I. C. McManus. "Handedness, cerebral lateralization and the evolution of language"

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Correction: On page 195, in the last paragraph of the section, **Broca, the lateralization of language, and its relationship to handedness**, the third line should read, "is proportionately more common in *left*-handers".

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Handedness, cerebral lateralization, and the evolution of language

I. C. McManus

Introduction

To those proverbial and seemingly almost ubiquitous biologists and anthropologists from Mars, visiting planet Earth and trying to make sense of the vast and diverse animal kingdom, one of the most difficult phenomena to explain would be language. In a fully developed, practical and useful form it would seem to be restricted to just the one species, *Homo sapiens*, where it is apparently correlated with such overwhelming technical advantages that without it civilization and technology would seem impossible, and indeed its organizational advantages would seem to threaten the very existence of many other species on the planet. Perhaps most problematic in explaining why only one species exhibits language would be that the brain, which embodies the central nervous system whence all complex behaviours stem, would seem to be not substantially different in any qualitative morphology from that of many other vertebrates, particularly from that of other primates. Our Martians might observe that the human brain, and especially the frontal lobes, is somewhat larger relative to body size than in other species, but the differences are not immense. Neither are there in human brains any obvious 'language organs', any sets of nuclei or particular gyri which are conspicuously absent in apes or primates.

Eventually one of the Martians, perhaps one of a more experimental turn of mind, would cease observing and instead begin a little vivisection on the single peculiar species with language. And from that would come what is really the strangest of all the truths about language—that in most of the humans studied, the faculty of language would be destroyed by removing the *left* half of the brain, but almost unaffected by removing the right half. And to mystify the Martian yet further, the two halves of the brain when viewed anatomically would be barely distinguishable. The shock would be all the more surprising because the Martian would know that the function of the left lung is similar to that of the right lung—to exchange gases—and that the function of the left kidney is the same as that of the right kidney—to excrete waste products—and so on; so why on earth (or indeed, for that matter, why on Mars) should language be functionally asymmetric in an anatomically symmetric brain? And just to clinch it, why is functional asymmetry of similar extent found in almost none of the other myriad different brains found on earth—with the exception of the asymmet-

rical control of song in birds (Nottebohm 1977) and possibly of 'speech' in parrots (Snyder and Harris 1997)? There can be little doubt that our inquisitive Martian would feel sure that lurking in the asymmetry of language, in the phenomenon of cerebral dominance, was an answer to the question of what had happened in the evolutionary past that resulted in just this single species having that most crucial and sophisticated of faculties, language.

Broca, the lateralization of language, and its relationship to handedness

The above account makes a few small exaggerations—'always' should sometimes be 'almost always', and so on—but the key observation is correct, and it dates back to the findings of Paul Broca in the 1860s (Broca 1865; Hécaen and Dubois 1969; Schiller 1979) who observed that in a series of patients with aphasia, a loss of language, there was a concomitant paralysis of the right side of the body. Since the central nervous system shows decussation, the left cerebral hemisphere controlling the right half of the body, and *vice versa*, the implication was that in most people language was present in the *left* half of the brain. The general principle was rapidly confirmed by other researchers, although it did become apparent that a small proportion of individuals, perhaps 10% or so, had their language disrupted by damage to the right rather than the left side. At first it was often assumed that these individuals were left-handed (Eling 1984; Harris 1991, 1993)—in effect restoring some form of conceptual symmetry to an otherwise asymmetric brain. But it soon became clear from observations of patients with brain damage, then later from studies of language function during intra-carotid sodium amytal testing (Woods *et al.* 1988; Milner 1994), unilateral electroconvulsive therapy (Kopelman 1982), and also from dichotic-listening tests (Bryden 1988) and visual tachistoscopic studies (Beaumont 1982; Strauss *et al.* 1985) that the true relationship between handedness and language dominance was more subtle and more complex. A consensus view of this relationship is that between 2 and 10% of *right*-handers have language in the *right* hemisphere, and between 20 and 30% of *left*-handers have their language in the *right* hemisphere.

Notice that a majority of right-handers *and a majority of left-handers* have language in their left hemispheres, and that although right-hemisphere language is proportionately more common in right-handers, the majority of individuals with right-hemisphere language are actually right-handed, because right handers are about ten times more common than left handers. In practice the situation is made yet more complex by the fact that a moderate number of left-handers seem to show some form of bilateral language, whereas that pattern is rare in right-handers (Snyder *et al.* 1990).

The nature of hemispheric specialization

The precise nature of hemispheric specialization is still far from clear, and is complicated by a number of observations. After Broca's discoveries in the nineteenth century, it was felt that the left hemisphere was the 'dominant' or 'major' hemisphere, and that the right hemisphere, often referred to as the 'minor' or 'non-dominant'

hemisphere, had no specific function. However, it soon became apparent that there was also a specific class of syndromes, typically the agnosias, but also including the constructional apraxias and other disorders of spatial organization, that were associated with right-hemisphere lesions. This led to the concept of *complementarity* between the hemispheres, with the left hemisphere principally processing verbal, sequential, analytic tasks, and the right hemisphere instead being spatial, parallel, or holistic in its approach. Analysis of the dissociations between different neuropsychological syndromes after right- and left-hemisphere lesions showed, however, that in a number of patients there could be verbal functions and spatial functions seemingly in the same hemisphere (Bryden *et al.* 1983). More recent work has used dichotic listening to measure ear advantages for verbal distinctions (typically with a right-ear advantage) and for emotional judgements (typically showing a left-ear advantage) in the same normal subjects at the same time, and shown that there was no correlation between the strength of the two forms of lateralization (Bulman-Fleming and Bryden 1994). The implication is that the lateralization of functions in the two hemispheres is independent, and seems to be complementary only because a majority of the population is left-hemisphere dominant for verbal tasks and right-hemisphere dominant for other tasks. The modal pattern in the population therefore misleadingly suggests causal complementarity rather than the true situation of mere statistical complementarity (Bryden 1990).

