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REVIEW

White-matter commissures: a clinically focused anatomical review

José Pedro Lavrador[1,2,3] · Vítor Ferreira[1] · Miguel Lourenço[1] · Inês Alexandre[1] · Maria Rocha[1] · Edson Oliveira[1,2] · Ahilan Kailaya-Vasan[3] · Lia Neto[1,4]

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Abstract

Purpose The objective of this review is to provide a structured approach to the main white matter commissures, their anatomic and radiological definition and disease implications.

Methods The Pubmed database and The JAMA Network were used for the literature review and the following terms were searched using Sort by: Best Match and Sort by: Most Recent: telencephalic commissure, forebrain commissure anatomy, fornix anatomy, commissure of fornix, posterior commissure, corpus callosum, commissural agenesis, Probst bundle, corpus callosum disorders review, corpus callosum diseases review, Marchiafava–Bignami, Alzheimer's disease and Forel commissure; 36 papers were selected, one excluded due to the language barrier.

Results The interhemispheric communication in the brain is achieved via the brain commissures, bundles of white matter linking the two cerebral hemispheres. Anterior white commissure (AWC)—related with olfactory and non-visual communication, hippocampal commissure—main efferent pathway of the hippocampus, connecting the hippocampal formation to structures beyond the temporal lobe, crucial in declarative memory formation and consolidation—and the corpus callosum (CC)—from the anterior commissure to the hippocampal commissure—are the main telencephalic commissures. Supramammilary commissure, posterior commissure, supraoptic commissure and habenular commissure are diencephalic commissures—unknown function, probably related to involuntary eye movements. Commissural agenesis (AWC is absent or impossible to recognize), Alzheimer's Disease (hippocampal commissure may contribute for disease dissemination) and agenesis of corpus callosum are some of the disturbances that involve the telenchephalic commissures.

Conclusions A comprehensive understanding of the clinic–anatomic correlation is pivotal to understand the pathology and therefore improve our diagnostic accuracy and treatment options, in the background of all patient management.

Keywords Corpus callosum · Anterior commissure · Hippocampal commissure · Diencephalic commissures

Introduction

The myelinated fibres composing the white matter are grouped into three classes: fibres interconnecting different cortical areas in the same hemisphere—association fibres; fibres that transverse the neuraxis, linking the cortex with caudal parts of the brain and spinal cord—projection fibres; and fibres responsible for the interconnection of both hemispheres across the midsagittal plane—commissural fibres [13]. Therefore, interhemispheric communication in the brain is assured by the brain commissures, bundles of white matter linking both cerebral hemispheres [32, 36].

The commissural fibres are categorized according to the brain structures they connect. The main commissural fibres at the level of the telencephalon—telencephalic commissures—are the corpus callosum, the anterior commissure

Collaborators: Afonso de Almeida, Afonso Amorim, António Urbano, João Chaves, Mafalda Cardoso, Mariana Almeida, Miguel Lança, Nuno Soares, Raquel Oliveira, Raquel Pinto, Sara Brito, Sara Nabais.

✉ José Pedro Lavrador
jose.pedro.lavrador@gmail.com

1 Anatomy Department, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

2 Neurosurgical Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal

3 Neurosurgical Department, King's College Hospital Foundation Trust, Denmark Hill, London SE5 9RS, UK

4 Neuroradiology Department, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal

and the hippocampal commissure (also known as commissure of the fornix or *psalterium Davidi*/David's lyre in older literature) [32, 36]. In the diencephalon, commissural fibres—diencephalic commissuresx—are also found: the habenular commissure, supraoptic commissure formed by *Meynert*'s and *Gudden´*s commissures (can also contain representatives of *Ganser´*s commissure) and posterior white commissure [16]. Even though anatomically distinct, their current function in the human being is not clearly defined.

The white matter diseases have their pathways in the bundles and tracts of fibres. Therefore, it is crucial to understand the white matter anatomy to predict their behaviour as well as the clinical symptoms that may occur. Multiple techniques have been developed to understand its architecture, namely advance MRI techniques (as diffusion tensor imaging—DTI) and dissection techniques (as Klingler technique) (Fig. 1).

In this review, the authors aim to perform a clinically focused anatomical review of the main findings regarding the white matter commissures, providing a scaffold for a scientific approach to their clinical relevance.

Materials and methods

The PubMed database was used for the literature review. The following terms were previously defined, while imposing some restrictions to limit our results: *telencephalic commissure*, using *Sort by: Best Match* and reviewing the results on the first three pages; and *forebrain commissure anatomy*, using *Sort by: Best Match* and reviewing at the results on the first nine pages. The phrase *white matter cerebrum review* was also searched for and sorted by *Best Match*, with the results of the first ten pages analysed; we also searched for *fornix anatomy*, using *Sort by: Most Recent*, regarding the articles on the first eight pages, as well as *commissure of fornix*, sorting the results by *Most Recent* and analysing the first seven pages. The term *posterior commissure* was also searched for and results were sorted by *Best Match*. Within the same database, we searched for the terms *corpus callosum* and *commissural agenesis* together to find the core data, using the filter *review* and ordering them by release date to find the most recent and complete articles. Furthermore, to find some specific data on the Probst bundles, the term *Probst bundle* was searched for, and the search was filtered through *case reports* to find specific data that would allow thorough comprehension of what these bundles represent in complete commissure agenesis. Moreover, the key terms *corpus callosum disorders review, corpus callosum diseases review* and *corpus callosum Marchiafava-Bignami* were separately searched for and sorted by *Most Recent*. The search *Fornix, Alzheimer's disease, pathology* was also made within the database. Beyond PubMed, we searched *The JAMA Network* for the terms *connections of the diencephalon*, and selected one article by title and abstract. We then searched for the term *Forel commissure* within the search engine *Google* and one book chapter was selected. *Habenular commissure review* was searched for and one article selected; *anterior commissure disorder* was also considered and two articles were selected. To complete our findings, a complementary search was made using PubMed for *indusium griseum*, sorting results by *Best Match*, as well as *corpus callosum anatomy*, with results *sorted by Most Recent*. The key terms *anterior commissure disorder* and *anterior commissure pathology* were also searched for, the latter using *Sort by: Best Match*. During this search, articles were selected based on their title and abstract, and most importantly on their relevance to our study.

