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Geschwind's Theory of Cerebral Lateralization: Developing a Formal, Causal Model

I. C. McManus
University College London and
St. Mary's Hospital, London
London, England

M. P. Bryden
University of Waterloo
Waterloo, Ontario, Canada

Geschwind and Galaburda (1987) have proposed a complex and influential model of cerebral lateralization that is based on the argument that increased fetal testosterone levels modify neural development, immune development, and neural crest development. The theory can explain many aspects of cerebral lateralization and its relation to learning disorders, giftedness, and immune deficits. This article clarifies the structure of the theory by presenting it as a causal-path model. The internal coherence of the model is then evaluated by assessing the central concept of anomalous dominance, the role of timing in the articulation of the model, and the invocation of nonlinear processes. Finally, the article considers the problems implicit in testing a "grand" theoretical model and derives some principles for assessing the *testability* of various predictions, given the practical constraints of sample size and the problems of measurement error.

In 1982, Geschwind and Behan published an article (Geschwind & Behan, 1982) in which they proposed that fetal testosterone slowed normal development in the left hemisphere, modified cerebral lateralization, disrupted early language development, and impaired immune functioning, thereby resulting in subsequent immune disorders. This theory made the clear, but counterintuitive, prediction that left-handedness should be associated with immune disorders, a finding that Geschwind and Behan reported in two survey studies. Since that initial article appeared, the model has been extensively elaborated in a series of three articles by Geschwind and Galaburda (1985a, 1985b, 1985c) and a subsequent book, *Cerebral Lateralization* (*CL*), that was based on those articles (Geschwind & Galaburda, 1987). In its final form form, as stated by Geschwind, the theory attempted to explain a vast range of correlations between conditions and processes that had not previously been linked, either empirically or theoretically. In this article we consider only the central theory as presented in Geschwind's works, recognizing that modifications have occurred in Galaburda's theorizing since that time (e.g., Rosen, Galaburda, & Sherman, 1987).

The Geschwind-Behan-Galaburda theory (henceforth the Geschwind theory) has provoked a great deal of interest among psychologists, neurologists, and other neuroscientists. Although some attempted to replicate the association between handedness, language disabilities, and immune disorders, and others searched for new correlations suggested by the theory, the vast majority of the several hundred citations of the articles during the 1980s were generally uncritical in their acceptance of the broad principles of the theory.

Although there have been detailed critiques of various aspects of the Geschwind theory (e.g., Bishop 1990; Satz & Soper, 1986), the fully developed version of the theory is sufficiently rich and complex to mean that there has not been any serious attempt to evaluate the model as a whole.

Popper (1963) has distinguished between "small" theories and "large" theories. The Geschwind theory is undoubtedly a large theory, not only accounting for its original data but extending that theorizing to such an extent that, if true, it would require a radical rethinking of many areas of biology and medicine, reinterpreting in passim such generally accepted areas as the biology of twinning (*CL*, pp. 139–140), the genetic basis of Down's syndrome (*CL*, pp. 94–95), and the neuropharmacology of psychoactive drugs (*CL*, pp. 214). The very size and complexity of the Geschwind theory however means, as we shall see later, that it is not open to simple "falsification" in Popper's sense: Rather, in the fashion described by Lakatos (1978), the theory has a concentric series of defensive hypotheses around it, which can be falsified without the central theory being effectively challenged.

Why has the Geschwind theory been so appealing and received so much attention? Although in part a function of the charisma and prestige of Geschwind himself, the theory is also successful because in being a large theory it manages to gather together a wide range of previously intractable neuropsychological phenomena under a single theoretical umbrella. This theory might perhaps be described as the "neuropsychology of individual differences," attempting to explain both variation within the normal range (such as why individuals differ at mathematics or reading), and at the extremes of the ability range (producing

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Correspondence concerning this article should be addressed to either I. C. McManus, Department of Psychology, University College London, Gower Street, London WC2 6BT England, or M. P. Bryden, Department of Psychology, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1.

both what Geschwind and Galaburda call a "neuropathology of superior intellectual functions" (*CL*, p. 65) and an account of mental subnormality and of conditions such as autism and of "idiots savants"). Before the Geschwind theory there was no general theory that explained all of these phenomena and their associations; extant theories typically appealed to specific and independent genes for each condition. In the theory's strength might also lie its weakness, for theories that integrate too many phenomena run the risk of explaining everything, and hence saying nothing and becoming untestable or vacuous. But here also is another facet of the Geschwind theory: It apparently keeps its feet firmly rooted in biological reality, with its emphases on neuroanatomical asymmetries, on histological abnormalities of cortex, and on handedness in relation to specific diseases. It thus sits firmly in the scientific mainstream, with its undoubtedly brilliant use of scientific induction to generate apparently plausible theories from unusual data, and then to make even more counterintuitive empirical predictions from the theory.

Needless to say, every one of these virtues is potentially a fault, and the theory has its detractors and skeptics. Its radical reinterpretation of neurobiology and its enormous breadth of vision mean that to a great extent it is explaining phenomena that had hardly been looked at previously by conventional neuropsychology, which instead had concentrated on its traditional theoretical core of language and cerebral dominance. There is thus often a paucity of evidence for critically assessing the theory. A final problem that arises from the breadth of the theory is its use of evidence from a host of biological disciplines and subdisciplines, so that few individuals, if indeed any, could conceivably have the expertise to assess the theory comprehensively; and in discussing the theory with other workers we have often heard the comment that Geschwind and Galaburda's (1987) use of evidence seems selective in those areas in which one has special expertise, but that the rest cannot be assessed. For the nonexpert, the temptation is always therefore to extract a small portion of the theory, use it for one's own purposes, and tacitly assume that the other parts are correct because they sound convincing.

In discussing the Geschwind theory with others, we have also been struck with how often people state that they do not really understand the ramifications of the theory. Although this is in part due to the fact that Geschwind died while the 1985 articles were still in press, leaving both the articles and the resulting book poorly organized, much of the problem arises from the wealth of the ideas and the sheer number of different links suggested at one point or another in the text.

In the present article we provide a critical reading and a clarification of the Geschwind theory, to show how the various processes and factors are interrelated. That such a description is necessary is a consequence of the diffuse, rambling, sometimes repetitious, and often poorly structured nature of the book itself. In doing so we develop our interpretation of the Geschwind model as a causal path theory, which provides a clarification of the theory and readily allows empirical predictions. In doing so, we at times impose our own interpretation on the Geschwind model, as well as provide a formal and testable version of it.

As a next step we then develop some logical predictions from the theory, to assess ways in which a theory as large and as complex can in principle be testable and falsifiable. We therefore show the general types of study that can provide the best tests of crucial aspects of the theory. In so doing it will become apparent that some parts of the theory can be altered or modified without destroying the fundamental principles at the center of the theory.

In many ways it would be logical at that stage to go on and evaluate the empirical evidence for each causal connection we have identified. However such an attempt would not only make this article prohibitively long, but in many ways it would be premature. Geschwind, Behan, and Galaburda provided some provisional or suggestive evidence for a majority of their claims. Most subsequent research has focused on the more obvious associations of the model, such as the relation between handedness and immune disorders (e.g., Bishop, 1986; Cosi, Citterio & Pasquino, 1988; Searleman & Fugagli, 1987; Smith, 1987; Urion, 1988; Van Strien, Bouma, & Bakker, 1987). There are also interesting studies relating developmental language problems to immune disorders (e.g., Burke, Yeo, Vranes, Garry, & Goodwin, 1988; Hugdahl, Synnevåg, & Satz, 1990) and to congenital limb malformation (Dlugosz et al., 1988). However, the tactics for evaluating the model suggested by our causal path analysis are necessarily rather more complex than simply determining the association between two variables, and adequate empirical studies are yet to be done.

The Geschwind Model of the Biology of Cerebral Lateralization

In this section we delineate the principal theoretical postulates of the Geschwind theory as they are found scattered through *Cerebral Lateralization* (Geschwind & Galaburda, 1987). Our model does not pretend to describe *all* of the biological links proposed by Geschwind and Galaburda, but instead concentrates principally on those routes that explain psychological phenomena related to lateralization, learning disorders, or intellect or account for associations between those phenomena and other biological or medical phenomena.

The model is summarized in Figure 1, which represents a conventional path diagram or causal model for the theory (Kenny, 1979). Although formally a path model, path coefficients for the strength of links are not shown, because in general there is no real indication of what they should be. Nevertheless, in principle these coefficients are knowable, and must be nonzero and positive (except in one or two cases where they are explicitly negative). Given that the coefficients are nonzero, the first law of path analysis (Wright, 1934) means that there are also nonzero correlations between any two variables that can be reached by traveling backwards through the model to an earlier node and then forward once more to a later node; that is, in effect, between most of the entities listed down the right-hand side of the diagram. The model therefore makes it clear that many pairs of variables will be statistically associated. Correlation alone does not of course mean that variables are necessarily causally related, except perhaps indirectly through some third variable. That view of the model is implicit for instance in Geschwind and Galaburda's (1987) own description of the association between anomalous dominance and developmental

