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The Neurobiology of Handedness, Language, and Cerebral Dominance: a Model for the Molecular Genetics of Behavior

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One of the great surprises that awaited neurology and psychology in the nineteenth century was the discovery that the two halves of what seemed to be the symmetric human brain did not have the same functional properties. In this sense the hemispheres differed from the two kidneys, the two lungs, the two adrenals, the two gonads, or indeed any of the other seemingly symmetric organs. Those with a knowledge of embryology will, of course, realize that strictly speaking the right and left chambers of the heart, which *do* have very different functions, are not symmetric in any deep sense, having evolved from the complex folding of a single tube.

The important insight concerning functional asymmetry was first clearly enunciated by Paul Broca, who, in 1863, described over 25 patients, all of whom suffered from what we would now call *aphasia*, or lack of speech, and *all* of whom had suffered from lesions to the *left* side of the brain (Berker et al., 1986) (although he had undoubtedly been anticipated by Wigan and Dax – for more detailed historical accounts see Harrington, 1987; Hécaen and Dubois, 1969; Hécaen and Lanteri-Laura, 1977). The implication seemed obvious (and indeed its broad principle is as correct today as it was when Broca first enunciated it): "Nous parlons avec l'hémisphère gauche" ("we speak with the left hemisphere"; Broca, 1865). Such violation of a symmetry that had been implicitly assumed since the time of Aristotle was at first shocking; and for a while attempts were made to explain it away using the only other known functional asymmetry, that of handedness, since the majority of the population is also right-handed. Such explanations would have restored a higher order symmetry to the brain, in which left-handers simply showed the reverse pattern of language dominance to right-handers; in fact, however, they do not and, as will be seen, the relationship is much more complex.

Nineteenth-century neurologists at first talked of the "dominant" or "major" hemisphere (which does the talking), and the "non-dominant" or "minor" hemisphere (which apparently did little of real importance, for of course it was the richness of language, that dubious gift of Babel, that determined man's uniqueness in the animal kingdom). Only as cases of right-hemisphere injury were studied more closely did it become apparent that the right hemisphere also had its own typical mode of functioning, usually involving the processing of complex visuo-spatial images in a holistic or parallel fashion, and characteristically resulting in the group of syndromes broadly known as the *agnosias* (which can, however, be associated with left-hemisphere or bilateral damage). The two hemispheres therefore seemed to show *complementary specialization*, although Bryden (1986a, b, 1990) has pointed out that a more accurate description is *statistical complementarity*, localization of the two types of function being independent, but appearing associated because each is highly biased in its distribution, one principally to the left hemisphere and the other to the right hemisphere. Modern neuropsychology (see e.g. Ellis and Young, 1988; Shallice, 1991) has now recognized a range of syndromes, many of which are lateralized, and some of which, such as prosopagnosia (deficits of face recognition), seem to require lesions in specific but different areas in both right and left hemispheres.

The Biological Problem of Asymmetry

Psychology is inevitably based in biology, in the sense that psychological functioning necessitates the existence of a neural substrate, of brain tissue, or "wetware" (just as the running of the "software" of a computer program cannot actually function in any real sense without appropriate "hardware"). If functional processes are asymmetric – and Broca's observation alone makes that conclusion indubitable – then it would seem probable that the underlying neural machinery is itself asymmetric. The problem might be biologically trivial in one sense if it were the case that exactly half of human beings spoke with their left hemisphere and the other half spoke with their right hemisphere. Chance alone might then determine in any individual person whether (s)he were right or left-brained for language, just as chance determines whether a molecule produced in a chemical (but not a biochemical) reaction takes the D- or the L-form. Chance does seem to underlie the asymmetry of many biological processes, so that, for example, almost precisely 50 percent of mice prefer to use their right paw and 50 percent prefer to use their left paw for reaching for food (Collins, 1985); and if one measures the width of the upper incisors (front teeth) in humans, then in half of individuals the right tooth is slightly larger, and in the other half the left tooth is slightly larger (Bailit et al., 1970). In each case there is the situation biologists call *fluctuating asymmetry* (Palmer and Strobeck, 1986), which results from small chance fluctuations during early development, so-called "biological noise," which eventually become magnified and fixed so that individuals are asymmetric but the population still shows symmetry.

With language dominance and with handedness in humans, however, the vast majority of the population (of the order of 90 percent) is lateralized in one particular direction, speaking with the left hemisphere and using the right hand

for skilled activities (although these are not always the same 90 percent of the population for each type of dominance). Such *directional asymmetries* present a severe theoretical problem both in biology, as in explaining why the heart is almost always on the left side (Brown et al., 1991; Brown and Wolpert, 1990), and in neurobiology. The essence of the problem is that directional asymmetries cannot just happen, they have to be *maintained* by something; just as when a ball is bouncing on the top of a fountain of water, it is the force of the water that maintains what is otherwise an inherently unstable situation. The biological baseline against which all asymmetries are assessed is fluctuating asymmetry, 50 percent right and 50 percent left, and it is the situation to which directional asymmetries will inevitably revert unless they are maintained. Since human handedness and human language dominance show clear, strong, directional asymmetry, three crucial questions are immediately raised: what is it in the development of the individual human organism, in its *ontogeny*, that creates this asymmetry? When in our evolutionary past, in human *phylogeny*, did this asymmetry arise? And what were the adaptive advantages that allowed and encouraged the evolutionary shift that has apparently made humans unique in the animal kingdom in having an asymmetric brain?

It is rare in psychology for high-level, complex behaviors to have clear biological underpinnings, and such situations create unusual opportunities for studying and understanding both neurobiology and cognition. If, as we will argue is probably the case, the biological underpinning arises from the action of a single major gene, then the scope for understanding language, one of the central characteristics that seems to distinguish humans from other animals, is immense, particularly given the advent of modern techniques of molecular biology, which allow the dissection of developmental and genetic processes in immense detail. Other authors have argued that the best hope for studying the molecular basis of behavior genetics is by studying such complex, multifactorial conditions as alcoholism (McClearn et al., 1991). Here we will argue that perhaps a better strategy for molecular behavior genetics, and for cognitive neurobiology, is in understanding the biological basis of human cerebral lateralization – of language dominance and of handedness. And indeed it is the understanding of handedness that is of central importance, since language dominance is intrinsically much more difficult to study in large numbers of active, sentient, living human beings, accurate assessment and classification being neither easy nor reliable (Bryden, 1988a). In contrast, handedness is readily assessed and easily studied in large numbers of people, and therefore provides an excellent surrogate for the study of language dominance. Once the biology of handedness is understood then an understanding of the biology of language will not be far behind, since handedness and language show functional linkage, and in all probability are controlled by the same gene.