For purpose of illustration, we have introduced DTI images reconstructed in the form of tractography and imagens of specimens dissected according to the Klingler technique.

With regards to the DTI, the subjects were imaged with a Philips Achieva 3.0 T X-series MRI scanner, using a standard eight-channel radiofrequency head coil. The imaging protocol included: a diffusion-weighted (DW) single-shot echo planar imaging (EPI) with one non-DW

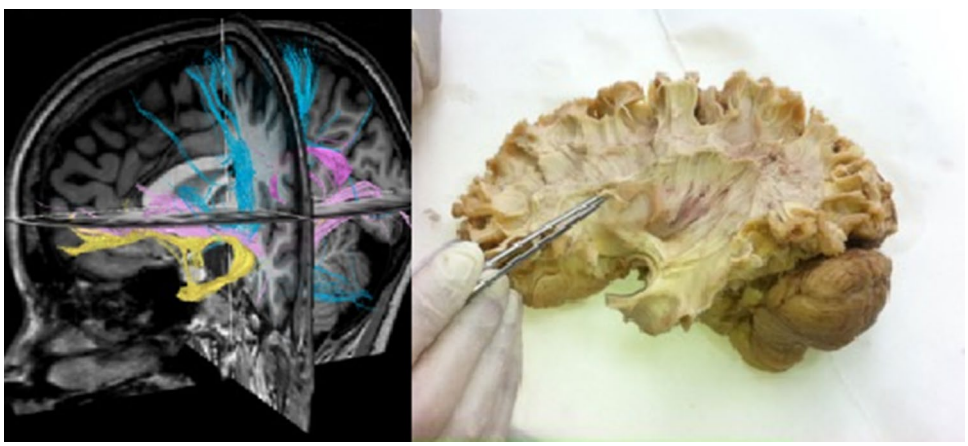

Fig. 1 Left: MRI head tractography demonstrating the pyramidal tract (blue), uncinate fasciculus (yellow), arcuate fasciculus (dark pink) and inferior longitudinal fasciculus (light pink). Right: Klingler technique revealing the uncinate fasciculus and the intra-hemispheric assotiation fibres (colour figure online)

image and 32 diffusion directions, *b* value of 1000 s/mm^2, reconstruction matrix 256 × 256, slice thickness 1.5 mm, TE/TR 64/7703 ms, FOV of 240 × 240mm2, 60 slices. A T1-weighted Spoiled Gradient Echo (SPG) image also was acquired: reconstruction matrix 512 × 512, slice thickness 1.5 mm, TE/TR 4.6/9.4 ms, FOV of 240 mm, 60 slices. The T1-3D and DTI data were transferred to an off-line workstation for analysis—StealthViz™ 1.3.0.34 Application with Stealth DTI™ Module by Medtronic Navigation. The DTI data were post-processed for co-registration and motion correction. Diffusion tensor elements and anisotropy at each voxel were calculated, and colour maps created. The colour-coded vector map results were superimposed onT1-3D images.

The white matter dissection was performed with spatulas and forceps with no magnification. Two specimens were used, preserved in 10% formalin for more than 1 month, and washed for several hours in fresh cold water before the dissection (specimens prepared according to the Klingler technique). The arachnoid and the pia-mater were removed with forceps and dissectors and the cortex was removed with the spatulas. The Frontal, Parietal and Temporal *operculum* were removed to expose the insular lobe and its cortex was removed as well (specimen in Fig. 1). A midline sagittal incision through the midline structures was performed to illustrate the medial surface of the hemispheres and their anatomy (specimen in Fig. 2).

Results

Brain commissures

Embryology

The *lamina terminalis* (membrane closing the anterior *neuropore*) is a pivotal structure in the development of the cerebral commissures. This structure provides a scaffold allowing the commissural fibres to cross from one side to the other in a morphological and phylogenetical organization.

The anterior commissure (*paleopallidum*) is the first to develop (primitive vertebrates) in the most ventral aspect of the lamina terminalis. The primitive hippocampus is located in the dorsal aspect of the anterior commissure and fibres connecting both hippocampal structures develop thereafter—hippocampal commissure. With the progressive development of the *telencephalon*, the major connection in between both hemispheres in the human brain (*neopallidum*) develops—the corpus callosum. This structure is located dorsally to the hippocampus formation. However, its rapid development and increase in size are responsible for pushing back and downwards the hippocampus, giving rise to the different components of the hippocampus [25].

Anterior commissure

Phylogenetically, the paleopallial anterior commissure is the oldest of the great forebrain commissures [32].

The anterior commissure is situated at the antero-inferior portion of the globus pallidus, within the *Gratiolet's* channel, near to the posterior part of the uncinate fasciculus, supero-anterior to the temporal horn of the lateral ventricle [30]. It crosses the midline in front of the anterior columns of the fornix, above the basal forebrain and below the medial and ventral portion of the anterior limb of the internal capsule [33] (Fig. 2). Both temporal regions, particularly the amygdalae are connected via its fibres. It is formed by two different portions: the anterior crus and the posterior crus. The first one is responsible for the connection between the olfactory systems of both hemispheres—olfactory commissure. This second part has more complex anatomy and a further division: a temporal portion and an occipital portion. The posterior crus of this commissure runs within Gratiolet's channel where it undergoes torsion, so that its superior fibres go to the temporal lobe and its inferior fibres reach the occipital lobe. Both extend to the level of the basal portion of the globus pallidus, at a 90° to