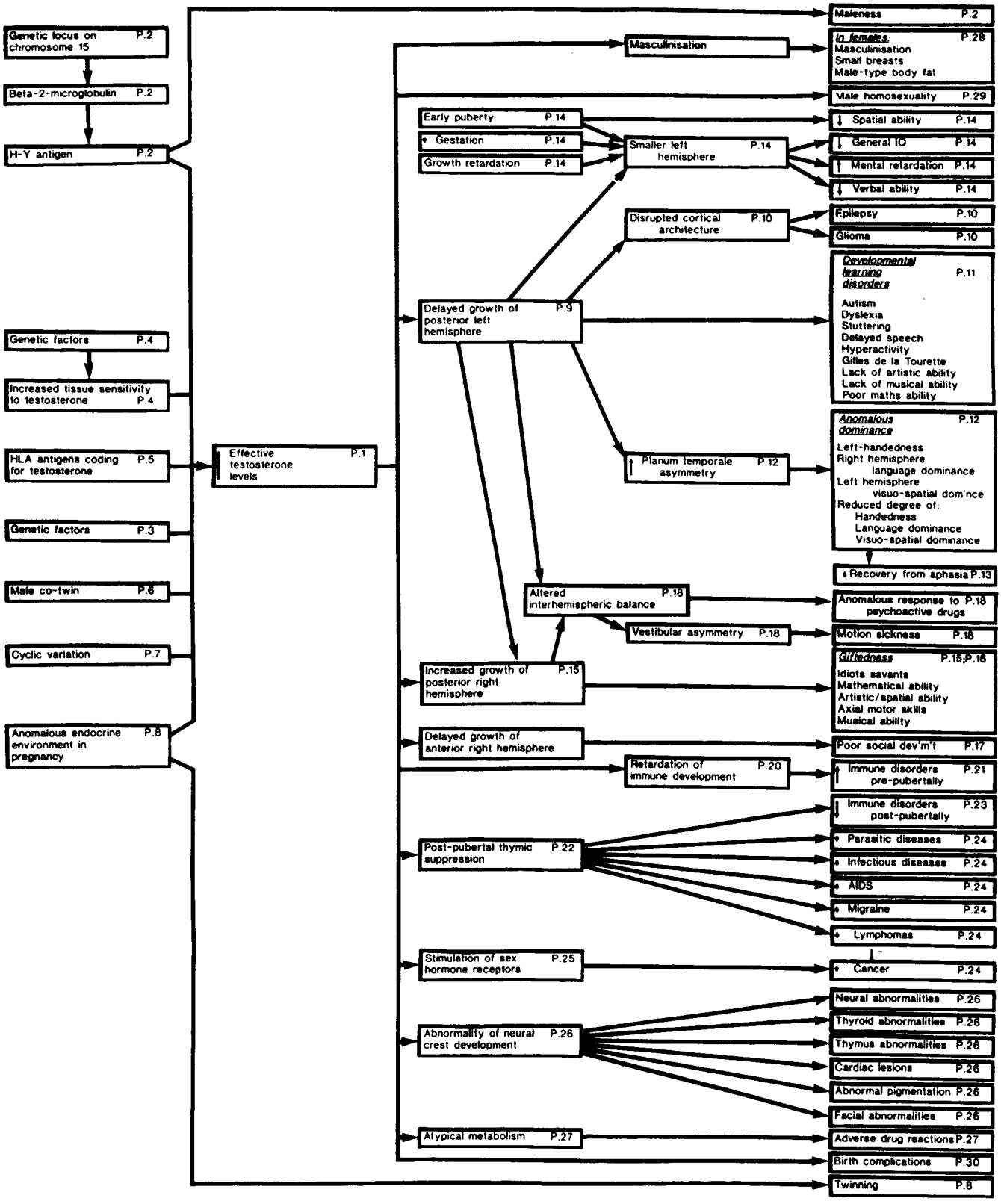

Figure 1. A structural model of the Geschwind model of cerebral lateralization: Numbered references within boxes (e.g., P. 16) refer to the specific postulates identified in the text, which should be studied for further information on each component of the model.

learning disorders where they say "these findings do not imply that non-right-handedness is the *cause* of the learning disorder; we regard non-right-handedness only as a marker of an alteration in dominance" (*CL*, p. 85; our emphasis).

The postulates of the model are subdivided and numbered for convenience. The numbers on Figure 1 correspond to the theoretical postulates, so that descriptions of each may readily be found in the text. For the purposes of exposition in describing the postulates, we have uncritically cited only references quoted by Geschwind and Galaburda (1985a, 1985b, 1985c, 1987) in support of their hypothesis, and we have neither added additional references nor assessed their worth as support for the statements made. Table 1 summarizes the citations in *CL* for each of the postulates of Figure 1. For convenience we will divide the postulates into four groups: those concerning testosterone, those related to neurological processes, those related to the immune system, and a miscellaneous collection of others.

Testosterone

Postulate 1: Individual differences in testosterone levels are the principal common cause of a range of individual differences, modifying among other things the developing brain and immune system. Testosterone lies at the theoretical core of the model. This is not surprising given that of the six empirical observations that Geschwind and Galaburda (1987) wished their theory to explain (*CL*, p. 10; the excess of left-handedness in males; the male-predominance in stuttering, dyslexia, and autism; but see Shaywitz, Shaywitz, Fletcher, & Escobar, 1990; superior verbal ability in women and superior spatial ability in men; left-handers and the learning disabled show superior right hemisphere abilities; left-handedness is more common in developmental disorders; and immune disorders are more common in nonrighthanders), three concern sex differences. Although testosterone is thought to be important in lateralization throughout life, the theory principally emphasizes its role during fetal development at certain critical times (and the precise timing is considered separately in a following section). In talking of "testosterone," Geschwind and Galaburda made it clear that they were principally concerned with "effective" testosterone, biologically active at the cellular level, excluding that bound to globulins (*CL*, pp. 13 and 107). There are individual variations in many factors that modify the individual fetus's testosterone levels, including other sex hormones (*CL*, pp. 11 and 107).

Postulate 2: The principal determinant of testosterone levels is the H-Y antigen, which determines maleness; the gene for beta-2-microglobulin on chromosome 15 may also be necessary for H-Y expression and be involved in familial dyslexia. The H-Y antigen, determined by a gene on the Y chromosome is the principal determinant of maleness and hence of testosterone levels (*CL*, p. 105; Haseltine & Ohno, 1981). Geschwind and Galaburda also followed Ohno (1977) in arguing that H-Y antigen expression is dependent on the locus for beta-2-microglobulin (B_2M) on chromosome 15, which is essential for immune responsiveness (*CL*, p. 119). They also invoked the B_2M locus as a possible mechanism in the linkage identified by Smith, Kimberling, Pennington, and Lubs (1983) between dyslexia and chromosome 15 (*CL*, p. 119). Geschwind and Galaburda emphasized that the H-Y antigen is not the only source of fetal testosterone, because female fetuses also have testosterone (*CL*, p. 11; and the distribution overlaps with that of male fetuses, *CL*, p. 107).

Postulate 3: Testosterone levels are under direct genetic control, both in males and in females. In explaining the apparently sex-limited pattern of expression of learning disorders, Geschwind & Galaburda (1987) proposed that genes might affect testosterone levels (*CL*, p. 87) so that "a female would be more likely to suffer from a learning disorder if she were subjected to high testosterone levels during development" (*CL*, pp. 87–88). Because "testosterone levels in male fetuses are [more] sensitive to environmental effects" (*CL*, p. 88), the heritability of learning disorders will be greater in females than in males.

Postulate 4: Altered tissue sensitivity to testosterone can occur in both female and male fetuses and may be under genetic control. As well as the testicular feminization syndrome, in which genetic males are insensitive to testosterone (*CL*, p. 107), Geschwind and Galaburda also claimed that some female fetuses have increased sensitivity to testosterone (*CL*, p. 13), which may be under genetic control. This mechanism is invoked to explain why female stutterers (who are assumed to have genetically inherited high testosterone levels), have a higher incidence of affected relatives than do male stutterers (*CL*, p. 88; Kidd, Heimbuch, & Records, 1981). As also for

Table 1
Summary of Textual References in Cerebral Laterilization (CL) to Support the Theoretical Postulates Indicated by Number in the Text and in Figure 1

Postulate	*CL* page number(s)
P.1	11, 13, and 107
P.2	11, 105, 107, and 119
P.3	87 and 88
P.4	13, 107, and 108
P.5	93, 94, and 119
P.6	141 and 142
P.7	218, 219, 220, and 221
P.8	141 and 142
P.9	11, 46, 98, 99, 100, and 207
P.10	13, 58–66, 86, 121, 186, 199, and 202
P.11	83, 84, and 87
P.12	70 and 73
P.13	74
P.14	94, 98, and 99
P.15	12, 65, 66, 97, 98, 99, and 102
P.16	11, 77, 78, 82, 87, 98, and 168
P.17	20–34, 206, and 207
P.18	213 and 214
P.19	151
P.20	13
P.21	13, 88–89, 118, and 123
P.22	13 and 122
P.23	13, 92, 96, 118, 122, 123, and 196
P.24	82, 91, 92, 124, 150, 175, 176, 180, and 198
P.25	181, 182, and 218
P.26	156, 157, 158, 159, 160, 161, 162, 163, 170, and 177
P.27	216 and 217
P.28	111, 141, 169, 171, 172, and 183
P.29	175
P.30	176 and 227

Note. P = postulate.

Postulate 3, no direct evidence was provided for the genetic hypothesis.

Postulate 5: There are loci in the major histocompatibility complex that alter the production and metabolism of testosterone (CL, p. 14). Genes in the major histocompatibility complex of the mouse affect testis weight, serum testosterone, testosterone-binding globulin, responsiveness to testosterone, and H-Y antigen expression on the thymus gland (*CL*, p. 119; Ivanyi, 1978). Surprisingly, Geschwind and Galaburda (1987) do not therefore predict that the human leukocyte antigen (HLA) haplotypes which underly histocompatibility should be related to anomalous dominance, and indeed they are concerned that an association will be taken as evidence *against* their theory (*CL*, p. 93). Instead, they emphasized that HLA genes must exert their ultimate effects through "particular chemical products," of which testosterone is a likely candidate (*CL*, p. 93).

Geschwind and Galaburda (1987) also mentioned that because parental HLA haplotype sharing is related to infertility, fetal loss, and fetal abnormalities (Faulk, 1981; Taylor & Faulk, 1981), then parental shared haplotypes may be more common in offspring with anomalous dominance (*CL*, p. 94).

Postulate 6: Testosterone levels will be higher in individuals, male or female, who have a cotwin who is male, and therefore also secreting testosterone (CL, p. 141). Female twins in opposite-sex pairs will be exposed to higher levels of testosterone due to exposure from their male cotwin (*CL*, p. 141), implying that female twins in opposite-sex pairs should have a higher rate of left-handedness. Additionally it is argued, without mechanism, that "Since male twins both produce testosterone, each will conceivably be exposed to higher levels than he would be if he were a singleton" (*CL*, p. 141). Such processes are used to explain the higher rate of dyslexia among twins (*CL*, p. 142; Bakwin, 1973).

