

The Neurodevelopmental Frontostriatal Disorders: Evolutionary Adaptiveness and Anomalous Lateralization

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The frontostriatal system (dorsolateral prefrontal cortex, lateral orbitofrontal cortex, anterior cingulate, supplementary motor area, and associated basal-ganglia structures) is subject to a range of neurodevelopmental disorders: Tourette's syndrome (TS), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), autism, and probably depression. The system is responsible for our adaptive responses (initiation, execution, or withholding) to environmental situations, and the above disorders, involving effectively excessive release or withholding of various types of response, are all a consequence of changes in specific frontostriatal regions. The disorders all have a genetic component, and their persistence in the genome indicates that their clinical manifestations may also be associated, perhaps in low levels in close relatives, with certain adaptive advantages in given situations. Thus *autism* is associated with computational careers, *depression* with literary creativity, *SCZ* with lateral thinking and the Odyssean personality, *ADHD* with an Ice-Age readiness to respond, *OCD* with a focused range of interests, and *TS* with competitive sports and jazz improvisation. The disorders are all highly comorbid, and which one predominantly manifests may depend on how the frontostriatal system happens to be compromised as a result of inherited genetic predispositions and environmental contingency. We review the adaptive nature of the various subclinical manifestations and the evidence for concomitant phenomena (possibly epiphenomena): alterations in structural, functional, and behavioral lateralization in each syndrome. Indeed it is not clear that altered lateralization in frontostriatal disorders of a neurodevelopmental origin generally has any adaptive significance; it may often simply serve as a *marker* for altered regulatory function of the frontostriatal system, alterations which in low genetic dosage or penetrance continue to play an adaptive role in clinically unaffected close relatives of probands, but which, in high dosage or penetrance in the probands themselves, are generally deleterious. © 2000 Academic Press

Human adaptability depends on conscious, volitional, intelligent, problem-solving behavior largely mediated by frontal regions, the ‘‘special work-

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shop of the thinking process" (Burdach, 1819, cited by Pennington & Ozonoff, 1996), where "executive processes" (Shallice & Burgess, 1991) are largely elaborated. Frontal or executive deficits all involve problems in goal-directed behavior, in novel contexts where there may be competing but often erroneous response alternatives. Patients may understand what is required of them, but fail because of perseveration, or impersistence, or because of lack of initiative or of intrusions of task-irrelevant behavior. The frontal lobes comprise the largest sector of the hemispheres and are often said (Blinkov & Glezer, 1968) to be larger and more developed in us than in other primates (though see Semendeferi, Damasio, Frank, & van Hoesen, 1997).

Flexible and adaptive behavior requires selection of just those sensory inputs, and generation of just those responses, that are immediately relevant. Because environment and goals continually change, we must be able to *attend* to currently relevant events, *switch* between cognitive strategies or response modes, *inhibit* inappropriate behaviors, and *select* and mobilize appropriate effectors (Allport, 1989). All this requires an efficient executive control system for coordinating and regulating multiple resources; the system involves the dorsolateral prefrontal cortex (DLPFC), the lateral orbitofrontal cortex (LOC), the striatum of the basal ganglia (BG), and the anterior cingulate (AC). Thus for any appropriate action to occur, we must decide *what* to do (the LOC may eliminate inappropriate alternatives), *how* to do it (via the DLPFC and the lateral premotor area), and *when* to do it (via the AC and supplementary motor area).

The frontostriatal system comprises the above regions of prefrontal cortex and the BG, whose input circuit (receiving information from the frontal cortex) is the striatum. Information is output from the BG, via the globus pallidus and thalamus, back to the frontal regions. Thus the system acts as a closed feedback loop, though it receives additional information from other cortical regions and is subject of a range of modulatory neurotransmitters. However, the exact role of the BG remains unclear: (1) Do they optimize patterns of muscular activity in target attainment (Brooks, 1995)? (2) Do they facilitate movement sequencing especially in response to internal cues (Brochie, Ianssek, & Horne, 1991)? (3) Do they "chunk" action or thought repertoires without conscious supervision, which may only be necessary under novel, difficult, or unfamiliar conditions when the DLPFC is involved (Graybiel, 1998)? (4) Are the BG involved in binding, facilitating the synchronization (in the gamma band) of cortical activity which underlies the selection and promulgation of appropriate groupings or sequences of thoughts or actions (Brown & Marsden, 1998)?

The frontostriatal system is subject to such neurodegenerative disorders of aging as Parkinson's (PD) and Huntington's (HD) diseases and such neurodevelopmental disorders of youth as Tourette's syndrome (TS), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), schizophrenia (SCZ), autism, and probably depression (including bipolar disorder). ADHD is perhaps the archetypal disorder of attentional

and inhibitory processes (Barkley, 1997), involving deficits in sustaining attention, in distractibility, and in impulsivity. However, all these diseases, striking in childhood or early adulthood, are characterized by selective losses of attentional and executive control and changes of motor function. They are all also, to a considerable extent, heritable and are typically associated with alterations in frontostriatal function and in the normal patterns of behavioral, structural, and functional asymmetry. Autism is in some respects a new candidate for such treatment, but many authors have reported the presence of movement disturbance symptoms, typically associated with striatal dysfunction, in individuals with autism; Leary and Hill (1996) thoroughly review such findings.

