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REVIEW

The Geschwind–Behan–Galaburda model (GBGM) of cerebral lateralization: a critique and prospective

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In the wake of, and as a complement to, a recently published major meta-analytic review of empirical support of the Geschwind–Behan–Galaburda model (GBGM) of cerebral lateralization (CL) the present brief essay attempts to present a critical assessment of the theoretical approach underlying the GBGM. The GBGM is criticized for having been misguided in its representation of the cerebral basis of handedness, and of the links between testosterone and immune function. Some guidelines are presented for the development of a general theory of CL, emphasizing animal research, greater interdisciplinary communication, a hierarchical model-building approach, and the relevance of neuropharmacology and psychiatry.

Keywords: Cerebral laterality – Endocrine – Handedness – Immune – Neurotransmitter – Geschwind-Behan-Galaburda model

INTRODUCTION

The Geschwind–Behan–Galaburda model (GBGM) of cerebral lateralization (Geschwind and Galaburda, 1985) is a far reaching theory of the effects of prenatal testosterone on the development of hemispheric specialization with thymic immunity acting as a mediator. The GBGM continues to inspire behavioural neurology. Evidence to that effect is the special issue in *Brain and Cognition* (Bryden *et al.*, 1994) which was entirely devoted to critical assessment of empirical evidence in support of the GBGM. That major review article, as well as the numerous commentaries, essentially led to the conclusion that there is virtually no support at all for the theory, at least as far as its claims regarding the development of hand dominance. The scientific community is coming to this conclusion after publication of several hundreds of research projects designed to test components of the theory, and yet seems to want to continue testing the model. It is the contention of the present essay that it is time to pass on to another paradigm of cerebral laterality, with an entirely different theoretical approach to the problem.

A first major problem with the GBGM was its heavy reliance on expeditive assessment of human handedness in a general model of cerebral lateralization (CL). As Bryden and colleagues have explained (1994), the biopsychosocial complexity of human handedness has been sorely underestimated. The problem with human handedness, as an index of CL, is that it is a bad measure when extracted summarily. The ease with which it can be documented is, however, precisely the reason why it has been so popular. However, this catch-22 situation has corrupted our understanding of the cerebral aspects of handedness.

Secondly, it seems disappointing, in hindsight, that the clinically based associations forming the centroid of the GBGM were drawn piecemeal, the authors not having bothered to survey, for example, sex and age curbs of *all* the autoimmune, allergic and infectious diseases systematically. If such had been done, using the biomolecular data available at the time, the GBGM would never have been born. For example, the GBGM would not have attributed such importance, as it did wrongly, to thymic mediation of

brain–immune developmental interactions (St Marseille and Braun, 1995).

Thirdly, more attention to animal research in neuroendocrinology and neuroimmunology would have helped inhibit some of the sweeping generalizations of the GBGM. For example, the effects of fetal androgens on CL could not plausibly have been reduced to slowing development of the left hemisphere. I elaborate on this in a later section. Furthermore, there was never any basis for reducing the GBGM selection of immune disorders to thymic atrophy in boys, and even less the latter to left handedness. On the other hand, normal development of the immune system does relate to CL in sex-dimorphic manner in non-human species (Tobet and Fox, 1989). This is certainly a stronger basis for model building than speculation about associational clusters of immune disorders and non-immune marginalities.

How might we now re-build a general model of CL? Contrary to the GBGM, a general model or theory of CL *must:* (1) be based on animal research as well as human research; (2) draw the relevant material from each scientific discipline systematically and exhaustively *prior* to interdisciplinary integration; (3) propose theoretical models hinging not on the weakest associational clusters first but on the stronger ones; and (4) cover *all* the relevant scientific disciplines including neuropsychiatry and neuropharmacology. These four points will now be argued in more detail with a few examples.

ANIMAL RESEARCH

There are many hundreds of specific findings of CL in animal research obviously forming a complex mosaic. One of the more developed programs of research, in this general domain, is the work of Glick and colleagues on the neurodynamics of asymmetric turning behaviour in rats. The behavioural, genetic, neuropharmacokinetic, neuroendocrinological, neuroanatomical, and developmental aspects of this paradigm are now amazingly advanced (Zimmerberg 1974; Glick and Shapiro, 1985; Shapiro *et al.* 1986; Glick *et al.*, 1988). This behaviour is clearly lateralized in its bodily expression as well as in its brain substrate and there is good fit between the two. The phenomenon is also sexually dimorphic, inherited, dopamine-mediated, and striatum-based. The paradigm has even been extended to the human (Bracha *et al.*, 1987) and, therefore, an extremely interesting candidate as a prototype for continued deepening of our bioscientific understanding of CL.