The differences between the two hemispheres have stimulated many investigators to look for a deeper, more primitive asymmetry. Perhaps the most interesting asymmetries are those reviewed by Nicholls (1994, 1996) which suggest that there are differences in temporal processing between the two hemispheres, the left hemisphere being able to distinguish small time intervals more accurately, be they in the auditory, visual, or tactile modes. The potential for explaining language dominance is that the perception of subtle phonemic distinctions often requires judgements of voicing and other features that differ in onset by perhaps only 20 ms or so. Although this is an attractive idea, it must be remembered that language and speech are not the same thing. Recent work on deficits in sign language after brain damage suggests that although sign language is essentially spatial rather than temporal, with very different timing characteristics, it is still based in the left hemisphere (Hickok *et al.* 1996). The possibility therefore arises that it is some high-level feature of language *per se* that is lateralized, rather than a low-level process to do with perception of speech sounds. One obvious possibility is grammar. It is possible that this also is connected with superior temporal processing, because the active, dynamic parsing of sentences requires fast timing of sequentially ordered words, perhaps also benefiting from a left-hemisphere temporal processing advantage; although it could be argued that grammar in sign language is spatial, it does include a temporal dimension, and it also seems to be quintessentially left rather than right hemispheric (Hickok *et al.* 1996). That possibility might also fit in with the proposal of Corballis (1991) that the principal advantage of the left hemisphere is as a 'generative assembling device' (GAD), which enables not just grammar, but also praxis in the form of complex motor actions, together with the decomposition of complex visual images into their components in the form of a 'visual grammar' (a position much influenced by Biederman's 1987 theory of 'geons').

A complete and adequate theory of cerebral lateralization must not only explain how and why language is typically located in the left hemisphere and visuo-spatial processing of complex images is typically located in the right hemisphere. It must also explain how these processes can be independently located so that in some individuals they are seemingly in the same hemisphere, so they can be either ipsilateral or contralateral to the writing hand. Finally, it must also be accepted that there are probably many lateralized processes in the brain which have not yet been discovered, or are only just being discovered. Perhaps one of the most surprising to psychologists must be the highly lateralized processes of encoding and retrieval of memory. Memory research has dominated psychology ever since the pioneering experiments of Ebbinghaus in the late nineteenth century, and particularly since the advent of the cognitive psychology revolution in the 1960s. Memory was felt to be reasonably well understood and unlikely to show any major surprises in its neural organization. However with the advent of positron emission tomography in the late 1980s there were many studies of subjects encoding and retrieving information, and to the amazement of some of the leading researchers in the field it was found that there were baffling asymmetries. In particular, for episodic memory, the left prefrontal cortex appears to be involved in encoding whereas the right prefrontal cortex is involved in retrieval. Just to confuse matters even further, for semantic memory it is the left prefrontal cortex that is involved in retrieval (Nyberg *et al.* 1996). (There is no information on whether the encoding of semantic information is lateralized, because it is virtually impossible to perform the necessary experiments.) The so-called HERA model (hemispheric encoding/retrieval asymmetry) poses many problems for neuropsychology and, given the importance of semantic memory in language usage, those questions are likely also to be important for understanding the evolution of language.

The nature of handedness

Handedness is a deceptively simple phenomenon. Most people use just one hand for writing, usually the right, and if asked their handedness will refer to that hand. In a few cases they might preface their answer by saying that at school they had tried to write with the left hand but had been persuaded or forced to use the right, and are therefore 'naturally left-handed'. And in other cases people will explain that they seem to do some tasks with their right hand and some with their left, making them ambidextrous; in practice, true ambidexterity, if defined as the ability to write equally well with either hand, seems to be almost unknown. The details of handedness, however, are more complex. Firstly, one must distinguish between *direction* and *degree* of handedness. Direction refers to whether it is the right or left hand that is dominant, and degree refers to the extent of that dominance. These two phenomena are logically separate although many studies have confounded them by calculating a single 'laterality index' and then carrying out conventional statistics (McManus 1983). Direction of handedness undoubtedly runs in families, but whether degree does so is not at all clear, some studies finding it that does and others that it does not (McManus and Bryden 1992).

A further complication in defining handedness concerns the difference between *preference* and *skill*. For example, I am right-handed in two distinct senses—when asked to perform a task I *prefer* to use my right hand, and when I carry out a task with each hand I am more *skilled* with my right hand. In principle either skill or preference could be prior to the other: Thus I might have an innate preference for the right hand, which makes me use it more often, and hence it becomes more skilled, or I may be innately more skilled with my right hand, making me prefer it for more complex actions. Teasing the two apart is not easy, but one intriguing piece of evidence has been found in children with childhood autism (McManus *et al.* 1992), and has recently also been replicated in children with fragile-X syndrome (Cornish *et al.* 1997). In these individuals there is a clear overall *preference* for the right hand but half the individuals are more *skilled* with the right hand and half are more *skilled* with the left hand. The implication is that preference may be developmentally prior to skill, with preference normally causing subsequent skill asymmetry. That is, preference is the fundamental asymmetry.

Yet another problem for handedness concerns its dimensionality—is it a single entity or are there several independent components to it? Traditional handedness inventories and questionnaires have implicitly assumed that all items are equivalent and that there is a single underlying component. That assumption has been challenged in recent years by factor analytical studies of questionnaires suggesting that there might be between two and four underlying dimensions (Healey *et al.* 1986; Liederman and Healey 1986; Steenhuis and Bryden 1989). These studies are almost certainly flawed, not least in that they take no notice of the highly skewed distributions of scores on the individual items, which are effectively binary, and which almost certainly result in the artefactual factor structures known in psychometrics as 'difficulty factors' (Corballis 1968; Maxwell 1977; Gorsuch 1983; Bernstein and Teng 1989). Far more substantial is recent work by Peters and coworkers suggesting that there is a subgroup of left-handers who write with their left hand but are better at throwing, among other things, with their right hand (Peters and Servos 1989; Peters 1990; Peters and Pang 1992). Recent questionnaire analyses have suggested that about one third of left-handers are inconsistently left-handed in this sense, and in addition about 1 or 2% of the population are inconsistent right-handers, writing with the right hand but preferring to throw with the left (Gilbert and Wysocki 1992; McManus *et al.* in press). This separation of handedness into two components, one intimately linked with written language and the other with throwing, has clear evolutionary implications, particularly given the work of Calvin (1982, 1983*a*, *b*) on the possible importance of throwing in hominid evolution (and in particular of the crucial importance of precise *timing* in throwing).