An understanding of the neurodevelopmental disorders also informs us of the mechanisms normally operating in preparation for action. Preparation for action crucially involves the frontostriatal system, in particular five regions of the frontal lobe and associated reentrant pathways via the BG. Clinical (lesion) studies indicate that dysfunction of the DLPFC, resulting in the dysexecutive syndrome, is particularly associated with impaired attention, "set" or overall processing capacity, and a lack of strategic or goal-oriented behavior, or the ability to defer, delay, or inhibit responses. Dysfunction of the LOC may result in euphoria, disinhibition, sporadic hypomania, impulsivity, and socially inappropriate behavior and lack of concern for others or for ethical principles, while dysfunction of the AC may result in social and emotional withdrawal or apathy and reduced initiative drive and vigilance (Pantelis & Brewer, 1996). Through the BG run five distinct parallel frontal-subcortical (cortico-striatal-pallidal-thalamic-cortical) circuits, involving the oculomotor, motor, dorsolateral prefrontal, lateral orbital, and anterior cingulate loops (Cummings, 1993). These parallel pathways provide a unifying framework for understanding similarities and differences of behavioral changes, particularly cognitive, attentional, affective, and motor, associated with diverse anatomical lesions and the various neurodegenerative and neurodevelopmental disorders. These disorders may involve structural (PD, HD, SCZ, and autism), metabolic, or neurochemical (PD, SCZ, TS, OCD, ADHD, and depression) changes at various points in a given circuit or in different circuits. Other regions (temporal, hippocampal, cerebellar, and amygdalar) may also be involved (e.g., in SCZ and autism). Thus whether, and what kind of, neurodevelopmental or neurodegenerative disorder manifests will be determined by genetic and probably epigenetic factors operating on a number of circumscribed regions, pathways, or circuits, anatomically or neurochemically defined. Indeed, at the *neurodevelopmental* level, there may even be a propensity to a range of such disorders (symptoms often overlap, the disorders are often comorbid, or there may be a raised risk of developing a given disorder in relatives of sufferers from *another* such disorder), with chance or environmental factors perhaps influencing which particular syndrome actually manifests.

We see therefore that TS, OCD, ADHD, SCZ, autism, and depression

have much in common, including a likely neurodevelopmental origin, an extensive overlap of symptoms and/or comorbidities, and frontostriatal involvement. The striatum, the input region of the BG, intervenes to process information automatically, without conscious representation, unlike the conscious, volitional thalamocortical system; it acts as a filter and for mediating stereotyped, rule-governed behavior.

Each of the five circuits has a direct and an indirect pathway. *At the level of the BG*, activation of the direct pathway tends to excite the thalamus and release behaviors, whereas the indirect pathway has a net inhibitory tendency (Alexander & Crutcher, 1990). Unwanted behaviors (tics of TS, hyperactivity of agitated depression or of ADHD, and certain positive symptoms of SCZ) may therefore arise from overactivity of one or more direct pathways, while overfocused preoccupations or obsessions (OCD, autism), rumination or motor retardation in depression, or negative SCZ symptomatology may reflect overactivity of one or more indirect pathways. *At a cortical level*, we may similarly contrast the AC and the LOC; the former may provide a "go" signal and the latter a stop signal, while the DLPFC mediates, modulates, combines, and controls these actions. *At a syndrome level*, we can contrast disorders of excess or insufficient activity (disinhibition vs inhibition) and of under- or overfocusing of attention.

COMORBIDITY, DIAGNOSTIC OVERLAP, AND SYMPTOM COMMONALITY

Comorbidity may be defined as "any additional clinical entity that has existed or may occur during the clinical course of an index disease" (see, e.g., Griez & Overbeek, 1997); it is currently very much a "hot topic" in psychopathology research (Mineka, Watson, & Clark, 1998). Thus there are problems in how we delimit a distinct clinical entity and how we determine whether a disorder may be a risk factor for, or a complication of, another disorder; there are problems with respect to causal and correlational relationships and categorization into super- and subordinate relationships; there are problems of multiple comorbidities and whether their effects may be multiplicative or additive; there is the problem of severity with respect to whether a more severe level of a disorder is likely to be associated with more comorbid conditions; there is the problem that key symptoms, which define theoretically quite distinct disorders, can often co-occur. It is not therefore surprising that clinicians and theoreticians fall into separate traditions of "lumping" and "splitting."

TS and OCD clearly have features in common, especially a repetitive and obsessional quality (Hollander & Stein, 1997), and they have been considered on the basis of familial findings as alternative manifestations of a common gene (Peterson, Leckman, & Cohen, 1995; Shytle, Silver, & Sanberg, 1996). Although distinct disorders, autism and TS share features too, e.g.,

echolalia and palilalia, rigid and ritualistic behavior, and abnormal motor stereotypies (Baron-Cohen et al., 1999). Moreover, TS and ADHD have many similarities in terms of behavioral disinhibition (Leckman et al., 1997; Walkup, Scahill, & Riddle, 1995). The symptoms of ADHD may overlap with those of SCZ, major depression, and bipolar disorder (Jensen, Martin, & Cantwell, 1997; Ratey, Middeldorp, Crispijn, & Leveroni, 1995; Tannock, 1998). There are many commonalities, including obsessive rumination, between OCD and depression (Hollander & Stein, 1997), while in children emerging bipolar disorder (mania) may be mistaken for ADHD (Biederman, 1998).

Mania has been linked with OCD (Baer, Minichiello, & Jenike, 1985), OCD with SCZ (Carey et al., 1986), and mania with SCZ (Nasrallah, 1997), while autism may overlap and/or be comorbid not only with TS (see above) and OCD but also with SCZ, ADHD, and depression (Bolton, Pickles, Murphy, & Rutter, 1998; Pennington & Ozonoff, 1996; Rapin, 1997).

