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Rainer W. Guillery and the genetic analysis of brain development

DR. Christopher A. Walsh

Division of Genetics and Genomics Howard Hughes Medical Institute Boston Children's Hospital Departments of Pediatrics and Neurology Harvard Medical School CLS15062, 3 Blackfan Circle Boston MA 02115, Christopher.walsh@childrens.harvard.edu

Abstract

Ray Guillery had broad research interests that spanned cellular neuroanatomy, but was perhaps best known for his investigation of the connectivity and function of the thalamus, especially the visual pathways. His work on the genetics of abnormal vision in albino mammals served as an early paradigm for genetic approaches for studying brain connectivity of complex species in general, and remains of major relevance today. This work, especially on the Siamese cat, illustrates the complex relationship between genotype and physiology of cerebral cortical circuits, and anticipated many of the issues underlying the imperfect relationship between genes, circuits, and behavior in mammalian species including human. This review also briefly summarizes studies from our own lab inspired by Ray Guillery's legacy that continue to explore the relationship between genes, structure and behavior in human cerebral cortex.

Keywords

Siamese Cat; genetics; brain development; cerebral cortex

When Ray Guillery died last April, neuroscience lost a great mind and a great person, a giant intellectual leader who was so understated that his remarkable contributions may not be as widely known as they should be. Those of us fortunate enough to have spent an extended period of time with him during our training believe that our careers bear his indelible imprint, if not being largely defined by his influence. In this piece I will try to capture Ray's approach to science and its effects on me, with apologies that there is no clear way to describe this other than being autobiographical. His thoughts and imprint live on, and readers unfamiliar with the man will undoubtedly find his way of thinking about the brain to be interesting and informative (Guillery, 2017).

I will never forget the first lab meeting when I heard Ray present. I was a first-year graduate student, and this meeting captures in my mind the essence of his genius, recognizable by those who knew him. He was teaching us about the phenomenon of transsynaptic degeneration, discovered by Bernhard von Gudden (Muller, 2001), whose work Ray was studying at the time: removing the eyes of newborn animals to understand how this manipulation affected the patterns of connectivity of the remaining eye. He told us not only about von Gudden's work, but the entire story of von Gudden, who was best known as the personal psychiatrist for "mad" Prince Ludwig of Bavaria, the benefactor of Richard Wagner, and the designer and builder of Neuschwanstein (the castle in Bavaria that is the

model for the Disneyland castle). And to cap it off, he told us the enduring mystery story of how von Gudden and Ludwig died together under the most mysterious of circumstances, drowned in 3 feet of water in the midst of controversy about Ludwig's fitness to lead the country (Guillery, 2011).

This was Ray. He was always putting science into a larger cultural-philosophical context, bringing in art and history and humor. We would talk science and philosophy over lunch in a subbasement conference room at the University of Chicago, eating our sandwiches and drinking black coffee. At some point I would make some poorly-informed philosophical generalization, and he would pounce on me and tell me I was shooting from the hip. We talked about Kuhn's "Structure of Scientific Revolutions" (Kuhn, 1962), and what really counted as a revolution in neuroscience and what did not. He told me about how 19th century neuroanatomists were influenced by their culture and intellectual traditions—those west of the Rhein river (such as Campbell, and Cajal) by the empiricists such as Berkeley and Hume, while those east of the Rhein (such as Kolliker, Brodmann, and the Vogts) by the idealists such as Kant. We can see this in the classification of cerebral cortical areas: Cajal describes 9 layers in some areas, and 5 layers in other areas, describing them one at a time as they appear under the microscope. In contrast, Brodmann postulates an over-arching developmental-functional-evolutionary "Uhrstruktur" of a conserved 6-layer structure—but nonetheless one that is subject to absence of layers in some places and duplication of layers in other places (Brodmann & Garey, 2006). Which system is better? How do we define which system is better? Though Ray loved to poke fun at the Germanic culture into which he was born, such decisions like this are based on scientific utility, and here he concluded that Brodmann's concept of a shared 6-layered structure has certainly been biological insightful and useful.

Of course, one of Ray's greatest scientific heroes was Ramon y Cajal, and he transmitted that love to me by talking about the man, his work, and his unique character as he had understood it (he himself never having met Cajal). When he indicated that anyone serious about neuroanatomy had to read Cajal's "Histologie du Systeme Nerveux" (at that time not available in English), I promptly embarked on teaching myself enough French so that I could stumble through it. Ray also encouraged me to take extra coursework in genetics, unusual for a budding neuroscientist, but which had a permanent influence on my future course.

Ray taught us Peter Medawar's credo that Science is the "Art of the Soluble" (Medawar, 1967). By that he meant to take an impossibly difficult problem—understanding the function of the brain, for instance—and find within that a problem that was interesting, but nonetheless "soluble" on some level—for which definitive data could be found, or a specific hypothesis disproven. The disproof of hypotheses was how Medawar writes that science moved forward, leading to his famous critique of psychoanalysis as being useless because it was essentially non-disprovable. It was not just this approach of finding soluble problems that influenced me, but the discipline of reflecting on how we we find soluble problems that has had a lasting effect. Medawar's books are still as timely now as then, and I recommend them to students and postdocs.

