Deviant Development of Lateralization and Cerebral Function

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leaves open the possibility of the same outcome. It is possible that if the dominant hemisphere is inactivated, the subdominant hemisphere can take charge and further elaborate behaviors in the control of which it otherwise would have had little or no role.

Before addressing empirical evidence on these issues, we should note one further point. A "developmental sequence" within an ability domain implies that the processes used to perform the act in question become increasingly efficient and sophisticated over time. But it is not implied that a given outcome is necessarily secured by the same apparatus at all ages. An important case in point has to do with certain forms of pattern detection, such as face recognition. There is evidence that children's ability to recognize faces is at an early age subserved by the left hemisphere, but that toward the end of the first decade the right hemisphere assumes responsibility for this accomplishment. It appears that this is because children switch their strategic approach to this task. Younger ones use analytic left-hemisphere strategies (and their performance exhibits the limitations of that approach). The right hemisphere subsequently matures to a sufficient extent to enable children to deploy more efficient, pattern-manipulating mechanisms which then supereode the analytic approach which they continue to rely on in their adult years. We will not in this discussion consider examples of this kind of strategic switch (of which there are few). Rather, we will attempt to discern the earliest signs of a developmental sequence and follow it through to its full mature expression.

CLINICAL IMPLICATIONS OF DEVIANT PATTERNS OF BRAIN ORGANIZATION

Can certain developmental deficits be explained by...
flawed development of brain organization? This discussion has to take its reference point from known facts of the customary pattern of brain organization at various developmental stages. If one such pattern was universal among normally functioning people, then it would be tempting to interpret any deviation as pathological and possibly of pathogenic import. However, normal individuals vary considerably in patterns of laterality. This is particularly true of that subset of the normally functioning population that is not right-handed and yet functioning within the normal range.

We are looking for brain-based factors sufficient to explain major developmental deficit, pulling the individual well down below the range of normal variation. Indeed, if a given pattern that occurs in a developmentally disabled group also occurs among persons within the normal range, then by exclusion that pattern cannot by itself explain the developmental deficit. We shall see that this exclusionary principle calls into question the whole proposition that anomalous laterality suffices to explain abnormal function.

This is not to suggest that abnormal laterality might not have pathological implications. Even if it is not the cause of a deficit, it could be a biological marker for a case antecedent both to it and to the cognitive or other deficit under scrutiny. As we shall see, the construct of "pathological left-handedness" holds promise of supplying such a biological marker.

THE VARIANTS OF ABNORMAL BRAIN ORGANIZATION

Hypotheses invoking the abnormal development of relationships between differentially specialized cerebral areas have been based on measures of peripheral and central laterality. Thus they almost uniformly invoke differences in the lateral specialization of the brain, that is in the relative role of the two cerebral hemispheres in control of behavior, rather than antero-posterior differentiation or other aspects of functional localization. This is simply because measures we can use in the intact individual are sensitive to the lateral sources of variation. Correspondingly our listing of types of anomalous organization relies upon the varieties of lateral specialization.

In the literature it is widely assumed that if a person has an appropriately specialized area in his brain, then when engaged in the relevant task he will automatically use that area to perform the task. However, this assumption may not be warranted. Perhaps some people activate inappropriate areas for purposes of the task, thereby entering into an inappropriate mental set performing with a deviant cognitive style. Thus possible anomalies of laterality include both deviant geography of the cortical processorstheemselves, and deviant relationships between them and the ascending influences from brainstem that enlist them selectively during cognitive functioning.