ADAPTIVE ASPECTS

Hammer and Zubin (1968) over 30 years ago asked whether an evolutionary perspective can help formulate questions crucial for an understanding of psychopathology and, in particular, whether disorders may even possess a positive adaptive significance, as one must account for the persistence of phenomena (in the genome) which have clear individual and group disadvantages. In a very modern approach, in answer to the paradox of continuing high rates of genetic transmission of an evidently maladaptive characteristic, they invoke the model of a balanced polymorphism—"an underlying entity or process which under different conditions has opposite adaptive significance, developing in ways which are advantageous to individual and cultural survival under some conditions, and disadvantageous under others" (p. 153).

They go on to note the sickle-cell complex as one of the best known medical examples of balanced polymorphism: in the environmental presence of malaria, the gene for sickle cell is advantageous, as heterozygous individuals are more resistant to malaria than those who are homozygous for normal hemoglobin. In the absence of malaria, sickling is disadvantageous because of the fatal anemia of those homozygous for the sickling gene. Other examples include the heterozygous forms of congenital adrenal hyperplasia protecting Yupik Eskimos against *Hemophilus influenzae* B infections, heterozygotes with Tay-Sachs disease having increased resistance to TB, and improved fetal survival with diabetes-linked human leukocyte antigens (see, e.g., Rison, 1998).

Hammer and Zubin (1968) also note that psychopathology is adaptationally disadvantageous to the individual, at least in the context of that individual's society (as mental illness is primarily defined by its disturbing impact on, and from, a given society), and that fertility rates are historically

lower, and morbidity and mortality higher, than those who are “well.” Thus they reason that a genotype which survives with a moderately high frequency, as does psychopathology, cannot be exclusively maladaptive. Nowadays, of course, we see a much clearer picture of familial patterns in psychopathology and, often, even evidence of positive or adaptive aspects in “subclinically affected” close relatives. Thus evolutionary biology provides a new framework for characterizing neurodevelopmental disorders. When human mental and behavioral phenomena are viewed from this theoretical perspective, a core assumption would be that natural selection has shaped our mental mechanisms in terms of adaptation and survival; many emotional and behavioral responses, particularly if persistent within populations, may not just be symptoms of a disorder, but rather may reflect adaptive responses to possible environmental demands (and see also Jensen et al., 1997).

Autism

There are reports (Baron-Cohen et al., 1998; Jarrold & Routh, 1998) of an overrepresentation of occupations that involve engineering, physics, and math (and possibly medicine, science, and accounting) among the fathers of individuals with autism. Thus a meticulous and obsessive attention to and interest in detail, quantification, and minutiae may characterize, adaptively, individuals closely related to probands with the disorder. The interest in detailed minutiae may also be reflected in findings (Plaisted, O’Riordan, & Baron-Cohen, 1998) that children with autism are better than controls at locating or disembedding target letters from a larger array (scatter) of letters. Similarly, Mottron and Belleville (1993) argue that individuals with autism lack the normal precedence in local–global processing. Indeed, we have found that individuals with autism and Asperger’s disorders may acquire a natural ability to select out detail, as they seem to lack the normal preference for focusing on the overall gestalt or configuration (Rinehart, Bradshaw, Moss, Brereton & Tonge, in press).

Depression

Post (1994) sought to determine the prevalences of various psychopathologies in outstandingly creative individuals and to test the hypothesis of a high prevalence of mental abnormalities in prominent living creative individuals. He determined the family background of 291 famous men of science, thought, politics, and art (including inventors, scholars, painters, sculptors, composers, novelists, and playwrights). All excelled, not only by virtue of their abilities and originality, but also of their drive, perseverance, industry, and meticulousness—what in the context of autism (above) might seem an obsessive attention to detail. Severe personality deviations were unduly frequent only in the cases of visual artists and writers; depressive conditions and alcoholism were noteworthy particularly in writers.

In bipolar disorder, essentially phases of depression alternating with phases of mania, unusual levels of energy may be available during periods of mania, and while this may sometimes be coupled with corresponding achievements (Jamison, 1993), the period may also of course be characterized by excess and disaster. According to the Roman writer Seneca 2000 years ago, *nullum magnum ingenium sine mixtura dementiae fuit* ("there has never been a great mind without some degree of madness"). How do we identify *magnum ingenium*, genius or talent? While productivity (number of publications, pictures, novels, sculptures, inventions, and so on) can clearly be quantified, judgements of quality depend upon peer review, the winning of prestigious awards, or inclusion in biographical dictionaries of notables such as *Who's Who*. Marzullo (1996) in fact employed a range of such biographical sources in his study of notable scientists, artists, musicians, and so on with respect to season of birth. The context of his research was a well-attested seasonality effect in SCZ, but he was also interested in the possibility of a heterozygote advantage for creativity in any gene influencing mood; he did in fact report a bias of season of birth in various categories of genius, which, however, was out of phase with that pertaining to SCZ. Presumably epigenetic (e.g., viral) factors would interact with any genetic determination.

Jamison (1993) reported on the frequency of psychiatric treatments received by a series of 47 living, prize-winning British poets, playwrights, novelists, biographers, and artists. Treated affective illnesses were found in 63% of playwrights and 15% of novelists. Unlike the poets, her prose writers had not received treatment for mania, but many reported periods of elation coinciding with high creativity. Creativity, high-energy states, intense emotionality, and risk taking are under certain circumstances socially advantageous (MacKinnon, Jamison, & DePaulo, 1997); a balanced polymorphism in this regard has long benefited both individual and society.