One of the many projects ongoing in Ray's laboratory at that time was the study of the Siamese cat (Guillery, 1969; Guillery *et al.*, 1974; LaMantia, 2018; Mason & Guillery, 2018; Taylor, 2018). Siamese cats are a temperature-sensitive albino mutation, hence their dark points, and they manifest abnormalities of the visual system that Ray and others described in albinos of many, apparently all, mammalian species, including humans (Guillery, 1971; Guillery *et al.*, 1971; Guillery & Kaas, 1973; Guillery *et al.*, 1975). In each albino, a majority of the retinal ganglion cell fibers from the temporal retina that would normally project to the ipsilateral (same side) lateral geniculate nucleus instead send their axons contralaterally—to the same spot but the wrong side of the brain. This creates a disorderly map of the retina in the LGN and, if transmitted unaltered to the cortex, a highly abnormal visual map on cortex in which a single cortical column would receive input from two different points of the same retina--in essence, data from two noncorresponding points in visual space—hence a fundamentally ambiguous visual map that would seem to prevent normal motor behavior (Figure 1). Yet, Ray and Jon Kaas showed that relatively normal visual behavior on the part of Siamese cats in their Midwestern colony reflects the suppression at the level of the cerebral cortex of much of the abnormal input, and Viven Casagrande showed that the visually guided behavior of Siamese cats is generally excellent (Guillery & Casagrande, 1977; Casagrande *et al.*, 1978). Even more amazingly, Hubel and Wiesel showed in their own "Boston" Siamese colony an alternative solution—a true developmental miracle--in which the globally abnormal visual map is recognized as abnormal prior to the eyes opening, and is reorganized to reconstruct at the level of the cortex an orderly map of the world (Hubel & Wiesel, 1971; Kaas & Guillery, 1973; Guillery & Casagrande, 1977; Cooper & Blasdel, 1980).

Thus, the Siamese cat presents two fundamental and fascinating problems in developmental biology. One relates to how retinal ganglion cells are instructed to project to one side or another of the brain, and what is the role of pigment—which is only detectably present in the pigmented retina and not in the neural retina—in this process? This issue is discussed elsewhere in this issue (Mason, 2018). And the second developmental problem, much more profound, is about how the 'non-genetic', or perhaps epigenetic, map reorganization (prior to visual experience) takes place. This latter question raised fascinating issues of the roles and limits of genetic explanations, taken up in a review article by Gunter Stent at the time.

"For the viewpoint that the structure and function of the nervous system of an animal is specified by its genes provides too narrow a context for actually understanding developmental processs and thus sets a goal for the genetic approach that is unlikely to be reached. Here 'too narrow' is not to mean that a belief in genetic specification of the nervous system necessarily implies a lack of awareness that in development there occurs an interaction between genes and environment, a fact of which all practitioners of the genetic approach are certainly aware. Rather, 'too narrow' means that the role of the genes, which, thanks to the achievements of molecular biology, we now know to be the specification of the primary structure of protein molecules, is at too many removes from the processes that actually 'build nerve cells and specify neural circuits which underlie behavior' to provide an appropriate conceptual framework for posing the developmental questions that need to be answered."(Stent, 1981)

To a naïve, second-year graduate student the non-genetic, compensatory alteration of thalamo-cortical pathways that occurs in Siamese cats, in which disordered mapping is either selectively suppressed or globally reorganized into a continuous map of visual space, harkened philosophically to Emanuel Kant's Critique of Pure Reason (Kant, 1998), in which he proposed that space, time and the categories are forms *imposed* by the mind (or brain) on the stuff of sensory experience. Hence, this forced visual reorganization represents a demand that the brain, or the "unity of consciousness" of Kant, can only function according to certain rules that in this case demand an orderly representation of visual space at all costs. Thus, neural mechanisms at the level of cortex demand orderly maps of the world, and when they are disrupted at the retinogeniculate level by albinism, they are reconstructed at the level of cortex by nongenetic mechanisms.