The ontogeny and phylogeny of handedness

Handedness in some form or other is found in most mammalian species. Thus a cat, for instance, when given food at the bottom of a can, will automatically use one paw to scrape out the food, and in most cases individual cats will consistently use the same paw. That is, individual animals show handedness, footedness, pawedness, or what-

ever. Where humans differ from most other animals is that they show a population-level asymmetry, with about 90% of individuals choosing to use their right hand, whereas in cats, mice, and other species about 50% of individuals use the right paw and 50% the left paw for skilled activities (Collins 1968; Fabre-Thorpe *et al.* 1993). Although there is some evidence that in mice there are minor differences between strains in the frequency of right paw usage (Signore *et al.* 1991), the proportions never differ dramatically from 50% or begin to approach the 90% found in humans. One exception is the toad, in which there is a population-level functional asymmetry approximating that in humans (Bisazza *et al.* 1996), but it would seem that this is secondary to anatomical asymmetries that are probably related in turn to the asymmetry of the cardiovascular and gastrointestinal systems (Naitoh and Wassersug 1996). There is also the intriguing problem of handedness (or more accurately 'footedness') in parrots, where there does indeed seem to be a population level asymmetry, but only, it seems, for Australasian parrots, perhaps representing an evolutionary cul-de-sac (Harris 1989; Snyder *et al.* 1996). Recent controversy has surrounded the question of whether there is a population-level handedness in primates (MacNeilage *et al.* 1987). Some of the evidence for this is statistically inadequate (McManus 1987; Marchant and McGrew 1991), and in other cases there is clear evidence of a lack of population-level asymmetry, notably in gorillas (Annett and Annett 1991; Byrne and Byrne 1991). However, recent evidence does suggest that right-handedness in great apes might be above 50% (Hopkins 1995, 1996), but still well below the 90% incidence found in humans, and perhaps restricted to bimanual rather than unimanual actions (Hopkins and Rabinowitz 1997). A conservative conclusion might be that there are weak population-level asymmetries for handedness in primates, in particular in chimpanzees, but that none of these shows the extreme 90:10 ratio evident in humans.

In the hominid evolutionary record there is only a little adequate evidence for the evolution of handedness, most of which has been excellently reviewed by Steele (1997). The literature is complex but two important conclusions seem to be possible, although there is still much controversy (Noble and Davidson 1996). The first is that right-handedness seems to have been present between about 1.5–1.6 million years ago, based on asymmetries of the post-cranial skeleton (Walker and Leakey 1993) and in the production of asymmetric artefacts in the form of stone tools (Toth 1985). From these data the only sensible estimate we can make of the incidence of left-handedness in the population is that *none* of the population was left-handed—the relative proportions of left- and right-handed tools are the same as those produced by a fully right-handed sample of modern humans, although the statistics are not totally compelling. Certainly, the conclusion that there was an excess of right-handers seems robust, particularly when coupled with evidence suggesting that cerebral asymmetries were also present at about the same time and are different in form from those in non-hominid primates (Holloway and de Lacoste-Lareymondie 1982). More problematic is evidence concerning the existence of left-handedness, and its proportion in the population. Recent only partially reported findings at Boxgrove suggest clear evidence of at least one left-handed flint knapper (Pitts and Roberts 1997, p.175) dating from about 500 000 years ago, but statistics have not yet been reported on the other 150-plus stone tools found (and additional evidence based on teeth (p. 265) or

butchery marks (p. 198) suggests right-handedness). The analysis of handedness as depicted in works of art by Coren and Porac (1977) suggest strongly that left-handedness has been present in proportions similar to those of modern populations for at least 5 000 years (i.e. from about 3 000 BC), and that figure is compatible with the data of Spennemann (1984) on a large sample of Neolithic stone tools with right-handed and left-handed wear patterns. A very specific early example of left-handedness is associated with 'Ötzi', the Neolithic hunter found in a glacier in the Italian Alps (Spindler 1994), dated to about 5 300 years ago; he was found to be carrying two arrows, one of which had clearly been fletched by a right-hander and the other by a left-hander (BBC television, *Horizon: A Life in Ice*, 6 February 1997). These data suggest that left-handedness in its modern proportions could have arisen at any time between about 1.6 million and 10 000 years ago.

Little need be said about the ontogeny of human handedness except to emphasize that its direction seems to be set up quite early, typically between 18 months and two years of age, although degree of handedness continues to develop throughout childhood (McManus *et al.* 1988) and possibly even throughout the adult life-span (Porac *et al.* 1990). It is also possible that handedness is set up in utero, and the elegant data of Hepper *et al.* (1991), using dynamic ultrasound imaging of human fetuses, suggest that 90% or more of human infants are preferentially sucking their right rather than their left thumb by 15–20 weeks of gestation (although as yet there has been no reported follow-up into childhood to demonstrate that fetal thumb-sucking does indeed predict child and adult hand-preference). Data such as these, together with the lack of evidence for intra-familial learning of handedness (Leiber and Axelrod 1981) and the suggestion that in adopted children handedness correlates more strongly with biological parents' handedness than with adoptive parents' handedness (Carter-Saltzmann 1981), support the idea that handedness is probably under genetic control, and is little influenced by social learning—at least in the absence of coercion.