The Study of Right- and Left-handedness: the Dangers of Symbolism

Interest in right and left, particularly in why most people are right-handed but a few are left-handed, can be traced back at least to Plato and Aristotle (McManus et al., 1986), and reflects a deeper interest in the symbolic functions of right and left that can be found in Homer, in the Bible, and in other mythologies. "Right"

is seen as good, correct, skilful, etc., in contrast with the sinister, evil, gauche, cack-handed nature of "left" – so that in the Bible, for instance, the (good) sheep are sorted on to the right hand whereas the (bad) goats are sorted on to the left. One consequence of this dual symbolic classification (Hertz, 1909, 1960; Needham, 1973) is that what are supposedly serious scientific studies of handedness sometimes either confuse symbolism with evidence, or are treated more seriously by other scientists or by the general public than their data strictly justify. An early example is the work of Lombroso, who tried to demonstrate that criminals were more likely to be left-handed (Lombroso, 1903) (although see Ellis, 1990, for a recent review). Recent examples are also common, and reflect ideas that refuse to die, and indeed are frequently cited in the scientific and popular literature, despite adequate evidence to refute them. Perhaps the best studied is the hypothesis, originally proposed by Bakan (1971, 1990), that left-handedness is the result of minor degress of brain damage due to birth trauma or birth stress. Large-scale prospective studies (McManus, 1981; Schwartz, 1990) have found no serious evidence to support the hypothesis, and a recent meta-analysis (Searleman et al., 1989) found almost no support for the theory. Nevertheless, claims still continue to be made on behalf of such a theory, as for instance in the variant that it is older mothers who have left-handed children (Coren, 1990), despite pre-existing evidence to the contrary (McManus, 1990) and a subsequent failure to replicate (Peters and Perry, 1992). A similar controversy is currently raging in the literature concerning the highly contentious suggestion that left-handers live less long than right-handers: despite the methodological inadequacies of the original studies (Coren and Halpern, 1991; Halpern and Coren, 1990, 1991) and the failure of other data sets to replicate the finding (Marks and Williamson, 1991; Wolf et al., 1991), serious and critical journals such as *Nature* (Pool, 1991) have devoted large amounts of space to the question, and thereby encouraged popular newspapers and magazines to report it extensively. Similar criticisms apply to the suggestion, based on a relatively small set of subjects, that homosexuals are more likely to be left-handed (McCormick et al., 1990); two large studies have failed to replicate the effect (Marchant-Haycox et al., 1991; Satz et al., 1991) yet, in an otherwise serious article (Barinaga, 1991), *Science* repeated a claim that cannot be empirically replicated.

A variant of the symbolism of "right–left" confounds it with the other potent dual symbolic classification of "male–female" (and is seen in part in the suggestion, dating back at least to the beginning of this century in the correspondence between Fliess and Freud, that homosexuals are more likely to be left-handed). That males and females differ in their lateralization seems likely from studies of deficits after unilateral brain damage (McGlone, 1980), and from the higher incidence of left-handedness in males than females, the male rate being 27 percent higher than that in females in a recent meta-analysis (McManus, 1991; Seddon and McManus, 1991). However, in recent years a very influential theory has dominated the neuropsychological literature, which combines not only laterality and sex differences, but also a vast range of diseases and other malformations in a "grand theory" of potentially awesome implication. What we will call the "Geschwind–Behan–Galaburda" (GBG) theory originated in a paper published in 1982 by Geschwind and Behan, and the theory was subsequently developed in a series of three very long papers by Geschwind and Galaburda

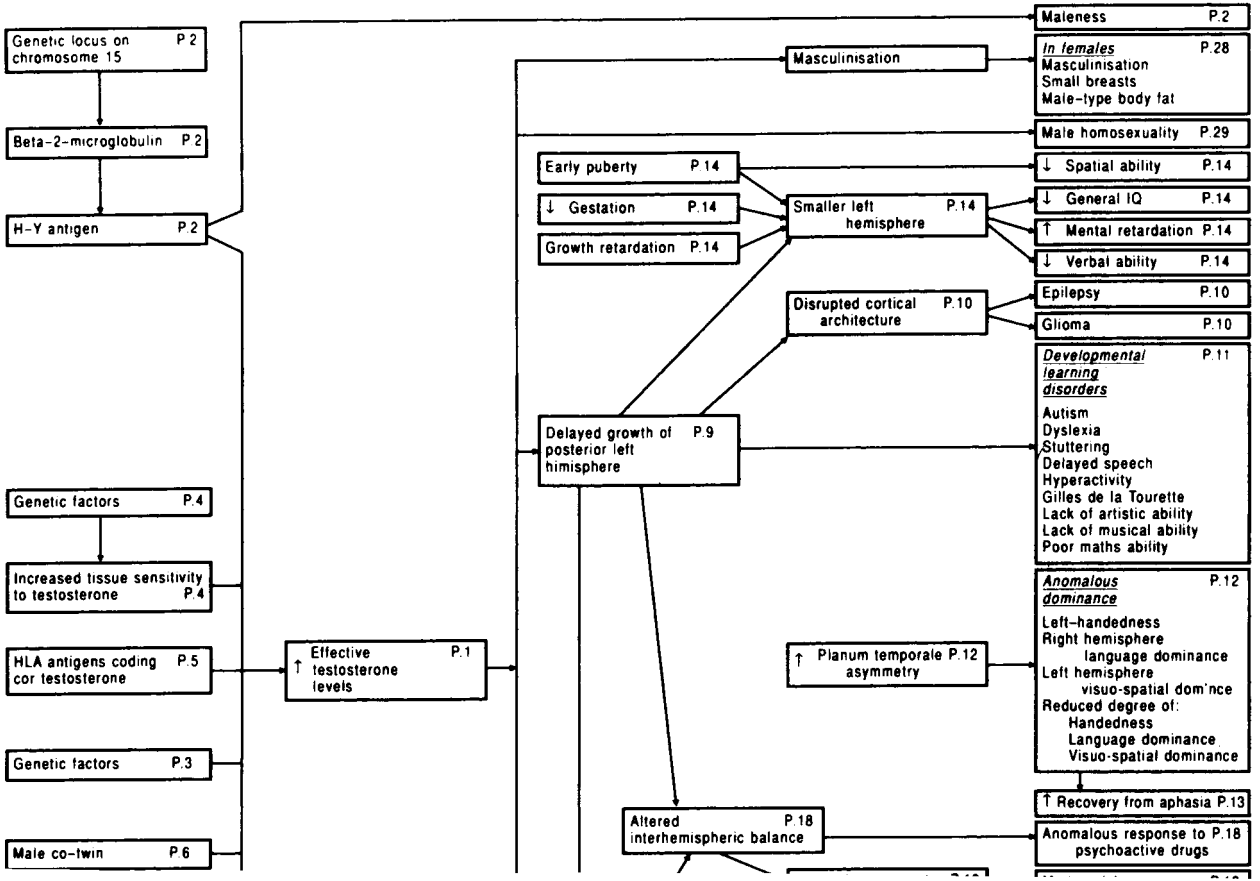
(1985a, b, c), and then in a book containing essentially identical material (Geschwind and Galaburda, 1987).