Back then, as I was casting about for a PhD thesis project, defining the biological instantiation of Kant's "a priori" knowledge in the thalamo-cortical reorganization of Siamese cats, did not seem to satisfy Medawar's dictum of the "Art of the Soluble" by a good bit. Even the seemingly simpler problem raised by the albino--defining how pigment might regulate axon crossing--seemed difficult and not well modeled by mice, where the genetics is good but the animals have only a puny uncrossed visual projection so that the magnitude of the effect of albino mutations is small. So my thesis with Ray settled for soluble problems. For example, working with Ray and Ed Polley, we described the timing and pattern of neurogenesis of the cat's retinal ganglion cells, finding that distinct subtypes (medium, large, and small) are generated sequentially within a given spot of the retina, forming multiple waves of production (Walsh *et al.*, 1983; Walsh & Polley, 1985). And Ray and I examined the pattern of outgrowth of retinal axons through the optic nerve, chiasm and optic tract in relation to these patterns of neurogenesis (Walsh & Guillery, 1985; Walsh, 1986; Guillery & Walsh, 1987a; b), finding that axons organized themselves in the optic system according to the sequence of production of the parent neurons (Torrealba *et al.*, 1981). Our thinking was that, even if these studies would not solve the albino problem (and they did not), they might be useful background for getting at it. Notably three papers from my PhD thesis with Ray (Polley & Walsh, 1984; Walsh & Polley, 1985; Walsh, 1986) were published without him as a co-author, which was as unheard of then as it is today, demonstrating Ray's tremendous generosity as a scientist and mentor.

Many studies from Ray's lab at that time were done on ferrets, an animal that Ray introduced into neuroscience as an ideal model to study development. While at Wisconsin, with its large veterinary school, he explored many different mammalian species in terms of their visual system organization, and in terms of genetically induced retinogeniculate abnormalities (Guillery, 1971; Guillery *et al.*, 1979; Linden *et al.*, 1981; Huang & Guillery, 1985). While their general brain and visual organization and timing of development resembles the cat and other Carnivora, ferrets are born in very large litters (6–12 kits), and only 40–42 days after conception, right in the middle of cerebral cortical neurogenesis (Jackson *et al.*, 1989), so that half of cortical neurogenesis occurs after birth, and much of retinogeniculate axon maturation occurs postnatallay as well (Cucchiaro & Guillery, 1984). He not only used them for postnatal manipulations, but also pioneered and described how remarkably amenable they are to fetal surgery.

Ray left Chicago for Oxford just as I finished my PhD, and at Oxford, he continued work on the organization and development of retinal projections to the thalamus, albino abnormalities, and thalamic structure (LaMantia, 2018; Mason & Guillery, 2018; Taylor, 2018). He also showed how sensory inputs wire into circuits that have already formed with their own internal logic, and studied how corticothalamic and thalamocortical projections organize and reorganize on their respective routes (Mitrofanis & Guillery, 1993; Guillery, 1995; Sherman & Guillery, 1996; Adams *et al.*, 1997; Molnár, 2018; Onat *et al.*, 2018). This work also resulted in his first book, with Murray Sherman, Exploring the Thalamus (Sherman & Guillery, 2001), and eventually to his second and final book (Guillery, 2017), where he increasingly thinks about relationships between thalamic and cortical and other connections, and how they relate functionally to our experience of the world.

I left Chicago soon after finishing my PhD with Ray, and continued to residency training in neurology at Massachusetts General Hospital, which at that time was a hotbed of pioneering human neurogenetics research, with the initiation of work to map and clone genes for Huntington's disease, familial Alzheimer's disease, and others (Martin, 1989). My subsequent postdoctoral fellowship with Connie Cepko involved learning molecular biology and more genetics, but was similarly descriptive from an anatomical point of view, with a focus on describing patterns of neurogenesis of cerebral cortical neurons using retroviral gene transfer. We developed libraries of retroviruses with DNA barcodes that could track clones of sibling cells regardless of where they migrated in the brain (Walsh & Cepko, 1988; Walsh & Cepko, 1992; Walsh & Cepko, 1993), so that we could extend methods she developed in the retina to studying the cerebral cortex. I continued to correspond with Ray about our findings, got his comments and support on some of our early papers, and adopted the ferret as an experimental animal for cerebral cortical cell lineage mapping as well after I started my own lab (Reid *et al.*, 1997; Ware *et al.*, 1999). In fact, our lab recently generated one of the first engineered neurological knockouts in ferrets, showing how much better they model defects of human cortical development than mice, and dedicated that paper to him posthumously (Johnson *et al.*, 2018).

My return to studying genes and cerebral cortical development—and now specifically human cerebral cortical development—started unexpectedly a few months after setting up my own lab in 1993. At a meeting in Venice I heard a short talk by Peter Huttenlocher, child neurologist and a former colleague of Ray's from the University of Chicago, and one of my teachers when I was in medical school there. Ray and Peter were good friends and both had suffered from the Nazi Regime as young children—Ray by escaping Germany in the middle of the night before the war (Sherman *et al.*, 2017), and Peter suffering through the war and its aftermath in Germany as a young child before leaving for America in the late 40s (Lin *et al.*, 2013). Peter presented a family with an inherited malformation of the cerebral cortex, called periventricular nodular heterotopia (Huttenlocher *et al.*, 1994)(Figure 2) which he already suggested was X-linked but lethal to males. When I heard him speak it seemed like an epiphany, one of those rare moments in science where I literally felt my heart race and my palms sweat, because here was a "soluble" problem in human developmental neurogenetics, to map and hopefully clone the gene responsible for the Huttenlocher syndrome. Peter had already shown that the gene was on the X chromosome, so how hard could it be to identify it, and then we could understand how that gene relates to the abnormal

cerebral cortical neuronal migration. Of course, this problem seemed soluble for the very reason that it lacked many of the subtleties and the Kantian scope inherent in understanding the wiring changes of the albino abnormality.