Human handedness, like animal pawedness, is not only testosterone-dependent. In fact, testosterone explains only a very small portion (barely significant) of the variance. Genetic factors are obviously tremendously important. Human research has not, however, been able to show, and probably cannot show, the specific impact of asymmetric *experience* with the hands on cerebral anatomical or neurochemical asymmetry. Fortunately, the issue can be addressed in animal research. Diaz *et al.* (1994) trained very young rats to reach for food with only one paw. They later analyzed adult brains of rats with such precocious forced right or left pawedness, and adult brains with right and left spontaneous (untrained) right or left paw preference. Rats with precocious forced pawedness had greater development of the primary motor cortex of the hemisphere contralateral to the trained paw. The paw area of the motor strip was thicker and contained fewer neuron cell bodies, suggesting greater synaptogenesis. No such hemispheric asymmetry was observed in the rats with spontaneous paw preference.

Another highly relevant animal research paradigm introduced by Renoux *et al.* (1983) consists of investigating lateralization of hemispheric control of the immune system. Though there have been some controversial findings (Barnéoud *et al.*, 1987; La Hoste *et al.*, 1989; Belluardo *et al.* 1990), numerous independent studies have now reported that lateralized cortical lesions have opposite effects on proliferation and response of various lymphocyte types, including types that are *not* thymodependent. This animal paradigm has developed very rapidly and now incorporates data relating it to mouse paw preference and gender (Neveu *et al.*, 1988) and to neuropharmacological asymmetries (Barnéoud *et al.*, 1988; La Hoste *et al.*, 1989). Four studies have recently begun to show that this CL also exists in humans (Lisianyi *et al.*, 1989; Khil'ko *et al.*, 1990; Kawaharada and Urasawa, 1992; St Marseille *et al.*, 1996). Geschwind and his colleagues were justifiably interested in prenatal steroid influence on brain development. However, virtually nothing was, or is yet, known directly about this in humans. The direct evidence can only, and therefore must, be obtained from animal research. Otherwise, the wildest of speculations will continue to emerge, unchecked, and intriguing marginalities will be given excessive status in the overall scientific research agenda.

ANALYSIS OF AVAILABLE DATA

The GBGM proposed a broad link between left handedness and immune disorders, via foetal testosterone

and atrophy of the thymus. This is a domain which exemplifies the importance of systematic and exhaustive analysis of available data prior to theorization. For example, there are numerous reports of menstrual, of gestational and of contraceptive modulation of immune and autoimmune activity, normal and pathological (Shoenfeld and Isenberg, 1989). Even more alarmingly for the GBGM, such male-prevalent traits as stuttering and high spatial ability are modulated by the menstrual cycle, in a manner specifically suggesting an estrogen factor (Silverman *et al.*, 1974; Nyborg, 1983, 1984; Hampson, 1990), and there are numerous other examples of modulation by estrogen of functions postulated to be cerebrally lateralized. Finally, even prenatally, male and female mammalian brains in areas such as the cortex and the corpus callosum differ not only in brain-testosterone but also in brain-estrogen dynamics (Sandhu *et al.*, 1986; Fitch *et al.*, 1991).

The GBGM made broad statements to the effect that testosterone slows left hemisphere development. Careful analysis of the literature available now (and some available then) suggests, across a wide range of developmental brain dynamics and species, including humans, that all three sex steroid classes (especially testosterone, but occasionally also estrogen and progesterone) have a *facilitatory* rather than *inhibitory* effect on brain development. Examples apply to neuronal proliferation (Wright and Smolen, 1983), neurotransmitter metabolism (Goudsmit *et al.*, 1990), neuronal migration (Kolata, 1979), myelination (Juraska and Kopcik, 1988), dendritic arborization and synaptogenesis (Menzies *et al.*, 1982; Ayoub *et al.*, 1983; Wright and Smolen, 1983), and resistance to neuronal mortality (Nordeen *et al.*, 1985; Swaab and Hoffman, 1988). The few relevant empirical results obtained in humans so far are in mixed directions. For example, umbilical cord androgens are significantly *negatively* related to spatial ability of the offspring at age 6 years, but only in girls (Jacklin *et al.*, 1988). This suggests the presence of critical steroid–steroid interactions in fetal brain development precluding exclusive focus on any one steroid in any general model of CL. Consequently, it appears obvious that isolation of fetal testosterone and neglect of female steroids in modulation of CL is theoretically counterproductive.

