Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity

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Abstract | Agenesis of the corpus callosum (AgCC), a failure to develop the large bundle of fibres that connect the cerebral hemispheres, occurs in 1:4000 individuals. Genetics, animal models and detailed structural neuroimaging are now providing insights into the developmental and molecular bases of AgCC. Studies using neuropsychological, electroencephalogram and functional MRI approaches are examining the resulting impairments in emotional and social functioning, and have begun to explore the functional neuroanatomy underlying impaired higher-order cognition. The study of AgCC could provide insight into the integrated cerebral functioning of healthy brains, and may offer a model for understanding certain psychiatric illnesses, such as schizophrenia and autism.

Interhemispheric transfer (IHT). Transmission of information between the cerebral hemispheres, typically assessed with laterally presented stimuli.

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The brain's complexity arises from its connectivity — this is highlighted by the disproportionate increase in white matter volume throughout primate evolution[1]. The largest connective structure in the brain is the corpus callosum; it consists of over 190 million axons that transfer information between the two cerebral hemispheres[2] (FIG. 1). The corpus callosum contains homotopic and heterotopic interhemispheric connections. Although there has been debate about whether the connections are primarily excitatory (integrating information across hemispheres) or inhibitory (allowing the hemispheres to inhibit each other to maximize independent function)[3], they appear to be primarily excitatory, and this is the focus of most research on interhemispheric transfer (IHT).

Corpus callosum function in humans was first investigated in classic studies of 'split-brain' patients, whose callosum is severed surgically for the treatment of epilepsy[4,5] (BOX 1). However, there is another population that provides valuable insight about the functions of the corpus callosum and the role of altered connectivity in neurodevelopmental disorders: individuals with developmental absence (agenesis) of the corpus callosum (AgCC) (BOX 2; FIG. 2).

AgCC encompasses complete absence as well as hypogenesis (partial absence) of the corpus callosum (BOX 3). This review covers a broad range of findings from research into AgCC, including animal models of callosal development, genetic and environmental contributions to AgCC, neuroimaging in acallosal humans, and neuropsychological outcomes in individuals with primary AgCC. Therefore, the interdisciplinary nature of this review provides a framework for bridging two once largely non-overlapping domains of neuroscience: genetics and neuropsychology.

AgCC is a complex condition, which can result from disruption in any one of the multiple steps of callosal development, such as cellular proliferation and migration, axonal growth or glial patterning at the midline. We review the molecular mechanisms underlying these processes. Later sections address behavioural and neuropsychological aspects of AgCC. We briefly examine research on IHT and alternative hypotheses regarding behavioural symptoms. Although the contribution of AgCC to our understanding of callosal function is complicated by concomitant anatomical changes (BOX 2), we suggest that AgCC might be a powerful model for understanding cortico-cortical plasticity in other neurological and psychiatric populations.

Development of the corpus callosum

Corpus callosum formation involves multiple steps, including correct midline patterning, formation of telencephalic hemispheres, birth and specification of commissural neurons and axon guidance across the midline to their final target in the contralateral hemisphere. Much of what we know about the stages of callosal development comes from animal models[6,7]. Several principal mechanisms have been proposed to regulate callosal formation.

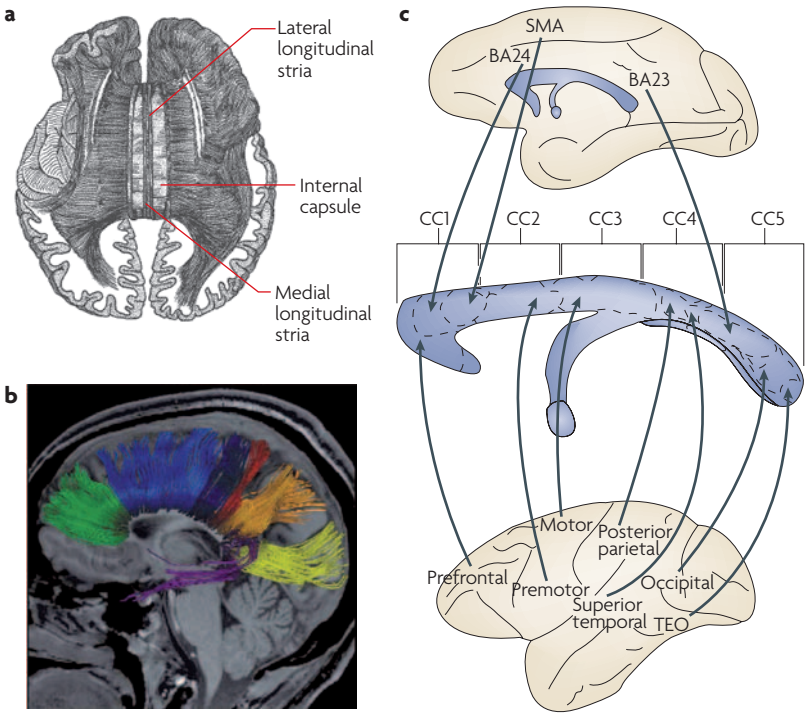

Figure 1 | **Neuroanatomy of the corpus callosum.** The human corpus callosum contains approximately 190 million axons. **a** | Organization of a human corpus callosum based on histological and neuroimaging findings. **b** | Diffusion MRI (dMRI) and tractography modelling provide important information about the corpus callosum fibre tracts and the cortical regions they connect. These dMRI data[144] of transcallosal fibre tracts in normal brains resulted in a new organizational scheme that describes corpus callosum structure, and suggested that much more of the corpus callosum is involved in premotor and supplementary motor coordination than previously thought. Fibres are coloured according to their projection areas: prefrontal lobe (green), premotor and supplementary motor areas (light blue), primary motor areas (dark blue), primary sensory cortex (red), parietal lobe (orange), occipital lobe (yellow), and temporal lobe (violet). **c** | In monkeys, researchers have been able to use chemical tracers to map the organization of cortical fibres passing through the corpus callosum, providing a level of detail currently unavailable in humans. BA23, Brodmann's area; CC, corpus callosum; SMA, supplementary motor area. Panel **a** modified, with permission, from REF. 145 © (2004) American Society of Neuroradiology. Panel **b** reproduced, with permission, from REF. 144 © (2006) Elsevier Science. Panel **c** modified, with permission, from REF. 146 © (2006) Oxford Univ. Press.

Diffusion MRI
(dMRI). This broad term covers both diffusion-weighted MRI data acquisition and image analysis of this data, including diffusion tensor imaging. The MRI signal is weighted by the amount of water diffusion within tissues. The weighting can vary with direction, allowing diffusion anisotropy arising from microscopic restrictions in biological tissues to be observed.

Pioneer axons
These are axons that innervate targets early in development and form a substrate for the guidance of later developing axons.

Guidance by pre-existing axon tracts. The first axons to cross the midline arise from neurons in the cingulate cortex. In mice, these pioneer axons cross the rostral midline at embryonic day 15.5 (REF. 8), providing a path for the fasciculation of later-arriving neocortical axons. In humans, pioneer axons express the guidance receptor neuropilin 1 (REF. 9), which can guide the axons themselves or the later-arriving callosal neurons from the neocortex. Cingulate cortex neurons also project axons into the rostrolateral cortex, perhaps to initially guide neocortical axons towards the midline. In more caudal regions of the corpus callosum, the hippocampal commissure, which in mice is formed a day earlier than the corpus callosum, may provide a growth substrate[10,11].

Midline glial structures. Multiple glial structures including the glial wedge, midline zipper glia and indusium griseum (FIG. 3) are present at the developing midline and are probably required for corpus callosum formation[12–15]. The glial wedge is a bilaterally symmetrical structure composed of radial glial cells that reside ventral to the corpus callosum at the corticoseptal boundary. It prevents callosal axons from entering the ventrally located septum, and once callosal axons have crossed the midline, repels the axons away from the midline into the contralateral hemisphere[13,16]. Guidance by the glial wedge occurs through both SLIT–ROBO and WNT–RYK signalling[13,16–18]. Midline zipper glia are found ventral to the developing corpus callosum at the septal midline. Their fusion at the midline has been suggested to be necessary for subsequent callosal axons to grow across the midline[19].