Postulate 7: There is cyclic variation in sex hormone production, which can explain the higher rate of birth of individuals with particular syndromes at different seasons. "Cyclic alteration in the production of sex hormones is likely to be important in many ways; for example it might affect the percentage of children with anomalous dominance born at different seasons" (*CL*, p. 219); the data of Badian (1983) are cited. Note is also made of the circannual variation in the birth rate of schizophrenics, mental defectives, and of eminent births (*CL*, p. 220). Other cyclic phenomena are also invoked: "Circadian phenomena" may differ in those with anomalous dominance (*CL*, p. 221); and "There is also a lunar cycle, which has been highly significant in the folklore of many cultures. This cycle probably has physiological importance, but convincing data on this point are very scarce" (*CL*, p. 218).

Postulate 8: "An anomalous endocrine environment in pregnancy might modify the later hormonal characteristics of the individual . . ." (CL, p. 93). Geschwind and Galaburda here seem to have referred to the influences of atypical maternal hormones (such as exogenous progestogens) on the developing fetus, acting by increased testosterone; examples cited include "masculinized females" (due to polycystic ovary syndrome) with raised luteinizing hormone levels (Jafee & Vaitukaitis, 1982) and abnormal exogenous hormones such as clomiphene or human chorionic gonadotropin (*CL*, p. 141). The effects of these hormones include an increased rate of twinning (even in the subfertile group with polycystic ovaries; *CL*, p. 142). Geschwind and Galaburda used the mechanism to explain increased rates of left-handedness in twins and in the mothers of twins (*CL*, p. 141). The excess twinning is presumably dizygotic (DZ), both because clomiphene induces nonidentical twins, and because populations differ far more in DZ than in monozygotic (MZ) rates, and it is DZ twinning that tends to be familial (*CL*, p. 140).

Neurological Effects

Postulate 9: In fetuses, testosterone "slows the growth of parts of the left hemisphere, so that . . . the corresponding regions on the right develop relatively more rapidly" (CL, p. 11). Geschwind and Galaburda referred principally to the left posterior regions associated with the planum temporale (*CL*, p. 207), and they emphasized that it is a slowing of left hemisphere growth rather than stimulation of right hemisphere growth (*CL*, p. 46). The experimental work of Goldman-Rakic and Rakic (1984) provides some underpinning, in that partial removal of fetal monkey cortex produces a compensatory hypertrophy contralaterally and in adjacent ipsilateral areas (*CL*, p. 99; photograph, *CL*, p. 100). The slower growth of the left hemisphere does not mean that it is necessarily smaller (*CL*, p. 98; see Postulate 14).

Postulate 10: Delayed left hemisphere growth results in a disruption of the normal cortical architecture of the left-hemisphere. "Markedly delayed neuronal migration and/or abnormal neuronal assembly" leads to "disrupted cortical architecture and neurons in abnormal locations" (*CL*, p. 13). Geschwind and Galaburda (1987) speculated that the normal process whereby axons find appropriate terminations is immunological and affected by testosterone:

> If the immune system provides anchoring sites for the processes of axons, then sex hormones, which affect the immune system, could lead to alterations in the formation of the nervous system. If the immune system provides markers for neural development, then immune suppression at a particular period might lead to disordered neural development. (*CL*, p. 121)

Disrupted left cortical cytoarchitecture causes developmental learning disorders in males (*CL*, p. 13), so far only described in dyslexia (*CL*, pp. 58–66), but implied as also occurring in autism and stuttering (*CL*, p. 86), and other developmental learning disorders (see Postulate 11).

Abnormal cytoarchitecture has two additional effects: "Embryonic rests are more likely to persist in anomalously dominant individuals because of delays in development" (*CL*, p. 199) and may provide the origin of cerebral tumors such as gliomas either provoked by or provoking other immune phenomena (*CL*, p. 199), so that "gliomas might result from immune attack at a cell rest" (*CL*, p. 186). Abnormal architecture, such as micropolygyria, may result in abnormal electrical activity, and may explain the increased epilepsy found in dyslexics, in language delay, in stutterers, and in autistic children (*CL*, p. 202; Dalby, 1981; Masland & Masland, 1981; Stefan, Milea, Magureanu, & Roman, 1981; Szondi, 1932).

Postulate 11: Delayed left-hemisphere growth is associated with an increased incidence of the conditions broadly called "developmental learning disorders." This broad category principally

includes developmental dyslexia, stuttering, delayed speech, childhood autism, and hyperactivity (*CL*, p. 83), and Giles de la Tourette syndrome should probably also be included (*CL*, p. 83). These conditions are linked by having an excess of males, a "rather similar pattern of inheritance" (*CL*, p. 84), and increased personal and familial left-handedness (*CL*, p. 84; Bishop, 1983; Boucher, 1977; Colby & Parkinson, 1977; Porac & Coren, 1981). The conditions may also show cotransmission, propositi with one condition having relatives with other conditions (e.g., Orton, 1925, for stuttering and dyslexia; Ludlow, Polinsky, Caine, Bassich, & Ebert, 1982, for dyslexia and Tourette syndrome; and Folstein & Rutter, 1977, for autism and learning disabilities). The group might also include "extreme lack of musical ability," "lack of artistic ability," (*CL*, p. 87), and "special difficulty in mathematics" (*CL*, p. 87), which, like superior mathematical ability, is said to be more common in males (*CL*, p. 87). Geschwind and Galaburda were not clear as to whether these disorders are all caused by abnormal cytoarchitecture (Postulate 10), or whether some may have a direct causal link only to delayed left hemisphere growth. The latter hypothesis is broader, and we have chosen to use it.

Postulate 12: Delayed left hemisphere growth results in "anomalous dominance." Anomalous dominance is a central theoretical construct in the Geschwind theory, and we devote a whole section to it later. Here we emphasize that it does not consist only of reversed handedness in the sense of left-handedness (which was the only description used by Geschwind & Behan, 1982), but instead comprises six separate components: *reversed handedness,* in the sense of left-handedness; *reduced degree of handedness* with anomalous dominance marked by deviations from strong laterality (*CL*, p. 70), so that evaluation of the Geschwind hypothesis requires "consideration of the entire distribution of laterality scores" (*CL*, p. 75); *reversed language dominance* (that is right hemisphere language dominance; *reduced degree of language dominance,* which can be present even in those who are left-hemisphere dominant for language (see *CL*, p. 70) and would presumably be assessed by dichotic listening or visual half-field studies; *reversed dominance for right hemisphere functions* (*CL*, p. 70); and *reduced dominance for right hemisphere functions* (*CL*, p. 70). *Standard dominance* refers to the absence of all of these features, and "the term *anomalous dominance* refers to those in whom the pattern differs from the standard form" (*CL*, p. 70); that is, if *any* feature differs. It should be noted that the concept of anomalous dominance is intertwined with that of structural asymmetries: We consider the question further in the section on Immune Effects.

Postulate 13: Individuals with anomalous dominance should have higher rates of recovery from aphasia. Geschwind and Galaburda cited Luria's (1970) finding that left-handers have a higher rate of recovery from aphasia and then argued that other groups, such as right-handers with developmental learning disorders or with first-degree relatives with learning disorders, will also have higher recovery rates (*CL*, p. 74). The causal relation between recovery and dominance is not clear, but because dominance occurs temporally before aphasia, we have made it causally prior.

Postulate 14: Delayed left hemisphere growth results in a smaller left hemisphere, which in turn results in decreased verbal ability. However other factors, such as a longer pregnancy, delayed puberty, or the absence of growth retardation can result in a lengthened growth period so that despite growing more slowly the left hemisphere can be larger and hence verbal ability be greater (CL, p. 98). Geschwind and Galaburda (1987) were not explicit on the causal relationships, but they did state that despite "growth of the left hemisphere being slowed to a greater extent in left handers," "it may attain a greater final size," when "the growth period is prolonged. . . . when pregnancy is longer than average or when puberty is late," even resulting in "left-handers [being] . . . found in increased numbers in . . . occupations demanding high talent, *including those in which verbal talents are necessary*" (*CL*, p. 98; our emphasis). Conversely, growth retardation, short gestation, and early puberty produce developmental disorders, "and in more extreme cases a distinctly inferior overall level of functioning" (*CL*, p. 94)—by which we understand reduced general intelligence and mental retardation (*CL*, p. 99). Finally, Geschwind and Galaburda argued that delayed puberty (specifically late menarche in females) is associated with higher spatial ability (*CL*, p. 98; Waber, 1981) and hence early puberty associated with decreased spatial ability.

Postulate 15: Delayed growth of the left posterior hemisphere "favours growth of cortical regions on the opposite side and of unaffected regions on the same side" (CL, p. 12; see also CL, p. 97). The compensatory mechanisms in the contralateral and adjacent hemisphere are seen as potentially beneficial, so that "even with excessive retardation of growth and the resultant migration abnormalities and learning disorders, high talents may exist as a result of compensatory enlargement of other cortical regions" (*CL*, p. 97). "When this increase in size is marked, superior or even remarkable talents may develop" (*CL*, p. 66), resulting in a "neuropathology of superior intellectual functions" (*CL*, p. 65). The definition of giftedness is not entirely clear, so that "it might [also] . . . be postulated that nonrighthanded populations are over-represented in *all populations with high talent*" (*CL*, p. 98), including "those in which verbal talents are necessary" (*CL*, p. 98; see Postulate 14). Giftedness also includes the phenomenon of idiots savants (*CL*, pp. 99 and 102).

Geschwind and Galaburda (1987) were vague as to when ipsilateral hypertrophy will occur;

> If the delaying influence acts only during the development of a particular cortical area, then one might expect hypertrophy of adjacent regions. . . On the other hand, if the retarding influence is present over a longer period, it may affect other areas in the same hemisphere and thus might diminish or prevent the hypertrophy of adjacent areas, although contralateral hypertrophy should still take place and indeed might even be enhanced. (*CL*, p. 99)

Postulate 16: Compensatory right hemisphere growth typically results in "giftedness" for those skills for which the right hemisphere is particularly involved. The evidence typically consists of an implicit assumption either that functions are located in the right hemisphere (or are adjacent to the left hemispheric language areas), or are associated with left-handedness, and hence with anomalous dominance. In no case is structural anatomical or histological evidence cited. Geschwind and Galaburda (1987) considered several specific skills:

1. *Mathematical ability.* Geschwind and Galaburda (1987) cited Kolata (1983), Benbow and Stanley (1983), and Annett

and Kilshaw (1982) as evidenced for an increased left-handedness in the mathematically gifted (*CL*, pp. 82, 87, and 98).