THEORETICAL MODELS BASED ON STRONG ASSOCIATIONS

Aside from left hemisphere dominance for language, behavioral aspects of human CL are very subtle and controversial. The solution then is not to focus on the more evanescent behavioral manifestations of CL, but rather on strong systemic (biological) associations which involve CL. For example, gender is obviously strongly involved in modulating immunity, but only weakly in CL. Female mammals clearly and consistently have stronger immune systems than males, except for IgE lymphocytes (Eidinger and Garrett, 1972), suffer less, and die less, from infections (Haber *et al.*, 1982; Messadié, 1993), and suffer much more from autoimmune diseases (i.e. overactive immune responses). One gets a clearer picture of this when one reviews sex-prevalences in autoimmune diseases, most of which are not covered by the GBGM. Furthermore, males (especially prepubertal) have much higher rates of allergic disease involving IgE overactivity (Marsh *et al.*, 1981). Starting from there, one is in a better position to blend in pieces of data relating the above to CL. Firstly, not all immune sex differences are thymodependent. Secondly, there is good reason to believe that sex steroids and certain neurotransmitters are integrated into asymmetric sex-dimorphic immunomodulatory brain systems, the prime chemical vectors possibly being serotonin (Ameison *et al.*, 1989; Farber and Beer, 1991; Kelly, 1991; Dinarello, 1993), and to a lesser extent, noradrenaline (Madden and Livnat, 1991; Roszmann and Carlson, 1991). It seems to be often thought that human cerebral functional symmetry of language is a unique exemplar of radical hemispheric functional asymmetry, a perverse effect of anthropocentrism. Singing is just as radically and universally left hemisphere-lateralized in several bird species as language is in the human (Nottebohm, 1989). Furthermore, scientific understanding of the underlying neural mechanisms (neurochemical, neuroanatomical, endocrinological, genetic, environmental, developmental) is far more advanced for birdsong than it is for human speech (or handedness). Of course, this is not to suggest that the investigation of birdsong can in any way replace investigation of cerebral specialization for speech, only that general theories of cerebral laterality must take into account animal research.

NEUROPSYCHIATRY AND NEUROPHARMACOLOGY

Neuropsychiatry

Another example of a strong relation involving a weak link with CL is the sex-prevalence bias for certain neuropsychiatric diseases. For example, anorexia nervosa and psychopathy are strongly female and male biased respectively (each by approximately nine

to one). Other common neuropsychiatric diseases, also very much sex-biased, include depression which is female preponderant and is clearly modulated by sex steroids (Meyer-Bahlburg and Ehrhardt, 1986) and hyperactivity and Gilles de la Tourette syndrome which are male preponderant. These syndromes are all the more relevant considering that they are all highly heritable and autosomal. The male-preponderant syndromes are virtually all manifest prepubertally and involve low anxiety and high turbulence. The female-preponderant syndromes are virtually all postpubertal and are stress-related and involve much anxiety. Even neuropsychiatric diseases which are not differentially prevalent as a function of sex over the full life-cycle tend to show the early onset bias for males and the late onset bias for females. These include schizophrenia (Seeman, 1982), motor disorders of the basal ganglia (Yassa *et al.,* 1989), and the obsessive–compulsive syndrome (Flor-Henry, 1990). All three of these syndrome profiles support a hypothesis of an oestrogen protection factor against diseases involving dopamine overactivity (see Haefner *et al.*, 1981; DiPaolo *et al.,* 1985).