Our lab dove into the mapping (Eksioglu *et al.*, 1996) and cloning of the *FLNA* gene responsible for Huttenlocher's periventricular nodular heterotopia (Fox *et al.*, 1998; Sheen *et al.*, 2001). And this led to similar studies of "double cortex" syndrome (Figure 3), another X-linked cortical malformation, and the identification of the *DCX* gene responsible for that disorder, and the finding that *DCX* is a uniquely specific marker of newborn neurons (Allen *et al.*, 1998; Gleeson *et al.*, 1998; Gleeson *et al.*, 1999). That led to studies of dozens of other genetic malformations of the cerebral cortex (Figure 3), and from there we ventured more broadly into study of genetic intellectual disabilities and autism spectrum disorders. So, in many ways my subsequent career—analyzing genes that are essential for normal formation and function of the human cerebral cortex—was a direct followup, and an ongoing tribute to, the ideas that Ray first brought out, to define how the cerebral cortex is defined developmentally by a set of genes. Yet what Ray's work had already shown was how these genes nonetheless do not account for many of the most interesting and mysterious aspects of human brain function.

Though the developmental basis for the albino misrouting is still not completely understood, the description of the cortical mapping abnormality of human albinos has progressed considerably with noninvasive imaging methods (Morland *et al.*, 2001; Hoffmann *et al.*, 2003; von dem Hagen *et al.*, 2005; Bridge *et al.*, 2014). Remarkably, humans (Guillery *et al.*, 1975; Guillery, 1990; Hedera *et al.*, 1994; Hoffmann *et al.*, 2003; Kaule *et al.*, 2014) as well as other primates (Guillery *et al.*, 1984), often show the sort of conflicting cortical maps described by Ray and Jon Kaas in the Midwestern Siamese cats, in which there are two noncorresponding and mirror-reversed maps of visual space overlapping in the same hemisphere of primary visual cortex (Guillery, 1990). Stated in other words, area 17 of the right hemisphere has a map of the left visual hemifield as the textbook would say, with the midline represented at the 17–18 border and eccentricities of the visual field moving from center to left periphery mapping away from the border. However, that same area 17 also has a second, overlapping map of the *right* visual hemifield, with the midline again at the 17–18 border, but now eccentricities from center to right periphery also mapping away from the border, overlapping the other, mirror reversed visual map. How do two mirror-reversed maps of noncorresponding points in visual space on the same suite of neurons make sense? And furthermore how do albino humans, despite decreased visual acuity and depth perception, develop normal reading ability (Cole *et al.*, 1987; MacDonald *et al.*, 2012; Bridge *et al.*, 2014; Huurneman *et al.*, 2016b; a; c; 2017), remarkably normal motor behavior, and largely neurotypical cognition?

These questions raise broader questions that remain unanswered despite studies of thousands of patients with abnormally formed brains, caused by specific genetic defects, which has only deepened the mystery about the tremendous range of shape and form of the human brain that is often compatible with remarkably normal intelligence, and outward appearance and behavior. The variety of patterns of human cerebral cortical development that are consistent with neurotypical cognitive and behavioral development is enormous, suggesting

that the "normal" pattern of human brain development can be amazingly broad and permissive. For example, in Huttenlocher's periventricular heterotopia, typical patients have normal IQ and are behaviorally and cognitively indistinguishable from normal, although there is an increased rate of dyslexia, and patients are often first diagnosed when they have a brain MRI scan for other reasons (Chang *et al.*, 2005; Chang *et al.*, 2007). Yet, these patients have large numbers of cerebral cortical neurons arranged in irregular blobs centimeters from their normal locations (Figure 2), usually structurally and functionally connected to the overlying cerebral cortex in bizarre patterns that belie the neat 6-layered structure of textbook cerebral cortex (Christodoulou *et al.*, 2012; Christodoulou *et al.*, 2013; Shafi *et al.*, 2015). Are patients using these abnormally located cortical neurons in conscious thought, or are they capable of normal conscious thought despite the apparent interference of these abnormally positioned neurons? The genetic aspect of this is the tremendously wide variety of shapes and sizes that the human brain can be transformed into by the action of highly penetrant, Mendelian genes, that can arrest neurons in the wrong place, damage a hemisphere, or more. An extreme example is presented by hemimegalencephaly, the abnormal overgrowth of one cerebral hemisphere, reflecting somatic, mosaic mutations (present in some neurons but not all neurons), in genes such as *MTOR*, *AKT3*, *PIK3CA*, and *PIK3R* that all encode members of the MTOR pathway regulating cell proliferation and growth (Poduri *et al.*, 2012; D'Gama *et al.*, 2015; D'Gama *et al.*, 2017). The pathologically enlarged hemisphere never functions properly because of the mutation, and is the source of intractable epilepsy beginning at birth. Now the common treatment is surgical removal, or surgical disconnection, of the entire hemisphere, since the opposite hemisphere usually is normal and does not contain the mutation. Yet following hemisphere removal, living on just one cerebral hemisphere, many of these children can develop cognitively and behaviorally remarkably well (Figure 4).