2. *Artistic and/or spatial ability.* Geschwind and Galaburda (1987) cited Peterson and Lansky (1974) for increased left-handedness in architects (*CL*, pp. 15, 82, and 98), engineers (*CL*, p. 98), and in artists Peterson (1979). Additionally, the first patient of Galaburda and Kemper (1979), a dyslexic, was also a "skilled metalsmith" (*CL*, p. 77). "The capacity of each half-brain to control its motor functions relatively independently may . . . [account] for the high rate of nonrighthandedness . . . in fields such as architecture and the other visual arts" (*CL*, p. 168). Whether artistic ability, spatial ability, or motor ability is the key common component is not clear.

3. *Athletic, dancing and other motor skills.* Geschwind and Galaburda followed Geschwind (1975) in arguing for two types of motor learning: pyramidal, involving fine manual skills of the contralateral limb, and axial, involving movements of the trunk and limb girdles. Axial control is particularly important for acquiring "high athletic or dancing talents." "In those with standard dominance [SDP] the programs for both types of dominance lie in the left hemisphere but . . . under conditions of anomalous dominance they may lie in separate hemispheres" (*CL*, p. 78). McLean and Ciurczak (1982) were cited for increased left-handedness in "professional athletes" (*CL*, p. 98)—in fact, baseball players.

4. *Musical ability.* This skill is not mentioned specifically, although Geschwind and Galaburda (1987) did discuss the superiority of nonrighthanders on musical tasks (Deutsch, 1978) and increased incidence of left-handedness in musicians (Peterson [1979], Byrne [1974], and Quinan [1922] were cited, and the contradictory evidence of Oldfield [1969] was noted; *CL*, p. 98). *Lack* of musical ability is also a developmental learning disorder (see Postulate 11).

Postulate 17: Testosterone delays the growth of the anterior part of the right hemisphere. Geschwind and Galaburda (1987) documented the general tendency for brains to show a larger right hemisphere anteriorly and a larger left hemisphere posteriorly (*CL*, pp. 20–34), and they speculated that "intrauterine effects on dominance [do not act] to slow development only in the left hemisphere but instead [act] on selected areas in the two hemispheres, namely, on left posterior regions and right anterior regions" (*CL*, p. 207), supporting this with evidence for similar patterns of atrophy in Pick's disease (*CL*, pp. 206–207). Delayed right frontal development, based on the cases of Weintraub and Mesulam (1983), results in "poor social development" (*CL*, p. 207).

Postulate 18: Alteration in the relative activities of the right and left hemispheres, caused by left hemisphere growth retardation and right hemispheric hypertrophic compensation, alters the hemispheric balance producing anomalous and idiosyncratic responses to psychoactive drugs. Because the left and right hemispheres differ in their emotional responses (Gainotti, 1972; *CL*, p. 213), Geschwind and Galaburda (1987) argued for differential hemispheric action of neurotransmitters, so that "if a drug produces opposing cognitive or behavioral effects on the two sides, then the net effect will alter when the dominant side is damaged" (*CL*, p. 214). This radical theory therefore argued against much conventional psychopharmacology:

> Because certain drugs are called antidepressants and others are described as antipsychotic, there is a common belief in a chemistry of mood or psychosis. These terms may be misnomers, however, and there may be no such special chemistry. It is possible instead that the usual actions of these drugs reflect the standard dominance pattern of the majority of the population. Those with different patterns of cerebral dominance might react in a quite different fashion. (*CL*, p. 214)

Postulate 19: "Alterations in hemispheric dominance relationships" result in "lateral imbalances produced in normally symmetrical neural systems," resulting in vestibular anomalies and conditions such as motion sickness (CL, p. 151). The concept of "hemispheric balance" is often applied metaphorically; here it is applied literally: lack of vestibular balance resulting in physical imbalance and symptoms (e.g., Ménière's disease). Geschwind and Galaburda (1987) speculated that "vestibular anomalies may derive from lateral imbalances produced in normally symmetric neural systems by alterations in hemispheric dominance relations" (*CL*, p. 151). Little evidence is presented except for associations between motion sickness and migraine (Barbas, Matthews, & Ferrari, 1983; Kuritsky, Zeigler, & Hassanein, 1981), and it was noted that conditions such as torsion dystonia and spasmodic torticollis may have anomalous vestibular systems and hence anomalous dominance. Finally, Geschwind and Galaburda noted that because the cortical representation of the vestibular system may be in the temporal lobes (Crosby, Humphrey, & Lauer, 1962), cytoarchitectonic defects may result in vestibular symptoms, and they noted that dyslexics have histological defects in this region (*CL*, p. 151).

Immune Effects

Postulate 20: Testosterone in utero has the effect of retarding the development of the immune system. "Testosterone . . . retards the growth of structures involved in immunity, such as the Bursa of Fabricius in the chick embryo (Warner, Szenberg, & Burnet, 1962) and the thymus gland in the rat post-natally (Frey-Wettstein & Craddock, 1970)" (*CL*, p. 13). Geschwind and Galaburda (1987) also said that "recent experiments in the rabbit by Behan . . . are consistent with similar retarding effects on the fetal thymus" (*CL*, p. 13). As yet, this work remains unpublished (P. Behan, personal communication, December, 1990).

Postulate 21: Retardation of the immune system increases susceptibility to immune disorders in prepubertal males (CL, p. 13). Immune retardation results in a higher rate of immune disorders in males, as is the case for atopic disorders of childhood (*CL*, p. 13), asthma, eczema, and hayfever (*CL*, p. 118). Geschwind and Galaburda (1987), "use the term 'immune disorder' to mean atopic disorders (the allergies, typically of childhood onset), autoimmune disorders, and other conditions in whose pathogenesis immunity plays a major role" (*CL*, pp. 88–89), but they noted that " 'immune disorder' is not a monolithic category but instead encompasses many conditions with different mechanisms" (*CL*, p. 123).

*Postulate 22: Testosterone suppresses the thymus in adult life, postpubertally (*CL, *pp. 13 and 122).* Geschwind and Galaburda (1987) cited Frey-Wettstein and Craddock (1970) and

Wasi and Block (1961) as evidence that testosterone in adults causes suppression and involution of the thymus (*CL*, p. 13).

Postulate 23: Thymic involution in adults in response to testosterone results in a lower incidence of immune disorders, especially in males. Geschwind and Galaburda (1987) used this to explain the apparently disparate effects whereby diseases such as lupus erythematosus and myasthenia gravis are more frequent in young females (*CL*, pp. 118 and 123), that the proportion of males rises with age, and that atopy is more common in males prepubertally and in females postpubertally (Crawford & Beldham, 1976; *CL*, pp. 13, 96, and 122). "[T]he post-pubertal male, despite a possibly greater propensity toward autoimmunity, is protected from it by his own hormones, whereas this masking effect is weaker before puberty" (*CL*, p. 92; see also *CL*, pp. 122–123). Geschwind and Galaburda stipulated that the precise timing of the testosterone excess in relation to ontogeny of the immune system and of lateralization will affect tissue systems differentially and will determine associations with anomalous dominance (*CL*, pp. 92); therefore, they "do not wish to imply that a general susceptibility to all forms of immune disorders will exist in all those with anomalous dominance" (*CL*, p. 92). The concept of immune disorders is broad enough so that "those with anomalous dominance . . . [may] also have a higher rate of immune complications of drugs or diseases" (*CL*, p. 196).

Postulate 24: Abnormalities of immune functioning should result in a range of other conditions with actual or possible immune deficits. A range of conditions is specified without it being clear of the precise immune mechanisms involved (so that the model includes links both to Postulate 19 and Postulate 21).

1. *Infectious diseases.* "Differences in the frequency of the allergic and immune diseases may well be paralleled by differences in susceptibility to infection. Females are less likely to die of infection than are males, and this must be attributable in good part to differences in the immune system" (*CL*, p. 124). Although initially Geschwind and Galaburda seemed to imply that infectious diseases should be less common in those with anomalous dominance and left-handedness (*CL*, pp. 82 and 124), they subsequently argued that

> patients with anomalous dominance may well be protected from certain infections while being more susceptible to others. Those with high IgE are susceptible to allergies but, may have an elevated level of protection against parasitic disorders (Marsh, Meyers, & Bias, 1981) which raises the possibility that many anomalously dominant individuals are resistant to these disorders. (*CL*, p. 198; see also *CL*, p. 150)

2. *Acquired immune deficiency syndrome (AIDS).* Some individuals have this immunological pattern as the result of a particular pattern of intrauterine hormonal experience (*CL*, pp. 175–176); as a result there is a "possibility that AIDS may attack a particular anomalous dominance group" (*CL*, p. 198).

3. *Malignancies of the lymphoid system.* The incidence of "some [immunologically] related conditions, such as lymphoid malignancies that have a close relationship to immune disorder, would also be elevated in the anomalous dominance population" (*CL*, p. 92) and also in their families (*CL*, p. 180).

4. *Migraine.* Geschwind and Galaburda (1987) stated that

> there is some support for the participation of immune mechanisms in at least some cases, for instance, a reported increase in the rate of migraine in lupus erythematosus. During attacks there is an asymmetrical distribution of mast cells (Thonnard-Neumann, 1969). In a recent report (Egger, Carter, Wilson, Turner, & Soothill, 1983) of a controlled study of treatment of childhood migraine with exclusion diets, the authors argue for an allergic mechanism. . . . Further studies will be needed to confirm the existence of an immune mechanism in migraine (*CL*, p. 91);

and that "we should note that migraine is related to all of the factors discussed: unilateral predilection, female predominance, and an association with left-handedness and learning disorders" (*CL*, p. 150).