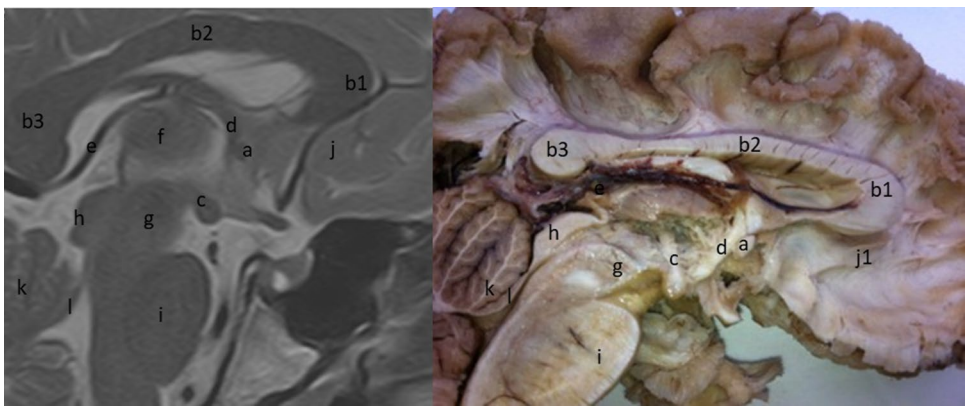

Fig. 2 Left: T2-weighted sagittal image. Right: medial aspect of the human brain dissected according to Klingler technique. a—anterior commissure; b—corpus callosum (b1—genu; b2—body; b3—splenium); c—mamillotalamic fasciculus; d—fornix; e—internal cerebral vein; f—thalamus; g—cerebral peduncle; h—tectal plate; i—pons; j—subgenual area (j1—subgenual córtex resected); k—cerebelum; l—superior velum medullaris

the optic radiation and medial to the uncinate fasciculus. Some fibres reach the uncinate fasciculus and the temporal pole; most of them course posteriorly joining the inferior longitudinal fasciculus and the sagittal stratum. This section of the anterior commissure covers the anterior and the central portion of the optic radiations [30].

From a topographical perspective, the anterior commissure is situated anterior to the columns of the fornix, superior to the optic chiasm and the lamina terminalis. Anterior to the anterior commissure, there is a region known as the ventral striatum, located in close proximity to the anterior perforated substance. Two grey matter nuclei can be identified in this area: the *nucleus accumbens* and the nucleus of *Meynert*. The nucleus of *Meynert* is a portion of the *substantia innominata* (which is located in front and under the anterior commissure and superior to the anterior perforated substance). The amygdalo-fugal fibres are also observed as they form the diagonal band of Broca [13, 30] (Fig. 3).

The clinical relevance of the anterior commissure is not well understood, but seems to be related to olfactory and non-visual communication [14]. In cases of corpus callosum agenesis or callosotomy, the AWC may partially take over the interhemispheric connection function normally undertaken by the CC, compensating for the lack of interhemispheric transfer [14].

Fornix

The fornix constitutes the main efferent pathway of the hippocampus, connecting the hippocampal formation to structures beyond the temporal lobe [7, 30]. It is part of the *Papez* circuit, along with the hippocampus, the mammillary bodies and the cingulum [21] (Fig. 4). It is part of the limbic system and therefore crucial in declarative memory formation and consolidation [34]. The fimbria represents the initial part of the fornix. It is located along the temporal horn on the ventricular surface of the hippocampal formation, arising

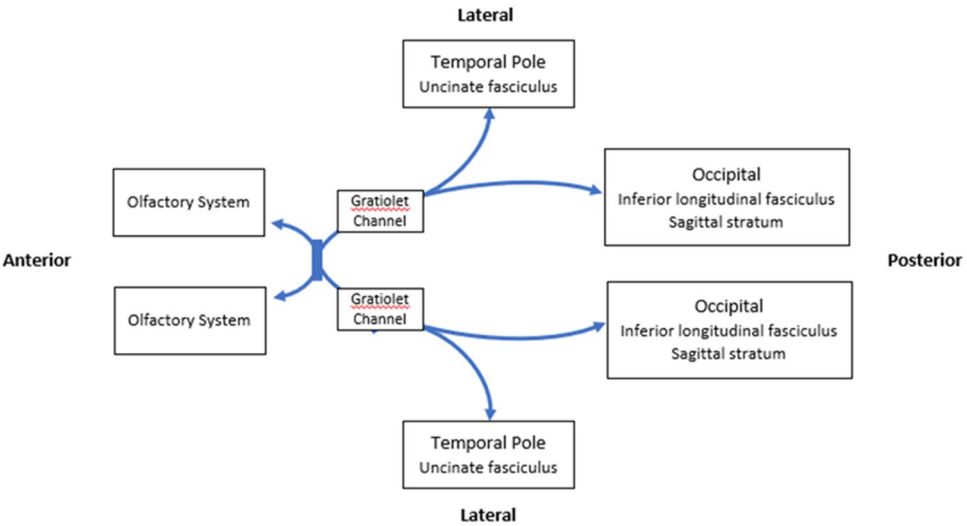

Fig. 3 Schematic representation of anterior commissure

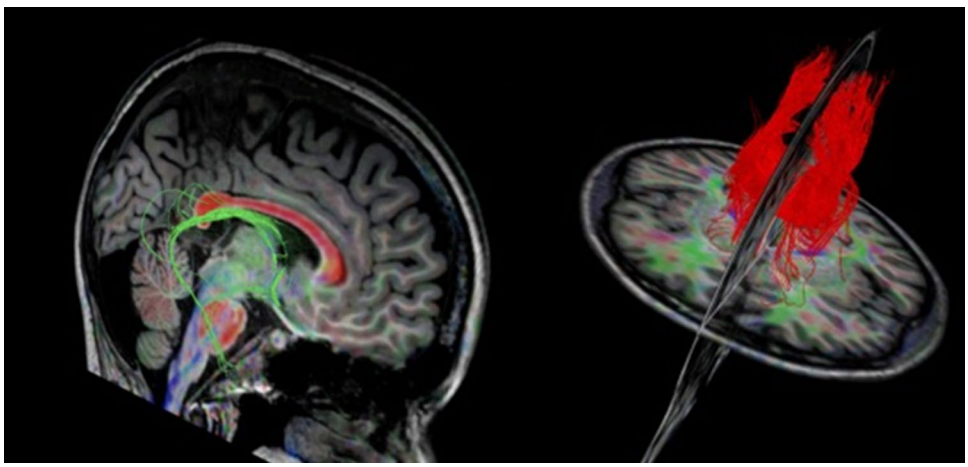

Fig. 4 MRI head tractography demonstrating the corpus callosum commissure (red) and the fornix (green) (colour figure online)

and becoming the crus of the fornix underneath the splenium of the corpus callosum. Both *crura* then course posteriorly to the ipsilateral pulvinar and arch superomedially. At this point, crossing fibres that establish the commissure of the fornix (also referred to as the hippocampal commissure) join the *crura* [30, 34].