Genetic models of handedness

The central tenet of this chapter will be that handedness is under genetic control, that the peculiar aspects of its transmission in families can readily be explained by a simple genetic model, and that genetic model can also explain the association of handedness with language dominance. The problem will then be to explain how those genes evolved. Any such explanation, however, will necessarily be a partial theory of the evolution of language itself.

The important thing in understanding genetic theories of laterality is to realize that they are heavily constrained by biology. All other things being equal, there is a strong tendency for organisms to be approximately symmetrical, not least because symmetric organisms can cope better with a physical world in which it is necessary to swim, stand, walk, run, etc., and in which information is as likely to come from one point as another (Dawkins 1997). Building a symmetric body does, however, pose certain problems, mainly because parts of the body that are physically distant from one another cannot readily influence one another. Thus if one considers the embryologi-

cal mechanisms that result in the eventual growth of a limb, complete with upper arm, forearm, hand, and fingers, then the development of the left arm is independent of that of the right arm. In effect each limb is like a ballistic missile, each being launched into space with its own in-built program, coded in the genes, which should result in a similar limb being built on each side. Of course, just as two precisely identical ballistic missiles would not land at exactly the same spot, so the limbs on each side will not be exactly the same size or shape, each being buffeted by a myriad of tiny forces and disturbances, broadly described as 'biological noise', which result in the limb being deviated randomly from its target. The result is that the two limbs will not be quite identical; one will be slightly larger than the other, for instance, and in half of individuals it will be the left limb that is larger, and in half the right that is larger. This is the situation known as *fluctuating asymmetry* and it represents the biological baseline from which all lateralities develop. In the absence of any other form of control a population will show fluctuating asymmetry, and in the presence of noise or other randomness, fluctuating asymmetry will tend to override *directional asymmetries*, returning the symmetry towards 50:50. An example in which the asymmetry is actually reversed is the phenomenon of pathological left-handedness (Satz 1972).

Producing directional asymmetry in a biological system is not easy, and it is perhaps therefore not surprising that very few systems under genetic control have been described. Quite the best understood is that of control of *situs*, the side of the body on which the heart is placed, from which also flows all other asymmetries of the viscera, normally resulting not only in a left-sided heart but also asymmetric lungs, a liver and an appendix on the right, a spleen and a stomach on the left, and so on, including a mass of smaller asymmetries, such as those of the testes and ovaries (McManus 1976; Mittwoch 1988). In about 1 in 20000 humans the normal situation of *situs solitus* is reversed to give *situs inversus*, with the heart on the right, and all other organs also reversed, resulting in an individual who is anatomically a mirror-image of the normal. A similar situation occurs in mice, produced by the *iv* mutation, which has been extensively studied; the gene has been located (Brueckner *et al.* 1989, 1991), and recently has been sequenced in its entirety and been shown to be a mutant form of dynein (Supp *et al.* 1997). Individual mice with the normal 'wild type', +/+, or with a single copy of the *iv* gene, +/*iv*, all have the heart on the left side, but homozygotes for the iv gene, with genotype *iv*/*iv*, show precisely 50% with their heart on the left side and 50% with their heart on the right side—that is, pure fluctuating asymmetry. A similar mechanism almost certainly underlies many cases of human *situs inversus*, which also runs in families (Afzelius 1979; Arnold *et al.* 1983), and in at least one case is based on the X chromosome (Casey *et al.* 1993), where there seems to be mutations in a specific zinc finger gene (Gebbia *et al.* 1997). The biological basis of *situs* is very similar to that proposed for the genetic control of handedness and language dominance in humans.

The problem for any genetic model of handedness is to explain several well understood observations:

(1) although left-handedness tends to run in families, it does so only weakly, almost half of all left-handers having no known left-handed relatives (McManus 1995*a*);

(2) two right-handed parents can have left-handed children in about 5–10% of cases;
(3) two left-handed parents have left-handed children in only about 25–30% of cases (McManus and Bryden 1992); and
(4) monozygotic (identical) twins often differ in their handedness, although the proportion of discordant pairs is slightly lower in monozygotic pairs than in dizygotic pairs (McManus and Bryden 1992).

I have proposed a simple model (McManus 1985a) which explains this pattern of inheritance. According to this model, there are two alleles, *D* (Dextral) and *C* (Chance). Individuals with two copies of the *D* allele, *D/D*, are all right-handed. Individuals with two copies of the *C* allele, *C/C*, show pure fluctuating asymmetry, with 50% being right-handed and 50% being left-handed. Heterozygotes, the individuals with one of each allele, *D/C*, are midway between the homozygotes in their expression, 25% being left-handed and 75% being right-handed. This model is successful at explaining why handedness runs only weakly in families, and why neither right-handers nor left-handers 'breed true'—right-handers can be of any of the three genotypes, *D/D*, *D/C* or *C/C*, and hence can transmit *C* alleles to their offspring, who might well then be left-handed; likewise left-handers will be either of genotype *D/C* or *C/C*, and because the *D* allele is necessarily much more common than the *C* allele (since right-handedness is much more common than left) many of the children of left-handers will have *D* alleles, making them more likely to be right-handed. Even those rare individuals who are of the *C/C* genotype will still only have a 50% chance of being left-handed. The discordance of monozygotic twins is also readily explained, because in individuals who are *C/C* (or *D/C*) handedness will partly be determined by chance factors and those chance effects will be statistically independent in the two developing fetuses, resulting in discordant pairs. The model has also been developed somewhat to account for known sex differences in handedness (McManus and Bryden 1992).

Annett has produced a slightly different genetic model of handedness, the right-shift theory, the central feature of which is also fluctuating asymmetry. This model can also produce a good account of family data (Annett 1985). Detailed comparison of the two models suggests to me that the McManus model is somewhat superior, both in accounting for the family data (McManus 1985a) and also in accounting for the phenotypic distributions (McManus 1985b); perhaps unsurprisingly, Annett claims the converse (Annett 1996).