Just as mysterious as the diversity of genetic abnormalities consistent with a relatively "typical" apparent experience of the world is the *diversity* of *abnormal* responses that can occur when the same highly penetrant genetic mutation occurs in different individuals. Many genetic mutations, including deletion or duplication of chromosome segment 22q11.2 (Fine *et al.*, 2005), or deletion or duplication of chromosome 16p11.2 (Weiss *et al.*, 2008; Hanson *et al.*, 2010) and certain highly penetrant point mutations--such as point mutations in *TSC2* (Numis *et al.*), *SHANK3* (Durand *et al.*, 2007; Guilmatre *et al.*, 2014), *CHD8* (Bernier *et al.*, 2014), and others--can cause a range of phenotypes in different individuals carrying essentially the same mutation. In most cases, individuals carrying such highly penetrant mutations are abnormal neurologically somehow, but the exact manifestations—whether intellectual disability, autistic symptoms, epilepsy, motor weakness, psychotic symptoms, or virtually no symptoms at all—are often remarkably variable between individuals with the same mutation, even from the same family (Manzini *et al.*, 2014). This variability of neurological manifestations of a shared genetic mutation again harkens back to Stent and to the Boston and Midwestern Siamese cats, where the neurophysiological and behavioral output of a given mutation reflects additional causes that we have yet to identify. Those many years ago, the Siamese cat already provided a way to conceptualize the neurobiology of such differences—that the same genetic mutation might have diverse effects on higher order cortical wiring in different individuals. But we know less about what these other

underlying causes of variability—or variable penetrance, in genetic parlance—might be. There are reasons to suspect that “common variation” at multiple sites in the genome might play a role, but I have always felt that the development of each complex brain is a singular history, in which the genes only establish initial conditions of a complex algorithm, and that stochastic, nongenetic, aspects of development might also play a role.

In his last year of life, Ray finished an amazing book that I recommend to all (Guillery, 2017), in which he proposed a plausible, unifying, neurobiological model to explain our private sense of self—i.e., a continuous internal sense of being and continuity. He presents a compelling argument that this psychological sensation reflects patterns of parallel recurrent projections through the brain, with central cortical centers essentially receiving a parallel report of outgoing motor signals via branched collaterals. His approach is radical in proposing specific connectomic pathways underlying some of our experiences that we think of as most uniquely human, while also suggesting that these same pathways—and perhaps analogous experiences—appear to be shared by other mammals. I find this model particularly appealing because it provides a simple explanation for how the wide variety of genetic forms of the human brain share certain common anatomical projection patterns that in turn might underlie commons patterns of thought. Ray’s book is completely neurobiological, while being admittedly speculative; but he has left us with a remarkable new vision that promises to move some one of the most “un-soluble” problems in neuroscience—those involving our experience of consciousness itself--into the realm of the testable.

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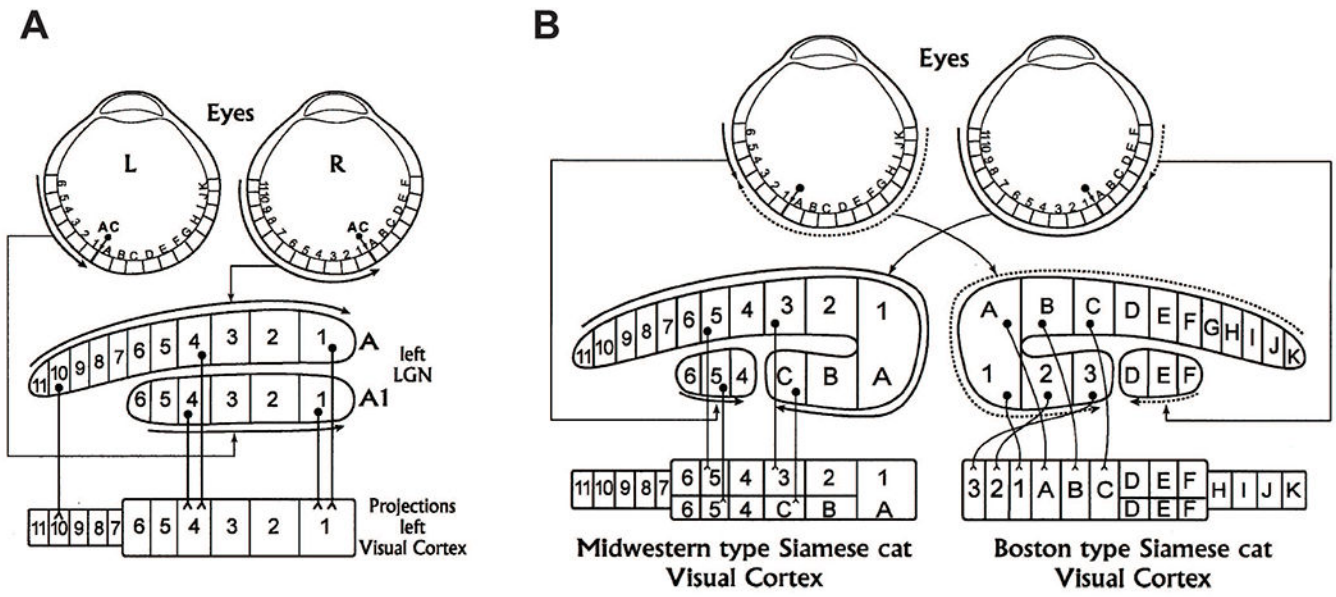