The hippocampal commissure is a triangular transverse structure with an anterior vertex and posterior base that originates from fornix fibres (approximately 20%) that cross the midline between the *crura*, posteriorly to the *septum pellucidum* and body of fornix and anteriorly to the forceps major [32] (Fig. 5). This structure's dorsal portion connects the subicular, entorhinal and parahippocampal cortices of either side of the hemisphere, although not the *hippocampus proper*. Its ventral portion, which would connect the Ammon's horns, was found to be vestigial [32].

Both *crura* then unite in the midline at the junction of the *atrium* and body of the lateral ventricle and below the *corpus callosum*, forming the body of the fornix, which courses forward along the superomedial border of the thalami and below the inferior border of the septum pellucidum [34]. At the level of the foramen of Monro, the fornix divides again laterally forming the columns of the fornix [21]. Most of the fibres of each column form the postcommissural fornix [7, 30] passing posterior to the anterior commissure to reach the mammillary bodies and the anterior thalamus via mammillothalamic tract of *Vicq d'Azyr* [7] (Fig. 5). These fibres originate from the subiculum of the hippocampus [34]. The precommissural fornix encompasses the remaining fibres, which pass anterior to the anterior commissure, ending within the septal nuclei and basal forebrain, the ventral striatum and the prefrontal cortex [7, 34]. These fibres originate from the pyramidal cell layer of the hippocampus and some from the entorhinal cortex and subiculum [34]. The precommissural fornix also contains projection fibres from the septum that reach the hippocampus [7]. Therefore, the fornix has both projection and commissural fibres [34]. It was recently observed by Christiansen et al. in an MRI-diffusion study [8] that fibres associated with the anterior hippocampus were predominantly located laterally within the body of the fornix, whereas fibres associated with the posterior hippocampus were located more medially. It is still unclear if these subpopulations participate in different cognitive functions and whether they are distinctly affected by pathology. This had been previously observed in monkeys and rats, but has now been confirmed in humans as well.

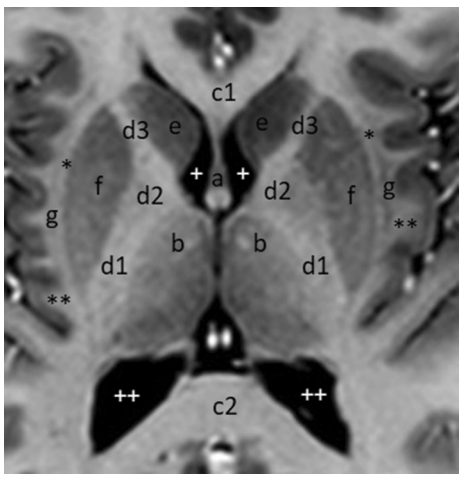

Fig. 5 T1—axial weighted MRI. a—fornix; b—mamillotalamic fasciculus; c—corpus callosum (c1—genu; c2—splenium); d—internal capsula (d1—posterior limb; d2—genu; d3—anterior limb); e—caudate nucleus (head); f—lenticular nucleus; g—claustrum; *external capsule; **extreme capsule; $^{+}$frontal horn of the lateral ventricle; $^{++}$atrium of the lateral ventricle

Corpus callosum

The *corpus callosum* (CC) consists of myelinated nerve fibres and connects the right and left cerebral hemispheres [29, 36] (Fig. 4). The CC involves the frontal and parietal lobes and extends from the anterior commissure (anteriorly) to the hippocampal commissure (posteriorly). This large commissure is anatomically subdivided in sequential segments: *lamina rostralis*, genu, body, isthmus, and splenium [32].

The *lamina rostralis* (or rostrum) extends from the anterior commissure (anteriorly) to the posterior inferior portion of the genu (posteriorly). It is superior to the septal area and borders the *septum pellucidum* anterio-inferiorly. The *lamina rostralis* incorporates fibres that have not been accurately studied but probably connect the fronto-basal cortex. The genu (knee) is located in the callosal abrupt change of orientation between the *lamina rostralis* and the callosal body.

The genu encompasses the fibres connecting the prefrontal cortex and the anterior cingulate area, forming the *forceps minor*. The ventral genu contains the fibres connecting the ventromedial prefrontal areas and the dorsal genu contains the fibres connecting both dorsolateral prefrontal cortices [32].

The callosal body extends horizontally from the genu to the isthmus and forms the superior limit of the *septum pellucidum*. The lateral fibres of the callosal body form the roof of the body of the lateral ventricles, inferior to the cingular bundle and superior to the inferior occipito-frontal fascicle. The fibres of the callosal body bridge the precentral cortex (premotor area, supplementary motor area), the adjacent portion of the insula, and the cingulate gyrus mostly. The *isthmus* is the narrowed part of the corpus callosum where the fornix meets the inferior callosal surface. The pre and postcentral gyri (motor and somatosensory strips) and the primary auditory area are connected through the commissural fibres of the isthmus [32].

The thickest portion of the corpus callosum is called the splenium (Fig. 2). It bulges in the ambient cistern, superior to the tectal plate, while the vein of Galen courses around it. The fibres pass through the splenium forming the forceps major and they participate in the *tapetum* or *sagittal stratum*, in the lateral wall of the ventricular atrium. These fibres can be divided into three groups: the superior, containing the commissural fibres from the posterior parietal cortex; the posterior, containing the commissural fibres of the medial occipital cortex; the inferior, containing the commissural fibres of the medial temporal cortex. The inferior surface of the splenium relates to the hippocampal commissure. Both left and right cingula course in an anteroposterior direction above the corpus callosum [13]. Above the corpus callosum, on the superior callosal surface, there is the *indusium griseum* (gray velum) which is a thin lamina of grey matter, covered on each side by two pairs of myelinated fibre bands called the medial and lateral longitudinal *striae*. The medial longitudinal *striae* are also called nerves of *Lancisi* [11, 32] (Fig. 6).

The known functions of the corpus callosum are: interhemispheric transfer of information, integration of inputs from one or both hemispheres, facilitation of some cortical activities, and inhibition of cortical functions. It was recently suggested that the integrity of the corpus callosum in humans is crucial and positively correlated with cognitive performance. Some findings support these concepts, namely the cognitive decline occurring is some patients after resection of the corpus callosum [12].