The relationship between handedness and language dominance

Earlier, I described the relationship between handedness and language lateralization. It is one of the successes of the modern genetic models of handedness that they naturally and elegantly produce the proportions illustrated by a simple extension of the models for handedness alone. In the model detailed above, all that is required is to postulate that the *D* and *C* alleles influence language lateralization in exactly the same way as they determine handedness. Thus *D/D* individuals are all right handed and are expected all to be left-language dominant. In contrast, *C/C* individuals show

fluctuating asymmetry for handedness and are expected also to show fluctuating asymmetry for language dominance, with half being left-dominant and half being right-dominant, and with handedness and language dominance again statistically independent, so that a quarter are right-handed and right-language dominant, a quarter are right-handed and left-language dominant, and so on for the four possible combinations. The *D/C* heterozygotes follow the pattern for handedness, so one quarter are right-language dominant and three quarters are left-language dominant, handedness and language-dominance again being statistically independent. Such a model not only produces almost exactly the proportions reported earlier, but can also be extended to consider the situation of there being two language centres, each being determined independently both of each other and of handedness. This extended model predicts very well the differences between aphasia occurring acutely after brain damage (if either centre is damaged), and chronically (when both centres have to be damaged), and also explains the fact that left-handers are somewhat more likely to recover from aphasia after brain damage than are right handers (McManus 1985*a*). A conceptually almost identical approach using the right-shift theory has also been put forward recently (Annett and Alexander 1996).

It can now be seen that this pleiotropy of the handedness gene, with independent effects on different cerebral lateralities resulting in what might be better called 'cerebral heterotaxy', can not only explain the association of handedness and language dominance but can also be invoked to explain many other problems of cerebral organization. Thus if the same gene determines some form of visuo-spatial functioning, which typically would be in the right hemisphere of *D/D* individuals, then one can see that in individuals with other genotypes it could instead be in the left hemisphere. And likewise, it might also be possible to explain the seemingly correlated but nevertheless independent location of writing hand and throwing hand to the right and left hemispheres. The genetic model therefore by means of a single, simple genetic mechanism—fluctuating asymmetry—can potentially explain much of the rich diversity of lateralized cortical organization for higher functions, and yet can also explain why many of the population—about 70% or so—will show the conventional textbook patterns of right-handedness, with language on the left, visuo-spatial function on the right, because they have the *D/D* genotype. The importance of diverse patterns of cortical lateralization is clear in conditions such as aphasia, and is now also becoming apparent in conditions such as stuttering, where positron emission tomography shows the presence of atypical speech-related centres in the right hemisphere (Fox *et al.* 1996).

The evolution of right handedness and language dominance

Thus far this chapter has argued that handedness and language dominance are under genetic control, with most individuals being right-handed and left-language dominant as a result of the effects of the *D* allele. Two things now need to explained: firstly, why do most individuals have the *D* allele, and secondly, why do some individuals have the *C* allele and hence are left-handed and right-language dominant. I wish to argue that what I will call the D^* allele is a specifically human innovation, that it

occurred some time before approximately 2.5 million years ago, when humans were becoming tool-users (Semaw *et al.* 1997) and properly bipedal, with locomotor bipedalism rather than postural bipedalism (Wood 1993), and that it was responsible for the right handedness found in *Homo ergaster*. Additionally, it was also responsible not only for right handedness but also for some form of early cerebral dominance, either for language or, more likely, for some form of proto-language. Before the evolution of the D^* allele I shall assume that handedness in hominids was 'determined' by what I shall call the C^* allele, which results entirely in fluctuating asymmetry in just the same way as does the C allele. For reasons that will become apparent later I will not however call it C, and neither will I wish to equate D^* and D. Either way, C^* is a null gene with no effect upon the development of handedness, so that handedness is 50% to the right and 50% to the left (as I presume is probably the case for most modern primates and particularly in their shared ancestors with the hominid line, although it is possible this proportion is 66:33, as has been suggested by Corballis 1997). The D^* allele must have had significant benefits for the early hominids and I presume that in some sense it was responsible for the shared characteristics of proto-language, throwing ability, manual dexterity, and the other characteristics which all seem to have co-evolved, and which might be intimately related neurologically and functionally (Calvin 1993). One possibility is that this gene directly affected the timing of processing in the left hemisphere, making it faster (perhaps even simply increasing what in a computer would be called the 'clock speed') and thereby making possible tasks such as accurate throwing, fine motor tasks, sophisticated locomotor bipedalism, and complex vocal gestures, all of which would benefit from greater processing power. Because these characteristics would be of enormous survival benefit to those carrying the D^* allele, it seems reasonable to assume that the D^* allele rapidly went to fixation, the C^* allele being eliminated from the gene-pool, and the entire early hominid population becoming right-handed (see Fig. 11.1).

Where did this D^* allele come from? As a general rule, new genes can only come from old genes, by mutation or, more likely, copying of an existing gene to a new location, followed by mutation. It has already been suggested that genes affecting laterality are surprisingly rare in biological evolution, a fact that tends to be forgotten principally because we are all so aware of the asymmetry in our own bodies and those of other vertebrates in the form of the heart. The genes and the control mechanisms which determine *situs* in vertebrates, including frogs, chicks, and mice, seem to be very similar (Ryan *et al.* 1998). They result in the otherwise morphologically symmetric early embryo showing a greater rate of growth in the cells on one side of the heart rudiment, causing it to kink to one side and eventually end up as a left-sided heart, with all other organs following the direction laid down by the initial cardiac asymmetry. A simple scenario for the evolution of the D^* allele is that a mutation occurred in a copy of one of the genes which normally causes the cardiac rudiment to grow slightly more on the left side. Instead, therefore, of causing the *heart* to grow slightly more on the left side, it caused early *neural* tissue to start to develop differently on the left side. That would have resulted in a directional asymmetry of precisely the kind required. Recent discoveries in the molecular biology of the control of *situs* make this situation quite feasible. Before the developing chick, frog, toad, or mouse