The Geschwind–Behan–Galaburda Theory of Lateralization

The GBG theory is complicated, as can be seen from our attempt (McManus and Bryden, 1991a) to reduce it to a causal, structural model (see figure 29.1), based on the published work of Geschwind, Behan and Galaburda (Geschwind and Behan, 1982; Geschwind and Galaburda, 1987). That the model in figure 29.1 is an oversimplification is undoubted, but it does at least make the theory tractable, and its testability can then be discussed (and we are at present preparing a critical review of the published evidence for and against the model). The absence of any independent substantial published evidence for the GBG theory has not prevented it already becoming a "citation classic," having been cited 370 times in scientific papers during the period January 1986 to June 1991.

The core of the GBG theory is that levels of testosterone in the fetus affect the relative growth of the right and left hemispheres, so that high testosterone levels, which of course will more typically be found in males than females, will result in the phenomenon of "anomalous dominance," which is defined as left-handedness, or right-hemisphere language, or left-hemisphere visuo-spatial ability, or a reduced degree of dominance for any of those characteristics, whichever hemisphere they may be in. Raised testosterone levels are also said to result in delayed growth of the posterior part of the left hemisphere, and thereby cause developmental learning disorders, such as autism, dyslexia, stuttering, hyperactivity, and poor artistic, musical, or mathematical ability. Finally, and most importantly for testing the theory, raised testosterone levels are postulated to result in modifications of immune functioning, so that there is an increased incidence of a wide range of pathological conditions, particularly those of an auto-immune nature, such as myasthenia gravis, ulcerative colitis, systemic lupus erythematosus (SLE), asthma, hayfever, and atopy, or of conditions that have a putative auto-immune status, such as migraine.

Although principally an exercise in theoretical biology, the GBG model keeps its feet on the ground by its apparent reliance on empirical data. The theory makes strong predictions that there should be associations between any of the measurable characteristics shown down the right-hand side of figure 29.1, and in their very influential 1982 paper, Geschwind and Behan reported the highly counterintuitive result that individuals with conditions such as myasthenia gravis, ulcerative colitis, and asthma are more likely to be left-handed. If correct, then those results would provide very strong evidence indeed for the GBG model – and would be totally inexplicable under any other current model of cerebral lateralization. Regrettably, however, those findings have not received the unambiguous support that a grand theory such as that of GBG really requires. Thus for instance, in two studies of allergic disorders one investigation (Smith, 1987) did find an increased incidence of left-handedness, whereas the other, a much larger and better controlled study (Bishop, 1986), found no association. Similarly, one study of ulcerative colitis and Crohn's disease (Searleman and Fugagli, 1987) did find an association as predicted, and another (Meyers and Janowitz, 1985)


Genetic locus on chromosome 15 P.2
Beta-2-microglobulin P.2
H-Y antigen P.2
Genetic factors P.4
Increased tissue sensitivity to testosterone P.4
HLA antigens coding cor testosterone P.5
Genetic factors P.3
Male co-twin P.6
↑ Effective testosterone levels P.1
Maleness P.2
Masculinisation
In females P.28
Masculinisation
Small breasts
Male-type body fat
Male homosexuality P.29
Early puberty P.14
↓ Gestation P.14
Growth retardation P.14
Smaller left hemisphere P.14
↓ Spatial ability P.14
↓ General IQ P.14
↑ Mental retardation P.14
↓ Verbal ability P.14
Disrupted cortical architecture P.10
Epilepsy P.10
Glioma P.10
Delayed growth of posterior left himisphere P.9
Developmental learning disorders P.11
Autism
Dyslexia
Stuttering
Delayed speech
Hyperactivity
Gilles de la Tourette
Lack of artistic ability
Lack of musical ability
Poor maths ability
↑ Planum temporale P.12 asymmetry
Anomalous dominance P.12
Left-handedness
Right hemisphere language dominance
Left hemisphere visuo-spatial dom'nce
Reduced degree of:
Handedness
Language dominance
Visuo-spatial dominance
↑ Recovery from aphasia P.13
Altered interhemispheric balance P.18
Anomalous response to P.18 psychoactive drugs