The usual reference point for discussion of anomalous laterality is the normal individual in whom the two hemispheres are, it is thought, maximally specialized, the left for verbal analytic function, the right for spatial parallel function. Although such a dichotomy is widely accepted, it is by no means clear that specialization reaches its maximum in the normal case. Thus a theoretically possible anomaly would be to have a hemisphere more specialized than is optimal for a particular form of processing. Such a principle in explanation of pathology has not been invoked. This leaves us with the possibilities that lateral specialization is: a) reversed, i.e., one hemisphere assumes to some or a great extent the function customary for the opposite; b) diminished, i.e., functions proper to one hemisphere are spread thin (through both or even the functions proper to both hemispheres are spread thin through both)

Clinical evidence suggests that both of these anomalies occur. The most extensive information comes from the work of Hecaen, D'Agostini, and Monzon-Montes. Although they confirm the usual pattern in right handers, that left hemisphere damage usually occasions aphasia and right hemisphere damage spatial deficit, they document even for right handers instances where damage to one hemisphere (in some cases the left, in some cases the right) caused major difficulties in both these usually conversely lateralized domains. In such cases, information is not available about what the functions of the other hemisphere might be. However we can deduce, both from experience with extensive hemisphere damage and with the transitory inactivation of most of one hemisphere through intracarotid amytal, that the one possibility of an "empty" hemisphere opposite the doubly involved one cannot be substantiated. The other hemisphere either houses both language and spatial abilities or at least one of those. Thus we have evidence in a few right-handers of these specialized functions usually localized in one hemisphere being "spread thin" across both.

The bilateralization of usually lateralized function appears to be much more common in the non-right-handed. In them, lesions of one hemisphere more frequently cause disabilities within both domains. It may not be an unrelated fact that left handers also tend both to sustain a broader range of cognitive deficits after lateral damage than right-handers, and to recover from them more rapidly. Bilateral representation of specific cognitive skills could both bring those tendencies about. Insofar as laterality tests such as dichotic listening, hemifield viewing, verbal-manual interference and cognitively determined conjugate lateral eye movements are valid indicators of the side of specialization, they also supply evidence that within non-right-handed groups specialization may be more bilateralized. Non-righthanders tend to show diminished asymmetry relative to righthanded groups, none at all, or even a tendency in the opposite direction. However, we know from a variety of sources that non-righthanders, although a minority, are far more heterogeneous in brain organization than are the majority of right-handed people. Thus a group outcome of "no lateral specialization," though it could reflect a population largely unilateralized for the function being examined, also could reflect a population divided into some lateralized in one direction, and some in the other. It would appear that one could get some idea of which of these is the case by looking at between-subject variance. However, this is complicated by the fact that non-righthanders also give more variable results on successive laterality tests within subjects.
It is well-known that giving a laterality test to an individual does not suffice to establish once and for all his lateral specialization for the function being tested. The test-retest reliability of such measures is imperfect, so that on repeated testing the answers may not be the same. In particular, Satz has shown that if a right-hander obtains a left-sided advantage in verbal lateral tests, the odds are still: 9:1 that he or she is lateralized like right-handers usually are, namely verbally on the left. It would then take four successive left-advantage outcomes on a dichotic listening test before it can be asserted that a right-hander is more likely lateralized in the opposite direction from the norm than lateralized normally. The imperfect test-retest reliability of laterality measures is aggravated among non-right-handers as Satz and colleagues have also shown. To understand these kinds of outcomes, which are not to be anticipated on the assumption of a one-to-one relationship between the direction of a lateral advantage and the identification of the more specialized hemisphere, we have to consider what factors other than hemisphere specialization might interact with specialization to generate a laterality effect.

Certainly the input paradigms (dichotic listening, hemifield viewing) are subject to fluctuations in attention that might happen to disadvantage input from one side. The subjects might even take the view that they were doing poorly with respect to one direction and voluntarily shift attention toward it. Incidentally, an advantage of the verbal-manual interference paradigm is that there are even more factors that can occur. In this method, subjects perform right or left finger movements while speaking. The speaking interferes disproportionately with the performance of the contralateral hand. But scores would fluctuate if the subject happens not to be exerting maximal effort when a particular voice-hand combination is being evaluated. Given that the normative finding is one of asymmetry, then by central tendency such random factors would diminish rather than increase the asymmetry of the outcome. This indeed is the usual, though not invariable, finding when developmentally disabled groups are measured. A further possible source of variability has to do with the distribution of background activity in the brain. As we have shown (Kinsbourne, Bruce R., unpublished data) whatever else the subject might be thinking of could alter the base-state of relative hemisphere activation and swing attention, and therefore the laterality advantage, in one or the other direction. Again, this is more apt to happen in input paradigms in which the subject is able to timeshare the work he has to do with whatever he might be thinking about than in the verbal-manual paradigm, where the experiment lasts only 1 or 2 minutes and the subject is fully engaged in the task.