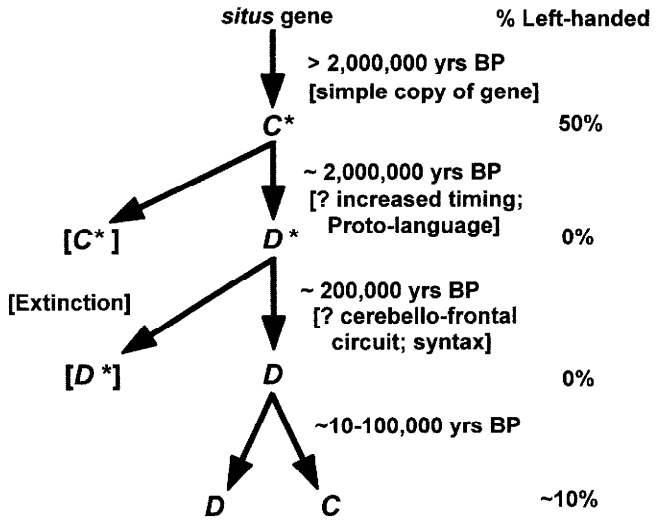

Fig. 11.1. A summary of the proposed evolution of the various genes underlying handedness and cerebral dominance for language. The *situs* gene is that found in all vertebrates which makes the heart be on the left side, and firstly a copy of that is made to produce the 'null' *C** gene. About two million years ago the *C** gene mutated to the *D** gene, which perhaps affected the timing of the left hemisphere and thereby enabled protolanguage, throwing, and tool-making, with the result that *C** gene rapidly became extinct, and almost all of the population were right-handed. About 200 000 years ago, the *D** gene mutated to the modern *D* gene, perhaps allowing a fronto-cerebellar circuit which resulted in proper syntax, and resulting in the *D** gene becoming extinct. Finally somewhere between 10 000 and 100 000 years ago the modern *C* allele mutated out of the *D* allele and the *D* and *C* alleles formed a balanced polymorphism, with about 10% of the population being left-handed.

shows any anatomical asymmetries, there are clear asymmetries in growth factors such as *sonic hedgehog, activin receptor IIa, cNR-1* (Levin *et al.* 1995), *lefty* (Meno *et al.* 1996), *nodal* (Colignon *et al.* 1996; Lowe *et al.* 1996) and *Vg1* (Hyatt *et al.* 1996); interestingly, the action of these growth factors has been shown to be downstream from the *iv* gene and also from the *inv* gene, which reverses lateralization completely (Yokoyama *et al.* 1993). Integrating all of these findings into a single ontogenetic model which includes both the *iv* gene and the X-linked situs mutations is not straightforward, but seems possible (Srivastava 1997).

If I am correct that the gene for handedness can only have mutated from some pre-existing gene, then the most probable scenario, following the finding of Supp *et al.* (1997), is that the *iv* mutation results from a mutation to axonemal dynein. This provides a direct test: The genes for handedness should be largely homologous with the sequence of the wild-type *iv* gene. Finding the gene ought therefore to be relatively straightforward. Take a core sequence from the DNA of the left–right dynein (*lrd*) specified by the *iv* gene, carry out a moderately low stringency screen of the entire human genome and look for DNA sequences which are close homologues of the *lrd* sequence, exclude any which are also present in the mouse genome because

they are not specifically human, and then look for linkage to handedness, or for the presence of mutations or polymorphisms in left-handers not present in right-handers.

The model described also provides an answer, albeit a prosaic one, to the question of why most people are right-handed rather than left-handed—it is ultimately because our heart happened to be on the left, that there were genes that made the left side grow more, and these could then make the left brain grow more. In other words, historical contingency plays a large part, as in so many evolutionary situations (Gould 1989). The answer to why the heart should itself be on the left side is complex and interesting, and seems to depend on events occurring about 550 million years ago (Jefferies 1986, 1991; Gee 1996), but that is another story.

If the above scenario is to be acceptable as an explanation, it is necessary to show that alteration of the normal route for producing cardiac asymmetry can result in alterations of neural development. At present not all the links in that causal chain are present, not least because it will probably be necessary to study morphogens in early human embryos, who have and express the modern *D* (or *C*) alleles, rather than in non-human embryos, who necessarily only have the ancient C^* allele. Nevertheless there are several suggestions that the mechanisms might be present. Firstly, it is now becoming apparent that the asymmetries of growth factors being found in early embryos are not restricted to the region that will form the future heart, but are also present asymmetrically in the floor-plate of the developing mid- and hind-brain (Meno *et al.* 1996), where one might speculate that they could be responsible for the otherwise bizarre asymmetry of cerebral decussation in the motor and sensory tracts, and adjacent to the developing notochord (Colignon *et al.* 1996). Additional evidence for the feasibility of the mechanism comes from the seemingly unlikely source of a mouse gene called *legless*, which causes the back legs to fail to develop (McNeish *et al.* 1988; Singh *et al.* 1991). When this insertional mutation was mapped it was shown to be at precisely the same location as the *iv* gene, and subsequently it was shown to be co-allelic with it, so that *legless/iv* heterozygotes are also more likely to show *situs inversus*. Of particular interest for the present story is that individuals of a *legless/legless* genotype also showed wide-ranging abnormal development of the brain (McNeish *et al.* 1988), in particular showing a failure of the normal differentiation of the two cerebral hemispheres. The *legless* mutation therefore confirms that abnormalities of a gene which normally determine *situs* can result in failure of normal neural development. If a further link is needed between laterality and limb development then it should also be remembered that *sonic hedgehog* is now deeply implicated in both (Tickle and Eichele 1994; Levin *et al.* 1995), although to complicate matters a knockout mouse lacking the *sonic hedgehog* gene does not seem to show abnormal visceral lateralization (Chiang *et al.* 1996).