Figure 1.

The Siamese cat abnormality, as an example of albino abnormalities in mammals. Taken from Kaas (Kaas, 2005) (with permission), the left panel illustrates the normal pattern of partial decussation of visual fibers from the retina to the geniculate, and their normal pattern of projection to visual cortex. The right panel summarizes the abnormal patterns of decussation seen in the Siamese cat, in which fibers from temporal retina that normally project ipsilaterally undergo abnormal crossing at the optic chiasm. This panel also illustrates the two ways in which this abnormal visual input is corrected at the level of the visual cortex, either by a relatively normal pattern of geniculocortical projection (along with relative suppression of the abnormal input) in Midwestern Siamese cats, or reorganization and re-mapping of the abnormal input in the Boston cats.

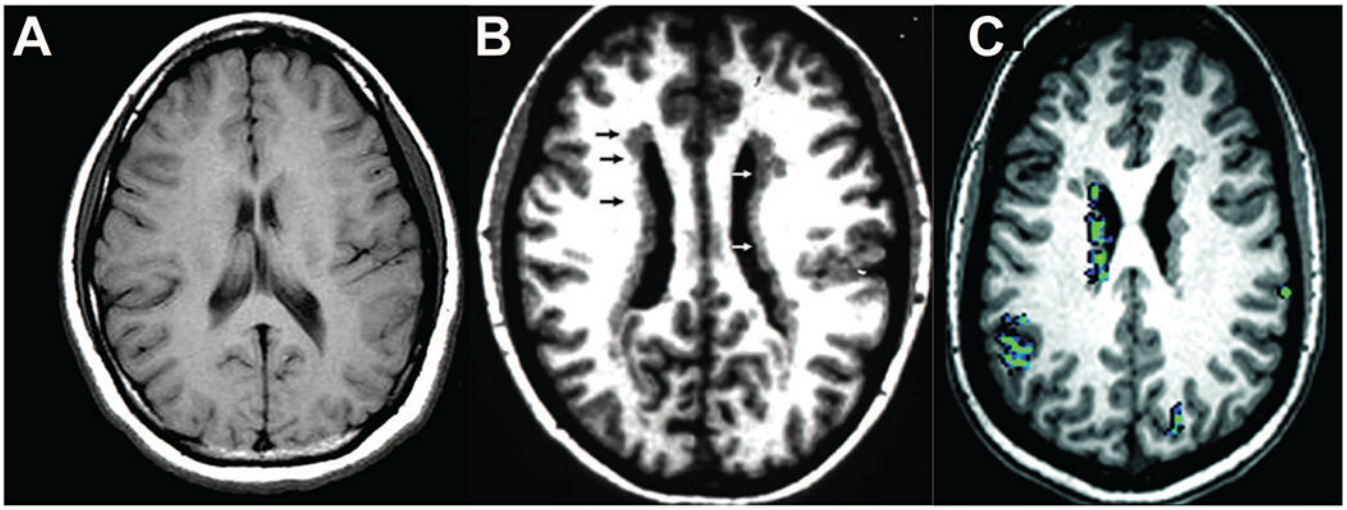

Figure 2.

Periventricular nodular heterotopia. The first image (A), shows an axial MRI scan from a normal individual, showing the normal configuration of the cerebral cortex, and ventricular lining. The ventricles show white matter signal right down to the ventricular surface, except for a small part of the ventricle shown on the left side where the body of the caudate nucleus appears near the ventricular surface. The middle image (B) shows an MRI scan of a woman with periventricular nodular heterotopia due to a mutation in the *FLNA* gene, in this case a *de novo* mutation not shared by her parents. The small arrows highlight the continuous lining of the ventricular surface on both sides with irregular nodules that show identical signal characteristics to normal cerebral cortex. Figure C is adapted from Christodoulou et al (2012) (with permission) and shows resting-state functional connectivity MRI with bold oxygenation level-dependent (BOLD) imaging. The periventricular nodules in this patient are highly active, and their activity is synchronized with overlying cortex, suggesting that these abnormally placed nodules are structurally and functionally integrated into cerebral cortical circuits.