Supramammilary commissure (Forel)

The supramammilary commissure corresponds to the posterior hypothalamic decussation of *Kolliker* and is located dorsal to the mammillary bodies, as if pushed between the two bundles of their afferent pathways. However, Forel's commissure has no relationship with them [3]. The commissural fibres distribute in the ventral part of the mesencephalic tegmentum after crossing at very acute angles, and they are undetectable at the subthalamic nucleus and the zona incerta. Thus, we do not know the origin and termination of these axons, which according to *Dejerine*, would form a connection between the two subthalamic nuclei, as well as between these nuclei and the opposite red nucleus and field of Forel [3].

Posterior commissure

In mammals, particularly in the human being, the posterior commissure is greatly reduced in size [16]. Anatomically, the posterior commissure is located in the posterior part of the third ventricle, composing the roof, floor, posterior wall and both lateral walls [27]. Its fibres interconnect the pretectal nuclei thus mediating the consensual pupillary light reflex. There are some myelinated and non-myelinated fibres connecting the pineal gland and the pretectal area. Some fibres are also believed to start at the posterior part of the thalamus and the superior colliculus continuing in the medial longitudinal fasciculus [27]. Functionally, the posterior commissure is a pathway for impulses related to eye

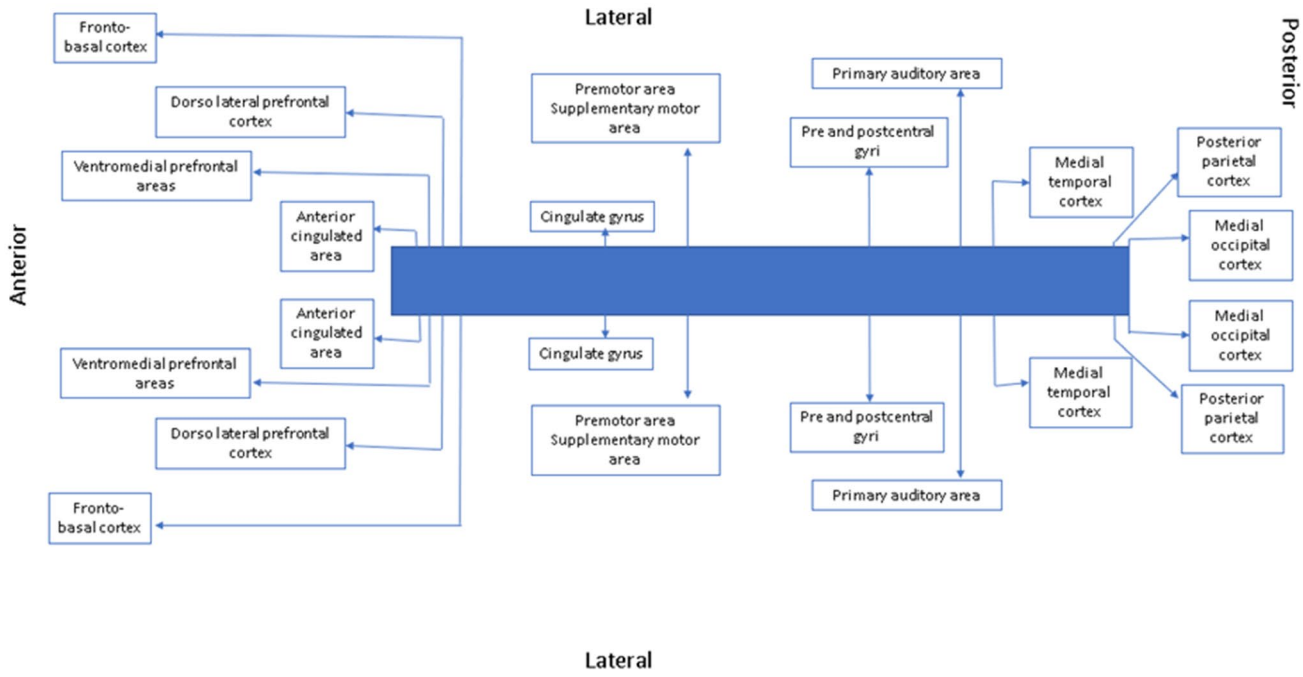

Fig. 6 Schematic representation of corpus callosum

movements, and there is a close relationship between the posterior commissure and the medial longitudinal fasciculus. It may also be related to the pupilloconstrictory pathways and the optic pathways (through fibres from cell bodies in the pretectal and neighbouring regions, including the dendrite of Müller cell M1). However, there is a relationship between the development of the cerebellum and the posterior commissure which suggests the more important functions of the commissure might be associated with posture and the integration of body movement rather than with movement of the eyes and visual influences [27].

Supraoptic commissure

The supraoptic commissure crosses the chiasmal ridge at the level of the optic decussation. Immediately behind it are the supraoptic or post-optic commissural systems [16]. These are divided in three main components. The most ventral division is indistinguishable from the optic tract—*Gudden*'s or the ventral supraoptic or ventral post-optic commissure. It interconnects the medial geniculate bodies and to some extent the inferior colliculi. Another supraoptic or post-optic commissural system is most frequently designated as *Meynert*'s commissure. It is a relatively complex system of fibres with no single nucleus of origin and no single nucleus of termination. The pos-toptic system, described by Herrick, is probably the forerunner of both Gudden's and *Meynert*'s commissures as found in higher forms and it may contain representatives of *Ganser*'s commissure as well [16].

Even though Meynert's commissure is a complex system in mammals, it forms a proportionately less prominent fibre bundle. Some of its more prominent bundles may be tectal fibres associating the superior colliculus with the contralateral ventral thalamus; intergeniculate fibres passing from one lateral geniculate body to the other (not thought to be present in all mammals); fibres connecting one lenticular nucleus with the contralateral subthalamic regions. *Foix* and *Nicolesco*, in their comprehensive recent account of the thalamus, listed a connection with the *substantia innominata of Reichert* [16].

The third member of the supraoptic commissural system is Ganser's commissure also known as *fibrae ansulatae*. The fibres interconnecting the subthalamic and the ventral thalamic regions of both sides run in this commissure. The periventricular grey caudal to the optic chiasm is likewise connected to this commissure as well as the fibres which arise in the nucleus of the median longitudinal fasciculus of one side, pass to the contralateral nucleus and possibly directly to the contralateral median longitudinal fasciculus [16].