The indusium griseum glia (IGG), which are dorsal to the developing corpus callosum, also express SLIT2 and may help guide commissural axons towards their site of midline crossing[13]. Recent work in conditional fibroblast growth factor receptor / glial fibrillary acidic protein (*Fgfr1*/*Gfap*) Cre knockout mice has shown the importance of these glia in corpus callosum formation[14]. When FGFR1 is selectively eliminated from glia (and not neurons), the corpus callosum fails to form. Further analysis showed that FGFR1 is required for the migration of the IGG and for the development of this midline glial structure[14]. However, when *Fgfr1* is knocked out earlier in development, all midline glial structures at the corticoseptal boundary fail to develop, suggesting that FGFR1 has a signalling role at multiple stages of callosal development[15]. Similarly, *Nfia*- and *Nfib*-knockout mice[20,21], whose IGG and glial wedge are absent or significantly reduced in size, do not form a corpus callosum. However, midline glia are not the only guidance mechanisms at the midline. *Fgfr1*$^{+/-}$ heterozygotes[15] and growth-associated protein 43 (*Gap43*)-knockout mice[22] do form midline glial structures (and express *Slit2*), but callosal axons fail to cross, suggesting that multiple mechanisms regulate callosal development.

The subcallosal sling lies dorsal to the glial wedge and ventral to the developing corpus callosum. When the sling is severed experimentally, the corpus callosum fails to form[19], suggesting a role for this structure in callosal guidance, although the first callosal axons cross prior to the formation of the subcallosal sling. In mice, the majority of cells that make up the sling prenatally are neurons[23], but in humans, whose subcallosal sling contains a large number of glia, the cellular origins of this structure are more complex[9] (FIG. 3). Finally, additional neurons that have been identified within the corpus callosum[24] may have a role in axon guidance.

Target recognition and selective pruning in the contralateral hemisphere. After crossing the midline, callosal axons grow into the contralateral hemisphere towards their designated target region, usually homotopic to their region of origin, and then innervate the appropriate cortical layer. Such processes probably involve both molecular recognition of the appropriate target region and activity-dependent mechanisms that regulate axon targeting to the correct layer and the subsequent refinement of the projection[25]. In cats and ferrets,

Box 1 | **AgCC and the classic 'split-brain'**

Surgical commissurotomies (split-brain) are typically conducted in adulthood for the treatment of intractable epilepsy, while AgCC is a brain abnormality present at birth. In patients with commissurotomy, all cerebral commissures including the anterior commissure are severed, whereas the anterior commissure is intact in almost all patients with primary AgCC. In patients with callosotomy the anterior commissure is not surgically severed[5].

Individuals with commissurotomy manifest a 'disconnection syndrome' that includes the absence of callosal transfer of sensory information[121,122], and a deficiency in bimanually coordinated motor activity[123].

The presurgical existence of a seizure disorder complicates interpretation of higher cognitive functions in split-brain cases. However, Roger Sperry comments that "speech, verbal intelligence, calculation, motor coordination, verbal reasoning and recall, personality and temperament are all preserved to a surprising degree in the absence of hemispheric interconnection"[4]. Nevertheless, deficits have been noted in cognitive processing time, arithmetic, abstract reasoning[4] and short-term memory[124]. Commissurotomized patients may also exhibit alexithymia[125].

Overall, patients with AgCC have better, although limited, interhemispheric integration than patients with commissurotomy on many forms of visual and tactile information[68,126]. The relative importance of age at onset of AgCC versus commissurotomy for interhemispheric transfer (IHT) is illustrated by the finding that patients with early callosotomy and children with AgCC show little evidence of a disconnection syndrome in IHT tests with simple tactile information, whereas adolescent and adult callosotomy patients show marked transfer deficits[127]. This suggests that neural plasticity in children may allow for reinforcement of alternative neural pathways and that presence of the anterior commissure alone may not be sufficient to explain residual IHT in AgCC. The extent to which this compensatory plasticity involves unique recruitment of anterior commissure fibres remains unclear.

Despite the difference in functional interhemispheric connectivity, commissurotomy and AgCC both result in impairments of reasoning in complex novel situations[128]. Social situations require extremely rapid processing of very complex information that is typically handled within lateralized regions (that is, lexical and affective processes) and therefore may be particularly sensitive to corpus callosum abnormality.

refinement of callosal visual projections occurs through the selective pruning of axons after eye opening[25–27]. Correct pruning and stabilization at the border of areas 17 and 18 (but to a lesser extent in other areas) requires visual input[28]. A similar refinement of developmentally exuberant projections occurs in the somatosensory cortex[25]. It is not yet clear whether defects in axonal pruning may affect corpus callosum size and contribute to callosal hypoplasia (BOX 3) in humans.

Animal models of AgCC

Animal models of AgCC provide a basis for identifying genes that may be involved in human AgCC. The inactivation of genes that causes AgCC in mice often also triggers neurological deficits in other large-fibre tracts such as the internal capsule, and consequently leads to death at birth in many cases. These phenotypes, mostly resulting from gene deletions, may be too severe to model human AgCC, and such gene deletions might also result in embryonic or perinatal death in humans. However, a number of mouse models exist in which AgCC is partially or fully penetrant, but the animals have normal lifespans. Strains such as 129 and BTBR have been used to map quantitative trait loci that affect corpus callosum size[29]. Recent studies have shown that the gene disrupted in schizophrenia 1 (*Disc1*) is homozygously inactivated in all 129 strain mice[30], and this genetic mutation may be causally linked to AgCC in these animals. Thus, inactivation of *Disc1* might be an important mechanistic link between schizophrenia and AgCC[31].

Finally, recent studies have used new tools for labelling and isolating functional subsets of neurons to identify markers that are unique to callosal projection neurons[32]. These studies have identified the gene LIM domain only 4 (*Lmo4*) as a candidate transcription factor for specifying callosal 'identity' to projection neurons. This approach will potentially lead to a greater understanding of how neurons acquire their functional identities.

Causes of AgCC in humans

Genetic causes. The genetics of AgCC in humans are variable, and reflect the underlying complexity of callosal development. Current evidence indicates that a combination of genetic mechanisms, including single-gene Mendelian mutations, single-gene sporadic mutations and complex genetics (which may have a mixture of inherited and sporadic mutations) might have a role in the aetiology of AgCC. Retrospective chart reviews and cross-sectional cohort studies report that 30–45% of cases of AgCC have identifiable causes. Approximately 10% have chromosomal anomalies and the remaining 20–35% have recognizable genetic syndromes[33] (TABLE 1). However, if we only consider individuals with complete AgCC, then the percentage of patients with recognizable syndromes drops to 10–15%, and thus 75% of cases of complete AgCC do not have an identified cause.

One example of AgCC associated with a Mendelian disorder is X-linked lissencephaly with AgCC and ambiguous genitalia (XLAG), which results from a mutation in the aristaless-related homeobox gene (*ARX*). The first description of this disorder included only male patients. However, females with mutations in ARX, can, because of X-inactivation, have clinical symptoms that range from none to spasticity, mental retardation and seizures. MRI scans of these female patients are either normal or show isolated AgCC with Probst bundles[34] (BOX 3). Male *Arx*-knockout mice also have AgCC and replicate many of the other clinical and anatomical findings in XLAG[35], including a significant reduction in cortical interneurons, which probably explains the severe and uncontrollable seizures experienced by patients with this condition[36].