Schizophrenia

Seneca's dictum *nullum magnum ingenium sine mixtura dementiae fuit* may properly perhaps be applied more to SCZ than to depression. Marzullo (1996) notes that the riddle of the epidemiological survival of SCZ stems from the incompatibility inherent in the following three observations: (a) SCZ has a large genetic component, (b) schizophrenics reproduce at rates considerably below normal, and (c) the incidence of SCZ is not apparently changing. While the first two observations would require the incidence of the disorder to be dropping rapidly over the generations, the third indicates that this is not the case. Is there a social or reproductive advantage of some sort for close relatives of propositi?

Leonhard and Brugger (1998) corroborate previous findings of a reduced left-hemisphere dominance for subjects scoring high on scales measuring proneness to schizophrenic behavior and thought (schizotypy). They propose

that this dominance failure, which is commonly observed in patients with acute signs of psychosis, facilitates the emergence of paranormal and delusional ideas by way of right-hemisphere associations involving coarse or global rather than focused semantic activation. Such an unfocused mode of semantic processing is also characteristic, they argue, of creative thinking; the use of the right-hemisphere semantic system may constitute a selective evolutionary advantage which allows the genes predisposing to SCZ to proliferate despite the obvious disadvantages of this devastating disease. Rison (1998) also asks whether SCZ-related genes can serve a beneficial adaptive role in terms of the "Odyssean" personality (cunning, aloof, suspicious, paranoid, resourceful, and atypical; see for example, Jarvik & Deckard, 1977) and whether altered function of the *N*-methyl-D-aspartate (NMDA) receptor is the molecular correlate of such adaptive significance. The NMDA receptor is one of a class of excitatory amino acid receptors with a role in a variety of neurologic phenomena such as learning and memory, synaptic plasticity and neuronal development, neurodegeneration, and SCZ. Indeed, it has even been suggested that the "superior capacity" of the hominid (compared to other primates) brain is related to a tolerable delay in switching from the fetal to the adult form of the NMDA receptor (Etienne & Baudry, 1990).

Karlsson (1968) studied an Icelandic kindred extending over seven generations and found that in addition to having a large fraction of schizophrenic individuals in the family, this group contained many highly gifted people. The SCZ genotype may lead not only to reduced resistance to stress, but also to a potential for versatile or imaginative inventiveness, lateral associations, and divergent thinking. Thus Spitzer (cited by Buchanan, Buckley, Tamminga, & Schultz, 1998) notes that patients with formal thought disorder, a symptom-complex of SCZ, exhibit increased rather than decreased semantic priming during lexical decisions, indicative of more widespread activation of associative networks. Finally in times of war and persecution, a seclusive, suspicious, and paranoid outlook on life may be of survival benefit. We shall see that a somewhat similar argument may apply with respect to ADHD.

Obsessive Compulsive Disorder

Patients experience problems in the natural inhibition of repetitive thoughts and actions (Rosenberg et al., 1997) and loss of self-regulation and control, compromised volition, stereotyped and perseverative ideas, obsessions and ritualizations of behavior (compulsions) (Koziol, 1994). Patients know their obsessions are irrational and their compulsions excessive and distressing, but they nevertheless persist, thereby manifesting a dissociation between knowing and doing. The repetitive behaviors, which cannot easily be resisted, ignored, or suppressed, are performed according to rigid "rules,"

often to reduce anxiety or distress (Carter, Pauls, & Leckman, 1995). There must be a feeling of force or invasion by the symptoms (as with SCZ) and (unlike paranoia or SCZ) some level of insight (Towbin & Riddle, 1996). Should the actions be in any way pleasurable, a diagnosis of obsessive compulsive personality (OCP) may be more appropriate.

OCD-like behavior may be reported after striatal damage (Purcell, Maruff, Kyrios, & Pantelis, 1998; Rosenberg et al., 1997), involving pathways thought to mediate key mammalian behavior routines of grooming, cleaning, nesting, reproduction, and avoidance of danger. Thus OCD behavior (hygiene, checking, hoarding, etc.) may represent an exaggeration or disinhibition of such normally adaptive species-specific behaviors (Wilson, 1998). If the orbitofrontal cortex is crucial for suppressing inappropriate behaviors, and given that the onset of OCD typically occurs during the period of normal development of such structures, then OCD may be seen as a neurodevelopmental disorder of an overactive orbitofrontal warning system (Hollander & Stein, 1997). While children lack the metacognitive capacities sufficient for self-report on obsessive ideation, normal childhood is replete with disinhibition, collecting mania, a fear of and fascination with dirt, scatology, repeated checking, and rituals (“not stepping on flagstone cracks or junctions”) (Carter et al., 1995; Palumbo, Maughan, & Kurlan, 1997), while tic-like behavior is also extremely common (Kurlan, 1994). Children’s repetitious play (seen to excess in autism); passion for sameness and uniformity with respect to clothing, food, stories, and bedtime routines, especially when stressed; and magical rituals merge with adult OCD behavior.