An interaction between task-related and concurrent unrelated mental activity can cause discrepant outcomes between individuals who adopt deviant mental sets which it is not intended to measure in the paradigm. This point is relevant to the application of laterality tests to problems of psychopathology.

If lateral asymmetries reflected hemisphere specialization directly, no differentially-greater variability in non-right-handers would be expected. Thus, the greater test-retest variability of non-right-handers itself reflects the difference in brain organization; not in the organization of the specialized cerebral areas, but in the projection of ascending activating systems from brainstem onto these cerebral areas. Not only is it logical to suppose that categorical mental set is adopted not spontaneously but by some selective activation system, but there is now substantial evidence for this. Ojemann has demonstrated at least lateral selectivity of thalamus-based ascending activating systems relative to the category of task orientation. It is possible that this lateral selectivity is diminished in some non-right-handers and may be absent in others. If so, then when such people adopt a mental set they might activate not only the appropriately specialized area, but also wide areas of functionally irrelevant brain at the same time.

The notion that more is activated in brain than is called for by the task posed has obtained dramatic support from recent studies in cerebral metabolism. It has become clear that during "cognitive activation" studies, posing a subject a task that challenges lateralized facilities uniformly causes increased metabolism in both hemispheres and is not always easy to show that the presumably specialized hemisphere is the one whose metabolism is more greatly increased. How this differs when it occurs in left-handers has not been explicitly studied. If we suppose that left-handers activate both hemispheres when given a task that calls for the specialized function of only one, then they differ from right-handers only in degree rather than in kind. That concept has additional explanatory value. If left-handers have a special facility for activating brain territories opposite those specialized for a given function, then it becomes understandable why they tend to recover relatively quickly from unilateral damage causing cognitive deficit.

In summary, lateral specialization may be reversed or diffused to the point of bilaterality for the specialized functions of either the left or the right hemisphere in left-handers. Additionally, activation patterns across the brain when entering into categorical mental sets may be widespread and/or variable in some people. Given that all these patterns had been observed in normal functioning people (albeit mostly non-right-handers), one wonders what pattern of laterality there might be, that induces substantial deficit in some cognitive skill (as opposed to minor fluctuation within the normal range). Certainly anomalous patterns of laterality in pathological groups almost always finds precedent in the normally functioning non-right-hander. Dyslexic groups have often and dysphasic groups usually been found to be less asymmetrical than normally functioning controls on one laterality paradigm or another. More interestingly, Obrzut, Hynd, Obrzut, and Leitgeb have demonstrated a tendency for reading disabled children not to adopt a particular categorical mental set as firmly as normal children (as indexed by their ability to switch attention between ears when a verbal mental set should institute attention virtually fixed toward the right). Whereas such clues should be followed up, our present state of knowledge warrants the viewpoint that if anomalous laterality patterns in developmentally disabled groups have some pathological significance this must be because of func-
tional convergence onto the same anomalous laterality pattern of different influences. Specifically, it might be that failure to lateralize or reverse lateralization can occur either as a harmless biological variant, bringing with it little or no cognitive cost, or as a consequence of early brain damage, which independently exerts a cognitive toll. In the latter case, the anomalous laterality may not be causally responsible for the cognitive deficit, but be a biological marker with respect to the latter's antecedents.

