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The duplicity of plasticity: A conceptual approach to the study of early lesions and developmental disorders

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Research on impairments of brain development has in the past been characterized by two empirical paradigms that examine developmental plasticity from very different perspectives. The early lesion paradigm, on the one hand, focuses on patients with gross structural brain damage acquired peri- or postnatally and investigates effects on cognitive, sensorimotor, and affective outcome. On the other hand, the study of developmental disorders, such as attention deficit disorder, dyslexia, or autism, proceeds from a diagnostic profile of cognitive-behavioral symptoms to the exploration of underlying neurodevelopmental disturbances. The two approaches shed light on the malleability of the developing brain in opposite, yet complementary ways.

On the one hand, research on the effects of early structural lesions has produced evidence for the brain's astounding capacity to compensate for loss of neural tissue. Extreme examples are studies of patients with resection or disconnection of a complete forebrain hemisphere. While extensive brain damage in *adults* results in severe and persistent region-specific deficits (as evidenced by aphasia following left perisylvian lesion; Kertesz *et al*., 1979; Pedersen *et al*., 1995), left hemispherectomy after early lesion[1] is often associated with good long-term language outcome if the right hemisphere is intact (Basser, 1962; Smith and Sugar, 1975; Ogden, 1988; Vargha-Khadem and Polkey, 1992; Vargha-Khadem *et al*., 1997). Likewise, congenital unilateral brain damage is typically associated with general intellectual outcome in the normal range, regardless of the side of lesion (Bates *et al*., in press; Muter *et al*., 1997; Stiles *et al*., 1997).

On the other hand, in the study of developmental psychopathologies and learning disabilities, cognitive-behavioral disturbances are typically salient, while the underlying neurological impairments remain mostly elusive. Even when neurological abnormalities can be identified, they are typically microscopic, subtle, or variable across individuals. For example, a few postmortem case studies on developmental dyslexia have shown neuronal ectopia and cortical microdysgenesis, especially in left perisylvian regions (Kemper, 1984; Galaburda, 1988; Galaburda *et al*., 1989). Yet it is unclear to what extent neuronal ectopia may occur even in *normal* ontogeny (Kaufmann and Galaburda, 1989). The histological findings in dyslexia may be related to atypical morphological asymmetry in the perisylvian region observed in some studies (for discussion, see below). Yet again, these morphological findings in dyslexia are subtle and sex or overall brain size appear to have a more robust effect on perisylvian morphology than diagnosis of dyslexia (Schultz *et al*., 1994).

Returning to the broader issue of theoretical approaches, the early acquired lesion paradigm predominantly illuminates *compensatory plasticity,* while the study of developmental disorders tends to emphasize the enhanced *vulnerability* associated with neurobiological impairments that occur at critical maturational stages. Accordingly, neuroimaging studies in patients with early acquired lesion will primarily seek to identify enhanced activations in regions outside a structural lesion. Such activations are assumed to reflect functional compensation and recovery. On the other hand, imaging studies in developmental disorders will typically look for an absence or abnormality of activation that is assumed to reflect a particular cognitive or affective impairment. This latter objective is reasonable because, in a prototypical developmental disorder, a discrete initial defect (due to genetic mutation or a neurotoxin, for example) will tend to affect multiple systems, thus reducing the potential for compensatory reorganization across brain regions or neurofunctional circuits.

While the above framework undoubtedly captures a fundamental difference between early structural lesion effects and developmental disorders, it is intellectually unsatisfactory that the two paradigms and the empirical data they produce are often discussed in complete isolation. After all, both empirical paradigms deal with impairments of the developing brain, which suggests that some principles are shared. The comprehensive concept for these shared principles is *plasticity*. Traditionally, this concept has often been related only to those brain adaptations that are beneficial in terms of cognitive-behavioral outcome. For example, in the words of Gregory and Taylor (1987) plasticity refers to an "ordered alteration of organization... that *makes some sort of sense*