Attention Deficit Hyperactivity Disorder

All the neurodevelopmental disorders may be seen as involving altered or extreme variants of normal behaviors, perhaps with perpetuation or prolongation of juvenile phenotypes into developmentally later phases of ontogeny. This may be particularly true of ADHD. Clearly, aspects of ADHD may prove adaptive if you are a migrant, nomadic hunter-gatherer, while OCD-like behavior may be more adaptive for a settled agriculturalist who has to look to the future. Thus the behavioral and emotional responses of a “disorder,” especially if relatively common, persisting in the genome, and possessing an inherited component, may not just be “symptoms” (as viewed from a particular societal perspective), but may, as we saw, instead be adaptive responses to environmental demands (and see also Jensen et al., 1997). Our ancestral environments varied in resource availability and safety, and ADHD’s classic triad of symptomatology—hyperactivity, disturbed attentional processes, and impulsivity—all are potentially and independently adaptive in certain circumstances (Jensen et al., 1997): (1) Hyperactivity is adaptive for exploring the environment, especially during times of scarcity. (2) Rapidly shifting attention is clearly adaptive for monitoring for possible

danger or threats, while overfocusing as in OCD could be dangerous in a risky environment. (3) Impulsivity, or a rapid reflexive response to environmental stimuli while not considering alternatives, may also be advantageous in risky, rapidly changing circumstances. Thus we might need to adjust the threshold and timing of responses as functions of the likelihood of payoff as a result of immediate, delayed, or withheld responding; costs and payoffs of false-positive or withheld responses also need assessing. Thus there may sometimes be advantages with impulsive, hair-trigger responses, maybe more in times of war than of peace, when hypervigilance is essential. Impulsive behavior is adaptive when time is critical. Indeed the personality characteristics of the good warrior (impulsive) and the good strategist (reflective) are very different, probably based on dopaminergic striatal mechanisms, and equally valuable to a society.

While schools and educational establishments demand focused, reflective, nonimpulsive, and measured behavior, the opposite is required by many forms of games and entertainment of a risk-taking nature and favored by those of a certain personality profile. Of course, as Jensen et al. (1997) observe, many modern occupations also still demand ice-age impulsivity and response readiness, for example, those of the soldier, air traffic controller, entrepreneur, emergency-room physician, or salesperson. ADHD is not the only "disorder" which is a product of society's norms and which would be considered adaptive in a simpler and more dangerous society; thus anxiety, depression, bipolar disorder (hypomania), Tourette's syndrome, and schizophrenia all convey additional adaptive advantages and involve probable neurodevelopmental and lateralization anomalies of the frontostriatal system.

Tourette's Syndrome

Leckman and Cohen (1999) ask, from the Darwinian viewpoint, whether there might be an advantage, however slight, in having the vulnerability to develop TS or OCD. They claim as clinicians to have observed that TS individuals are "in a special way. . . . sensitive to the feelings and experiences of others, and have a thinner barrier to stimulation. . . . they are thus more empathic. . . . a special gift" (p. 149). Being aware of dangers, from the internal or external milieu, may, they believe, protect both the individual and those with whom he is bonded.

We (Georgiou et al., 1997) have found that patients with TS, compared to controls, when tested on a graphics tablet and assessed in terms of movement kinematics, were in certain respects more force efficient than controls, making fewer cycles of acceleration and deceleration. Tourette's support groups are noteworthy for their use of, success with, and enjoyment of song and dance, rhythmic physical activity, ball playing, and so on. Sacks (1986) describes "Witty Ticky Ray" who was a remarkable musician: ". . . a weekend jazz drummer of real virtuosity, famous for his sudden and wild extemporizations, which would instantly arise from a tic or a compulsive hitting of a

drum, and would instantly be made the nucleus of a wild and wonderful improvisation, so that the 'sudden intruder' would be turned to a brilliant advantage'' (p. 94).

According to contemporary accounts, the 18th-century English lexicographer Samuel Johnson suffered from various vocal and motor tics, with facial grimacing, finger twirling, head tilting, shoulder shrugging, gesticulations, loud vocalizations, and bizarre rituals on going through doorways—the opposite of the Parkinsonian freezing under similar circumstances. Sacks (1992) suggested that Mozart may too have suffered from TS; he was hyperactive and given to tics, sudden impulses, odd motor behaviors, echolalia, and palilalia, with a love of nonsense words and a head full of melodies—like Johnson, with his head full of words. We can ask, with Sacks, whether Mozart and Johnson were creators and innovators in their fields *despite* TS or *because* of it. TS may therefore be a continuum with two ends: one (stereotypic) extreme involves simple motor tics and vocalizations, iterations, and perseverations, which are largely a nuisance and an irrelevance; the other extreme perhaps involves elaborations, playful mimicry, extravagant impudent inventiveness, audacious dramatizations, surreal associations, uninhibited inventiveness, incontinent reactivity, stimulus hunger, imagery, and exuberant art. Sacks saw this latter extreme to be a source of inspiration in language, music, art, athletics, and games, a usefully harnessed disorder.

Since, despite the existence of a highly heritable component in the disorder, any TS gene is neither necessary nor sufficient on its own to cause TS, we must invoke the concept of genetic vulnerability (Peterson et al., 1995), with tic behaviors on a continuum with normal behavior; vulnerability genes may be turned on and off at specific developmental points, and environmental influences may affect developmental timing and expression of frontostriatal and limbic circuitry. Again, TS may be seen as an excessive expression or abnormal persistence of normal developmental characteristics. This of course may also be true of the other neurodevelopmental disorders of the frontostriatal system.