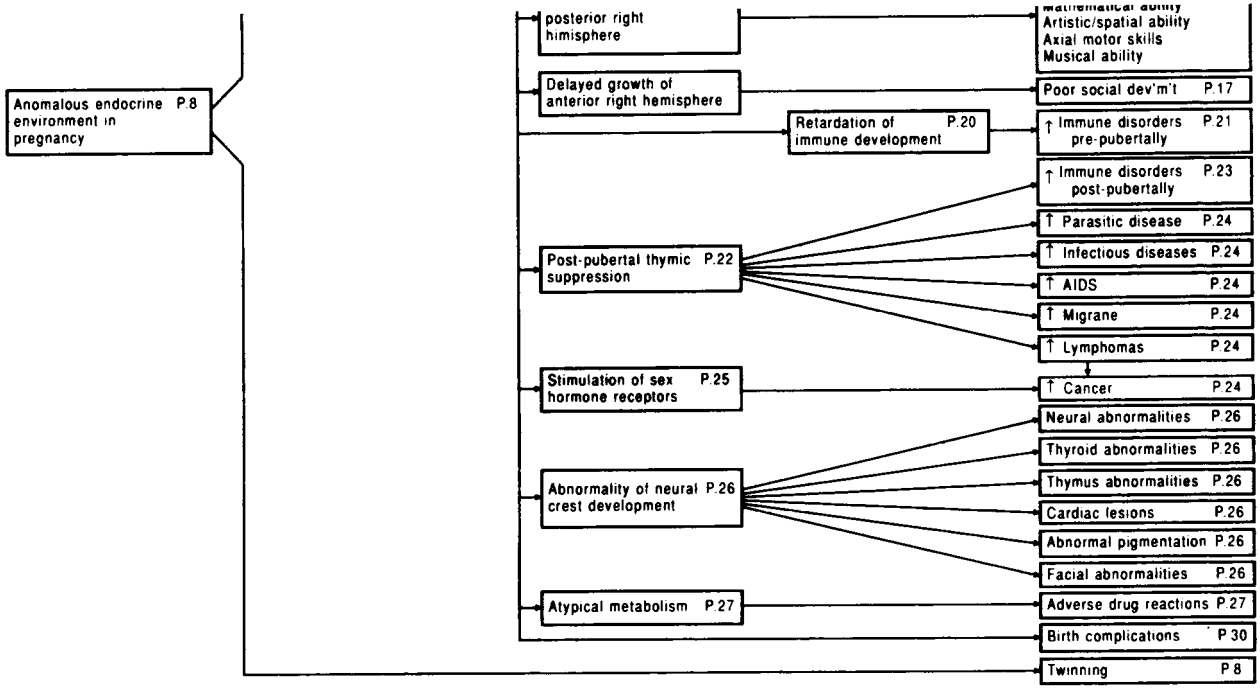


Figure 29.1 A summary diagram of the model proposed by Geschwind, Behan and Galaburda, (based on Geschwind and Galaburda, 1985a, b, c, 1987). Arrows between boxes indicate direct causal links. Reprinted with permission from I. C. McManus and M. P. Bryden (1991) Geschwind's theory of cerebral lateralization: developing a formal, causal model, *Psychological Bulletin*, 110, 237–53.

und no association. In contrast, neither of two studies of systemic lupus ythematosus found any association with handedness (Salcedo et al., 1985; hur, 1986). In yet further distinction, two studies (Cosi et al., 1988; McManus al., 1990) of myasthenia gravis in three populations each found evidence that t-handedness was *less* common than in the general population. A recent, more stematic review of the association of diseases with left-handedness (Bryden and cManus, 1992), using meta-analytic techniques, found suggestive evidence that ere are positive associations of left-handedness with thyroiditis, Crohn's disease d colitis, negative associations with myasthenia gravis, eczema and urticaria, id no association with a wide range of conditions, including systemic lupus ythematosus and diabetes among others. Taken together such data are hardly rong support for the GBG model.

Summarizing the status of a theory as complex as that of the GBG model, as hown in figure 29.1, is difficult in a few words. Probably it is best to say that t is clearly a brave attempt at grand theorizing in neurobiology; that if it is true t is of immense importance in integrating a wide range of otherwise seemingly lisparate conditions; that it receives its strength in its prediction of highly ounterintuitive and unlikely associations between handedness and a range of lisease conditions; that independent attempts at replicating those associations ave, however, been far from consistent, sometimes contradictory and sometimes latly refuting the predictions of the model; and accordingly it is probably premature at the moment to attach too much credence to the theory as a whole, while simultaneously accepting that the theory has been immensely influential in recent years in stimulating research into the biology of lateralization, and into the neurobiological factors underlying such conditions as mathematical and artistic ability. Perhaps the best summary in a few words is that of Galaburda, one of the proponents of the model, who, when asked whether, "The story that we left-handers are more liable to autoimmune disease, more intelligent, etc., is all nonsense?", replied, "There is no evidence to support the claim in the original observations that left-handers are more vulnerable to autoimmune diseases in general, although they may be more susceptible to some types of allergies" (Galaburda, 1991). Nevertheless, Galaburda (1990) has pointed out that there is somewhat stronger evidence for an association between learning disorders and auto-immune disorders, as the GBG theory would also predict.

What Are Right- and Left-handedness?

It was the great nineteenth-century neurologist Hughlings Jackson who said that "the study of the thing caused must precede the study of the cause of the thing" (Wilson, 1908). One of the major problems of the GBG theory is its rather uncritical acceptance of the concept of "anomalous dominance" (McManus and Bryden, 1991a). Here we will briefly look at some of the problems of classifying, measuring, and defining right and left-handedness; more extensive accounts will be found elsewhere (McManus, 1984, 1991; McManus and Bryden, 1991b).

At an everyday level handedness refers to two separate phenomena: if a person is right-handed then he is usually right-handed in the sense that he is more *skilled* at using his right hand for complex motor tasks (of which writing is the most lateralized), and he *prefers* to use his right hand for even relatively unskilled

tasks which either hand could in principle carry out (for instance, picking a sweet out of a bag). In general the two phenomena are highly correlated, those with a preference for one hand also being more skilful with it. Which then comes first? It may be that we prefer to use our right hand, and as a result it gets more practice and hence becomes more skilful; or it may be that the right hand is intrinsically more skilful and hence we prefer to use it (Morgan and McManus, 1988). These hypotheses are difficult to disentangle, but recent evidence (McManus et al., 1992a) that a majority of children with autism are right-handed, and yet those right-handed children are as equally likely to be more skilful with the left hand as with the right, suggests that preference asymmetry comes before skill asymmetry during development, and thus it is preference that is probably primary, with skill differences being a secondary phenomenon.

The extent of preference can be measured more quantitatively, typically by questionnaires asking about 10, 20, or 30 tasks, or by performance, in which individuals carry out a range of tasks. The distributions of scores on such tests are typically bimodal, and it is helpful to differentiate the *direction* of handedness (right versus left) from the *degree* of handedness (if you are right-handed, are you strongly or weakly right-handed?). Very little is known about degree of handedness, although there is evidence that it strengthens during early childhood, and may show some evidence for running in families (Bryden, 1982, 1988b; Porac and Coren, 1981), although not all studies find that result (McManus, 1985a). In general, studies of handedness refer to the direction of handedness, and simply classify subjects as right- or left-handed. A meta-analysis of 88 such studies, combining data from 284,665 subjects, found an overall incidence of left-handedness of 7.78 percent, with little evidence that methods of measurement had any significant influence upon the incidence; however, there was a higher incidence of left-handedness in younger subjects and in those born in more recent cohorts, although these two effects could not be disentangled statistically.