Other Effects

Postulate 25: There will be decreased rates of cancer. This results from at least two mechanisms. First, because immune disorders result in an increased rate of lymphoid tumors, these individuals will as a result of simple actuarial arithmetic necessarily have a lower rate of other cancers; for instance, Geschwind and Galaburda (1987) stated that in "celiac disease (which has a high rate of nonrighthandedness) [where] there is a higher than expected death rate from all malignancies. This is the result of an increased number of lymphomas and other unusual gut tumours; the rates of lung and breast cancer are diminished" (*CL*, p. 181). Second, "several tumours may carry sex hormone receptors, for example, cancer of the breast . . . melanomas, meningiomas and astrocytomas (but no[t] oligodendromas)," and early testosterone may affect their development, so that "it would be interesting to look for lateral predilection or association with anomalous dominance in all of these cases" (*CL*, pp. 181–182). Note, however, that it is now not clear whether carcinoma of the breast should have a lower incidence in anomalous dominance (because of its lower occurrence in celiac disease) or a higher rate (because of its sex hormone receptors). Finally, two further mechanisms are implied when it is pointed out that "the anomalous dominance population will differ from the much larger standard dominance population in fetal exposures to many substances [presumably both hormonal and carcinogenic], and this population may therefore have a different distribution of malignancies even in very late life" (*CL*, p. 218) and that "the hormonal atmosphere in utero may well permanently alter expression of genes or alter genes themselves (for instance, by methylation)" (*CL*, p. 218).

Postulate 26: Testosterone alters the embryological development of the neural crest, resulting in a range of minor and major structural abnormalities. Geschwind and Galaburda (1987) stated that the neural crest is important in the embryogenesis of the nervous system, including dorsal root ganglia, autonomic ganglia and several cranial nerve ganglia, the leptomeninges and dura in the forebrain, and pigmented cells throughout the body, and the connective tissue of the thymus gland and the skin and bones of the face. Neural crest lesions result in impaired development of the thymus and thyroid, and in cardiac lesions (*CL*, pp. 156–157). The neural crest is important in the Geschwind theory because "indirect evidence exists that sex hormones play a role in crest development"—albeit, the caveat is added that "to our knowledge [this has] not yet been studied directly" (*CL*, p. 157). The only substantive evidence cited is that

melanomas "are known in some instances to carry estradiol receptors" (*CL*, p. 157), as may meningiomas, and that neurofibromatosis typically worsens in puberty, particularly in females (*CL*, p. 158). Because adrenal steroids also affect neural crest development, it is surmised that sex steroids will also (*CL*, p. 158; see also p. 159).

Because the neural crest is responsible for the development of many tissues, particularly pigmented tissues, abnormal testosterone or other sex hormones might be implicated in abnormal aortic arch (*CL*, p. 158); transposition of the great vessels and congenital heart block (*CL*, p. 158); harelip (*CL*, p. 158); asymmetry of the external ear canals (*CL*, p. 159; which is included elsewhere in the broader category of "skeletal anomalies"; *CL*, p. 170); facial hypoplasia (*CL*, p. 160); scoliosis (*CL*, pp. 160–161); pale eye pigmentation (*CL*, p. 162); light colored hair (*CL*, p. 162); strabismus and esotropia (*CL*, p. 162); pigmentary anomalies (*CL*, p. 163); premature greying or whitening of the hair (*CL*, p. 163); and perhaps acne (as is implied in the diethylstilbestrol [DES] case history on *CL*, p. 177).

Postulate 27: Testosterone in pregnancy can alter metabolic processes and result in adverse drug reactions. Geschwind and Galaburda (1987) stated that

> since exposure to certain substances during intrauterine or early postnatal life may produce permanent alterations in the metabolic pattern, individuals subjected to unusual hormonal influences in pregnancy, who will frequently develop anomalous dominance, might have a different pattern of drug reactions from those not subjected to these influences. (*CL*, p. 216).

In consequence, "many drugs that are more toxic to males might also be more toxic to females with anomalous dominance than to females with standard dominance" (*CL*, p. 217).

Postulate 28: Testosterone can result in masculinization in females both physically and behaviorally. Geschwind and Galaburda (1987) several times referred to "masculinized females," sometimes referencing literature describing women with the polycystic ovary syndrome (Stein-Leventhal syndrome; e.g., *CL*, p. 141), and other times they implied a far broader definition, as when they use a criterion of smaller breast size (*CL*, p. 169), or a masculine distribution of body fat (*CL*, p. 171). Because the masculinizing effects of DES in utero are also referred to in relation to behavioral processes (*CL*, pp. 111–112), we assume that Geschwind and Galaburda were using the term in both the physical and the psychological sense. In all of these cases Geschwind and Galaburda linked masculinization with anomalous dominance:

> Masculinized females, who by our hypothesis should have a high rate of personal and familial anomalous dominance, have elevated levels of luteinizing hormone (Jaffee & Vaitukaitis, 1982). Since their offspring may have greater exposure to masculinizing effects in utero, they [i.e. the offspring] may have an elevated rate of left-handedness [*CL*, p. 141]; MVP [mitral valve prolapse] females have on the average smaller breasts than controls (Rosenberg, Derman, Grabb, & Buda, 1983) which suggests a masculinizing effect and therefore raises the possibility that this group will have a high rate of anomalous dominance. (*CL*, pp. 169 and 183)

Masculinization and anomalous dominance are also linked in the conditions of benign intracranial hypertension (*CL*, p. 171) and polycystic ovary syndrome (*CL*, p. 172).

Postulate 29: High testosterone levels early in fetal development result in homosexuality in males. "Ward and Weisz (1980) and Dörner, Gotz, and Docke (1983) have shown that, in rats, stress in midpregnancy causes the male offspring to have permanently low free testosterone levels and homosexual behaviour" (*CL*, p. 175). This potentially results in the "paradoxical conclusion that a group with low free testosterone levels in adult life should have a high rate of anomalous dominance," but that is resolved by a detailed examination of "the experiment of Ward and Weisz (1980) showing that when the pregnant rat is stressed, testosterone first *rises* to higher than normal levels in male fetuses and then drops to permanently low levels" (*CL*, p. 175).

Postulate 30: High testosterone levels are in some unspecified way the cause of birth complications and birth stress (CL, p. 176). Geschwind and Galaburda (1987) pointed out that a high rate of birth complications has been claimed for "left-handedness (Bakan, 1977), autism (Coleman, 1976) and other childhood learning disorders, and schizophrenia (McNeil & Kaij, 1978)," although they noted that "many of these data are in dispute" (*CL*, p. 176). However, they argued that since cytoarchitectonic disorders develop early in pregnancy they cannot be caused by obstetric damage, and hence

> it seems to us that difficult birth is much more likely to be a parallel manifestation rather than the cause of these disorders; in other words, the same influences that alter brain development also lead to disturbance of the birth process. This view implies that all, or nearly all, of the children who later turn out to be autistic would still suffer from this condition even if birth trauma were avoided. (*CL*, p. 176)

Similarly, in considering the question of whether particular birth positions are related to subsequent handedness, they again reverse the conventional causal order and suggest that "head position at delivery is not the cause of functional asymmetry but is itself the result of the existing asymmetry of the brain, which will have a distinct association with future handedness" (*CL*, p. 227).

Thus far we have uncritically described the principal causal model that we find in the Geschwind hypothesis. In the remainder of this section we wish to be more critical in assessing some theoretical ramifications of the model, ramifications that are close to its heart. In particular, we wish to consider the following: the concept of anomalous dominance; the role of timing in determining the events of the model; the occurrence of nonlinear processes in the model; the genetic model underlying the theory; and the evolutionary model underlying the theory. Each of these conditions the way in which the model was developed, how it might be applied, how it might be critically evaluated, and has its own logical implications (and in some cases, contradictions).

The Concept of Anomalous Dominance

Geschwind and Galaburda (1987) attached great importance to the concept of *anomalous dominance* (AD), which they distinguish from the *standard dominance pattern* (SDP), and that they said they had derived principally from the genetic theory of Annett (1978; *CL*, p. 236). They also made it clear (*CL*, p. 70) that they were referring to dominance in a broad sense, and not merely to handedness. SDP is defined as "strong left hemi-

sphere dominance for language and handedness, and strong right hemisphere dominance for other functions" (*CL*, p. 70); we refer to this pattern as RLR (i.e., strongly right-handed, strongly left-language dominant, and strongly right visuospatial dominant). AD is defined as "those in whom the pattern differs from the standard form" (*CL*, p. 70). Therefore, AD includes not only those individuals with completely reversed dominance (LRL) but also those who differ from the SDP with respect to the lateralization of one (LLR, RRR, or RLL) or two (LLL, LRR, or RRL) of these major functions. Strength of lateralization is also important in Geschwind and Galaburda's definition, because "there are continuously distributed degrees of language lateralization and handedness" (*CL*, pp. 69–70; and presumably also there are degrees of right hemisphere lateralization as well). It would therefore seem that individuals with weak left-hemisphere dominance for language (i.e., RlR—with the lower-case letter indicating weak dominance), weak right-handedness (rLR), weak dominant right-hemisphere functions (RLr), or any combination of these would also be included as cases of AD.

One of the dangers of the Geschwind and Galaburda (1987) definition of anomalous dominance is that it becomes overinclusive (*CL*, p. 70). They estimated that 30–35% of the population will show AD, although they later claimed that the SDP population is "much larger" (*CL*, p. 218) than the AD population. As a very minimum, and assuming a high covariation between the defining characteristics, the AD population must be at least as large as the number who are left-handed, or the number who have right hemisphere language, or the number who have left hemisphere visuospatial functions. Although perhaps 10% of the population fit the first two categories, current best estimates suggest that some 35% of the population have left hemisphere visuospatial dominance (Bryden, Hécaen, & de Agostini, 1983). Thus, at least 35% of the population must be AD. When degree of lateralization is included, so that people with weak lateralization are included in the definition of AD, the figure must become even higher. Given that right-handers are nearly 10 times more common than left-handers, then even a fairly liberal definition of weak lateralization for right-handedness would mean that r—individuals would easily outnumber L—individuals (and similarly for language and visuospatial dominance). We note that Schacter, Ransil, and Geschwind (1987), as described in *CL*, p. 75, suggested that a cutoff of 70 on the Oldfield Handedness Battery differentiated AD from SDP. Examining the original data of Oldfield (1971) for the Edinburgh Inventory, approximately 35% of right-handers will fit into the category of AD *on this criterion alone* (although using a modified Edinburgh Inventory, Schacter, Ransil, and Galaburda are cited by Geschwind and Galaburda as finding that only 25% of respondents scored less than 70; *CL*, p. 85). When combined with 10% of the population who are L—, plus perhaps another 10% who are RRR or RLL, and 35% or so who are RRL (see above), and an unknown proportion who are RlR or RLr, it may be that as many as 60% or 70% of the population would be showing AD.