ANOMALIES OF BRAIN LATERALIZATION

All the neurodevelopmental disorders under consideration are characterized by early onset (not later, usually, than young adulthood), strongly familial tendencies (though subject also to environmental factors in how, or indeed if, they manifest), frontostriatal involvement at various levels, a potentially adaptive nature (at least under certain circumstances or maybe at low genetic "doses") and, finally, anomalies of lateralization. It is to this last feature that we now turn.

Autism

There is evidence of deviations from the normal pattern of left–right morphological asymmetries in the parieto-occipital regions of autistic brains (for

review, see Bishop, 1990). Similarly, Fein et al. (1996) review recent studies indicating failure of young autistic adults to show normal metabolic brain asymmetries (both resting state and task activated) and altered or reversed patterns of lateralized electrophysiological measures. A left-hemisphere language deficit has long been hypothesized (Sanua, 1986), but this position is extensively criticized by Fein et al. (1984); moreover Ozonoff and Miller (1996), studying performance on pragmatic language aspects, thought normally to be mediated by the right hemisphere, conclude in favor of right-hemisphere damage. Sanua (1986) and Bryson (1990) also review the evidence of reduced, reversed, or delayed asymmetries in behavioral and hand-laterality tasks; Annett (1997) considers the latter in more detail from a genetic viewpoint. Haznedar et al. (1997) report that regions within the right anterior cingulate are significantly smaller in relative volume, and metabolically less active, in autistic patients than in normal subjects, while Teitelbaum et al. (1998) find evidence of movement disturbances in the early months of life in autistic children, which typically occur on the right side of the body. Similarly, Rinehart, Bradshaw, Brereton, and Tonge (submitted) found a left-hemisphere anomaly in autism which was evident across three separate neurobehavioral paradigms. Using a choice–reaction-time visuospatial task where participants responded to left and right pointing arrows, children and young adults with autism were consistently slower at making rightward responses. Further, when performing a serial choice, reaction-time, button-pressing task, the autism group was slower at rightward compared to leftward movements. Finally, in an inhibition of return task where participants were presented with a visual cue followed by a target, both of which could appear at either the right or the left side of the screen, the autism group was less likely to anticipate a target after receiving a rightward cue, while the control group made equal numbers of anticipation errors following leftward or rightward cues.

Depression

At a functional level, early imaging studies generally assessed resting values during periods when the patient's mental state was unknown; they reported hypofrontality, especially of the left DLPFC, and reduced striatal, left temporal (amygdala), and cingulate activity, sometimes with increased orbitofrontal perfusion, which perhaps corresponded to increased inhibitory processes (for review see Rogers, Bradshaw, Pantelis, & Phillips, 1998). Left-sided anterior lesions may induce prolonged or severe depression and a "catastrophic" reaction, while right-sided damage may be associated with indifference, euphoria, or even mania (Derix & Jolles, 1997; Rogers et al., 1998). In bipolar disease volumetric reductions in the left amygdala are reported (Drevetz, 1999). Pettigrew and Miller (1998) seek to explain the mood shifts seen in bipolar disorder in terms of the cognitive style associated with a

currently activated hemisphere—left hemisphere activation being associated with confidence, elation, or even mania and right-hemisphere activation with caution, apprehension, or even depression.

Schizophrenia

Structural imaging and neuropathological studies frequently show ventricular enlargement which is more pronounced on the left, with loss of gray matter, especially frontal and temporal and on the left (for reviews see Egan & Weinberger, 1997; Travis & Kerwin, 1997); reductions in size of the superior temporal gyrus on the left may correlate with positive symptoms (Gur & Pearlson, 1993). Anomalous BG activity, in particular reduced left lenticular activation, is also reported, along with increased blood flow in the left globus pallidus (Early, Haller, Posner, & Raichle, 1994), which would account for our finding of inhibition of rightward-directed activity analogous to a subtle form of right neglect (Downing et al., 1998, and see also Posner et al., 1988). Maruff and Currie (1996) review the evidence for biased turning behavior in SCZ. Crow (1997) likewise provides a comprehensive review of the large literature on anomalies of language lateralization in SCZ. In a very recent study, Kwon et al. (1999) find that patients with SCZ have reduced left planum temporale gray matter and a reversal of planum temporale asymmetry, which they believe may underlie an impairment in language processing in the disorder.

Obsessive Compulsive Disorder

Lateralization of neuroanatomical abnormalities has been suggested by several studies of both prefrontal cortex and caudate nucleus, but there is no clear predominance in one or other side of pathology (see Cohen, Hollander, & Stein, 1997, for review). Strong evidence of visual-constructional relative to verbal impairment suggests right-hemisphere hypofunction (relative to left-hemisphere hyperfunction). Conversely, Flor-Henry (1983), on the basis of EEG and neuropsychological tests, proposed that dominant (left) frontal lobe dysfunction was most characteristic of OCD. Likewise, studies of adult and childhood OCD (reviewed by Hollander, Liebowitz, & Rosen, 1991) find raised prevalence of left-handedness.

There are also reports, reviewed by Cohen et al. (1997), of a lack of normal right-sided dominance in simple line bisection and body-turning tasks, and various electrophysiological studies suggest left-hemisphere overactivity or overresponsiveness. Similarly, Rauch et al. (1994) report increased blood flow in the right caudate in situations unique to OCD provocation (i.e., not occurring during simple *phobic* provocation). Nelson, Early, and Haller (1993) used the Posner task and found decreased inhibition of return for left visual field targets and no inhibition of return for right visual field targets.

Clearly, the exact nature of changes in laterality in OCD remains to be determined.