Another syndrome caused by a single-gene mutation with considerable overlap between the human and animal phenotype is CRASH syndrome (corpus callosum agenesis, retardation, adducted thumbs, spastic paraplegia and hydrocephalus), which is accompanied by diminutive corticospinal tracts within the brainstem. CRASH is caused by mutations in the L1 cell adhesion molecule (*L1CAM*) gene that codes for a transmembrane cell adhesion protein broadly expressed in the CNS. Mice with *L1cam* inactivation show complete or partial AgCC, hydrocephalus, small corticospinal tracts, reduced neuron numbers and additional abnormalities in the elaboration of apical dendrites from cortical pyramidal neurons[37]. Recent work suggests that inhibition of L1CAM homophilic binding can cause hydrocephalus, but that preventing corpus callosum

Commissurotomy
Surgical procedure that involves severing the corpus callosum as well as the anterior commissures (can also include severing of posterior and hippocampal commissures). This is the original 'split-brain' procedure as reported by Roger Sperry.

Callosotomy
Surgical procedure that involves severing only the corpus callosum, either in part or in its entirety, leaving other commissures intact. This has also been described by some as a 'split-brain' procedure.

Alexithymia
Impairment in the expression of one's feelings and mood states. A dominant hypothesis is that alexithymia arises from compromised connection between the language processing in the left hemisphere and affect processing in the right.

Box 2 | **Prevalence and features of AgCC**

Agenesis of the corpus callosum (AgCC) encompasses a broad range of diagnoses. A synthesis of recent neonatal and prenatal imaging studies suggested that AgCC occurs in at least 1:4000 live births[129,130], and other imaging studies[131,132] demonstrated that 3–5% of individuals assessed for neurodevelopmental disorders have AgCC.

Complete and partial AgCC probably result from disruption of the early stages of callosal development, which could have genetic, infectious, vascular or toxic causes[65,133–135]. Further heterogeneity in AgCC can arise from concomitant abnormalities in the anterior commissure. A recent study reported that the anterior commissure was small or absent in 60%, yet enlarged in 10% of AgCC cases[136]. The latter cases may provide insight into brain plasticity, as it has been suggested that interhemispheric connections in AgCC could be re-routed through the anterior commissure[68,137]. This idea is indirectly supported by better clinical outcomes in individuals with a normal or large anterior commissure (E.H.S., unpublished observations).

The contribution of AgCC to our understanding of callosal function is complicated by concomitant anatomical changes, including colpocephaly and Probst bundles. It is possible that cognitive and behavioural differences between AgCC and split-brain patients arise from these other anatomical differences. Colpocephaly refers to the dilatation of the posterior aspect of the lateral ventricles, frequently including the temporal horns. This does not represent hydrocephalus[138], but may signify the reduction of ipsilateral cortical association tracts[139]. Probst bundles are the misrouted callosal axons that run parallel to the interhemispheric fissure and can also be observed in cases of partial AgCC. Apparently within the Probst bundles, a structure called the sigmoid bundle has been recently identified in several cases of partial AgCC[140] (FIG. 2). This long, heterotopic commissural tract appears to connect the left frontal lobe with the right occipitoparietal cortex.

Other brain malformations can also be associated with AgCC[136]. One AgCC autopsy study documented a lack of pyramidal tract decussation, suggesting a more global disorder of midline crossing[141]. This pattern is also observed in many animal models of callosal agenesis[7,142,143]. All concomitant anatomical abnormalities, including changes in commissural fibres outside the corpus callosum, may be relevant to clinical outcome.

formation also requires the disruption of heterophilic interactions with other proteins, including integrins[38]. Gene dosage effects have also been observed in mouse knockout models for the genes deleted in colorectal carcinoma (*Dcc*) and *Gap43*. Here, heterozygote mice show partial AgCC whereas homozygote knockout mice have complete AgCC with additional anomalies[22].

Andermann syndrome, an autosomal recessive condition prevalent in the Saguenay-Lac-St-Jean region of Quebec, presents with callosal hypoplasia or AgCC, cognitive impairment, episodes of psychosis and a progressive central and peripheral neuropathy. It is caused by mutation of the KCl cotransporter KCC3 (REF. 39). *Kcc3*-knockout mice display neurodegeneration, and also have hearing loss and progressive neuropathy[40]. However, in contrast to ARX and L1 mouse mutants, they have normally formed corpora callosa. Interestingly, some patients with KCC3 mutations also have a fully formed corpus callosum, and there is even phenotypic variability within families, suggesting that additional genetic influences are at work.

The variable effects of gene inactivation on callosal development in mice and humans are also evident in Meckel–Gruber syndrome (MKS3). In humans, the mutation of meckelin (the gene in MKS3) causes occipital encephaloceles, hepatic ductal cysts and polydactyly. In mice, mutation of the same gene causes AgCC, hydrocephalus and cysts within the kidney[41]. TABLE 1 shows other disorders associated with callosal agenesis that have a clear recessive pattern of inheritance but for which the causative gene has not been identified.

In spite of the progress of research into single-gene Mendelian causes of AgCC, in most individuals with AgCC there is no clearly inherited cause or a recognized genetic syndrome, suggesting that AgCC can be caused by sporadic (*de novo*) genetic events. One salient example of this is Mowat–Wilson syndrome (MWS), which, in addition to AgCC, causes Hirschsprung disease, congenital heart disease, genitourinary anomalies, microcephaly, epilepsy and severe cognitive impairment[42]. MWS is caused by heterozygous inactivating mutations in the gene zinc finger homeobox 1b (*ZFHX1B*) on chromosome 2q22, which codes for SIP1 (SMAD interacting protein 1)[43]. AgCC is not observed in all MWS cases, suggesting that haploinsufficiency or gene dosage of SIP1 interacts with other genetic polymorphisms to alter callosal development[42].

Aicardi syndrome is another disorder probably caused by sporadic mutations, in this case on the X chromosome. Only observed in females and XXY males with Klinefelter syndrome, this disorder consists of AgCC, infantile spasms and chorioretinal lacunae. Patients with Aicardi syndrome show a constellation of additional cerebral and ophthalmological abnormalities, so it is likely that the mutation participates widely and early in prosencephalic development. By inference, it is likely that other cases of AgCC are caused by haploinsufficiency at other genetic loci. This is supported by many reports of patients with AgCC who have sporadic chromosomal mutations, with particular loci identified repeatedly[44]. Recent data obtained using microarray-based comparative genomic hybridization demonstrate that patients with AgCC have chromosomal deletions or duplications that are smaller than those that can be detected using conventional cytogenetics[45]. Indeed, in collaboration with the California Birth Defects Monitoring Program, we have shown that the risk of having a child with AgCC is nearly threefold higher for mothers aged 40 and above, which is consistent with causal sporadic chromosomal changes (E.S., unpublished observations).

As noted for the single-gene disorders discussed above, not every patient displays AgCC, indicating that many cases of AgCC might be caused by polygenic and other complex interactions. Moreover, the abundance of case reports of AgCC associated with specific diseases (partially listed in TABLE 1) probably also reflects complex underlying mechanisms. This is exemplified by a recent report examining the MRI findings of individuals with Sotos syndrome, which is caused by haploinsufficiency of the *NSD1* gene. In this study, only one patient had complete AgCC and the other 35 patients had either diffuse hypoplasia or thinning of the posterior body of the corpus callosum[46]. These findings suggest that some genes, often referred to as modifier genes, only partially contribute to callosal formation. Common disorders that affect behaviour and for which the influence of many modifier genes is the likely mode of inheritance include autism and schizophrenia[47,48]. Moreover, as there are many reports of AgCC or abnormally formed corpora callosa in patients with autism and schizophrenia[49,50],

Mendelian
A trait resulting from changes in a single gene that has a significant effect on the phenotype and is inherited in a simple pattern that is similar or identical to those described by Gregor Mendel. Also referred to as monogenic.