A criterion of "anomalous," which runs the risk that a substantial majority of the population will be included within it, does not seem pragmatically useful or biologically realistic. In many ways the concept of AD reminds us of Luria's concept of "latent left-handedness" (Luria, 1970), which we have both criticized elsewhere (Bryden, 1989; McManus, 1983) on theoretical and empirical grounds, because the strong claims for such a broadly defined concept (see e.g. Sakano, 1982) render the concept too imprecise to be scientifically useful.

Individual Versus Population Dominance and Functional Versus Structural Dominance

The concept of AD, which as defined refers solely to *functional* dominance, is intertwined with the concept of *structural*, anatomical asymmetry in the brain, and results in some confusion of terminology and description, which is further confused by descriptions being applied either at the level of the individual or of the population. It is clear that Geschwind and Galaburda (1987) believed that anatomical asymmetries underlie the functional asymmetries. Anatomical structures may show one of three states: right dominant, left dominant, and symmetric, all three types being seen in the planum temporale, in which 65% of brains are larger on the left, 11% larger on the right, and 24% are symmetric (Geschwind & Levitsky, 1968). To account for the development of a functional dominance in individuals who do not show anatomical asymmetry, Geschwind and Galaburda invoked the concept of random dominance (Annett, 1978): "The more nearly symmetry is achieved in some particular region, the more likely there will be random dominance for the function subserved by that region" (*CL*, p. 69). As a consequence, in the subpopulation of individuals without functional dominance, there is functional dominance for each individual, but there is no population functional dominance.

AD is defined in terms of three separate features: atypical handedness, atypical language dominance, and atypical visuospatial dominance, with atypicality being defined either as reversed dominance or weakened dominance. Such a definition can only be useful, over and above the information given by its constituent measures, if it provides some theoretical gain in terms of conceptual simplicity or improved predictive power. The concept of AD can be viewed in two related ways: either it implies that high-order interactions are necessary in fitting a log-linear model to the six-way classification table of individuals or it implies that in a latent class analysis (McCutcheon, 1987) that a model with two latent classes (AD and SDP) is an improved fit over a simpler model fitted to the six-way classification table. And whether viewed as a latent class or an interactional model, the improved description should correlate better with some external criterion than do any of the individual components making up the definition, either jointly or separately. Thus if altered immune functioning is claimed to occur in AD (see Postulates 20 to 24), then compared with SDP (RLR) there should separately be shown to be altered function at an equal rate and higher rate in each of the anomalous groups, rLR, RlR, RLL, and so forth. In effect, this means that because AD is defined as an interaction, a full factorial design is necessary to demonstrate the existence of the interaction; in the absence of the demonstration of interactions then any of the subcomponents may actually be better correlates. If AD is to be useful theoretically, then it must convey some "added value" over a conceptually simpler description based on its component parts.

In its absence the multiple criteria for AD merely mean that researchers run the risk of Type II errors due to multiple significance testing of each of the separate components of AD.

Taken overall, Geschwind and Galaburda (1987) did not seem to provide convincing evidence that the concept of AD provides sufficient additional theoretical advantage to mean that it provides a useful addition to the measurement tools available to neuropsychology. Whether it might do so is an empirical question that has not as yet been addressed; until then it is probably inappropriate to sample multiple components without combining them systematically and appropriately.

A final problem in understanding the concept of AD is whether it is a discrete or a continuous variable. Although continually talked about in *CL* as a discrete entity (e.g. "subjects with anomalous dominance," *CL*, p. 151), Geschwind and Galaburda (1987) also commented that "within the group with learning disorders, *one might expect degrees of anomalous dominance*, perhaps with corresponding variations in disease association" (*CL*, p. 150, our emphasis). To our knowledge, none of the empirical studies of the Geschwind hypothesis, either by Geschwind or other workers, have attempted to assess degree of AD, or have demonstrated that increasing degree of AD is associated with increasing association with other conditions.

The Role of Timing in Determining the Events of the Model

Although Figure 1 implies a specific temporal sequence of events, it says little about the precise timing of those events. If an elevation in fetal testosterone occurs at the $n + 1^{th}$ gestational week rather than at the n^{th}, does this alter the way in which subsequent events unfold?

Geschwind and Galaburda (1987) made frequent reference to timing, and it is frequently invoked to explain the absence of associations that might otherwise be expected from the general model. Thus,

> there is another reason why lefthandedness will not be present in many individuals in whom growth of the cortex has been delayed. There is no reason to assume that the delaying effect will be present all through gestation. . . . In some cases the as yet unknown substrate of handedness may have developed during a period in which there is no significant retarding effect. A delaying influence appearing later . . . may slow the formation of later-developing regions (for instance the temporal speech area). If this type of pattern occurred frequently, one might find anomalous dominance for language more often than for handedness. (*CL*, p. 15)

The broad implication seems to be that the right hemisphere develops earlier and is vulnerable for a shorter time, so that its typical functions are far less often disrupted than are those of the left hemisphere (*CL*, pp. 15 and 46); there is thus a "greater conservatism of [posterior] right hemispheric function"; that is, "the appearance, after left-sided lesions, of syndromes typically observed after right posterior hemisphere lesions is less common [than the occurrence of aphasia after right hemisphere lesions]" (*CL*, p. 45). Differences in timing are also used to explain why

> in some cases delayed development of the speech region leads to superior development of the adjacent posterior region in the same hemisphere, whereas in others the opposite side enlarges. Whether these differences might result from variations in timing or duration of the delaying influences, or from other factors, is not known. (*CL*, p. 104)

Physiological support is cited for differential timing from the observation that

> estradiol receptors are present in the cortex in the postnatal rat, but apparently not in adult life, and the same is true for enzymes involved in steroid metabolism, thus suggesting that sex hormone effects are prominent only during a certain period of development (Kolodny, 1984). (*CL*, p. 109)

The timing of the development of the immune system is also invoked to explain the predominant association of gut and thyroid disorders with anomalous dominance:

> The fact that . . . the most common immune disorder found in strongly left-handed individuals involved the bowel and thyroid may give important clues to the timing of the causative events. . . . Suggesting that particular forms of learning disability have strong associations with certain types of immune disorder. (*CL*, pp. 121–122; see also *CL*, pp. 92, 184)

Similarly, the different rates of left-handedness in those with right and left-sided harelip are related to "the times when the anlage of the lip is being formed in relation to when the neural areas that control handedness are being laid down" (*CL*, p. 159).

We find it difficult to evaluate Geschwind and Galaburda's (1987) emphasis on differential timing. They were undoubtedly correct in asserting that tissues will vary in their susceptibility to different influences during the complex sequencing and interactions of embryogenesis. However, although such an assertion is a theoretical certainty, the precise (or even approximate) timings of the influences that they mention are not stated and are, we suspect, unknowable within the present status of the theory and within the current limits of experimental embryology. That leaves timing differences as powerful but, at least at present, unfalsifiable explanations of awkward absences of correlations, providing additional free parameters in the model. Of course, further advances in embryology may well alter this situation.

The developmental timing of events provides yet another instance of the underspecification of the theory and the strength of its defenses. By arguing that the timing of the specific events has been altered, one can both encompass new observations and dismiss those that do not fit the existing model.

The Occurrence of Nonlinear Processes Within the Model

Causal path models are usually linear models, and the model of Figure 1 is encapsulated only in terms of linear processes (although other processes can be incorporated). The Geschwind model makes frequent reference to nonlinear processes, typically quadratic or "U-shaped relationships" (*CL*, p. 102), with distributional extremes being more similar to one another than to those in the middle of the range. These curvilinear relationships are used to explain why the nonsignificance of many of the correlations implied by Figure 1 need not be crucial for the model: Thus,

> among dyslexics one might find a higher proportion with superior 'Gerstmann talents' than among controls, as well as a higher proportion with poor abilities of this type than among controls. A simple assessment of the mean scores on tests of these abilities might obscure the elevated frequency of dyslexics at both extremes. (*CL*, p. 101)

Likewise, in considering autistic children and idiots savants, "the mean level of performance has little significance in relation to a population with an excess of members at both the upper and lower ends of the distribution" (*CL*, p. 102). Similarly, "the apparent contradiction in the findings concerning spatial talents of left-handers might be resolved if they were found in excessive numbers at both high and low levels of spatial function" (*CL*, p. 102). It hardly needs stating that such hypotheses *might* be correct, but such processes should only be invoked in the presence of satisfactory measurements of the nonlinear functions. Merely to introduce them to explain negative results is just to double the number of free parameters in the model.

Nonlinear processes are invoked on several occasions for explaining the relationship between laterality and physical disorders. "Certain classes of immune disorders are most frequent in left-handers, others are most frequent in right-handers, and still others affect both types of individuals equally" (*CL*, p. 124); and "the anomalous dominance population may be resistant to most infections but more highly susceptible to others" (*CL*, p. 125). In the specific case of the skeletal anomalies claimed by Lombroso in criminals and mental defectives (Durfee, 1974; Ferrero, 1911; Lombroso, 1903),

> it is possible . . . that the distribution is bimodal, with an elevated rate of anomalies occurring both in the very talented and in the very disadvantaged, and a low rate in the general population. This is similar to what has been suggested for anomalous dominance—for example, that left-handedness is very frequent both in mental defectives and in very talented groups. (*CL*, p. 170)

Causal mechanisms within the body of the model may also be nonlinear, as was seen earlier in Postulate 15 (*CL*, p. 99) in which delayed left hemisphere growth either results in hypertrophy or diminished growth of ipsilateral cortex. Empirical testing is made more difficult when it is noted that high testosterone levels in utero result both in high levels of testosterone in adult life and also in low levels (caused by "damage to the testes," *CL*, p. 174), so that adult testosterone levels may be either raised or lowered.