Habenular commissure

The habenular commissure integrates the habenular complex. This is part of the dorsal diencephalic pathway system combined with the *stria medularis* and the *fasciculus retroflexus*. It starts in the anterior portion of the medial forebrain bundle and travels via the *stria medularis* to the habenular complex. Efferent fibres reach the midbrain *tegmentum* via the *fasciculus retroreflexus*. This shows that the habenular complex is an important connection between the limbic forebrain and the midbrain. The habenular complex is a small area adjacent to pulvinar, the superior colliculus and haulm of the pineal gland. In mammals, the habenular commissure consists on a medial and a lateral nucleus on each side and the habenular commissure which connects the nucleus of each side [22] (Fig. 7).

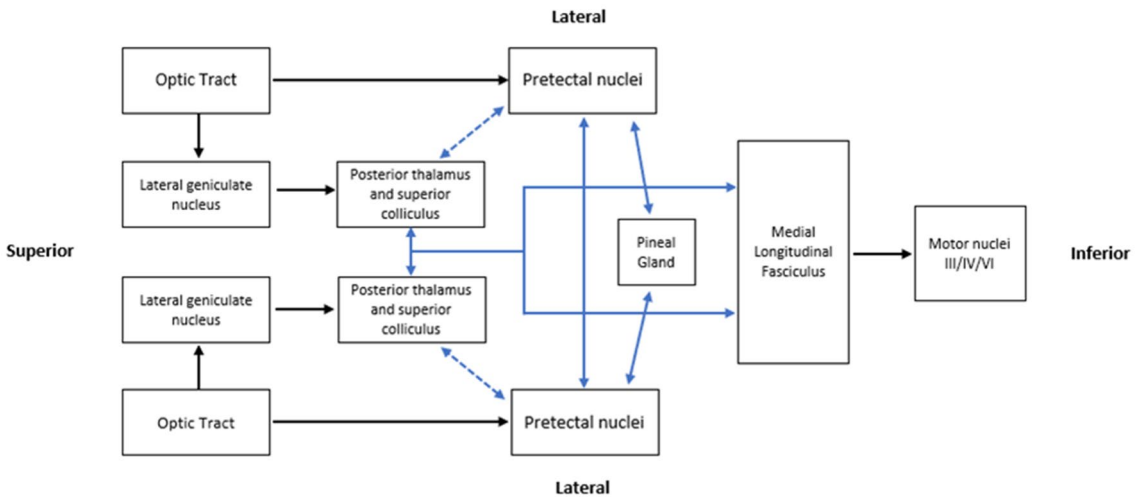

Fig. 7 Schematic representation of habenular commissure

A brief summary of the dienchephalic commissures is described in Table 1.

Discussion

Clinical correlations

Anterior commissure

Considering the classical comissural agenesis, the anterior commissure (AC) is absent or so thin that it is impossible to identify in approximately 50% of cases (isolated commissural agenesis is uncommon). It is hypothesized that this finding results in incomplete formation of its neocortical part (AC has cortical projections to areas to where the CC does not project) [38]. When there is an AC, it is abnormally located in more than a third of the reported cases (38%). This can result in the AC being found halfway between the optic chiasm and foramen of Monro, low on the *lamina terminalis* and, occasionally, posterior to the columns of the fornix [3].

Different pathologies have been implicated in morphological and physiological changes in the AC: genetic (mutations in *Pax6*), trauma (diffuse axonal injury) and neuropsychological disorders (schizophrenia) [3, 9, 37].

The relation between AC and CC has an evolutionary imprinting with CC taking over most of the functions played by AC. Therefore, it is unsurprising that different studies support the compensatory role of AC in callosal agenesis, as a regressive compensatory mechanism [10]. The compensatory roles played by these two structures become apparent in attention studies. The allocation of attention to action depends on neocortical systems and in the association with subcortical formations such as the basal ganglia and the thalamus. The role of the AC has been studied in relation to tasks in which certain forms of attention are required, such as visual attention. Visual attention in acallosal patients has been a subject of studies since the 1960s. In 1995, *Corballis* sought to investigate a deeper connection between visual integration and attention. To explain mixed findings in acallosal research, he proposed a binary visual attention organization: one part involved in the perception of forms—automatic and localized in each hemisphere—and another concerning movement and location—voluntary and subcortical [38]. By crosscutting the CC, the transmission of attention-related information between cortical pathways is predominantly annulled. Nevertheless, subcortical pathways and/or the AC could still take part in the mediation of the attention-based assimilation regarding visual data. Therefore, it is thought that the AC has a potential role in the connection between vision, attention and action.

Corpus callosum

In the *classic* comissural agenesis, the corpus callosum fibres are not absent but organized in an heterotopic manner [32]. These fibres gather up and form a parasagittal bundle, entitled *Probst* bundles, described by Probst in 1901. These bundles represent the re-routed callosal fibres, and are easily observed in T1 and T2 images due to its dense myelinization [32]. Taken together with the absence of the corpus callosum, the classic commissural agenesis is also characterized for an absence of the hippocampal commissure and changes in the anterior commissure in half of the cases. These bundles represent longitudinal tracts that travel from the frontal to the occipitoparietal lobes, connecting them. In the case of total corpus callosum agenesis, these bundles do not connect, whereas in cases of partial corpus callosum agenesis, a connection between these bundles is established through the remaining parts of CC [4].

There are imaging characteristics that allow us to identify a corpus callosum agenesis, namely: sulci radiating into the medial surface of the hemisphere and a complete or partial absence of the callosomarginal sulcus, as well as the cingulate gyrus in the sagittal view; reduced white matter volume, primarily along the midline, enlargement of the third

Table 1 Dienchephalic commissures: brief summary

Diencephalic commissures	
Supramammilary commissure (Forel)	Subthalamic nuclei Subthalamic nucleus and the contralateral red nucleus and field of Forel
Posterior commissure	Pretectal nuclei Pretectal nuclei and pineal gland Posterior thalamus and superior colliculus and medial longitudinal fasciculus
Supraoptic commissure	*Gudden's commissure* medial geniculate bodies *Meynert's commissure* superior colliculus and the contralateral ventral thalamus; lateral geniculate bodies (probably not present in all mammals); lenticular nuclei; lenticular nucleus and the subthalamic region *Ganser's commissure* subthalamic and the ventral thalamic regions of both sides; periventricular grey caudally to the optic chiasm; median longitudinal fasciculus nuclei
Habenular commissure	Habenular nuclei