Retrospective chart reviews
A retrospective analysis of medical records of a group of individuals with a particular condition or disease, typically used to study rare diseases for which prospective identification and follow up are difficult.

X-inactivation
Early embryonic inactivation of the genes in each cell on one of a female's X chromosomes (may also occur in males with Klinefelter syndrome who have more than one X chromosome). The result is that dosage of X-chromosomal gene products is equivalent to those in typical males (who ony have one X chromosome).

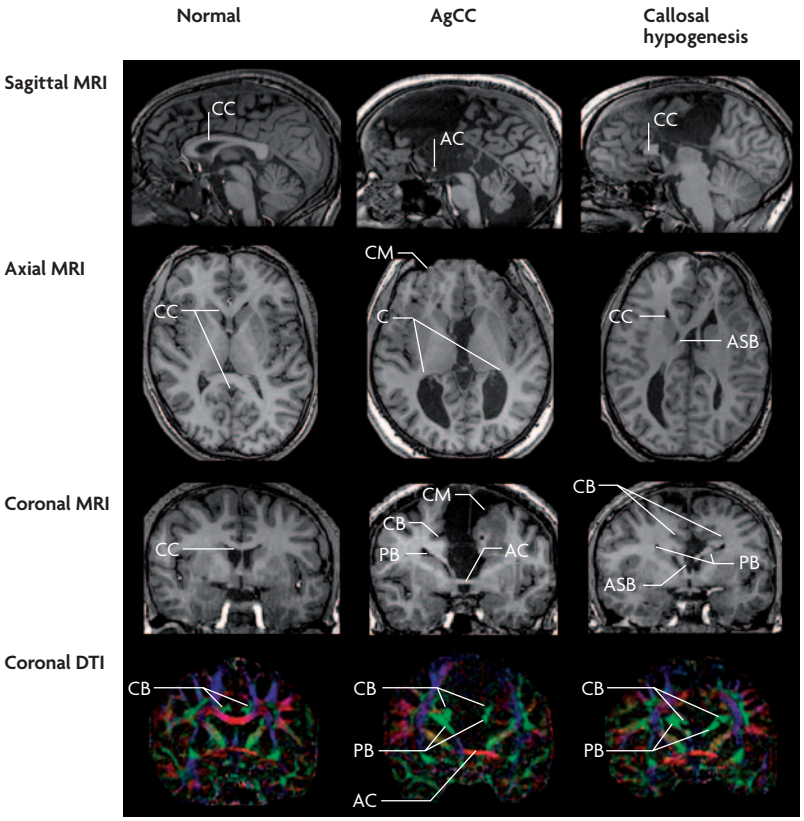

Figure 2 | **Examples of neuroanatomical findings in AgCC.** Neuroanatomical features of agenesis of the corpus callosum (AgCC) and callosal hypogenesis revealed by MRI and diffusion tensor imaging (DTI). Structural T1-weighted MRI (top 3 rows) and directionally encoded colour anisotropy dMRI (bottom row) are shown from a normal young adult male volunteer (left column), a young adult male with AgCC (middle column), and a young adult male with callosal hypogenesis (right column). The DTI images encode fibre orientation in white matter tracts using a three-colour scheme such that fibre pathways with predominantly left–right orientation are displayed as red, anteroposterior orientation as green, and craniocaudal orientation as purple. AC, anterior commissure; ASB, anterior sigmoid bundle; C, colpocephaly; CB, cingulum bundle; CC, corpus callosum; CM, cortical malformation; PB, Probst bundle.

it is possible that the modifier genes that affect callosal development overlap significantly with those that cause these neuropsychiatric disorders.

Environmental factors. Finally, it is important to note that environmental factors might contribute to AgCC as well. While much less is known about these than the genetic factors we have reviewed above, one clear example of environmental influences on callosal development is provided by fetal alcohol syndrome (FAS). Both clinical and experimental evidence indicates that alcohol exposure *in utero* decreases gliogenesis[51] and glial–neuronal interactions[52], processes that are vital for corpus callosum development[53]. Additionally, a growing body of literature suggests that ethanol disrupts the transcription and biochemical function of L1CAM[54–56], implicating an interplay of environment and genetics in AgCC. The incidence of AgCC in FAS is approximately 6.8%[57], with an even higher incidence of corpus callosum malformations short of complete AgCC. In many FAS cases, the corpus callosum is hypoplastic; this may result not only from the disruption of early events in callosal formation, but also from later dysregulation of axonal pruning. Such mechanisms might also cause callosal hypoplasia in other disorders such as schizophrenia and autism[25,31]. Other environmental factors may also influence postnatal and prenatal callosal development, including musical training[58–60], hypothyroidism[61,62] and enrichment or deprivation of experience[63].

Behavioural impairment in AgCC

Consistent with the broad range of genetic factors involved in AgCC, the cognitive, behavioural and neurological consequences of AgCC are wide-ranging. One approach to defining clinical subsets of the AgCC patient population is to categorize individuals according to specific neuroanatomical findings, and subsequently relate these to the behavioural symptoms within these groups. For example, a number of studies have suggested that the presence of polymicrogyria, pachygyria (abnormally broad gyri) and heterotopia, detected using MRI, correlates with moderate to severe developmental delay[64,65]. However, matching specific behaviours to anatomical groups is difficult given the diversity of symptoms in patients with similar antomical findings.

The comparison between complete and partial AgCC has revealed conflicting data, with multiple studies showing no difference in behavioural and medical outcomes between the two conditions, whereas one earlier study reported a worse outcome for individuals with complete AgCC[66]. One hospital-based study reported that just under a third of patients with AgCC were developmentally 'normal' or only mildly delayed[65]. A longitudinal study of 17 children prenatally diagnosed with isolated AgCC showed that nearly all patients had at least mild behavioural problems[67]. This suggests that isolated AgCC, even when not ascertained clinically, still causes behavioural and cognitive impairment. Parents often report that when their child was diagnosed with AgCC, they were told that the prognosis was unclear, ranging from severely delayed to 'perfectly normal'. However, as more individuals with primary AgCC are identified and assessed with sensitive standardized neuropsychological measures, a pattern of deficits in higher-order cognition and social skills has become apparent even in the so-called 'normal' individuals with AgCC.

Connectivity deficits. Historically, most research with patients with AgCC focused on the consequences of callosal absence, with the expectation that patients with AgCC would exhibit a 'disconnection syndrome' similar to that seen in commissurotomy patients[4]. The classic disconnection syndrome (BOX 1) involves the complete lack of IHT and interhemispheric integration of sensory and motor information presented independently to each of the hemispheres[4], with surprisingly subtle behavioural consequences in everyday life.

Studies using tachistoscopic presentation of visual stimuli and studies of evoked potentials provide the most compelling information about functional connections and IHT in AgCC at various stages of sensory processing. FIGURE 4 illustrates the visual cortical disconnection

Meckel–Gruber syndrome, type 3
(MKS3). Patients typically have renal cysts, CNS malformations, hepatic ductal dysplasia/cysts and polydactyly. MKS3 is caused by mutations in the gene meckelin (also known as TMEM67).

Encephaloceles
A neural tube defect (NTD) that results in a sac-like protrusion of brain tissue and overlying meninges. These NTDs are frequently associated with other brain or craniofacial malformations, and clinically with broad-ranging neurological problems.

Box 3 | **Key diagnostic definitions in AgCC**

Complete AgCC. A congenital condition characterized by total absence of the corpus callosum.

Hypogenesis of the corpus callosum. Also known as partial AgCC, this is a congenital condition characterized by partial absence of the corpus callosum. The absence must be evident from birth and not be representative of a degenerative condition.

Hypoplasia of the corpus callosum. Condition in which the corpus callosum is fully formed, but is thinner than expected for age and sex of the individual.