Skill asymmetry is typically measured with tests such as the Annett pegboard (Annett, 1970), which produces a unimodal, approximately normal distribution of difference scores between the hands, or by tapping tasks, such as that of Tapley and Bryden (1985), which typically produce bimodal distributions of scores (McManus et al., 1992b; Tapley and Bryden, 1985), and which can also be broken down into components of direction and degree.

To summarize, handedness is a complex activity, with components of skill and preference, which varies in direction and degree, and can be assessed by performance measures or questionnaires. Our view is that the principal measure relevant to the genetics of handedness is the direction of preference, which can most readily be assessed by questionnaire methods.

Environmental Factors and Pathological Left-handedness

Many studies have looked at possible environmental influences upon handedness (Harris, 1990; Porac et al., 1990), and in general there is relatively poor evidence that they are of importance. An important subgroup of possible environmental causes of left-handedness concerns pathological factors, typically arising *in utero*, during delivery or in early infancy. That such factors can be of some influence

is suggested by the increased incidence of left-handedness in children with mental retardation (particularly in those with very low intelligence) (Pipe, 1990). Although the concept of "pathological left-handedness" is not entirely uncontroversial (Harris and Carlson, 1988; McManus, 1983), it now seems probable that about one in twenty cases of left-handedness can be regarded as "pathological" in origin (Bishop, 1990). The precise nature of the pathology responsible for these cases is not clear, but probably it can be attributed either to early asymmetric brain damage, impairing functioning of what would otherwise have been the dominant hemisphere, or to an increased level of "developmental noise," perhaps owing to chromosomal or other defects during early ontogenesis and tissue formation, which disrupts the normal directional asymmetry and replaces it with fluctuating asymmetry, and hence results in an increased incidence of left-handedness (Batheja and McManus, 1985).

With the exception of the minority of left-handers that can be ascribed to pathological causes, there is very little solid evidence that other environmental factors modify handedness; and in particular the lack of a correlation between handedness and social class (McManus, 1981), and the extremely small correlation with intelligence (Hardyck et al., 1976; McManus and Mascie-Taylor, 1983; McManus et al., 1992b) strongly militate against the environmental influence of a range of factors, such as environmental deprivation or social disadvantage which are strongly associated with low social class and low intelligence. In recent years researchers have therefore looked for evidence that handedness is under genetic control, and although there are still some workers who are willing to propose strong environmental models for handedness, with almost no genetic influence (Collins, 1991; Provins, 1990) most workers now seem to accept that handedness is partly or principally under genetic control. That conclusion would seem to be supported by cross-cultural evidence which suggests that the incidence of left-handedness does not differ significantly between cultures (Connolly and Bishop, 1992; McManus and Bryden, 1991c; Seddon and McManus, 1991), although there is currently still controversy on this issue and opinions do differ (Ardila et al., 1989).

Genetic Models of Handedness

Although a genetic model of handedness was suggested as long ago as 1912 (Ramaley, 1913), and many models have been proposed since then (see McManus and Bryden, 1991b), at present there are only two models that seem to be accepted as having any real success in accounting for the family and twin data. Although probably the more popular in terms of its citations, one of these models, the "right shift theory" of Annett (1985), seems to us to be unsatisfactory for a number of reasons. The model suggests that there are two alleles, RS + and RS −, which are responsible for individuals differing in their extent of "right shift." Individuals differ principally in the extent of skill differences between the hands, those who are strongly right shifted (RS +/+) showing much greater

with the right hand and half are more proficient with the left hand. The relationship of preference to skill is essentially arbitrary, and reflects the position of a criterion, which can be altered by social and other factors, such as methods of measurement. For reasons of space the model will not be discussed in greater detail here, although elsewhere we have considered it extensively (McManus and Bryden, 1991b). We do, however, note briefly as criticisms of it that: it argues that genes determine skill rather than preference, whereas evidence suggests it is actually preference that is primary (McManus et al., 1992a); it does not provide an adequate description of observed distributions of differences between the hands in skill, which are frequently bimodal rather than unimodal (McManus, 1985b); on formal testing it provides a less adequate fit to family and twin data than does the other contending model (McManus, 1985a); it does not adequately explain the "maternal effect" (McManus and Bryden, 1991b; McManus, 1991), whereby left-handed mothers are more likely to have left-handed children than are left-handed fathers; and in its recent extension and development (Annett, 1991a, b, c; Annett and Manning, 1989, 1990a, b), it makes unrealistic assumptions about the differences in intellectual ability between heterozygotes and homozygotes (McManus et al., 1992). The model we will discuss further here, that originally proposed by McManus (1979, 1984, 1985a), and developed by us in McManus and Bryden (1991b), although indubitably far from perfect, does account for a reasonable number of phenomena, is relatively straightforward in its genetics, and has immediate implications for neurobiology and neuropsychology.

Any adequate genetic model of handedness must explain two crucial empirical results: that handedness runs in families, albeit not very strongly (summarizing data from 72,600 offspring in families, left-handedness was present in 9.5 percent of the children of two right-handers, 19.5 percent of the children of one right- and one left-hander, and 26.1 percent of the children of two left-handers); and that despite discordant twin pairs (one right- and one left-handed) being more common in dizygotic than monozygotic twins, there is still a very high proportion of monozygotic twin pairs that are discordant (21.7 percent of 2,900 pairs in our review; McManus and Bryden, 1991b). If a model also wishes to explain sex differences, which it probably should do given the statistical reliability of the sex differences, then it must also explain why the incidence of left-handedness is about 27 percent higher in males than females, and why if one parent is left-handed, then a left-handed mother produces a higher proportion of left-handed offspring (21.9 percent) than a left-handed father (16.8 percent) – the "maternal effect."