A final important point is that the modern *D* allele cannot be the same as the human genes controlling *situs solitus*. Although there is no doubt that cardiac asymmetry is the primary asymmetry which determines as a secondary consequence many of the asymmetries of the human body, handedness is not so caused. The evidence for this comes primarily from two large-scale studies (Cockayne 1938; Torgersen 1950) in which it was found that the incidence of left-handedness is almost exactly the same in individuals with *situs inversus* as in the rest of the population with *situs solitus*. The clear implication is that two entirely separate genetic systems are

involved. Almost nothing is known at present about cerebral organization in *situs inversus*, too few cases having been described (Woods 1986). It should be emphasized that although no phenotypic correlation is proposed between handedness and *situs*, there is of course a strong evolutionary correlation in the sense that the gene sequences responsible are probably very similar indeed.

Language and proto-language

Jean-Jacques Rousseau speculated in his *Essay on the origin of languages* that what must have come first was a language of the passions or of primitive instinct, and that only later would come the complex grammatical structures necessary for articulating abstract thoughts (Norris 1987). There is now a growing consensus (Donald 1991; Leakey 1995; Maynard Smith and Szathmáry 1995; Bickerton 1996; Noble and Davidson 1996) that during human evolution there are at least two broad stages. The first stage, some 2 million or so years ago, when humans first started tool-making and using some form of proto-language, was followed by a remarkable period of technological stasis—as Schick and Toth (1993, p. 284) remark: "considering that we see the Acheulean spread across thousands of miles, lasting almost one and a half million years, and continuing through considerable biological change among hominids, this conservatism is absolutely astounding". The Acheulean was followed suddenly by an "evolutionary explosion" (Corballis 1992) perhaps 30–40 000 years ago, when language might have started to be present in a form which would be recognizably modern, and when it might also have been associated with an anatomically modern larynx which would support a complex vocal language (Lieberman 1991); after this there was the diversification of languages presently found (Cavalli-Sforza *et al.* 1988). The implication must surely be that if the evolution of proto-language and its associated right-handedness and cerebral lateralization was the result of the mutation of a key developmental gene that made the left half of the brain grow differently, then the most likely explanation of the equally sudden onset of modern language was that a further mutation of the D^* gene had occurred, and that it produced the modern D allele. This allele provided the neurobiological substrate for a rich, grammatically complex language that was modern in form, and had the generativity which would also enable complex analyses of visual objects and manual skills (Corballis 1991). Just as the D^* allele rapidly took over the gene pool with the extinction of the C^* allele, so we must presume that the D allele would have soon also gone to fixation, eliminating the D^* allele.

Thus far no consideration has been given to the question of *how* in neurobiological terms it is possible for single mutations to change cognitive functioning qualitatively. For the evolution of the D^* allele no obvious mechanism is available at present, although some relatively low-level change in the migration patterns of developing central neurones or their proliferation kinetics (Rakic 1995; Caviness *et al.* 1997) could well change their interconnectivity or other properties, with dramatic effects perhaps on timing or the nature of the neural calculations for which they are optimized. The shift from the D^* to the D allele is of greater interest, not least

because Bickerton (1996) has proposed that this specifically involves a novel connection between the cerebellum and the fronto-lateral cortex, via the thalamus (Leiner *et al.* 1991; Fiez *et al.* 1989, 1997), and that this connection is responsible for syntax. The evidence in favour of the hypothesis is broad, covering not only the fact that agrammatism can occur after thalamic and cerebellar lesions, but also that the cerebellum has been shown to have been implicated in other high-level cognitive functions (Leiner *et al.* 1989, 1991; Barinaga 1996), including defects of timing (Nicolson *et al.* 1995). The relationship to handedness is made all the more interesting by the fact that in autism, fragile-X, and Rett's syndrome there not only seem to be unusual abnormalities of handedness, but neural imaging suggests that there are anatomical anomalies in the cerebellum (McManus and Cornish 1997). This is therefore a prime site for the *D* allele to work. Certainly, current work on cortical embryology is entirely compatible with the idea that a single mutation could radically alter the way that neurons in different parts of the brain interconnect, and result in a profoundly different form of functional organization (Molnar and Blakemore 1995); as Humphrey (1992) has pointed out, a tiny change such as allowing 'sensory' inputs to monitor internal neural states rather than external events can transform the life of the mind.

The evolution of left-handedness

If the scenario of the previous paragraphs is correct, there remains the mystery of why left-handedness should occur at all. Primitive, pre-hominid left-handedness was the 'result' (if the non-action of a null gene can be so-called) of the C^* allele. But modern left-handedness cannot possibly result from some atavistic reversion to the primitive C^* allele, because if the above story is correct then right-handedness and proto-language, and then language proper, have been intimately linked in cerebral terms. If left-handers were merely carriers of the C^* genes then they should be expected not even to have proto-language, to have difficulties in throwing, to have poor manual coordination, etc., none of which, of course, is true, despite a few occasional attempts to stereotype sinistrals in such a fashion. The only conclusion must be that the modern *C* allele is a further mutation of the *D* allele, presumably relatively recent in time, which enables the allele to have most of its beneficial effects on neurobiological development but does not require the locus of the effects to be in the left hemisphere. Far from the *C* allele being a reversion, it must be more recent in origin than the *D* allele, with new advantages of its own. We can do little at present to date this mutation except to state that it was almost certainly present in its modern form by 5000 years ago, since when there seems to have been a stable proportion of left-handers in the population (Coren and Porac 1977).