Isolated AgCC. Neuroanatomical description which includes complete absence of the corpus callosum, without other confounding brain abnormalities such as polymicrogyria, heterotopia or schizencephaly. Individuals with isolated AgCC frequently have colpocephaly and Probst bundles.

Primary AgCC. Primary AgCC refers to a symptom profile which includes isolated AgCC and generally intact intellectual functioning, as indicated by full-scale IQ ≥ 80.

Anterior commissure. Small band of approximately 50,000 axons that connect the cerebral hemispheres. The anterior commissure connects the temporal lobes and is located at the base of the fornix.

Probst bundles. Misrouted callosal axons that run parallel to the interhemispheric fissure and can be observed both in cases of complete and of partial AgCC.

Colpocephaly. Dilatation of the posterior aspect of the lateral ventricles, frequently including the temporal horns. This does not represent hydrocephalus but may represent the reduction of ipsilateral cortical association tracts.

Sigmoid bundle. A long heterotopic commissural tract found in some cases of partial AgCC. It appears to connect the left frontal lobe with the right occipitoparietal cortex.

effects in AgCC, as well as the limits of these disconnection symptoms. As shown by visual evoked potentials, there is a complete lack of IHT at the level of early visual processing in AgCC[68]. The hemispheric disconnection of the primary visual system in patients with AgCC results in a unique pattern of deficits in laboratory tasks that involve comparisons across the two visual fields: intact comparisons of simple stimuli and impaired comparisons of complex stimuli. Despite the lack of transfer of early visual information, individuals with AgCC display a normal ability to make comparisons of simple and easily encoded stimuli, indicating an intact interhemispheric transfer of simple or familiar information. For example, they exhibit an intact interhemispheric Stroop interference effect[69] and the typical bilateral field advantage for comparison of familiar and easily encoded visual information across hemifields[68]. These findings confirm that information can be transferred between the hemispheres in AgCC. One theory to explain the preserved capacity for IHT of simple stimuli in patients with AgCC is that simple information can be transferred via other connecting pathways, such as the anterior commissure. Structural and functional exploration of these alternate pathways for IHT is a crucial frontier in AgCC research.

By contrast, the capacity for IHT may be limited by task complexity. For example, the performance of patients with AgCC when comparing tachistoscopically presented visual information is significantly less accurate for more visually complex, less familiar and less easily verbalized stimuli[68] (FIG. 4). Similar limitations in IHT in patients with AgCC were evident on other tasks that required transfer or integration of the products of more complex cognitive operations, required more rapid processing and relied on less prior experience[68,70–72]. Taken together, these studies indicate that there is a greater reliance on the corpus callosum for rapid and effective interhemispheric interactions as task requirements increase (for example, when stimuli become more complex or response criteria become more constrained).

The question remains, however, about what causes the behavioural disturbances evident in primary AgCC. Studies using dichotic listening[73,74], positron emission tomography[75] and functional MRI (fMRI)[76] have revealed that language lateralization is normal in patients with primary AgCC and is in some cases even exaggerated. Although there is no published evidence for normal or abnormal localization of other higher cognitive functions in this population, we can suggest that, if localized functioning in the cortex of patients with primary AgCC is normal, a lack of information transfer between localized processing regions in opposite hemispheres could contribute to behavioural difficulties. This would leave callosal disconnection as a viable explanation for the behavioural disturbances in patients with primary AgCC.

Neuropsychological impairment. The major anatomical feature of primary AgCC is the absence of the corpus callosum, and it is presumed to be the cause of the cognitive and behavioural changes in these individuals. However, colpocephaly (BOX 3) and Probst bundles are common in people with primary AgCC (and never in those without AgCC), and together with other more subtle anatomical changes probably also affect behaviour. Functional and anatomical imaging approaches, coupled with incisive neuropsychological assessments, may in the future be able to map the neural processes and neuropathology associated with AgCC onto specific behavioural anomalies. For now, we begin by describing the general symptom profile found in primary AgCC.

Primary AgCC has a surprisingly limited impact on general cognitive ability. Although the full-scale IQ can be lower than expected based on family history, scores frequently remain within the average range[77]. Interestingly, in an unexpectedly large number of persons with primary AgCC (as many as 60%), performance IQ and verbal IQ are significantly different[77,78]. However, there is no consistency with respect to which of the two is more affected. Impairments in abstract reasoning[79,80], problem solving[81–83], generalization (the ability to extrapolate from one case to others)[84] and category fluency (the ability to list multiple items that belong to a semantic category, for example, names of animals)[80] have all been consistently observed in patients with primary AgCC. Data from large sample sizes suggest that problem solving abilities become more impaired as task complexity increases (W.S.B. and L.K.P., unpublished observations). While neuropsychological research into domains such as memory, attention and spatial skills is under way in large samples of patients with primary AgCC, currently published results in these domains are limited to a few case studies that do not yet provide consistent findings.

The most comprehensively examined higher cognitive domain in patients with AgCC is language. Overall,

Polydactyly
The anatomical variant of having more than the normal number of digits on the hands or feet. This is observed in approximately 1:500 births and is usually inherited as an autosomal dominant trait with variable penetrance.

Hirschsprung disease
A developmental disorder of the enteric nervous system resulting in absence of the neuronal ganglion cells in the distal colon, which in turn results in a functional obstruction of the colon. Can present with a dramatically distended colon (megacolon) or with bowel perforation. It is a cardinal feature of Mowat–Wilson syndrome.

Haploinsufficiency
A clinically evident symptom arising when one of the two copies of a gene is mutated, leaving a single functional copy and a presumed reduction in the level of the encoded protein.