The McManus (1985a) model of the genetics of handedness proposed that there is an autosomal locus, at which there are two alleles D (for dextral) and C (for chance). (For those who are not used to the terminology of genetics, *autosomal* means that the genes are not located on the X and Y chromosomes, the sex chromosomes, but on the other chromosomes which are paired. *Alleles* are the individual units of inheritance, essentially being long strings of DNA bases. The *gene-pool* of the population may contain many types of allele for a particular *locus*, or site on a chromosome, but each individual will have only two alleles at any locus, one originating from each parent, and each located on one of the two chromosomes in the pair. Together the two alleles comprise the individual's *genotype*, and are contrasted with the individual's *phenotype*, which represents the functional, structural or behavioral characteristics displayed by the

individual – handedness in this case. For an introduction to basic genetics see Cavalli-Sforza and Bodmer, 1971, and Weaver and Hedrick, 1989.) In the model, individuals with the DD genotype are all right-handed (and left-brained for language and right-brained for visuo-spatial processing). Genotype CC individuals show no systematic genetic control over the direction of their handedness, and hence fluctuating asymmetry alone determines whether they are right or left handed, and hence precisely 50 percent are right-handed and 50 percent are left-handed (see table 29.1); the model can also be extended to describe language dominance, and in the CC genotype 50 percent are right-brained for language and 50 percent are left-brained for visuo-spatial processing, the chance processes all being independent (see table 29.2). The manifestation of the heterozygotes, the DC genotype, is not specified *a priori* in the model, but model fitting finds that an acceptable fit is only obtained if the manifestation is midway between the two homozygotes, so-called "additivity" or "semi-dominance": there is therefore a 25 percent chance of a DC individual being left-handed and a 75 percent chance of being right-handed. Among other implications of this model are that little can be said with certainty about an individual's genotype based on his or her phenotype (handedness); right-handers can be DD, DC, or CC, and left-handers can be DC or CC. This is an inevitable consequence of the model containing a chance element in the form of fluctuating asymmetry, and fluctuating asymmetry seems to be necessary for any adequate genetic model of biological asymmetry (McManus and Bryden, 1991b; McManus, 1991). Formal fitting of such a model shows that it predicts well the proportions of left-handers found in the different types of family (McManus, 1985a). It also explains the high degree of discordance in monozygotic twins by making the biologically plausible assumption that the chance processes of fluctuating asymmetry in DC and CC genotypes occur independently in each member of a twin pair, and hence discordance occurs at predictably high rates (McManus, 1985a).

Table 29.1 The model of McManus (1985a) for the genetics of handedness, showing the proportion of right- and left-handers produced by each of the three genotypes

Genotype	*Frequency in population*	*% Left-handers*	*% Right-handers*
DD	0.7140	0	100
DC	0.2620	25	75
CC	0.0240	50	50

$p(C) = 0.155; p(D) = 0.845$

As it stands, the model of McManus (1985) cannot explain sex differences i the incidence of left-handedness. McManus and Bryden (1991b) (see also McM nus, 1991) proposed that a sex-linked modifier gene, located on the X chrom some, would account for men having a higher incidence of left-handedness (ju as genes on the X chromosome account for the higher incidence of color blindne and hemophilia in males). However, in the McManus–Bryden model, unlike tl case of hemophilia or color blindness, it is not being suggested that the D ar C alleles themselves are on the X chromosome (as stated earlier, they a

autosomal). Instead there is a second gene which is located on the X chromosome, which is a *modifier gene*, acting to prevent the normal action of the D allele, and thereby making it act as if it is a C allele (see table 29.3). Modifier genes (Hartl and Clark, 1989; Moody, 1975; Roughgarden, 1979) are common in biological systems, and probably act by methylation (Bird, 1983; Weaver and Hedrick, 1989). Since the modifier gene acts as a recessive gene, it is more likely to have its effect in males (who only have one X chromosome), than in females (who have two X chromosomes). Left-handedness will therefore be more common in males. More interestingly, when the model is worked through mathematically, the hypothesis of a modifier gene also predicts that left-handed mothers will be more likely to have left-handed offspring than will left-handed fathers (intuitively this can be seen because female left-handers are more likely to be left-handed because they are truly DC or CC genotypes, whereas males are more likely to be left-handed because they are "phenocopy left-handers," probably of genotype DD, and are only left-handed as a result of the action of the modifier gene).

Table 29.2 The model of McManus (1985a) for the genetics of handedness and language dominance, showing the proportion of individuals with each combination of handedness (right or left) and language dominance (right or left) in each of the three genotypes.

Genotype	*Frequency in population*	*R hand, L lang (%)*	*R hand, R lang (%)*	*L hand, L lang (%)*	*L hand, R lang (%)*
DD	0.7140	100	0	0	0
DC	0.2620	56.25	18.75	18.75	6.25
CC	0.0240	25	25	25	25

$p(C) = 0.155; p(D) = 0.845$

Table 29.3 The genetic model of McManus and Bryden (1991b), showing the proportions of left-handers expected in each combination of the autosomal genotypes (DD, DC, CC) and the sex-linked modifier genotypes (M, m in males; mm, mM and mm in females). Note that the effects of the DD, DC and CC genotypes are identical to those shown in table 29.1, except in the m genotype in males and the mm genotype in females, where in each case the genotype acts as if it were the CC genotype, producing fluctuating asymmetry.

	Males		*Females*		
	M	*m*	*MM*	*mM*	*mm*
Frequency of modifier genotypes in population	0.955	0.045	0.9120	0.0860	0.0020
Autosomal genotype (%)					
DD	0	50	0	0	50
DC	25	50	25	25	50
CC	50	50	50	50	50

$p(m) = 0.045; p(M) = 0.955$
$p(C) = 0.135; p(D) = 0.865$

The Genetics of Cerebral Dominance for Language and Visuo-spatial Processing

Although neuropsychologists are principally interested in the neural expression of functional specializations, such as language and other high level cognitive processing, almost no studies that can properly be called genetic have been carried out on them, principally due to the practical difficulties involved. Language dominance is difficult to assess reliably in single individuals, and there are logistic problems in testing whole families, so that only one study has ever looked at dichotic listening within families (Bryden, 1975). Similarly, although it has been known for over two decades that the planum temporale is structurally asymmetric, being larger in the left hemisphere than the right (Geschwind and Levitsky, 1968), it is only recently that the asymmetry has been shown to be different in right- and left-handers (Steinmetz et al., 1991; Witelson and Kigar, 1991), and as yet there are still no studies examining whether the pattern of asymmetry runs in families.