From there, one is in a solid position to explore meaningful hypotheses about CL, such as various sorts of sexually dimorphic hormonally mediated asymmetric hemispheric fragilities including pharmacological hemispheric imbalances. For example, there is overwhelming evidence that serotonin-mediated brain mechanisms are more fragile in female than male mammals including humans (Goodwin *et al.*, 1987; Anderson *et al.*, 1990; Haleem *et al.*, 1990).

Neuropharmacology

Having touched upon the importance of neuropsychiatry, let us insist on that of neuropharmacology. The GBGM makes little mention of neurochemical asymmetry. This is one domain where progress has been phenomenal in recent years. Several dozen chemical hemispheric asymmetries involving several neurotransmitters, and applying always to a subregion of the hemisphere (rarely to the entire hemisphere in non-human species), have been reported to apply to samples of animals of various species in a wide variety of cortical and sub-cortical areas, sometimes crossing over from one area to another. Some of these effects have been shown to interact with gender (Ross *et al.*, 1981; Robinson *et al.*, 1985; Drew *et al.*, 1986; Lipsey and Robinson, 1986). Furthermore, oestrogen receptors are asymmetrically distributed in rat cortex, and the asymmetry is crossed as a function of sex (Sandhu *et al.*, 1986). Androgen receptors are also distributed asymmetrically in male rhesus monkeys but not in the females (Scholl and Kim, 1990). These neuroendocrinological phenomena may be part of the basis for sex differences in neurotransmitter asymmetries. Hemispheric chemical asymmetries and sex differences in whole-brain neurochemical activity have also been found in the human. Such effects seem to involve acetylcholine (Amaducci *et al.*, 1981), GABA (Post and Goodwin, 1975; Rossor *et al.,* 1980), noradrenalin (Oke, 1978; Reynolds, 1983; Biegon, 1991), serotonin (Post and Goodwin, 1975; Reynolds and Czudek, 1987; Demeter *et al.*, 1989; Frecska *et al.*, 1990; Arato and Frecska, 1991), and dopamine (Post and Goodwin, 1975; Reynolds, 1983). [See also Glick *et al.* (1982).] The only sex-dimorphic neurotransmitter asymmetry we are aware of involves serotonin (Frecska *et al*, 1990; Arato and Frecska, 1991). Common sense dictates that such phenomena are much more likely than anatomical asymmetries or handedness (i.e. the GBGM) to be involved in immune system modulation or neuropsychiatric syndromes. Anatomical asymmetries can only be linked to behavioural asymmetries (c.f. GBGM) by *analogy.* What we need to determine is the *chain of causation*, or in other words, the sequence of mechanisms.

CONCLUSION

In light of all of which precedes, it seems to me that one research program which should retain our attention in view of building an integrative theory of CL, is the following experimental animal research agenda: we need to determine the effects of targeted steroid manipulations on relevant neurotransmitter activity (see DiPaolo *et al.*, 1981; Heritage *et al.*, 1981, for examples) and *vice versa* (see Dorner *et al.*, 1987; Dorner, 1988, for examples) as a function of precise intra- and interhemispheric loci in a developmental (especially prenatal) context. The timing, as well as intensities and durations of these manipulations will have to be very carefully controlled because acute and chronic, and low and high dose developmental manipulations often have opposite effects (see Biegon and McEwen, 1982; Haefner *et al.* 1991). Furthermore, steroid–steroid developmental brain dynamics (Diamond *et al.*, 1973; Maclusky and McEwen, 1978; McEwen, 1981) will have to be taken into account as well as neurotransmitter–neurotransmitter dynamics (see Tucker and Williamson, 1984; Stanley *et al.*, 1985), some being agonistic and others antagonistic. It would be fastidious and futile to do this independently of a well-structured behavioural paradigm. Though right and left paw preference are equally distributed in non-human mammals, paw preference is probably

more akin to human hand preference than has been hitherto recognized (Bianki, 1988). In any event, the animal model presents certain basic advantages over the human model: paw preference is less affected by brain disorders (i.e. pathological left handedness), by cultural pressures, by biases due to learning and practice, and arbitrariness of measurement parameters than is human hand preference. Ironically, this brings us back to our starting point, namely handedness and the brain, but this time perhaps on more solid footing. One thing is for sure, never again will a general model of CL be presentable as a matter of whole hemispheres, of a single sex steroid, or of a single immune organ.

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