Attention Deficit Hyperactivity Disorder

Imaging studies indicate anomalies or loss of normal asymmetries in the lateral ventricles, striatum, globus pallidus, and anterior frontal regions (Castellanos et al., 1996; Mataro et al., 1997), with reduced metabolic activity in left frontal and parietal regions and anomalous electrical activity on the left (Tannock, 1998). At a behavioral level, in a letter-cancellation task, children with ADHD behaved similarly to adults with left neglect after right-hemisphere damage (Voeller & Heilman, 1988), with an abnormal preponderance of left-sided errors. In various versions of the Posner orienting task, anomalous patterns of lateralization have also been reported (Carter et al., 1995; Epstein et al., 1997; Nigg, Swanson, & Hinshaw, 1997), while in a computerized line-bisection task, children with ADHD, off medication, bisected lines significantly to the right (compared to the normal slightly leftward bias), with methylphenidate normalizing performance (Sheppard, Bradshaw, Mattingley, & Lee, 1999).

Tourette's Syndrome

MRI studies of TS adults have reported left-side volume reductions of various regions of the BG (Hyde et al., 1995; Peterson et al., 1993; Singer et al., 1993). TS individuals may also fail to show the normal leftward bias in line bisection (Yazgan, Peterson, Wexler, & Leckman, 1995). In an as-yet-unpublished study (Sheppard, 1999) from our laboratory, children with TS, like the unmedicated children with ADHD (above), showed a reversal (i.e., a rightward deviation) of the normal pattern of a leftward transection in a computerized line-bisection task. Moreover, TS children, unlike controls, showed lateralized performance in a separate reciprocal button-pressing motor-inhibition task. This task involved the ability to follow visual cues (internal LEDs underneath each next button to be depressed in the sequence) and depress the buttons as fast as possible in a reciprocal (left, right, left, right) pattern. During each trial, at an unpredictable time and sequential location, participants were cued to press the button in the opposite ("oddball") direction to the next expected move and thus to inhibit the next expected move of the sequence as well as to *reprogram* the direction of that move. The TS children in this task showed a *rightward* preference in movement execution times (MTs, or the time in flight between consecutive buttons) such that movements in a rightward direction were significantly faster than those in a leftward direction.

Another task examined the ability to efficiently move toward targets under conditions requiring different types of inhibitory control. Different aspects of inhibition were incorporated into the task so that the effect on movement

parameters could be examined. The basic task involved the movement of a special stylus from a center start position toward either a left or right target according to the presentation of a visual cue (illumination of an LED directly above the left or right target). Although a performance asymmetry, in *movement execution*, of faster *rightward* movements was shown consistently for both ADHD and TS children as well as controls, a performance asymmetry in *movement latency* was only shown by the TS group. The TS children showed slower movement latencies for unexpected compared to expected targets for *rightward* movements only. For *leftward* movements the TS children were equally slow for expected and unexpected targets.

Further evidence of the possible consequences of altered subcortical/cortical volumetric asymmetries for TS children was unexpectedly found in another task within the same series of experiments. A local–global task was conducted in which the TS children failed to show the normal pattern of priority of processing at a global level; this is usually a consistent and robust finding in traditional local–global paradigms, reflective of earlier processing of global stimulus features (Navon, 1977). There has been recent electrophysiological evidence suggesting a left-hemispheric specialization for processing at a local level and a right-hemispheric specialization for processing at a global level (Proverbio, Minniti, & Zani, 1998). The presence of altered subcortical asymmetries in TS could, therefore, have conceivably affected local–global processing such that a sensory precedence for global information was no longer shown.

Finally, in an analysis of kinematic (movement) profiles with a graphics tablet involving goal-directed movements of a handheld stylus, we found reduced asymmetries in force efficiency in adult TS subjects (Georgiou et al., 1997).

DISCUSSION AND CONCLUSIONS

Flexible and adaptive behavior requires selection of relevant sensory inputs and generation, at exactly the right moment, of appropriate responses. We therefore need to attend to what is relevant, switch between various possible response modes, inhibit inappropriate behaviors, and select and mobilize appropriate effectors. To these ends, the inhibitory mechanisms of the LOC eliminate inappropriate, though often prepotent, responses; the executive decisions of the DLPFC permit us to decide how to initiate the remaining, appropriate, behaviors; the AC (perhaps in conjunction with another, medial, motor structure, the supplementary motor area, see, e.g., Cunnington, Bradshaw, & Iansak, 1996) allows us to initiate action; and the BG provides essential back-up facilitation with respect to filtering, sequencing, chunking, scaling, and binding movements. These structures are the essential components of the frontostriatal system, which in many ways determines our personalities as reserved or outgoing, focused or distractible,

cautious or risk-taking, “sane” or paranoid. (We probably should not think exclusively in dichotomies, but the powers of language seem to have been built around polar or antithetical opposites.)