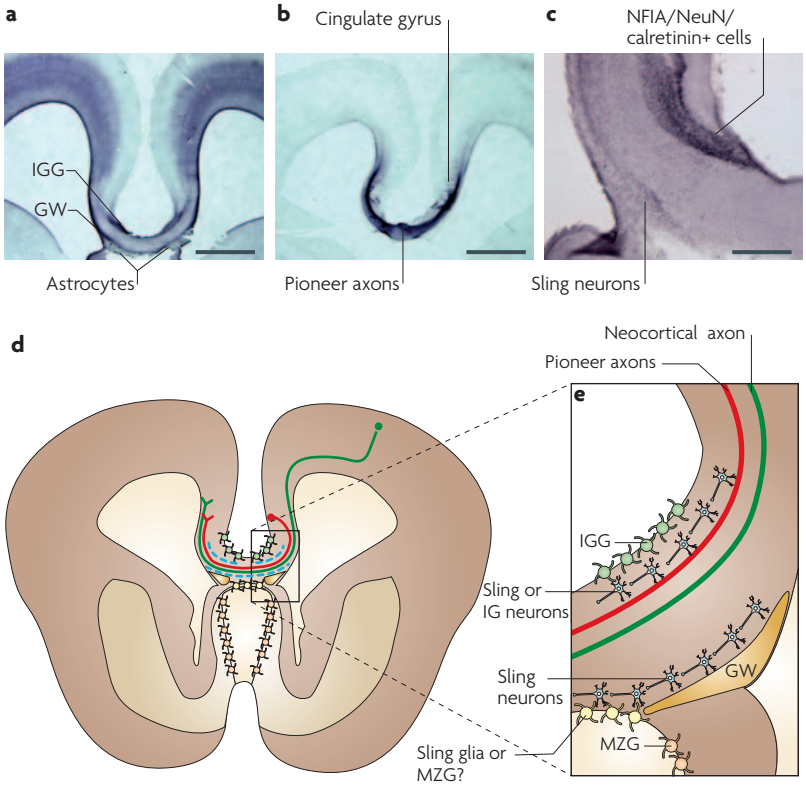

Figure 3 | **Corpus callosum development.** Midline structures support the development of the corpus callosum in the human brain. Panels **a**–**c** depict coronal sections of human fetal brains at 17 weeks gestation. Panel **a** is labelled with an anti-glial fibrillary acidic protein antibody, panel **b** with an anti-neuropilin 1 (NPN1) antibody and panel **c** with an anti-nuclear factor 1a (NFIA) antibody. Several midline glial structures are present at the cortical midline, including the glial wedge (GW; **a**), the indusium griseum glia (IGG; **a**) and the midline zipper glia (MZG; **d**,**e**). Pioneer axons, which form an additional potential guidance mechanism, express the guidance receptor NPN1 (**b**,**d**,**e**) and arise from the cingulate gyrus (**b**). In addition, the developing human brain contains subcallosal sling neurons, stained here with an antibody to NFIA (**c**). Developing human and mouse brains differ in two significant ways at the midline. First, in humans, differentiating astrocytes are found across the entire width of the midline (**a**,**d**,**e**). These cells can either be part of the subcallosal sling or an extension of the MZG. Second, a population of NFIA/ neuronal-specific nuclear protein (NeuN)/calretinin positive cells is present above the corpus callosum in humans (**c**), but not in mice. It is unclear whether these cells are similar to the subcallosal sling neurons or whether they might form neurons in the IGG (**e**). Scale bars: **a** and **b**, 3 mm; **c**, 400 mm. Panels **a** and **b** modified, with permission, from REF. 9 © (2006) Wiley and Sons.

Klinefelter syndrome
A genetic syndrome defined as a 47, XXY karyotype in a phenotypic male. Patients frequently have small testes, minimal sperm production, breast enlargement in puberty and psychosocial problems.

Chorioretinal lacunae
Punched out lesions in the pigmented layer of the retina that cluster around the optic disc that are pathognomonic for Aicardi syndrome.

individuals with primary AgCC have intact general naming (for example, naming objects from line drawings[85,86]), receptive language (for example, comprehension of sentences[78,86]) and lexical reading skills[87]. However, impairments have been reported in the comprehension of syntax and linguistic pragmatics[88,89], and in phonological processing and rhyming[86,88–90]. With respect to linguistic pragmatics, persons with primary AgCC are impaired in the comprehension of idioms, proverbs, vocal prosody[91,92] and narrative humour[93]. Within humour, they exhibit difficulty in overriding literal interpretation bias and are poor at using context to infer meaning[92–94]. Patients with primary AgCC also show marked difficulties with expressive language, for example in the verbal expression of emotional experience, which is consistent with a diagnosis of alexithymia[95]. In a study of a large sample of AgCC patients with adequate expressive language skills, parents consistently described 'meaningless' or 'out-of-place' conversation as particularly common[96]. Interestingly, recent studies of language support the dynamic dual pathway model, according to which syntax and semantics are lateralized to the left hemisphere and prosody to the right hemisphere[97–102]. In this model, the corpus callosum is the main path for coordination of this lateralized information, particularly for coordinating syntactic and prosodic information[97–99], the very areas of linguistic weakness evident in AgCC.

Parents of individuals with primary AgCC consistently describe impaired social skills and poor personal insight as the features that interfere most prominently with the daily lives of their children[96,103–105]. Specific traits include emotional immaturity, lack of introspection, impaired social competence, general deficits in social judgment and planning, and poor communication of emotions (for example, individuals prefer much younger friends, have a marked difficulty generating and sustaining conversation, take all conversation literally, do not take perspective of others, and are unable to effectively plan and execute daily activities such as homework, showering or paying bills[96,105]). Consequently, patients with primary AgCC often have impoverished and superficial relationships, suffer social isolation and have interpersonal conflict both at home and at work due to misinterpretation of social cues.

Responses of adults with primary AgCC on self-report measures also suggest diminished self-awareness[104]. The patients' self-reports are often in direct conflict with observations from friends and family. One potential factor contributing to poor self-awareness may be a more general impairment in comprehension and description of social situations. For instance, when asked to generate stories about social pictures, adults with primary AgCC provided stories lacking in logic, narrative content and social understanding[106]. It appeared that they had difficulty recognizing the implications of pictures depicting social scenes, imagining a sequence of events, and organizing relevant ideas in order to present an appropriate narrative. Similarly, when presented with highly provocative social pictures (for example, photos of mutilations), adults with AgCC tended to underestimate the emotional valence and intensity of the pictures, particularly for negatively valenced pictures[107]. Taken together, the neuropsychological findings in primary AgCC highlight a pattern of deficits in problem solving, in social pragmatics of language and communication and in processing emotion.

AgCC and neuropsychiatric disorders. The deficits in social communication and social interaction in patients with primary AgCC overlap with the diagnostic criteria for autism (from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; *DSM-IV*[148]). Furthermore, people with primary AgCC may display a variety of other social, attentional and behavioural symptoms that can resemble those of certain psychiatric disorders. Psychiatric diagnoses are based on clusters of behaviours, which are very complex and probably

Table 1 | **Syndromes associated with AgCC***

Syndrome	Salient features
With identified genes‡	
Andermann syndrome (*KCC3*)	AgCC, progressive neuropathy and dementia
XLAG (*ARX*)	Lissencephaly, AgCC, intractable epilepsy
Mowat Wilson syndrome (*ZFHX1B*)	Hirschsprung disease, AgCC
AgCC with fatal lactic acidosis (*MRPS16*)	Complex I and IV deficiency, AgCC, brain malformations
HSAS/MASA syndromes (*L1CAM*)	Hydrocephalus, adducted thumbs, AgCC, MR
AgCC seen consistently, no gene yet identified	
Acrocallosal syndrome	AgCC, polydactyly, craniofacial changes, MR
Aicardi syndrome	AgCC, chorioretinal lacunae, infantile spasms, MR
Chudley–McCullough syndrome	Hearing loss, hydrocephalus, AgCC, colpocephaly
Donnai–Barrow syndrome	Diaphragmatic hernia, exomphalos, AgCC, deafness
FG syndrome	MR, AgCC, craniofacial changes, macrocephaly
Genitopatellar syndrome	Absent patellae, urogenital malformations, AgCC
Temtamy syndrome	AgCC, optic coloboma, craniofacial changes, MR
Toriello–Carey syndrome	AgCC, craniofacial changes, cardiac defects, MR
Vici syndrome	AgCC, albinism, recurrent infections, MR
AgCC seen occasionally (partial list)§	
AgCC with spastic paraparesis (*SPG11*)	Progressive spasticity and neuropathy, thin corpus callosum
Craniofrontonasal syndrome	Coronal craniosynostosis, facial asymmetry, bifid nose
Fryns syndrome	CDH, pulmonary hypoplasia, craniofacial changes
Marden–Walker syndrome	Blepharophimosis, micrognathia, contractures, AgCC
Meckel–Gruber syndrome	Encephalocele, polydactyly and polycystic kidneys
Microphthalmia with linear skin defects	Microopthalmia, linear skin markings, seizures
Opitz G syndrome	Pharyngeal cleft, craniofacial changes, AgCC, MR
Orofaciodigital syndrome	Tongue hamartoma, microretrognathia, clinodactyly
Pyruvate decarboxylase deficiency	Lactic acidosis, seizures, severe MR and spasticity
Rubinstein–Taybi syndrome	Broad thumbs and great toes, MR, microcephaly
Septo-optic dysplasia (DeMorsier syndrome)	Hypoplasia of septum pellucidum and optic chiasm
Sotos syndrome	Physical overgrowth, MR, craniofacial changes
Warburg micro syndrome	Microcephaly, microopthalmia, microgenitalia, MR
Wolf–Hirschhorn syndrome	Microcephaly, seizures, cardiac defects, 4p –

*Reliable incidence data are unavailable for these very rare syndromes. ‡Gene symbols in brackets. §Many of these may also consistently have a thin or dysplastic corpus callosum, such as Sotos syndrome or agenesis of the corpus callosum (AgCC) with spastic paraparesis (*SPG11*). The overlap between AgCC and these conditions is still under investigation. Other gene symbols are omitted from this section. 4p –, deletion of the terminal region of the short arm of chromosome 4, defines the genotype for Wolf–Hirschhorn patients; *ARX*, aristaless-related homeobox gene; CDH, congenital diaphragmatic hernia; *KCC3*, KCl co-transporter 3; *L1CAM*, L1 cell adhesion molecule; MR, mental retardation; *MRPS16*, mitochondrial ribosomal protein S16; *SPG11*, spastic paraplegia 11; *ZFHX1B*, zinc finger homeobox 1b.