In principle we have no objection to nonlinear processes in modeling, and there are numerous instances of such models in biology. However, it is typically true that to a first approximation the world is often linear (Dawes, 1979), and hence in the first instance models should therefore be couched in linear terms. Invocation of nonlinear processes should only occur when there is substantive statistical evidence for their necessary existence on the basis of measured data. If used merely to explain awkward results, then they simply multiply the total number of parameters and run the serious risk of making complex models completely untestable. Thus, in the absence of strong empirical evidence requiring a more complex description, we have chosen in Figure 1 to represent the Geschwind model as a linear model.

The Genetic Model Underlying the Geschwind Theory

Genetic models of handedness and lateralization are popular because they explain the undoubted tendency for handedness to run in families. Geschwind and Galaburda (1987) acknowledged their debt to Annett's (1978) genetic model of handedness (e.g., *CL*, p. 126), but they added that their "views on the detailed genetic mechanisms involved in laterality differ from those of Annett" (*CL*, p. 126), although they did not "wish to overemphasize the differences between [their] interpretation and that of Annett" (*CL*, p. 69). However, our reading of *CL* is that those differences are in fact profound, although not in the particular manner emphasized by Geschwind and Galaburda who said that

> our ideas and Annett's differ chiefly in their fundamental assumptions. Annett postulates the absence of a gene for right cerebral dominance and instead the existence of one that favours a "right shift." . . . Our own formulation in some respects resembles that of Corballis and Morgan (1978) who postulate the existence of a "left shift" [influence] . . . though it also differs from theirs in several ways. (*CL*, p. 127)

From a strictly *genetic* perspective (but not an evolutionary perspective) that distinction strikes us as merely semantic. Just as a pair of alleles, P and p, may be more conveniently described as P being dominant to p, rather than p being recessive to P, so there is no strictly genetic distinction between Geschwind and Galaburda's and Annett's views. In fact, the difference arises because essentially Geschwind and Galaburda's model is not a genetic model at all in any strict sense. Geschwind and Galaburda did not propose that there are separate alleles at a single locus that principally determine the likelihood of left-handedness; instead their model argued for an initial *Ur*-laterality that is identical for all individuals ("the basic pattern of most brains includes a larger left side," *CL*, p. 127) and that manifests in the presence of an appropriate hormonal environment as right-handedness, left-language dominance, and right-hemisphere dominance for visuospatial functions. Deviations from that condition then arise principally because of variations in hormonal levels. The model is essentially one that is formally equivalent to those described by Harris and Carlson (1988) as a "pathological model," although the term *pathological* is perhaps inappropriate because Geschwind and Galaburda emphasized the benefits and advantages that can accrue from the deviations from the norm or standard pattern (see below on the evolutionary model), and they did not invoke conventional pathological factors such as birth stress.

Geschwind and Galaburda's (1987) model is perhaps best described as an *environmental model*, rather than a genetic model, with the principal correlate of lateralization being the early hormonal environment. That environment is itself partly under genetic control, but that hardly justifies the model being classed as a genetic model in the classic sense. To Geschwind and Galaburda, genetic factors were not the principal cause of phenotypic variation: "We will argue that the number of nongenetic factors involved in the determination of laterality is so large that no purely genetic theory will be able to deal with them" (*CL*, p. 128). In addition, Geschwind and Galaburda also speculated that maternal cytoplasmic factors may also be important (*CL*, pp. 129 and 131), as also may be vertical transmis-

sion of maternal hormonal anomalies (*CL*, p. 177). Conventional heritability estimates must therefore be low under the Geschwind hypothesis. The Geschwind model does not have any *direct* genetic component, in the sense that phenotypic variation is a direct result of genotypic variation; however, insofar as the principal causal pathway, the level of testosterone, is itself partially under genetic control, then the model can be described as having some *indirect* genetic component. Therefore, as we show later, tests of the model can be couched in terms of familial correlations.

The Evolutionary Model in the Geschwind Theory

Two separate evolutionary features of the model must be distinguished: whether laterality is evolutionarily recent or ancient and the nature of the selective pressures that might have resulted in the current situation.

To Geschwind and Galaburda (1987) it seemed that the biologically and evolutionarily normal situation is of asymmetry, present throughout the mammals (*CL*, p. 21), but present in some form in invertebrates, and "even single-called organisms" (*CL*, p. 20). In man and other mammals this takes the form of predominant left-sided and left-hemisphere advancement. Left-handedness and atypical asymmetry is then a deviant form derived from the standard animal model for which the one particular asymmetry is the norm. This model contrasts with the implicit evolutionary model of Annett (1985), in which random dominance is the norm in nonhuman species, and it is right-handedness and left hemisphere dominance that have evolved recently in evolutionary time. Annett's model implied the mutation of a new gene that produces right-handedness, and in consequence readily allows the possibility that a substantial proportion of the population may not carry that gene. Geschwind and Galaburda's model invoked an archaic asymmetry, and hence had problems with genes that override such a pattern to produce random dominance.

Geschwind and Galaburda (1987) referred on several occasions to the evolutionary pressures acting on their model, and they made it clear that merely because the group with high testosterone levels would have increased rates of some diseases, they would not necessarily be at a selective disadvantage (*CL*, p. 81). Instead they emphasized that the groups with high incidences of disability would also be the same groups in which would be found individuals of high talent and that the benefits for those talented individuals would outweigh the disadvantages for those with disabilities (*CL*, pp. 95 and 103). The mechanism may be difficult to detect because the main selection is occurring because of that small number of individuals who are in the tails of the distributions of ability (*CL*, p. 103). Geschwind and Galaburda also stressed that the selective advantages of high testosterone, manifesting through increased talents, may have had a different balance with the concurrent disabilities (such as dyslexia) during the preliterate evolution of human societies (*CL*, p. 83). Geschwind and Galaburda also invoked a group selectionist argument in which, "the pattern of cortical development may . . . reflect a mechanism that is advantageous *to the population as a whole,* since it leads to a great diversity of patterns of lateralization, and therefore of patterns of talent" (*CL*, p. 143, our emphasis). It should be noted, however, that group selectionist arguments remain a matter of some controversy within contemporary genetics and evolutionary theory (Sober, 1984). Geschwind and Galaburda also involved a nondirectional, stabilizing mode of selection in which it is argued, in the general context of neural asymmetry, that "mild degrees of diminished fusion [of the two sides of the nervous system] might lead to the formation of superior individuals who may be close to the goal of optimal, cognitive capacity, that is, the ideal balance between separation and fusion" (*CL*, p. 168). This is not a group selectionist mechanism, and it does not rely on occasional individuals with high talents, but instead seems applicable to all individuals. Finally, it is suggested that this lack of fusion may be a necessary precursor of the evolution of consciousness (*CL*, pp. 167–168).

Testing the Geschwind Model

Figure 1 makes it clear that the Geschwind hypothesis is complex. Testing it is therefore not an easy matter, because the model contains many free parameters; many more, in fact, than are available in the degrees of freedom of the data against which the model may be tested. Considered overall, the model is therefore underdetermined, so that the entire model cannot be put to any reasonable test. However, merely because a model is underdetermined overall does not mean that all of it is undetermined. Thus, the model makes clear predictions about the correlations between each of the items arrayed down the right-hand side, and Geschwind and Galaburda exploited that prediction by taking pairs of items for which a nonzero correlation had a low a priori probability based on extant biological theory and then demonstrated that significant correlations were indeed present in empirical data. Such observations therefore globally validate the broad causal routes within a large portion of the model, despite the detailed routes not being evaluated.

If the Geschwind model is to be tested then clear predictions need to be made. We have used a formal path analytic model to assess the relationships between variables and to determine constraints on the values that empirical correlations may take, both at the top and the bottom end. In developing the model we assume that all path coefficients are positive (as a result of the way we have defined the variables in Figure 1). We treat the model as if all variables are normally distributed, although in practice we accept that many are categorical and that therefore a model should be couched in terms of logistic regression coefficients rather than conventional path coefficients: This difference makes no substantive difference to the arguments.

The key starting position for our development is that the strongest evidence in favor of the *entirety* of the Geschwind model is derived from correlations between widely separated items (such as that between-handedness and immune disorders), the existence of which implies the existence of nonzero path coefficients for all intermediate stages. Thus in Figure 2, the correlation between myasthenia and left-handedness, r, is $e \times d \times h \times i$, and if this is significantly nonzero, and e, d, h, and i are not allowed to be negative, then it must be the case that $e > 0$, $d > 0$, $h > 0$, and $i > 0$ (because if any *were* to be zero then it is necessarily the case that $r = 0$). Hence, the empirical observation implies the existence of and is compatible with the existence of the intervening processes.

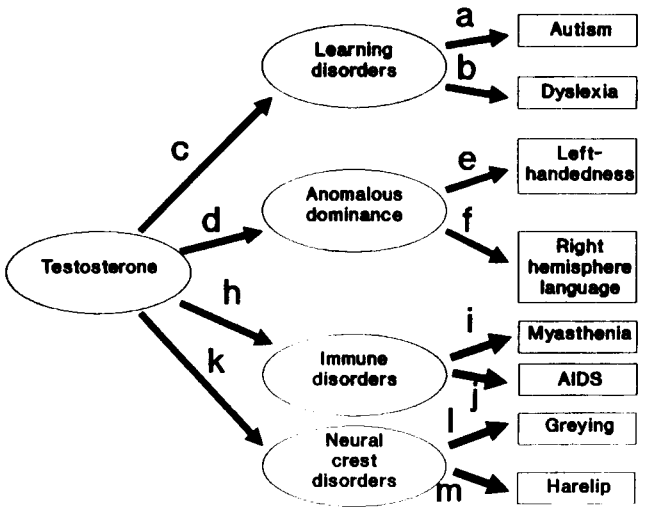

Figure 2. A formal path model for a reduced version of several components of the Geschwind model, to illustrate the principle of testability. (AIDS = acquired immune deficiency syndrome.)