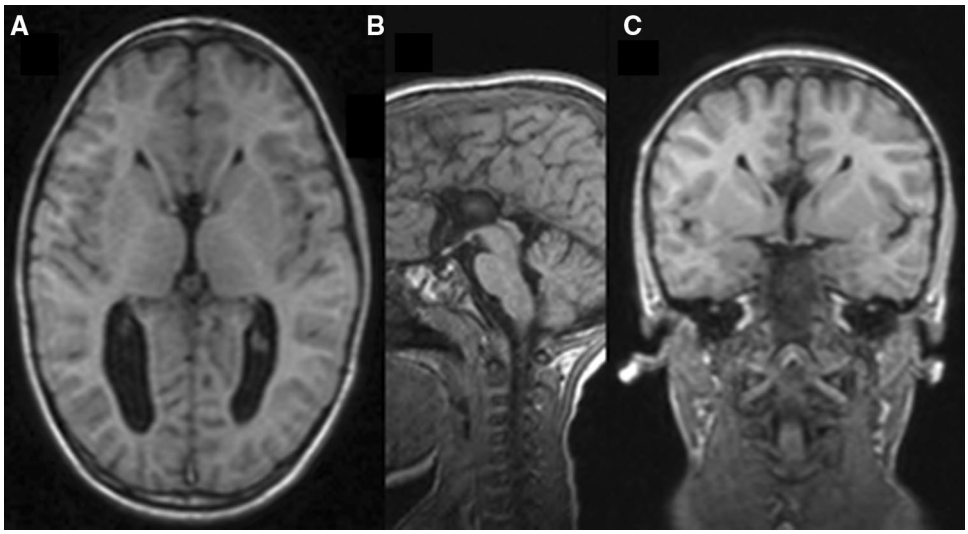

Fig. 8 T1 Weighted MRI (**a** axial; **b** sagittal; **c** coronal) showing Agenesis of Corpus Callosum

and fourth ventricles—best appreciated on coronal images; and enlargement of the posterior part of the lateral ventricles—colpocephaly—best appreciated in an axial images [29] (Fig. 8).

A somatotrophy of the fibres that constitute the Probst bundle has been described. The fibres originating in the frontal pole, more specifically the prefrontal area, run along the inner side of the bundle, whereas those originating more caudally, such as in the motor or premotor area, travel in the more lateral part [20]. These may constitute the reason that

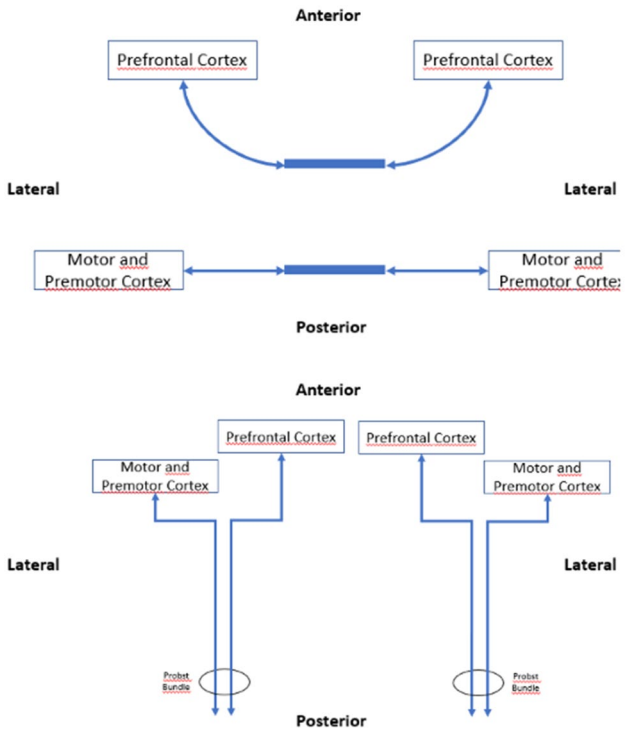

Fig. 9 Schematic comparison between corpus callosum and Probst fibres

the fibres originating in the more anterior part of the frontal cortex travel across the corpus callosum in its anterior part, the genu, whereas the ones originating more caudally cross its body, in a more posterior zone [35] (Fig. 9). Although, in the compete forms, no significant communication exists between both hemispheres, a neglect syndrome is quite rare in this patients due to brain plasticity allowing each hemisphere to compensate for the functions normally spread across both of them. However, some more complex activities, such as language and social skills, may exhibit minor disturbances [6].

Multiple acquired pathologies may affect as well the CC: phacomatoses (neurofibromatosis, bourneville's disease), tumors (glial lesions, lymphoma, metastatic), inflammatory diseases (multiple sclerosis, Marburg, acute disseminated encephalomyelitis, Susac syndrome), infectious diseases (HIV encephalopathy, progressive multifocal myelopathy, Lyme disease, subacute sclerosing panencephalitis, streptococcus meningitis), vascular (stroke, arterio-vascular malformations, cavernoma, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy—CADASIL), traumatic (diffuse axonal injury), toxic (Marchiafava–Bignami disease), metabolic (adrenoleukodystrophy, meta/orthochromatic leukodystrophy, muchopolysaccharidosis), iatrogenic (radiotherapy), reversible lesion (seizure, reversible posterior encephalopathy, and hypoglycemia) [2, 5, 15, 19, 28].

Fornix

Alzheimer's disease (AD) is a neurodegenerative disease characterized by an early stage of mild cognitive impairment (MCI) that can progress to dementia [31]. There are two pathways that try to explain Alzheimer´s neuropathology: the extracellular plaques formed by amyloid-beta (Aβ) and the intracellular neurofibrillary tangles made of

phosphorylated microtubule and protein tau (p-MAPT) [28]. Furthermore, AD can be characterized in National Institute on Aging/Alzheimer Association (NIA/AA) stages B0, B1, B2 and B3 according to neurofibrillary degeneration [23]. Recent studies have been focused on phospho-tau/MAPT (p-MAPT) neuropathology considering the fact its regional propagation appears to be correlated with the degree of cognitive impairment in AD [24]. Novel imaging studies suggest that the axonal injury caused by p-MAPT followed by increased diffusion in the fornix allow the evaluation of disease progression from the hippocampal formation [1, 26].