Nevertheless, most genetic models of handedness have been partly conditioned by known data on cerebral dominance for language, and the models of Annett (1985), McManus (1985a) and McManus and Bryden (1991b) make explicit predictions about the relationship between handedness and language dominance. The key result that these models attempt to explain is that right-hemisphere language dominance is relatively rare in right-handers (about 5 percent of individuals) as compared with left-handers (about 35 percent of individuals); and it will be noted here that left-handers are *not* simply mirror-images of right-handers. The McManus–Bryden model copes with this situation by the simple method of assuming that in the CC genotype (and in the DC genotype also) there are separate and independent random processes that determine whether an individual is right-or left-handed and right- or left-hemisphere language dominant.

The McManus–Bryden model also has further implications for linguistic and other cognitive processes because of the presence of the modifier gene, which sometimes acts to prevent the normal action of the D allele. Calculations suggest that the modifier gene is fairly common, and it forms about 5 percent of genes in the gene-pool, and therefore will be expressed in about 5 percent of men (but in a far lower proportion of women, in fact $0.05^2 = 0.25$ percent). If this postulated gene indeed exists, and it operates by turning off a gene that normally acts to govern the way in which another particular gene affects the lateralization of the developing brain, then it is easy to see that the same modifier gene might also modify the action of other genes affecting high level cortical functions – such as those perhaps concerned with visual processing, speech output, or social interaction. The failure of such genes to act in a normal fashion might then result in conditions such as dyslexia, stuttering, or autism; and it should now be apparent that these conditions should not only run in families, and be more frequent in males (as has been pointed out for modifier genes in general by Comings and Comings, 1986), but should also be associated with left-handedness, as indeed has also been postulated for each of them (Bishop, 1990).

Where Did the Gene for Handedness and Language Dominance Come from, and How Do We Find It?

Genes do not just happen; they can only evolve by mutation from other genes. The gene for handedness must have arisen in some such way, and it is of great interest for understanding the evolution of humans, and their differences from the apes, particularly in characteristics such as handedness, language and social interaction, to ask when and how the gene arose. Genes that determine biological asymmetry are surprisingly rare, and the only clear, well-understood case in vertebrates is the gene for ensuring that the heart is normally on the left side of the body (as opposed to the rare situation, *situs inversus*, in which it and all of the other visceral organs are on the opposite side to normal). The most likely origin of the handedness gene is therefore that it represents a mutation in a copy of the *situs* gene, slightly modified so that it acts upon the brain rather than the heart. (It should be noted here that handedness cannot result from the action of the gene for *situs* itself, since left-handedness is no more common in individuals with *situs inversus* than in normal individuals (Torgersen, 1950)). Since population level handedness (i.e. most individuals are right-handed) is not present in the apes, as neither is language, then a parsimonious hypothesis for the evolution of the handedness gene is that it has evolved sometime since the point, probably between two and three million years ago, when *Homo* diverged from the other apes (Hill et al., 1992). That handedness has existed throughout the past five millennia, during recorded history (Coren and Porac, 1977), and there is suggestive evidence of it existing far earlier than that (de Castro et al., 1988), implies that the development of the handedness/language gene might itself have been partly responsible for the divergence of man from the apes. That hand skill was indeed a key process during the divergence of *Homo* and the apes is shown by the near simultaneity in the fossil record of the earliest evidence of stone tools, presumably requiring a high level of manual dexterity for their manufacture (Hill et al., 1992), and the occurrence of the characteristic changes in the morphology in the temporal bone of the skull (Wood, 1992), and hence by implication in the underlying temporal lobe of the brain, where important areas for language perception are now located.

Such a broad evolutionary hypothesis allows the possibility of a quick way of finding the handedness gene, which otherwise would be very difficult to find in the human genome owing to its gene having a product which is probably expressed only for a few days during early ontogeny (and it is known that at least several thousand genes are expressed during early development of the fetal brain; Adams et al., 1992). The method does require that the *situs* gene is identified, and that is indeed almost the case, molecular geneticists having reached within a million base-pairs or so of the murine version of the gene (Brueckner et al., 1989, 1991). Once that mouse gene is identified then the human *situs* gene should be almost identical, and the human gene for handedness should be very similar although not identical to the *situs* gene. The genome can therefore be searched for genes that show homology to the *situs* gene, and one of these is likely to be the handedness gene. Other homologues might be the putative genes for hand-clasping, arm-folding (McManus and Mascie-Taylor, 1979), and eye-

dominance, all of which also appear to be under genetic control, and in all probability have mutated from the handedness gene (McManus, 1991). It might also be a fair prediction that since the *situs* gene is concerned with the fundamental layout of the region of the embryo around the branchial arches, then both the *situs* gene and the handedness gene may well contain homeobox sequences (Holland, 1988; Hunt et al., 1991; Leckman et al., 1991; Weaver and Hedrick 1989), a very ancient set of DNA sequences which seem to be central to early morphological development in both the animal and plant kingdoms (Gehring, 1987; Vollbrecht et al., 1991), and which are particularly concerned with development of the head and neck (Chisaka et al., 1992). An alternative approach to finding the handedness gene may capitalize on the fact that Wilm's tumor of the kidney often results in hemihypertrophy, in which one side of the body grows more quickly than the other (Björklund, 1955; Smithells, 1965); since Wilm's tumors are known to produce growth-promoting factors (Beierle et al., 1971), and the genes for such factors are expressed in human fetal brain tissue (Adams et al., 1992), it is possible that the Wilm's tumor gene represents a mutation of a gene or genes normally responsible for asymmetric brain development, so that known genetic markers for Wilm's tumor (Pelletier et al., 1991), or for other conditions resulting in asymmetric growth (Chemke et al., 1983), may also be markers for the cerebral dominance gene.

It should be noted that in using the shorthand term "a gene for handedness, language and cerebral dominance" we are not implying that the existence of language is dependent upon one and only one gene. That would be developmental nonsense. Clearly in order to have language one also requires many other genes that determine the basic structure of cerebral cortex, that organize motor control, and produce a functional larynx. However, we do mean that the majority of the variance between species with and without language may be ascribed to the presence or absence of a specific gene, which we can then regard in somewhat simplistic fashion as a "gene for language." No doubt when we have studied it in much more detail it will be apparent that it is several or even many genes.

What Will Happen When the Handedness/Language Gene Is Isolated?

Finding the DNA sequence of genes is the beginning not the end of the interesting part of developmental and evolutionary biology. From an evolutionary perspective, finding the genes will allow one to look for close and distant homologues in primates and other species, thereby providing an understanding of the origin of the gene, and an assessment of the effects of its precursors upon nonhuman cognition – and perhaps resolving the continuing controversy as to whether nonhuman primates show functional laterality.