PATHOLOGICAL LEFT-HANDEDNESS

Since the left hemisphere jointly controls movement of the right hand and verbal- analytic cognitive function, sufficiently extensive lesions of that hemisphere could impair right hand dexterity sufficiently to occasion a shift of preference to the left hand, and at the same time prejudice the development of left hemispheric cognitive processing. In the extreme case this is not what happens. After early total left hemispherectomy, the preferred hand necessarily is the left, but language function remains normal in its development sequence and even attains an end point within the normal range. Evidently the right hemisphere, when left hemisphere verbal processes are not available, is fully or nearly fully capable of subserving that function. And that use of the right hemisphere does not crowd out the spatial functioning proper to it. At least in some cases, the single hemisphere appears to maintain both verbal and spatial abilities within the normal range. The fact that the loss even of the whole hemisphere is insufficient to cause serious impairment of language development indicates that lateralized disorder cannot be used as an explanatory principle for a developmental language deficit. Instead, one would ordinarily invoke bilateral disease, that is, impairment both of the predestined substrate for language development and homologous areas on the other side that could otherwise compensate. However, the unilateral disease could account for language delay if it were conjoined with some other factor that precluded right hemisphere compensation. One possibility is that the right hemisphere's ability to compensate varies considerably from individual to individual and the rather few cases of left hemispherectomy that have been studied and shown to support good language development are not necessarily representative of all individuals. Another possibility is that the right hemisphere is not necessarily released for purposes of compensation merely by virtue of some damage to the left. In the first place, there is evidence that the left-sided damage has to impinge substantially on the classical language area for right hemisphere compensation to result.12 Even that may not be sufficient, as it has been shown for instance by Hutt, Hutt and Ounstead that children with focal epilepsy of early origin perform less well in language tasks if their epileptic focus is on the left rather than on the right.12 Thus, with the rather circumscripted lesions causing an epileptic focus (and no gross lateralized neurological disability) it seems that compensation is at best incomplete, perhaps because the left hemisphere retains primary responsibility for language processing. And yet in similar situations, hand preference does seem to shift from right to left. Satz and colleagues have shown that children with focal epilepsy are more likely to be left-handed if their foci were acquired early and were on the left. Pathological lefthandedness overriding the biological disposition to prefer the right hand by damage to its left-handed cortical control center, could be a marker of early left hemisphere damage, sufficient to prejudice left hemisphere ability to support language development, but insufficient in extent to release the compensatory potential of the right hemisphere from inhibition.13

Conceding that pathological lefthandedness could be a marker for impaired left hemisphere development in certain individuals, the question is how to identify such cases, and how important is this mechanism in accounting for a variety of developmental delays?

An obvious way of trying to identify the pathological lefthander has been attempted repeatedly; that is to locate him within that subset of left-handers called "sporadic," because there are no other sinistrals among close relatives. However, differences between sporadic and "familial" lefthanders are bewilderingly diverse and often in opposite directions from study to study. It may be that the picture is complicated by another effect, postulated by Bakan14 and more recently by Geschwind and Behan15 to the effect that early brain damage is more likely to occur in families with sinistral members than in families that are purely dextral. If this were the case, then pathological lefthandedness would not exist in isolation as a counterpart to the familial type. Instead, it would most frequently swell the numbers of sinistrals in a family in whom sinistrals are already present.

It is not yet certain whether sinistrality is a risk factor for early brain damage. Bradshaw-McAnulty, Hicks, and Kinsbourne16 suggest that it might. They studied the well-known increased prevalence of nonrighthandedness among the mentally retarded, confirming and extending the finding of Hicks and Barton17 that the proportion of lefthandedness increases with decreasing levels of mental function within this group. It was found that the probands showed a much higher rate of sinistrality than did their parents and relatives. Thus, familial sinistrality is insufficient to account for the prevalence of lefthandedness in the mentally retarded, and pathological lefthandedness is an attractive explanatory device to account for this increased prevalence. Furthermore, the correlation between the hand preference of the proband and his or her parents, which in a normal population is significant, was quite insignificant; again a relationship consistent with pathological lefthandedness. However, it was also found that the less righthanded the parents, the more likely they were to have offspring among the more severely affected of the mentally retarded. This suggests that a tendency of sinistral parents to bear children vulnerable to severe brain damage complicates the situation. The tentative conclusion was that the excess of lefthandedness among the mentally retarded was due to pathological lefthandedness swelling the ranks of nonrighthanders among individuals at least some of whom were more than usually vulnerable to such damage, because of some factor relative to familial sinistrality.