[1] *The different meanings and implications of the broad term* early lesion *will be discussed later in this chapter. Roughly, this term will be used in the sense of an acquired structural damage affecting one or several brain regions before these have fully matured.*

biologically or to the investigator" (ibid.: p623 [our italics]). We will argue that this view of plasticity is too narrow and that the concept should be understood as encompassing both beneficial *and detrimental* effects of developmental brain impairments. We will thus attempt to approach early brain-behavioral disturbances from two complementary angles, considering a coexistence and interaction of effects of compensatory reorganization and vulnerability, and examine what these principles may imply for functional neuroimaging. We will begin with evidence indicating vulnerability effects in nonhuman animals and human patients with early structural lesions and will then discuss the interaction of vulnerability and compensatory events in developmental disorders, with exemplary focus on autism, developmental language impairment, and dyslexia. The discussion of early lesion studies will set the stage for another theme of this chapter, which is the distinction between *bottom-up* and *top-down* approaches, i.e. approaches that are predominantly informed by evidence on biological causes versus those informed by cognitive-behavioral outcome. Early lesion studies are characterized by relatively good knowledge of the neuroanatomical causes of outcome deficits. In fact, animal lesion studies by definition include bottom-up information and proceed from a known pathogenic event (for example, a surgical resection) to behavioral outcome. Finally, we will argue that an analogous bottom-up approach is essential for the elucidation of biological mechanisms underlying developmental disorders.

Effects of early structural lesion

Animal studies

A simple statement about maturational plasticity that is often referenced in the literature is the 'Kennard principle', epitomized in the phrase: 'the earlier the lesion, the better the outcome' (all other things being equal; cf. Teuber, 1974; Rudel *et al*., 1974). This principle grossly refers to the work of Margaret Kennard on the effects of age at lesion onset in monkeys (Kennard, 1938; Kennard, 1940; Kennard, 1942) and, in particular, her finding "that cortical lesions made on young animals have less effect on behavior than have similar lesions in adults" (Kennard, 1938: p.490). Many more recent animal studies provide overall support for the Kennard principle. For instance, Kolb and Tomie (1988) found that rats sustaining hemidecortication showed better recovery on visuospatial navigation and motor tasks when surgery was performed at postnatal day 1 compared to day 10. Focal resection of somatosensory cortex in neonatal rats results in reorganization of receptive barrel fields around the lesion, whereas such plasticity is not seen in rats undergoing surgery after postnatal day 10 (Seo and Ito, 1987). Removal of primary visual cortex (areas 17 and 18) in cats leads to enhanced development of intracortical connectivity (MacNeil *et al*., 1996) and of connections with the superior colliculus (Sun *et al*., 1994) at postnatal day 1 (and to a lesser degree at day 28), but not in adulthood. This anatomical plasticity is reflected in better behavioral outcome (in visual depth perception and orienting) following resection in the first days of life as compared to later resection (Shupert *et al*., 1993).

On the other hand, there are drawbacks to maturational plasticity. Reviewing the effects of lesions in the superior colliculus of the neonatal hamster, Schneider (1979) showed that plastic reorganization of retinal afferents results in partial sparing of visually guided behavior, but may also lead to severe deficits (for example, turning the head in the wrong direction in response to a visual stimulus). Schneider concludes that earlier damage is indeed related to greater reorganizational potential, but that "[c]hanges in brain structure occur as a result of the workings of developmental cellular mechanisms, *irrespective of whether the result is functionally adaptive*" (ibid.: p.578).

The animal literature on cortical lesions has also made it clear that the Kennard principle applies only to gross comparisons between damage to the mature and the developing brain, but not when different time windows *within* development are considered. Unfortunately, comparison of data from different species is complicated by the fact that neurodevelopmental stages occur at different conceptual and postnatal ages in different mammalian species (Kolb, 1995; Villablanca *et al*., 1993b). Thus, the rat and hamster brains are more immature at birth than is the cat brain, which is in turn slightly more immature than the brain of a human neonate. In rats, Kolb and colleagues found *less* functional sparing when bilateral frontal or parietal resections were performed at postnatal day 1 compared to day 10 (roughly corresponding to lesions at human gestational month 5 versus postnatal month 6; Kolb and