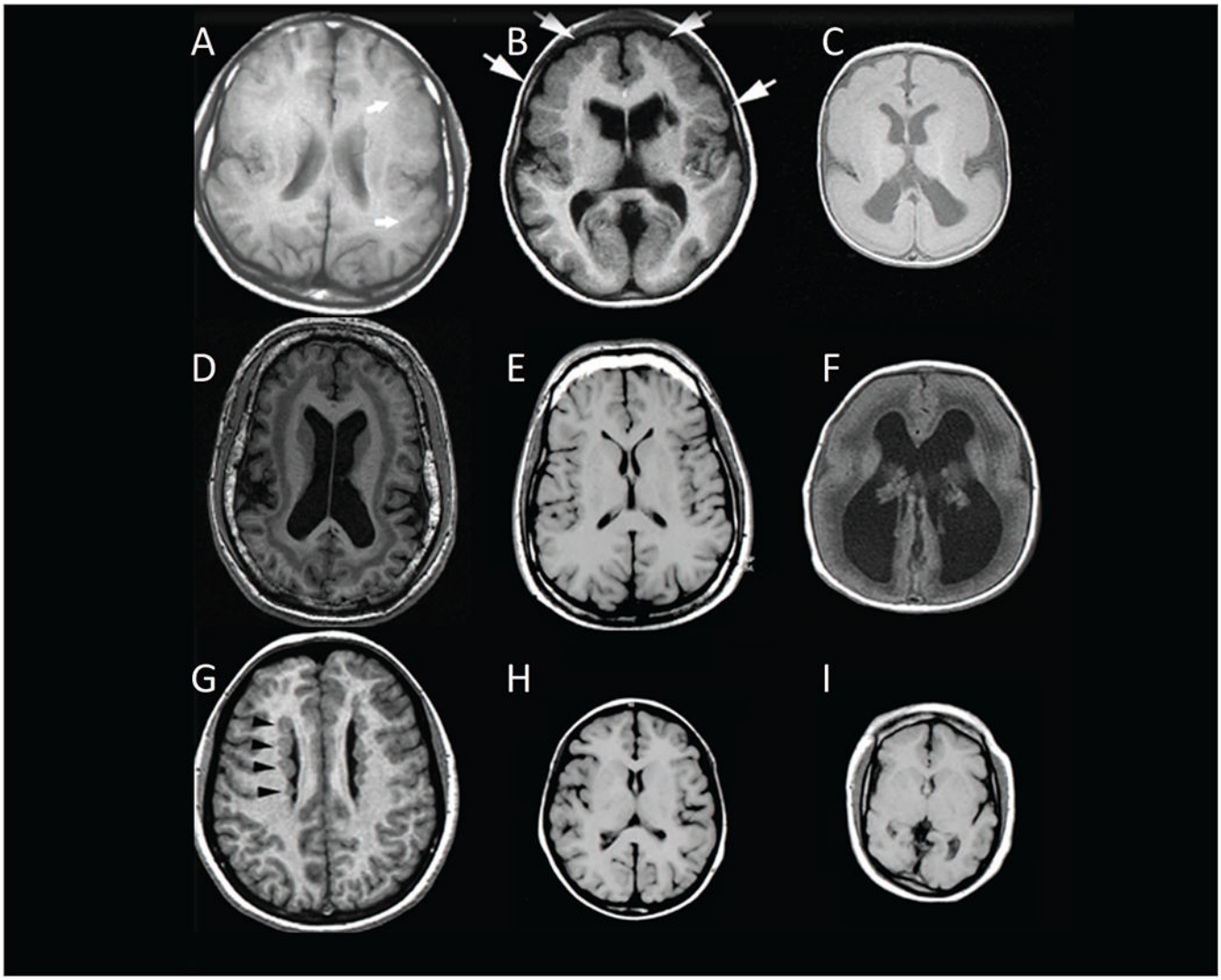

Figure 3.

Diverse human brain malformations. The panel shows axial MRI scans from a normal individual (E) surrounded by MRI scans of brains from 8 individuals with Mendelian disorders of cerebral cortical development. A, perisylvian polymicrogyria, presents with normal patterns of cortical folding frontally and posteriorly, with disrupted gyral folding in the perisylvian region (arrows). These patients have a wide range of intellectual and epilepsy phenotypes from almost normal to severely epileptic and intellectually disabled. B shows bilateral frontoparietal polymicrogyria, reflecting biallelic mutation in *GPR56*, associated with severe intellectual and motor disability. C shows classical lissencephaly, with a smooth, thick cortex, reflecting abnormal neuronal migration, and associated with intractable neonatal epilepsy, severe motor disability, and usually early death. D shows “double cortex” syndrome, in this case due to a female with heterozygous mutations in the X-linked *DCX* gene, and again showing a very wide range of phenotypes, generally proportional to the thickness of the abnormal subcortical band of neurons, and including intellectual disability and seizures. F shows Walker-Warbug lissencephaly, also associated with severe disability,

intractable epilepsy, and early death. G shows periventricular nodular heterotopia, with the abnormally located neurons highlighted by arrows, and associated with *FLNA* mutation. This condition is generally associated with normal intelligence and variable seizures, and with some patients being clinically asymptomatic altogether. H shows primary microcephaly, in this case due to biallelic mutation in *ASPM*, and associated with a cortex that is 50–60% reduced in volume, but relatively normally patterned, with normal cortical thickness, and associated with good motor function, intellectual disability, but usually some language development. I shows a patient with complex microcephaly with simplified and abnormal gyral patterning, in this case reflecting biallelic mutation in WDR62, and associated with more severe intellectual disability and motor delay.