Microarray-based comparative genomic hybridization
(CGH). A method that compares the quantity of DNA across the whole genome between two individuals. Two DNA samples are labelled red and green, respectively, and are both hybridized to a slide that has an array of many thousands of spots containing DNA from unique places in the genome. The colour ratio at each spot determines the relative amount of DNA present between the two samples.

Sotos syndrome
Also known as cerebral gigantism, this is a genetic disorder that results in early physical overgrowth and cognitive impairment. Most cases are caused by haploinsufficiency of the gene *NSD1*, which is a coregulator for steroid receptors.

Heterotopia
In general, this term refers to the displacement of neuronal cell bodies into the white matter.

Tachistoscopic
Presentation of visual stimuli more rapidly than the eyes can move. Tachistoscopic presentation thus results in a visual stimulus being perceived in only one hemisphere; representation of the image in the opposite hemisphere will require interhemispheric transfer of information.

Stroop interference effect
A measure of reaction time when identifying one feature of a stimulus, while inhibiting a dominant tendency to identify it according to an interfering feature (for example, the normally increased reaction time when naming the ink colour of the word "red" printed in green ink).

Bilateral field advantage
The normal decrease in reaction time when comparing two stimuli presented in opposite visual hemifields, compared with presentation of both within one hemifield. The reason for this advantage is dual processing, that is, each hemisphere only has to process one stimulus. Without efficient interhemispheric transfer, there cannot be such an advantage.

involve multiple neural mechanisms[108]. Examination of symptom overlap between psychiatric disorders and AgCC may help to isolate the symptoms that are directly caused by a dysfunction in cortico-cortical connectivity.

There are also structural similarities between AgCC and some psychiatric disorders. Indeed, structural correlates of abnormal brain connectivity are evident in essentially every psychiatric disorder that has been examined. For example, several studies have found altered morphology of the corpus callosum in schizophrenia patients, including changes in size and shape, as well as microstructural changes in callosal regions that are revealed by diffusion MRI (dMRI)[31]. There are also a number of reports of complete AgCC in patients with schizophrenia[50,80,109], underscoring a direct connection between AgCC and schizophrenia and countering claims that the smaller anatomical changes in the corpora callosa in patients with schizophrenia are not causally related to the condition. Corpus callosum size, especially its anterior sectors, is also decreased in some cases of autism[110,111]. Moreover, in one study, 8.5% of individuals with AgCC had a diagnosis of autism, compared to only 1% of their siblings[112]. Microstructural

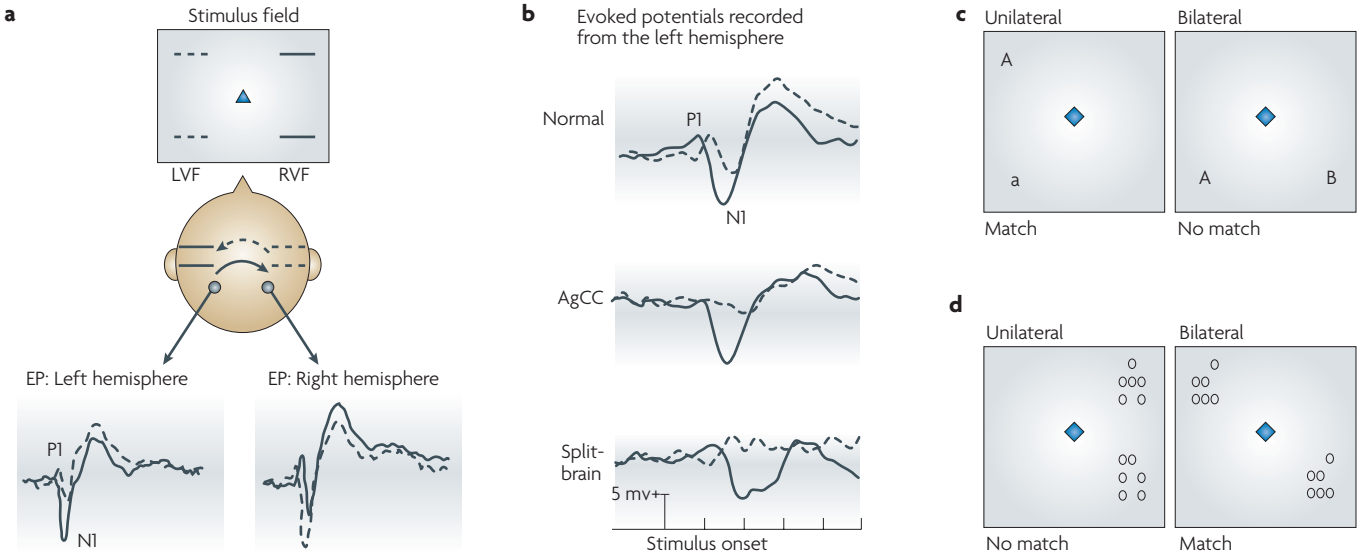

Figure 4 | **Interhemispheric transfer in AgCC.** Illustration of interhemispheric transfer (IHT) limitations in individuals with agenesis of the corpus callosum (AgCC). Panels **a** and **b** show an absence of interhemispheric conduction of the early visual evoked potential components that index sensory activity in the extrastriate visual cortex (that is, P1 and N1 components), in both patients with commissurotomy and individuals with AgCC[68]. **a** | Visual evoked potential (EP) recording paradigm. Right visual field (RVF) stimuli (top, solid lines) first result in evoked responses from locations within the left hemisphere (bottom left), and then following IHT (middle, solid arrow) evoke responses in right hemisphere locations (bottom right). The bottom panels show samples of typical evoked potentials from the left and right hemisphere recording locations within a healthy brain in response to the RVF (solid lines) and left (dashed lines) visual field (LVF). **b** | Comparison of left hemisphere evoked responses to stimuli in the right (solid lines) and left (dashed lines) visual fields. In the normal brain (top), the delay created by IHT is indicated by the later and smaller P1 and N1 components to the LVF stimuli (dashed lines) compared with RVF responses (solid lines). P1 and N1 components for LVF stimulation are absent in left hemisphere recordings of both the person with AgCC (middle) and the patient with commissurotomy (bottom), indicating that the corpus callosum is necessary for the IHT of visual information. **c**,**d** | Experimental conditions that reveal limitations in the ability to compare visual information from right and left visual fields[68]. Each square is an example of a stimulus used in a letter- (**c**) and dot pattern- (**d**) matching task. While participants looked at a central fixation point (solid diamond), two stimuli to be matched were flashed tachistoscopically in various configurations (bilateral or unilateral) in each trial. Patients with AgCC could make bilateral letter matches as well as control participants (presumably by using extra-callosal pathways). However, patients with AgCC could not successfully match bilaterally presented dot patterns, which is a more complex task that cannot use semantic simplification, suggesting that there is a limit on information transfer via non-callosal pathways. Panel **a** modified, with permission, from REF. 147 © (1993) Elsevier Science.

Anterior commissure
A small band of approximately 50,000 axons that connects the cerebral hemispheres. The anterior commissure connects the temporal lobes and is located at the base of the fornix.

Dichotic listening
A research method testing language lateralization by simultaneously presenting different auditory input to each ear. The degree to which individuals preferentially recall information from one ear or the other is an indication of which hemisphere is dominant in language processing.