More interesting will be the study of the process of ontogeny within the developing organism. Any gene that determines lateralization, and that presumably must be acting early during fetal development, must manifest because the gene's product is being expressed during embryogenesis. Techniques such as *in vitro* hybridization for mRNA, which allow one to visualize directly where and when a DNA-derived specific sequence is being actively transcribed, will tell *when* the handedness/language gene is active, and in particular, *where* in the

brain it is active. It will be of immense interest to know which parts of the cortex or subcortical areas are intrinsically asymmetric because of the action of the gene (and we note that although the evidence on apraxia and other high-level motor defects (Heilman, 1979) might suggest that handedness *must* be the result of cortical action of a gene, it is at least plausible that the gene instead acts on the basal ganglia, perhaps on the globus pallidus (Kooistra and Heilman, 1988), or on brainstem neurotransmitters, in the substantia nigra (Glick et al., 1977; Glick and Shapiro, 1985), or perhaps, in view of its influence on timing and force control, on the cerebellum (Ivry et al., 1988; Rosenbaum, 1991). The study of brain activity during the learning of a simple motor task involving the fingers (Seitz et al., 1990) finds evidence of altered activity in the premotor areas, supplementary motor areas, and primary motor areas of the cortex, in the basal ganglia (putamen and globus pallidus), ventrolateral thalamus, red nucleus, substantia nigra, pontine nuclei, and cerebellum. If the gene does indeed act upon cortex, how do the areas which it influences relate to our knowledge of functional activity in adults derived from conventional neuropsychology?

Identification of the gene for handedness/language will also allow the identification of allelic subtypes, of which presumably one will be the allele responsible for left-handedness; and that will immediately allow resolution of the conflicting claims of the McManus–Bryden and Annett models of handedness. Of greater scope will be the potential for assessing whether the miscellaneous range of conditions that have putatively been linked to handedness – such as dyslexia, stuttering, autism, schizophrenia, etc. – are really related: if they are, then individuals with the conditions should show a different pattern of genotypes to those without the condition. The hypothesis of an association with handedness immediately becomes rigorously testable, particularly when it is explicit, as in Crow's hypothesis that the gene for schizophrenia is specifically a mutation of the normal cerebral dominance gene (Crow, 1990a,b).

The final possibility which will arise from knowing the sequence of the handedness/language gene will perhaps at first sound like science fiction; in reality though it will have enormous potential for really understanding how this gene actually functions. Even if, at present, we are talking about a development that may be a decade or more away, the *Gedanken* (thought) experiment that it stimulates should wonderfully concentrate the minds of neuropsychologists as to the origins, purpose and function of this gene. Transgenic experimentation allows the transfer of genetic material from one species to another. If humans are unique in having handedness/language, and that is due to the presence of a particular gene, then the immediate and deceptively simple question arises as to what would happen if that gene were put into a species, such as a mouse, which does not have it. If the gene really produces directional asymmetry for handedness, then transgenic mice in which the human gene has been introduced should become right-pawed as a population, rather than, as at present, showing fluctuating asymmetry. More interestingly the transgenic mice may also show some of the cognitive capabilities that are assumed to be the ground for language processing; perhaps, say, in terms of symbolic manipulation (Corballis, 1991; Donald, 1991). It must of course be emphasized that these transgenic mice are extremely unlikely to show language as such, or to be able to talk (and this will be a relief for those who contemplate the nightmarish spectre of domestic cats, particularly whinging

Siamese, that talk to us directly, and thereby control our lives even more successfully than they do at present!). Mickey Mouse will therefore remain a creation of fantasy rather than biology. Language, it must be remembered, is, despite its biological roots, in very large part a cultural process, and therefore transgenic mice would be very unlikely to speak English or any other specific human language. More critically, speech also requires a highly evolved vocal apparatus with a very specialized laryngeal structure (which is not even shown by the apes (Lieberman, 1991), hence the failure of nineteenth-century attempts to teach monkeys to speak). The perception of speech may also require specialization of the auditory cortex in a form that is not generally available in the animal kingdom – in particular, in some form of categorical perception. Nevertheless, if the handedness gene is in any way responsible for language then mice with that gene should show different functional cognitive capacities from those without the gene. Whether it is in the existence of categorical perception, the presence of syntactic processing, the ability to comprehend other minds, or any of the other putative cognitive processes that distinguish humans from other species, the possibility of having the question answered will force us to consider the precise nature of that question far more seriously. Finally, the practical application of such a technique may mean that deliberately created mutations of the gene in transgenic mice might also allow the development of successful animal models for a wide range of human conditions, such as dyslexia, stuttering, autism, and schizophrenia. Even before the mice exist they will provide a fascinating intellectual challenge to psychologists, who will need to consider what they really believe is going on in the biology of handedness, cerebral dominance and language.

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BRAIN DEVELOPMENT AND COGNITION

A Reader

Edited by
Mark H. Johnson

BLACKWELL
Oxford UK & Cambridge USA

1993

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First published 1993

Blackwell Publishers
238 Main Street, Suite 501
Cambridge, Massachusetts 02142, USA

108 Cowley Road, Oxford OX4 1JF, UK

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Library of Congress Cataloging-in-Publication Data

Brain development and cognition: a reader/edited by Mark H. Johnson.
p. cm.
Consists of a collection of classic articles and commissioned chapters.
Includes bibliographical references and index.
ISBN 0-631-18222-5 (alk. paper). — ISBN 0-631-18223-3 (pbk.: alk. index)
1. Cognitive neuroscience. 2. Cognition in children.
I. Johnson, Mark H. (Mark Henry), 1960– .
[DNLM: 1. Brain—growth & development—collected works. 2. Brain—growth & development—essays. 3. Cognition—physiology—collected works. 4. Cognition—physiology—essays. 5. Neuronal Plasticity—collected works. 6. Neuronal Plasticity—essays. WL 300 B81238]
QP360.5.B73 1992 612.8'2–dc20 92–17620 CIP
DNLM/DLC
for Library of Congress

British Library Cataloguing in Publication Data
A CIP catalogue record for this book is available from the British Library.

Typeset in 9½ on 11pt Ehrhardt
by Pure Tech Corporation, Pondicherry, India
Printed in Great Britain by T. J. Press Ltd, Padstow, Cornwall

This book is printed on acid-free paper