A serious possibility with the Geschwind model is that although in principle there may be many predicted correlations between variables, in practice these may not be detected either because the sample size is insufficiently large or the measures are not sufficiently reliable to allow the correlation to be statistically significant. This problem can be circumvented if we consider those correlations that have already been found by Geschwind. Whatever the uncertainties of reliability of measurement, it must be the case that a replication study of similar size will have some reasonable power to detect similar differences. We therefore consider parts of the model as *testable* if, by making logical deductions from the model by means of path analysis, we find that other path coefficients are of similar magnitude, and hence will be detectable using similar sample sizes and similar measurement methods to those already used by Geschwind. We argue for a set of such propositions:

1. *If correlations have been demonstrated between distant blocks of the model then testable correlations should also be found within blocks.* In Figure 1 it is clear that there is a broad cluster of terms which have been called "learning disorders," all of which are presumed to share a common mechanism (so that, for instance, autism and dyslexia are both derived by a similar mechanism, of which delayed left posterior hemisphere growth is the principal one). Consider a generic version of this process as in Figure 3a in which three measured variables A, B, and C are derived from a latent process Y, and another three measured variables D, E, and F are derived from a second latent process Z; and assume that latent processes Y and Z are derived from a third process X. Let there be a distant correlation, r_{AD} across clusters between, say, A and D, which will then take the value $a \times g \times h \times d$; and consider also a within-cluster correlation between A and B, r_{AB}, which will take the value $a \times b$. For simplicity consider the situation in which path coefficients within and between each of the clusters are approximately equal in size, such that $a = b = c = d = e = f$. It is then the case that

$$r_{AD} = a \times g \times h \times d$$

therefore,

$$r_{AD} = g \times h \times a^2$$

and

$$r_{AB} = a \times b = a^2$$

therefore

$$r_{AD} = g \times h \times r_{AB} \qquad (1)$$

Given that g and h must be less than or equal to 1 (and in general $g < 1$ and $h < 1$) then $g \times h < 1$ then $r_{AD} < r_{AB}$. Because, however, r_{AD} has already resulted in a significant correlation, then it must also be the case that r_{AB} will result in a correlation at least as large, and therefore, as long as a similar sample size is used, then this correlation should also be detectable and significant. The prediction therefore in the model of the existence of r_{AB} is therefore *testable.* The derivation by relaxing the assumption of equality between a, b, c, d, e, and f is essentially similar although more complex: As long as each variable enters into at least one demonstrable long-range correlation then all pairs of short-range correlations must also be testable.

2. *Items within clusters may be negatively correlated, but this can be detected and studied by examining relationships between family members.* The derivation just shown would be complicated if it were the case that significant *negative* correlations might exist between the members of a cluster. This is possible if the items are mutually incompatible; so that for instance a diagnosis of autism precludes a simultaneous diagnosis of dyslexia (be it for neurological, nosological, or empirical reasons). This can be represented as mutual negative causal relations between, say, A and B, as in Figure 3b. Equation 1 would not then apply, and there could be a zero or negative value of r_{AB} despite a positive r_{AD}. This consideration forces one to ask the nature of the causal relationships represented in Figure 1; and, in fact, they represent relationships within the ontogeny of single indi-

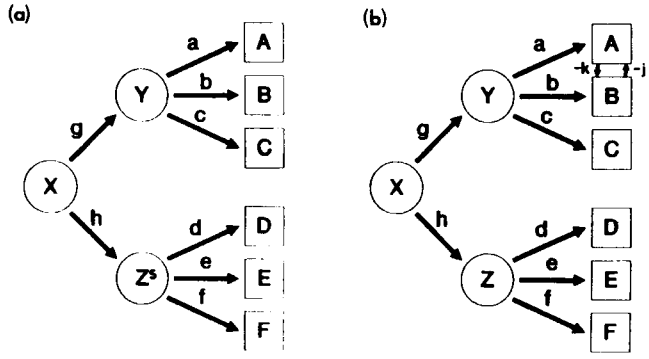

Figure 3. (a) A formal path model for the association of phenotypic characters, A, B, C, D, E, and F, organized within two clusters determined by separate causal processes, Y and Z, which are themselves determined by a common causal process, X. (b) A development of the model of (a) in which two phenotypic characters, A and B, are assumed to be mutually exclusive and hence negatively correlated one with another.

viduals. However, Geschwind and Behan (1982) have argued that these conditions are also associated in the sense that the relatives of individuals who suffer from one condition are more likely to suffer from another; and specifically that the relatives of left-handers with learning disorders are more likely to suffer from immune disorders. The situation can be represented in Figure 4, in which two relatives with similar causal paths are represented, but are linked through a common genetic mechanism. Consider a group of propositi selected for having learning disorders in whom there should be a correlation, $r_{LH\text{-}ID(r)}$, between left-handedness in these individuals and immune disorders in their relatives, estimated by the equation $r_{LH\text{-}ID(r)} = a \times d \times g \times d \times b = a \times b \times d^2 \times g$. By contrast the correlation between left-handedness and immune disorders in the propositi, $r_{LH\text{-}ID(p)}$, should be $r_{LH\text{-}ID(p)} = a \times b$. Therefore, $r_{LH\text{-}ID(r)} = r_{LH\text{-}ID(p)} \times d^2 \times g$, and hence, because $d^2 \times g < 1$ because $d < 1$ and $g < 1$, then $r_{LH\text{-}ID(r)} < r_{LH\text{-}ID(p)}$. If the reverse relationship applies then it must be the case that there is a negative causal association between the separate measures, and hence that Proposition 1 does not apply.

Negative associations between items might occur for many reasons: Categories might be logically exclusive; they might be pragmatically exclusive (as for instance if it is difficult to diagnose dyslexia in the presence of autism); or they might be causally exclusive—with perhaps some form of threshold process, whereby intermediate degrees of pathology result in one condition whereas more severe pathology results in the other condition. The key conclusion though is that these associations do not prevent the model being testable: If longer range associations are testable between relatives then shorter range associations should also be testable by an argument analogous to Proposition 1.

3. *If several correlations are legitimately testable, then the existence of other testable correlations can also be inferred.* Consider the simplified model shown in Figure 5. Results suggest that there is a correlation, r, between learning disabilities and handedness (see Postulate 11), between handedness and immune disorders, s (see Postulate 21), between learning disorders and immune disorders, q (see *CL*, p. 91), and between handedness and neural crest disorders, p (see Schacter et al., 1987). The question therefore arises whether there may be a testable association between learning disorders and neural crest disorders (represented by t in Figure 5). One can derive the equations from Figure 5 that $p = b \times d$; $q = a \times c$; $r = a \times b$; $s = b \times c$; and $t = a \times d$. By rearrangement, $t = a \times d = (r/b) \times (p/b) = r \times p/b^2$, and $q = a \times c = (r/b) \times (s/b) = r \times s/b^2$. Therefore $b^2 = r \times s/q$, and hence $t = (r \times p)/(r \times s/q) = p \times q/s$. Given that p, q, and s are all positive correlations in the range 0 to 1, then t will also be a positive correlation of the same order of magnitude as p, q, and s. If p, q, and s are all testable, then it is also the case that t will be testable. The association between learning disorders and neural crest disorders is therefore testable.

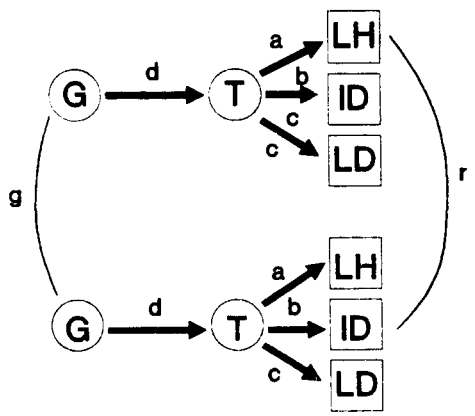

Figure 4. A formal path model for the association of phenotypic characters LH, ID and LD (left-handedness, immune disorders, and learning disorders, respectively) within related individuals. (Within individuals the phenotypic characters are determined by a single causal process, T, which is under genetic control, G, the genetic component being shared between related individuals.)

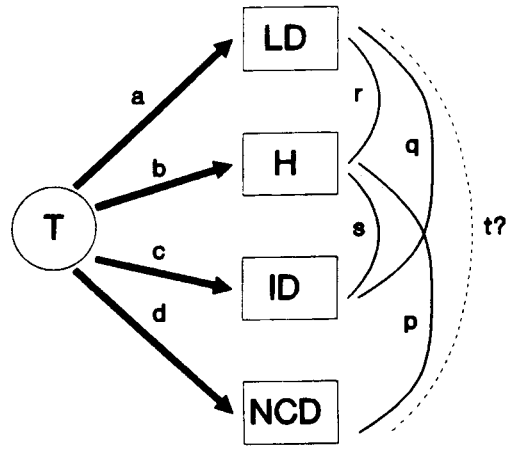

Figure 5. A formal path model for the empirical associations (represented by known correlations p, q, r, and s, and an unknown correlation, t, between four phenotypic characters, LD, H, ID and NCD (learning disorders, handedness, immune disorders, and neural crest disorders, respectively) determined by a common causal process, T.

Conclusion

We began this work intending to carry out an evaluation of the empirical evidence for the Geschwind model. However, it soon became apparent that the authors made such a sufficiently diverse number of claims and speculations that the nature of the model which was being tested was itself not clear. As a result we developed the causal path model shown in Figure 1, primarily with the intent of guiding our own further analyses of the model.

In developing Figure 1 three additional points became evident. First of all, the figure itself serves as a guide to what is important in an empirical analysis of the Geschwind model. It indicates that there should be positive correlations between those variables listed on the right-hand side; it shows how and why the correlations between closely-linked clusters should, in general, be greater than those between clusters separated by several nodes; and it indicates the benefits that would accrue from an analysis of familial relationships.

As a second point, the analysis provided in the present article has indicated to us that a full empirical analysis of the Ge-

schwind model would be premature. As we have indicated, much more work remains to be done in classifying and specifying the concept of anomalous dominance. Until that is done, there will remain many ways in which the theory can be modified on a post hoc basis to account for negative evidence. Therefore, the present analysis serves primarily as a guide to what new research needs to be done and what analyses might be most valuable.

Finally, in specifying the model in greater detail we have shown by specific example both the strengths and weaknesses of a "grand theory." Such a large theory clearly generates new and unexpected hypotheses; but it also runs the risk of having so many free parameters that it can explain everything but at the price of being unfalsifiable.

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