Like all advanced neural structures, the frontostriatal system constitutes a flexible, balanced network controlled by feedback loops, neural and neurochemical. Neurochemically, the neurotransmitters dopamine, serotonin, norepinephrine, glutamate, and γ -aminobutyric acid (GABA) are the major players and are subject to disturbance from various disease processes, neurodevelopmental (with which this article is concerned) or neurodegenerative. Structurally, the direct (excitatory or facilitatory) and the indirect (inhibitory) pathways of the BG release or inhibit responses at a relatively automatic level, while at a more conscious level the AC (and related SMA) and the LOC respectively initiate or restrain behaviors. The (at least partial) success of medication for the various neurodevelopmental disorders (serotonin selective reuptake inhibitors for OCD and depression, dopamine agonists for ADHD, dopamine antagonists for SCZ and TS, and noradrenergic medications for depression) testifies to their status as disorders largely of neurochemical imbalance rather than as due to major structural changes, as in PD, HD, and Alzheimer’s disease. Indeed, these aspects, and the fact that their onset is early rather than late and that they may have adaptive aspects at least for clinically “unaffected” close relatives, indicate that they may lie within or closely adjacent to the spectrum of normal human behavior. Thus we are all subject to depression, paranoid jealousy or suspicion, urges to commit the socially unacceptable, to tread on the cracks in the pavement or to avoid them, to throw caution to the winds—or to dedicate our lives obsessively to the pursuit of an arcane line of knowledge. We are sociable or otherwise, outgoing or introverted—and while these *traits* may be fairly consistent at a personal or even family level, from time to time our moods (or medications) may change our momentary *states* of mind. It is tempting to link *traits* to fairly permanent *structural* configurations of the frontostriatal system and *states* to more variable neurochemical balances, but this may be oversimplification.

The neurodevelopmental disorders are all highly comorbid: OCD and ADHD with TS; ADHD and depression with OCD; TS, ADHD, and OCD with autism; ADHD and mania (if not depression) with SCZ. Which disorder manifests may depend upon *how* the frontostriatal system happens to be compromised as a result of inherited genetic predispositions and environmental contingency. Similarly, a range of related behavioral phenotypes are associated with the different disorders: attentional dyscontrol with ADHD; inhibitory dyscontrol with ADHD and TS; overfocusing with OCD, depression, and autism; motoric hyperkinesia with TS; hypokinesia with depression and SCZ; thought disorder and paranoia with SCZ. However, all involve, to a greater or lesser extent, the frontostriatal system and, perhaps often epiphenomenologically, alterations in lateral asymmetries—reduced, reversed, or

delayed at a behavioral, morphometric, electrophysiological, or functional level.

An increasingly important concept in evolutionary theory and in medicine is that of a balanced polymorphism—an underlying entity or process which under different conditions has adaptive significance, developing in ways which are advantageous to survival under some conditions and disadvantageous under others. Natural selection may have shaped our mental mechanisms in terms of adaptation and survival; many emotional and behavioral responses may not just be symptoms of a disorder, but rather may reflect adaptive responses to possible environmental demands. Thus evolutionary pressures have molded the prefrontal systems (structural and neurochemical) that govern our predispositions, and changing pressures differentially advantage different predispositions. It is part of the adaptability of *Homo sapiens* as a generalist species (Bradshaw, 1997) that different individuals should differentially cope with the ever-changing demands of the environment. Some individuals may lie on or beyond the extremes of what we currently define as normality, but aspects of their behavior are likely to be preserved in the genome for posterity, in closely related individuals, and at most mark them as “different.”

Because the frontostriatal system is so closely bound up with fundamental aspects of human behavior, it will be closely involved in a range of directed perceptuomotor processes. We are laterally more or less symmetrical organisms with paired organs that include the hemispheres of the brain. Fundamental motor processes (fine, praxic manipulation of objects, and language and communication), perceptual processes (pattern processing and face recognition), and emotional phenomena (mood and expression) are all lateralized more or less quantitatively and consistently to one or other side of the paired hemispheric structures (Bradshaw, 1989). This is not the place to debate the reasons for this lateralization (economy of processing space? avoidance of interhemispheric competition?) except to note that it is phylogenetically very ancient (Bradshaw & Rogers, 1993). While communicative and praxic processes are left-lateralized in many primate and infraprimate species, even more ancient right-lateralizations of spatial and emotional behaviors are known (Bradshaw & Rogers, 1993); the latter lateralizations may indeed have determined where the former should “go.” It is noteworthy that anomalies of lateralization are consistently evident in the largely *functional* (neurochemical?) neurodevelopmental “disorders,” but are conspicuously absent in the largely neurodegenerative *structural* disorders (PD and HD) of old age. Future research should pay close attention to the presence, and direction, of anomalies of perceptual, attentional, and motor lateralization in people suffering from these disorders. The fact that medication not only controls the clinical manifestations of the disorder, but also often “corrects” the anomalous lateralization suggests that the *expression* of many asymmetries has at least partly a neurochemical basis, which may modulate any underlying

ing *structural* asymmetries, as may be particularly the case with SCZ. It is not clear that altered laterality in these frontostriatal disorders of neurodevelopmental origin often has any adaptive significance *per se*; it may simply be a *marker* for changing regulatory function of the frontostriatal system, changes which in low genetic dosage or penetrance continue to play an adaptive role in clinically unaffected close relatives of probands, but which, in high dosage or penetrance in the probands themselves, may be deleterious in a currently constituted society. Research should also document perceptual, attentional, and motor *superiorities* in relatives of probands of the various disorders as well as in probands themselves. In this way we can determine the nature of the selective pressures operating upon individuals to perform optimally in a range of possible societies or environments. Because evolution is typically a slow process, operating over many generations, and because generation time in humans is at least 20 years, clearly a cross-sectional approach is needed (across individuals, societies, and environments) rather than a longitudinal approach, with as wide a range as possible at all three levels. Only thus can we eventually determine how the bounds of our personalities are molded by structure and function in the frontostriatal system and by the pressures of environment and society of which we are part.

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