The origins of left-handedness are more complex still because left-handedness represents what in genetics is called a *balanced polymorphism*, with two separate phenotypic forms each being present in the population at quite high frequencies. Genetic theory (Cavalli-Sforza and Bodmer 1971) is entirely clear that balanced polymorphisms which result from the actions of two separate alleles in the gene-pool cannot maintain themselves spontaneously. If the two alleles have even slightly

different fitnesses then the less fit will inevitably be removed from the population; and indeed even if the two alleles have precisely identical fitnesses then by random genetic drift resulting from populations being of finite size then, just as surely, one or other of the alleles will be eliminated. Balanced polymorphisms therefore cannot just passively happen, but must be actively maintained by equally balancing forces. It is like a pencil being balanced on its point—by chance one may just happen to get it poised there for a fraction of a second but the apparent stability is ephemeral, and is in reality only metastability, and the slightest unequal push from an air molecule or one side or other will provide a turning moment which will rapidly grow by positive feedback and push the pencil off balance so that it falls over. The pencil can only be maintained on its point for any length of time by equally balanced forces such as two fingers holding it in position. Likewise with a balanced polymorphism, there must be forces maintaining the instability, or the polymorphism will disappear by genetic drift in a few instants of geological time. Occasionally, polymorphisms are maintained by frequent new mutations, but that seems an unlikely explanation for handedness.

The most common explanation for balanced polymorphisms is in terms of heterozygote advantage, which in the case of handedness would mean that D/C individuals are fitter than both D/D and C/C individuals. This would not mean that left-handers are fitter than right-handers (because the inheritance is additive, with heterozygotes midway in proportion of left-handedness between the homozygotes, the fitness of left-handers will be precisely the same as the fitness of right-handers), but rather that *some* left-handers and right-handers (the D/C genotypes) are fitter than the other right- and left-handers. At present there is no clear idea what the advantage might be. Annett and coworkers have proposed that homozygotes might have intellectual problems, with lower IQ, as well as specific problems with reading (Annett and Manning 1989; Annett 1995; Annett *et al.* 1996); detailed calculations suggest, however, that there are severe problems with that model which as yet have not been adequately circumvented (McManus *et al.* 1993; McManus 1995*b*). Additionally, a series of empirical studies has failed to find the postulated increased intelligence of individuals with moderate degrees of handedness (Klicpera and Gasteiger-Klicpera 1994; Corballis and Palmer 1996; Natsopoulos *et al.* 1997; Resch *et al.* 1997). Perhaps the problem is that, although it is tempting to assume that any advantage associated with genes to do with handedness must be neurological or psychological in its effect, that is not in fact the case. The proposed fitness advantage ultimately only has to mean that the heterozygotes have more children and grandchildren, and that might be because they can run faster, digest food more efficiently, have better thermo-regulation, or a myriad of other effects all of which could result in biological advantages. Balanced polymorphisms can also be affected by sexual selection, and Crow (1989, 1993) has argued that cerebral specialization for language might be explained in terms of sexual selection. Specifically he argues that the genes for cerebral dominance and handedness (and also the genes for psychosis, which he suggests are mutations of the normal cerebral dominance gene (Crow 1990b)), might be located in the homologous regions of the X and Y chromosomes. That theory produces some highly counter-intuitive patterns of inheritance of handedness in families in relation to the sex of offspring, and, to what I confess is my surprise, the predictions have been found correct in a very large sample of families (Corballis *et al.* 1996). The data do not,

however, yet give totally compelling support for the handedness/cerebral dominance gene being on the sex chromosomes; Bryden and I have previously argued that the gene itself could be autosomal and it is merely a modifier gene that is on the X-chromosome (McManus and Bryden 1992).

Testing the model and its predictions

Evolutionary models are very easy to produce—there are usually far more explanatory variables than there are data points, and as a result the models always seem convincing. Or to put it more crudely, they are often merely 'Just So' stories (Gould and Lewontin 1979; Pinker and Bloom 1990; Barkow *et al.* 1992)—nice stories or fairy tales but hardly science in any serious sense of the word. Steve Jones is even blunter about the problems of evolutionary theories:

> Evolution is to allegory as statues are to birdshit. It is a convenient platform upon which to deposit badly digested ideas (*New York Review of Books*, July 17th, 1997, p.39).

So is the above model testable? I think so, mainly because molecular genetics is progressing at an enormous rate. The first step of course must be to find the genes responsible for handedness, and if the above scenario is correct they should show strong homologies of sequence with the genes controlling *situs*. More interestingly, they should also produce gene-products which control growth asymmetrically in the early nervous system, and that should certainly be the case in humans. Intriguingly, this might also be the case in a transgenic mouse with the human gene inserted; if so, then we will also have an excellent model system for studying brain lateralization experimentally. A further possibility is that a wide range of human pathologies will show abnormalities of sequence in the *D* or *C* alleles, which will be responsible for atypical nervous system development. It is also possible that, as Crow (1990*b*) has suggested, schizophrenia is due to a mutation of the cerebral dominance gene—and the analogy presumably extends to the hundreds of diseases and conditions produced by minor sequence changes in the haemoglobin gene, such as sickle-cell anaemia. Supporting Crow's suggestion is the important finding that schizophrenia does indeed seem to involve an abnormality of cerebral dominance (Crow 1990*a*). There is also a group of other conditions which are characterized by atypical lateralization, problems of communication, and interestingly also tend to occur more frequently in males, namely, autism (McManus *et al.* 1992), dyslexia (McManus 1991; Eglinton and Annett 1994), and stuttering (Bishop 1990), and these are also good candidates for explanation in terms of abnormalities of the cerebral dominance gene. Finally there is a growing group of defects (Gopnik 1991; Van der Lely and Stollwerck 1996) that seems to be specific to grammar itself; these seem to run in families, suggesting that they also might be explained in terms of abnormalities of the cerebral dominance gene. Of course none of these findings would explicitly prove the relationship of the evolution of the gene to the evolution of language, but it is more than possible that detailed study of the sequences of the genes and analogous genes in modern humans and modern apes and primates would provide crucial insights into the evolution of language.

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