et al., 2019). Fine motor tasks, when the simultaneous use of both hands is required, such as typing, using utensils, playing musical instruments, or buttoning clothes, may also become more challenging. Thirdly, various cognitive functions also decline due to age-related CC atrophy and can affect everyday activities. Reduced processing speed (e.g., Fling et al., 2011a) can hinder quick reactions to environmental changes, crucial for activities like driving, crossing the street, or responding to emergencies. Poorer executive function (e.g., Di Paola et al., 2011) can interfere with time management, problem solving, or multitasking such as cooking while talking on the phone. Furthermore, poorer memory (e.g., Fan et al., 2019) can complicate following conversations, remembering instructions, or recalling past events. Finally, cognitive impairments can lead to withdrawal from social activities due to embarrassment or frustration over memory lapses or communication difficulties. This can lead to social withdrawal and isolation. Difficulty in regulating and recognizing emotions (e.g., Orlando et al., 2023) can lead to increased irritability, anxiety, or depression, impacting relationships and overall well-being.

These challenges clearly underscore the importance of early detection and interventions to mitigate the effects on daily functioning, to reduce reliance on caregivers or assistive device, and to improve the quality of life for older adults. Early detection of CC atrophy might be of particular interest for detecting and classifying individuals in the early stages of Alzheimer's disease. Previously described as a disease of the grey matter localized in the hippocampus (Ball et al., 1985), it is now widely accepted that Alzheimer's disease is associated with significant atrophy to white matter tissues of the brain (Frederiksen et al., 2011b; Kao et al., 2019; Nasrabady et al., 2018; Vermersch et al., 1994; Zhu et al., 2014). Existing literature has evidenced reduced callosal white matter density and integrity in Alzheimer's disease patients relative to cognitively healthy controls (Delvenne et al., 2023; Di Paola et al., 2010; Hallam et al., 2008; Hanyu et al., 1999; Thomann et al., 2006). Callosal atrophy is even correlated to dementia severity, suggesting that disrupted inter-hemispheric communication likely contributes to development of dementia syndromes (Pantel et al., 1999). Measuring the degree of CC atrophy in older people may therefore help diagnose the disease or risk of disease earlier, and initiate treatments that can help manage symptoms and significantly delay its progression (Rasmussen and Langerman, 2019). Given the link between late-onset depression and CC atrophy (Ballmaier et al., 2008; Cyprien et al., 2014; Touron et al., 2022), early detection of CC degeneration may also help mental health professionals assess the causes for mood disorders in the older population. Assessment of callosal integrity may similarly identify those at higher risk of mood-related difficulties, meaning in principle they could be screened more frequently in primary care or specific mental health services to ensure timely treatment. In the same vein, physical therapists and occupational therapists can incorporate assessments of inter-hemispheric communication and sensorimotor integration to support the development of person-centered interventions to target specific motor deficits due to callosal degeneration.

6. Future research directions

Future research directions in the study of age-related atrophy of the CC are therefore essential for advancing our understanding of its implications and developing effective interventions. Here, we identify several key areas for future exploration.

6.1. *Functional implications*

Examining how CC atrophy specifically impacts different cognitive and sensorimotor domains can provide a more nuanced understanding of its clinical significance. Research should focus on identifying which functions are most vulnerable and how they relate to everyday activities and quality of life. Additionally, studying the compensatory mechanisms that older adults employ to counteract the effects of CC atrophy can reveal adaptive strategies. Understanding these mechanisms can guide the development of interventions that enhance compensatory processes. Exploring the concepts of cognitive reserve and resilience in relation to CC atrophy can also help identify factors that protect against functional decline. Research can focus on lifestyle, educational, and occupational factors that contribute to maintaining cognitive and motor functions despite CC degeneration.

6.2. *Longitudinal studies*

Most of past research have used cross-sectional studies and shown correlations between CC integrity and functions. However, the causality is often undetermined. Conducting longitudinal studies to track the progression of CC atrophy over time in individuals can provide valuable insights into the natural course of degeneration and its impact on cognitive and sensorimotor functions. This line of research studies could help identify early biomarkers and predictors of decline.