Syntax
Grammatical arrangement of words and phrases in a sentence, which affects relationships of meaning. For example, changing the placement of a word or phrase can change the meaning.

Linguistic pragmatics
The processes that allow one to go beyond the literal meaning of language and actually interpret the speaker's intended meaning. This may involve utilizing second-order meanings, body language, vocal inflection, context and other factors.

Valence
A continuous scale from pleasant to aversive.

changes in the corpus callosum have also been found in patients with Tourette's syndrome[113] and attention deficit hyperactivity disorder (ADHD)[114,115]. One recent study provides evidence linking genetic changes in *KCC3* (the gene mutated in Andermann syndrome) with bipolar disorder[116], even though these patients did not have evident changes in callosal anatomy. As more causes of AgCC are identified, we anticipate that further genetic correlations between AgCC and neuropsychiatric disorders will be found.

The functional consequences of structural changes in brain connectivity, which might be revealed by dMRI analysis[117] including diffusion tensor imaging (DTI), contribute to cognitive impairment. Functional connectivity studies show that the strength of the correlations between brain activation in different regions and anatomical abnormalities is strikingly task-dependent. For example, children with ADHD show a disturbed transcallosally mediated motor inhibition[118]. Functional connectivity studies in patients with AgCC might reveal the means by which these highly atypical brains attain such apparently 'typical' interhemispheric interaction. In turn, understanding the functional limits of such connectivity may contribute to knowledge about psychopathological conditions with apparent corpus callosum involvement.

AgCC, like many psychiatric disorders but unlike callosotomy, results from abnormal development of connectivity. It may therefore be able to shed light on the behavioural and cognitive consequences of abnormal connectivity during development in general, as well as on potential compensation due to early intervention — a topic that is now receiving much interest, especially in studies of autism[119]. Of course, most people with autism, schizophrenia or ADHD do not typically have gross absence of the corpus callosum. Nonetheless, insofar as AgCC models one specific component (namely, altered connectivity) of what is likely to contribute to the cognitive symptoms of these psychiatric diseases, it may allow us to isolate a subset of symptoms that arise primarily from altered connectivity. Because disorders as complex as autism are not likely to

have a single correct explanation[108], finding clear genetic and neuroanatomical models that can dissect particular aspects of such disorders may be invaluable. Considering all of the above, AgCC might be a powerful model for studying behavioural and cognitive aspects of a number of psychiatric disorders.

Integrating findings across disciplines

We have emphasized the genetic and developmental nature of AgCC, and described its cognitive neuropsychology. How can data from these different domains best be synthesized? In linking genes and development to behaviour and cognition, one approach is to postulate multiple intermediate traits or endophenotypes, a compelling concept that has been developed to dissect the causes of complex psychiatric disorders[120]. One category of endophenotype is the anatomy. We propose that the principal anatomical endophenotype in AgCC is the absence of the corpus callosum. Regardless of the diverse genetic and developmental factors that result in AgCC, callosal absence in itself may directly lead to the behavioural and cognitive symptoms we have described in this review. However, additional neuroanatomical factors such as Probst bundles, colpocephaly, abnormal ipsilateral connections and abnormal cortical folding may well contribute separately to the clinical outcome of patients with AgCC by functioning as independent endophenotypes within the AgCC clinical complex, as well as contributing to other disorders such as schizophrenia and autism.

Thus, the endophenotype concept as applied to AgCC proposes that the abnormal neuroanatomy is generated by genetic and environmental factors operating on development, and that the neuroanatomy in turn generates the behavioural phenotype seen in AgCC. Such a picture offers intriguing possibilities for drawing parallels with psychiatric illness. Are there sets of genetic mutations or environmental factors that might contribute both to AgCC and to psychiatric illnesses such as schizophrenia and autism? Are there sets of cognitive and behavioural impairments that are common to both AgCC and those psychiatric illnesses? Commonalities at either the genetic, environmental, anatomical or behavioural level would provide preliminary support for hypotheses that callosal and other cortico-cortical white matter tract impairments are central to these disorders. We therefore suggest that geneticists, anatomists, cognitive neuroscientists and psychiatrists need to collaborate closely to take full advantage of the insights that AgCC can offer into understanding psychiatric illness.

Conclusions and future directions

Research on AgCC holds great promise for multiple scientific disciplines. In the field of genetics, much needs to be learned about the mode of inheritance. Most current data point to sporadic and polygenic inheritance. Identification of additional fully penetrant genetic causes will provide important insight into callosal development and function. As these genetic causes are illuminated, understanding the range of behavioural phenotypes that correlate with the genetics may be particularly useful for informing family planning decisions, for understanding related psychiatric conditions and for developing early intervention strategies for children whose developmental trajectories can be more accurately predicted.

The biological basis of AgCC is complex; this is reflected by the large number of human congenital syndromes associated with AgCC. It is perhaps one of the most complicated neurological birth defects simply because so many developmental processes are involved in the final readout of a fully formed corpus callosum. It is this observation that makes AgCC a plausible model for many other neurological and psychiatric illnesses with neurodevelopmental components. Callosal development can be affected by defects in cellular proliferation and migration, axon growth and guidance, glial development and patterning at the midline. Understanding the basis of the many disorders associated with AgCC, such as schizophrenia and autism, requires not only the identification of genes that regulate each of these processes but also a deep understanding of the function of each of the genes and how they work together in separate and overlapping molecular pathways to produce a corpus callosum.

AgCC is also particularly interesting to those studying network plasticity and compensation, as it does not result in the classic disconnection syndrome seen following surgical disconnection in adulthood. Careful integration of imaging and electrophysiology methods may provide important information about the intra- and interhemispheric connections in AgCC, similar to current work with split-brain patients[5]. In turn, AgCC provides a powerful test-bed for the integration of methods such as dMRI, fMRI and electroencephalograms to examine effective connectivity: given the demonstrable gross absence of specific structural connectivity, how does this translate into the functional deficits? Generating a functional map of AgCC brains will inform crucial questions about cortical and subcortical reorganization: where are particular functional regions (for example, specific visual areas and areas involved in language) located? To what extent do their locations differ from those in healthy brains? Are there some functional regions whose anatomical location remains relatively invariant, and are there others that can shift location more variably? Such questions have been much investigated in studies of plasticity in animal brains; next to nothing is known about this in the human brain.

Of course, the people most invested in AgCC research are the individuals and families who deal with this condition. Neuropsychological and behavioural characterization of AgCC may help clarify distinctions between it and various behavioural diagnoses (for example, autism, Tourette's syndrome and ADHD). Methods from cognitive neuroscience will be the most fruitful route to understanding the mechanisms underlying the cognitive and psychosocial characteristics that are common in primary AgCC. In turn, by using this information clinicians can develop more nuanced interventions for key deficits in AgCC, such as social skills, problem solving and planning, with the goal of enhancing the everyday lives of individuals affected by this disorder.

Diffusion tensor imaging
(DTI). Anisotropic diffusion within tissues is modelled as a second-rank tensor, which can be calculated from diffusion-weighted MRI acquired in six or more non-collinear directions. The tensor at each point in the image can be visualized as an oriented and scaled ellipsoid. More simply, quantities such as the mean diffusivity and fractional anisotropy can be calculated from the tensor and visualized as conventional images. The tensor contains information about likely axonal fibre direction and can be used to create virtual fibre tracts through the DTI, reflecting structural connectivity in white matter.

Endophenotype
A characteristic that is a subset of a particular condition and may be shared by individuals who do not have the full disorder.

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Competing interests statement
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DATABASES

The following terms in this article are linked online to:
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
ARX | *Disc1* | *Fgfr1* | *Gap43* | *Gfap* | KCC3 | *L1CAM* | *Nfia* | *Nfib* | SLIT2
OMIM:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
autism | schizophrenia

FURTHER INFORMATION

Corpus callosum research program: http://www.emotion.caltech.edu/AgCC
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