These results are compatible with the propagation of p-MAPT neuropathology from hippocampus to the basal forebrain nuclei via the fornix (early AD) [31]. However, they also suggest that p-MAPT neuropathology can also move from the basal forebrain into the hippocampal formation [31]. The projections from nucleus basalis of Meynert to the hippocampal formation through the fornix allow the correlation between tauopathy in the nucleus basalis of *Meynert* and p-MAPT-positive axons in the fornix [31]. Forniceal tauopathy is correlated with this pathology in the septum but not significantly correlated with tauopathy in anterior thalamic nucleus and *nucleus accumbens*. This may be explained by the propagation of p-MAPT neuropathology via other pathways (for example via the *amygdala* if we consider the *nucleus accumbens*) or could correspond to axonal loss. The investigator´s findings support the theory of AD-related p-MAPT neuropathology propagation from the hippocampus to the basal forebrain via the fornix in NIA/AA stages B2 and B3 of neurofibrillary degeneration [31].

To the best of our knowledge, there are two reported cases of patients presenting with memory impairment with subsequent recovery following traumatic injury of the fornix crus. Neural reorganization occurred: an abnormal neural tract from the right crus, proximal to the discontinuous crus, passed through the splenium of the corpus callosum to connect with the inferior longitudinal fasciculus. This reflects a different adaptive mechanism—abnormal tract formation—when we compare this with the relationship that is established between AC and CC—the regressive compensatory mechanism [17, 39].

Surgical correlations

Fornix and CC are structures often implied in neurosurgical pathologies either by harboring lesions requiring surgical resection or given their relation with common surgical approaches.

The third ventricle is a common place for intraventricular developmental lesions (colloid cysts) or tumors (craniopharyngioma) to develop and the fenestration of the floor of the third is a routine procedure nowadays to treat obstructive hydrocephalus (Fig. 10). The approaches to the third ventricle (both open surgery via craniotomy and the endoscopic approach) require dissection and splitting of the choroid fissure or entry in the third ventricle via the foramen of Monro. Both these procedures imply the gentle manipulation of the fornix and they may cause transient (or rarely permanent) short-term memory impairment [40].

The section of a part of the CC may be used as route to access the ventricular system in the inter-hemispheric approaches or maybe the treatment itself in cases of refractory epilepsy surgery. Possible complications of this procedure include the dissociation syndromes [18].

Conclusion

Both telencephalic and diencephalic white-matter commissures are important in the study of neuroanatomy, neurophysiology and neuropathology and critical in the clinical approach to the white-matter diseases. Sharing and

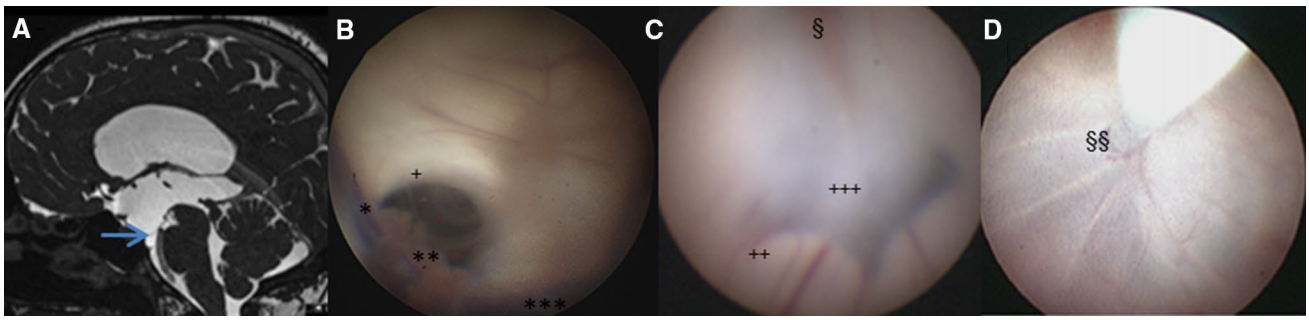

Fig. 10 Endoscopic third ventriculostomy—**a** sagital FIESTA sequence revealing the downward displacing of the floor of the third ventricle—arrow (factor of good response to the third ventriculostomy). **b–d** Endoscopic procedure. **b** Right foramen of Monro coming into view (endoscope in the right lateral ventricle) with the septal vein(posteriorly), the fornix (superiorly and anteriorly) and the choroid plexus (posterior aspect of the foramen). **c** Floor of the third ventricle (triangular shape) defined posteriorly by both mamillary bodies and anterioly by the infundibulum. **d** Endoscopic baloon creating a stoma at the floor of the third ventricle, anteriorly to the mamillary bodies and posteriorly to the infundibulum. *Septal vein; **choroid plexus; ***striatal vein; $^{+}$fornix; $^{++}$mamillar body; $^{+++}$floor of the third ventricle; §infundibulum; §§neurobaloon©

spreading information between both hemispheres allowed the specialization to occur. Nevertheless, when this communication is broken both abnormal tract formation and regressive compensatory mechanisms take over to compensate for this loss, as a memory of our phylogenetical evolution.

Olfactory and non-visual communication, declarative memory formation, interhemispheric transfer of information, integration of inputs from one or both hemispheres, facilitation of some cortical activities, inhibition of cortical functions and cognitive performance are some functions performed by the telencephalic commissures. The diencephalic commissures are vestigial in humans and their functions are not well understood, probably related to involuntary eye movements.

The white-matter tracts are a pathway for disease extension and spreading. Even though the congenital abnormalities of the white matter commissures are rare, they are critical to understanding their function. Isolated anterior commissure agenesis, partial or complete corpus callosum agenesis, Marchiafava–Bignami and Alzheimer's diseases are some examples supporting the importance of these structures. Deeper research in this field might be the key to find out different approaches to improve the treatment of new patients suffering from old diseases.

Author contributions LJP: Protocol/project development, Manuscript writing/editing. FV: Data collection or management. LM: Data collection or management. AI: Data collection or management. RM: Data collection or management. OE: Manuscript writing/editing. KVA: Manuscript writing/editing. NL: Data collection or management, Protocol/project development. AA: Data collection or management. AA: Data collection or management. UA: Data collection or management. CJ: Data collection or management. CM: Data collection or management. AM: Data collection or management. LM: Data collection or management. SN: Data collection or management. OR: Data collection or management. PR: Data collection or management. BS: Data collection or management. NS: Data collection or management.

Compliance with ethical standards

Conflict of interest The authors whose names are listed immediately above certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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