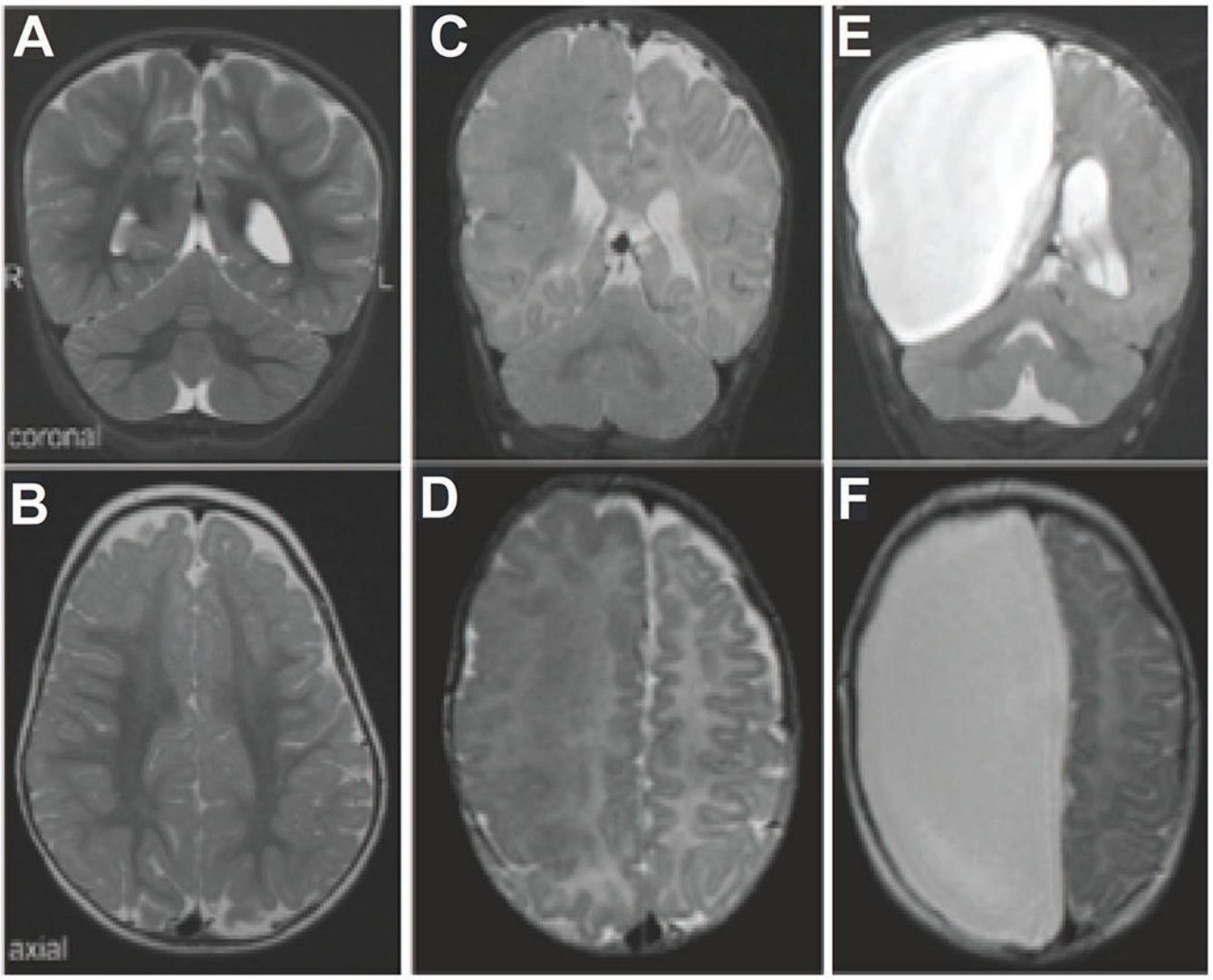

Figure 4.

Hemimegalencephaly before and after hemispherectomy. The entire right hemisphere was removed because of intractable epilepsy, replaced by mere cerebrospinal fluid (bright white). The child, who had suffered dozen of seizures a day, and was weak on the left because of the abnormal hemisphere, did very well after the surgery, going on to learn to walk, speak fluently, and read at grade level. Adapted from Poduri et al (Poduri *et al.*, 2012).