6.3. *Biological, genetic and environmental factors*

Investigating the underlying biological mechanisms driving CC atrophy, such as inflammation, oxidative stress, and vascular changes, can offer a deeper understanding of the processes involved. Exploring the genetic predispositions and environmental influences that contribute to CC atrophy can help identify individuals at higher risk and lead to personalized prevention and treatment strategies. There is indeed strong evidence of genetic correlations among most callosal subregions, suggesting callosal structure is significantly heritable (Jahanshad et al., 2013; Kochunov et al., 2010; Woldehawariat et al., 2014). Sex differences in CC size have also been documented (Prendergast et al., 2015; Shiino et al., 2017; Suganthy et al., 2003), although recent studies have

shown that individual differences in brain size could account for apparent sex differences in the anatomy of the CC (Jäncke et al., 2015; Luders et al., 2014). Heterogeneity in callosal structure is also affected by environmental influences. Macrostructural and microstructural abnormalities have been associated with both chronic alcohol use and consumption within a 'normal' range (Estruch et al., 1997; Pfefferbaum et al., 2006). Moreover, chronic smoking has been correlated with reduced FA in the left anterior CC (Paul et al., 2008; Zhang et al., 2011) and associations between higher Body Mass Index measurements and axonal degeneration in the CC body have also been reported (Xu et al., 2013). Therefore, future research should focus on exploring the role of genetic markers and modifiable lifestyle factors on CC atrophy, which could then inform personalized interventions for promoting brain resilience and cognitive vitality in ageing populations.

6.4. *Intervention studies*

Developing and testing interventions aimed at mitigating CC atrophy and its effects is crucial. At present, there is limited existing evidence focusing specifically on measuring the degree and subregions of age-related CC atrophy and implementing tailored interventions to mitigate the decline in functional abilities. However, a wealth of literature focusing on specific motor, cognitive and psychosocial interventions to improve functional outcomes in older adults associated with generic global decline has been demonstrated. In terms of motor interventions, multicomponent impairment-based walking exercise has been evidenced to improve strength, flexibility and endurance for walking in older populations to mitigate the mortality and morbidity associated with age-related changes to gait (Brach and VanSwearingen, 2013). Research suggests multi-component exercise interventions comprised of strength, balance and endurance training appears to be optimal to decrease falls risk and improve postural stability, balance, gait ability, and confidence in older adults who are physically frail (Brach and VanSwearingen, 2013; Cadore et al., 2013; Mahoney et al., 2019). Whilst research investigating the benefits of physical therapy on older adults experiencing motor impairments due to callosal atrophy is limited, benefits of physiotherapy, such as aerobic exercise and higher cardiorespiratory fitness, have been associated with increased structural CC integrity (Ibrahim et al., 2011; Loprinzi et al., 2020; Tarumi et al., 2022). Thus, research should focus on the development of interventions to mitigate motor changes associated with callosal degeneration in old age as well as to prevent or delay CC atrophy if implemented earlier in life. In terms of cognitive interventions, benefits of cognitive training among older adults to improve performance on a range of cognitive tasks, including verbal episodic memory, reasoning and executive functioning, have been evidenced among cognitively healthy and cognitively impaired populations (Bahar-Fuchs et al., 2019; Gooding et al., 2016; Hill et al., 2017; Hyer et al., 2016; Li et al., 2016; Willis et al., 2006). This supports the findings that regular engagement in stimulating cognitive activities can prevent or slow down cognitive decline and even reduce the risk of developing dementia (e.g., Marioni et al., 2012; Verghese et al., 2003). Nevertheless, there is currently a lack of research on the effects of cognitive training on CC integrity and inter-hemispheric communication. Although some cognitively demanding activities have been shown to increase the size of the CC during development, like musical training (Schlaug et al., 1995) or learning a second language (Negin et al., 2016), there are currently very few studies examining how those activities throughout the lifespan may preserve the CC in aging (Hanna-Pladdy and MacKay, 2011). Future research should therefore explore the effects of specific cognitive activities on the CC size and integrity in normal aging and how they may influence the preservation of cognitive functioning

7. Conclusion

In conclusion, age-related changes in the CC represent a significant aspect of brain aging, with profound implications for sensory processing, motor coordination, cognitive functioning, and emotional regulation. The atrophy of the CC, evidenced through both volumetric and microstructural decline, disrupts inter-hemispheric communication, leading to functional impairments that can diminish the quality of life for older adults. While the anterior regions of the CC are particularly vulnerable to degeneration, the resulting decline in functional connectivity affects various domains, from slower sensory integration and motor coordination to reduced cognitive efficiency and emotional stability. These changes underscore the importance of early detection and interventions to mitigate the effects of CC degeneration. Future research should focus on longitudinal studies, underlying mechanisms, and the role of biological, genetic and environmental factors to better understand CC atrophy and develop targeted strategies for prevention and treatment, ultimately improving the well-being and independence of aging populations.

CRediT authorship contribution statement

Jean-Francois Delvenne: Writing- Original draft preparation, reviewing and editing. **Ella Malloy**: Writing- Original draft preparation

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