How might one detect the pathological lefthander in more general populations, given that we exclude the
category of individuals with hard neurological evidence of left hemisphere damage? Satz, Orsini, Saslow and Henry, have attempted to delineate such a syndrome. Notably, they cite circumstantial evidence for the view that minor damage of the left motor strip, insufficient to embarrass the right arm in neurologically identifiable fashion, but sufficient to shift hand preference, also measurably impairs the growth of the limbs on the right.

Extensive, though confusing, literature exists on human anatomical asymmetries and some studies consider how these asymmetries interact with hand preference. Asymmetries favor the bones and muscles of the right arm and leg, though the left femur and left pectoralis major muscle constitute notable exceptions. Although some studies have failed to find symmetry relationships to interact with hand preference (LeMay M, Kido DK, Kinsbourne M, unpublished data) none find the right-sided limbs to be smaller or shorter than the left. Satz and colleagues pick out a subset of left-handers who actually have shorter soles of the foot and narrower palms of the hand on the right than on the left, as a sign of pathological lefthandedness. By similar logic, Bishop argued that even if not neurologically impaired, the right hand should show some performance deficit if handedness had shifted to the left for functional reasons. She examined fingertapping data from a large group of apparently normal children and picked out a subset of about 1% who were not only left-handed but had fingertapping rates on the right side that were significantly lower than the finger tapping elicited from the left hand of dextrals. Her estimate is that this 1% of the population indicates the prevalence of pathological lefthanders in the general population.

The methodologies in the Satz and the Bishop studies are clearly applicable to such subsets of the general population as dyslexics and developmental dysphasics, but the studies in question have not yet been completed. Pending such work it remains uncertain whether the increased incidence of left-handedness in these conditions indicates pathological lefthandedness or a vulnerability of members of sinistral families to the disorders in question, or both. Similar uncertainties apply to stutterers who are also described as including more than the expected number of left-handers but have not yet been studied in ways to clarify this issue. In summary, lefthandedness can, when it is pathological, constitute a biological marker for a disordered left hemisphere, although at this time the claims can only be made on statistical grounds and individuals so affected cannot yet with certainty be identified. The presence of sinistralism in a family may itself be a biological marker of vulnerability to a number of developmental disorders.

AMBIGUITY AND MIXED DOMINANCE

Under the influence of Lenneberg’s progressive lateralization hypothesis it has often been suggested that individuals with cognitive delays will also have delays in institution of laterality, both peripheral and central. Ambiguity was regarded as an immature form, on the view that it perpetuated a presumed lack of hand preference among infants. Mixed dominance, an incongruity in side of preference for hand, foot, eye and ear, could similarly be loosely regarded as resulting from incomplete developmental lateralization of the underlying functions.

Across many studies it has been hard to pin down any real difference between the left-handed and the ambidextrous. These groups seem to exist on a continuum, and the cut-off point depends on the selection criterion (e.g., questionnaire) used to characterize a population. It has not been possible to show that ambidextrous people differ from more fully left-handed individuals in the incidence of sinistrality in their family or indeed in their susceptibility to a variety of developmental disorders. Some recent evidence does suggest that those sinistrals who write with an “inverted” posture (such that the thumb holding the pen is angled below the line of the thenar eminence) are more often ambidextrous than those who write in non-inverted posture, comparable to the usual posture of the right hand in writing. Inverters differ from noninverters in a number of other intriguing ways. In particular, their lateralization characteristics seem more heterogeneous. On noninvasive testing, they appear to have diverse lateralization for different aspects of language function (visual, auditory, expressive) rather than be uniformly lateralized or bilateralized. Dexterity also does not uniformly favor the preferred hand. The fact that the inverted posture is relatively more common among males than females also fits with the pathological implication in that males are more liable to the developmental disorders that are characterized by increased prevalence of non-righthandedness. Nevertheless, the overlap in all relevant characteristics between noninverters and inverters, as between the ambidextrous and the lefthanders, is considerable, so that at best these variables are secondary to some more clear-cut differentiating factor yet to be discovered.

Ambidexterity and mixed dominance were invoked by Orton as indices of a failure of lateralization causing rivalry between the two hemispheres in the control of reading and writing and even of speech. It is thus accounted for developmental language and reading disorders. In spite of intensive research efforts during the subsequent four and a half decades, it has not proved possible to support even the general outlines of this notion, let alone the particular mechanism that Orton suggested. In the case of stutterers there is some evidence, admittedly based on individual cases rather than group studies, that suggest control of speech by both hemispheres. Stuttering may even resolve if one hemisphere is disqualified from a controlling role by brain damage. Nevertheless, if there is any relationship between developmental deficit and ambidexterity or bilaterality or central cognitive representation, it is too tenuous to be used as an explanatory concept at this time.

Mixed dominance is, if possible, more complicated still. Claims for an excess of such cases among the developmentally disabled have been disconfirmed as often as they have been confirmed, and the reverse has even been claimed: that the mixed dominant are better beginning readers than the strictly lateralized (Kerschner JR, unpublished data). It has not been possible to identify any specific pattern of lateral organization in the brain.
that corresponds to mixed peripheral dominance.23

LATERALITY AND PSYCHOPATHOLOGY

Absence of reliable hand preference is very common in one type of developmental psychopathology. In infantile autism, up to more than half of the children are non-right-handed. This is apparently not simply a function of their mental retardation. Their hand preference is inconsistent rather than strictly left-handed and this inconsistency suggests impaired inter-hemispheric communication. Blackstock and Malvestuto have reported that autistic children prefer to listen with their left ear to a source of speech as well as to a source of musical sound, whereas normally functioning children tend to use their right ear to listen to the words.24 But, given the impenetrable nature of the mental processes of autistic individuals, it is unclear with what mental set these largely nonverbal children were listening to the words. So we do not know whether they were using their right brain incongruously for purposes of verbal processing, or whether they were employing a deviant right hemispheric processing strategy for this stimulus material. A study in which the children respond discriminatively to the verbal stimuli rather than just listen to them could clarify this issue. Blackstock has also claimed greater size of left-handed than right-handed limbs among autistic.23 If this is so, left hemisphere damage could be a factor. However, the few autopsies that have been done on autistic individuals have not revealed such damage.

In general, laterality measures and phenomena have not revealed anomalies of structure in psychopathology.22 Another type of laterality finding holds more promise. It is in psychopathology that the usefulness of laterality measures as event-related indicators of differential hemisphere activation comes into its own. The literature is rife with reports of deviant laterality outcomes in various psychopathological groups, but still more impressive is the gross disagreement between studies and even between paradigms within studies as to how the laterality bias is to be construed. Although some reviews have made general claims for a rightward bias on laterality measures in schizophrenia and a leftward bias for depression, the literature gives ample grounds for claiming right, left or no bias for each of these two major groups of psychosis. Perhaps trying to arrive at some statement about fixed laterality biases in psychopathological groups is not the best use for this form of measurement. Instead, what is more impressive, and ultimately perhaps more revealing is the immense variability of laterality findings between different samples of a given psychosis and even within subjects on repeated testing. We have already noted that left-handers are more variable than right-handers. Individuals with psychopathology, regardless of hand preference, are much more variable still. Furthermore, even within the same session, two laterality measures, ostensibly measuring the same construct of language laterality, namely dichotic listening for word and for nonverbal syllables have been found to give opposite outcomes and even on retesting to fluctuate completely out of phase (Wexler B, unpublished data).

appears that with remission or effective treatment, this variability may be reduced. Laterality tests may turn out to be sensitive indicators of an instability of brain-based control mechanisms that could have a major role in the pathogenesis of severe psychopathologies.

REFERENCES