Tomie, 1988; Kolb and Whishaw, 1989; Kolb, 1990; Kolb *et al*., 1996). Studying cats, Villablanca and colleagues (1993a,b) observed good recovery after left frontal cortical ablation at postnatal days 8-14, but severe sensorimotor impairments after similar ablation during the third gestational trimester. The anatomical correlates of lesion timing effects are generally concordant. Early postnatal focal resection in rats results in cortical thinning throughout the remaining hemisphere (Kolb *et al*., 1989). Prenatal unilateral frontal ablation in cats leads to hypoplasia of the entire lesioned hemisphere and bilateral abnormalities of gyral and sulcal formations (Villablanca *et al*., 1993a).

Kolb and colleagues conclude from a review of studies in rats, cats, and monkeys that there are two periods of optimal compensatory potential, one during neurogenesis and one during maximal synaptogenesis (Fig. 1). On the other hand, they find the cerebrum specifically *vulnerable* to insult during the periods of neuronal migration and differentiation (Kolb, 1995; Kolb *et al*., 1998). In contrast, Villablanca *et al*. (1993b) propose that there is only a single "optimal developmental period" (when brain damage is associated with good recovery) occurring after neurogenesis is mostly achieved and while neuronal differentiation, synaptogenesis, and selective neuronal and synaptic loss are most pronounced. However, some caution is required with regard to Figure 1. It is hard to translate the above scenarios into human developmental time, since species differences conceivably involve more than some unitary index of brain maturity. Instead, there are probably species-specific differences in the precise chronological interaction of regionally differing maturational stages. These complex schedules will determine the nature of anatomical and functional recovery after brain damage at a given point in time. What the Kolb and the Villablanca scenarios have nonetheless in common is the finding that time-plasticity curves are *non*-monotonic and that the Kennard principle requires modification.

Human neuropsychological studies

This general conclusion from animal studies is reflected in human neuropsychological studies of early lesion effects. Again, gross comparison of lesion-onset effects in childhood and in adulthood supports the 'Kennard principle' of greater early plasticity. However, many studies suggest that the long-term outcome of congenital or early postnatal unilateral lesions is characterized both by a potential for compensatory 'restitution' *and* by delayed emergence of latent deficits (cf. Rudel *et al*., 1974). The latter applies above all to damage in brain regions that normally participate in higher cognitive functions. Such lesions may result in deficits only by the time these cognitive functions are normally acquired, as exemplified in social deficits observed many years after early frontal lobe damage (Grattan and Eslinger, 1991; Eslinger *et al*., 1992; for related animal data, see Goldman *et al*., 1970). A cross-sectional study on children and adolescents with congenital hemiplegia by Banich *et al*. (1990) indeed suggested that intellectual deficit *increases* with time since lesion onset, presumably due to slowed cognitive development. However, these findings may have been skewed by an uncontrolled clinical heterogeneity of the sample (especially by the inclusion of seizure patients) and were not replicated in a better-controlled longitudinal study (Muter *et al*., 1997). Nonetheless, several groups have further reported that patients with unilateral lesion occurring before age 1 year showed worse intellectual outcome than patients sustaining lesion after age 1 year (Woods, 1980; Riva and Cazzaniga, 1986; Strauss *et al*., 1992; see also Nass *et al*., 1989). Aram and Eisele (1994), who also found lower verbal IQ (VIQ) and performance IQ (PIQ) in patients with unilateral lesion onset before age 1 year (compared to patients with lesion in childhood and adolescence), relate this finding to a "greater vulnerability of the immature brain" (ibid.: 93). Findings from an extensive sample (N=1,185) of patients with a history of intractable epilepsy presented by Strauss *et al*. (1995) further showed that seizure onset was a major predictor of long-term intellectual outcome. Onset before one year of age tended to be associated with low VIQ and PIQ (regardless of the side of lesion), and there was a positive correlation between age at onset and outcome on IQ measures. This finding was not confounded by seizure duration.[2]

The above findings from human studies on early lesion effects are reminiscent of the chronological schedule proposed by Kolb (1995) that suggests a window of vulnerability in humans around birth and extending

into the first postnatal year (Fig. 1). However, it should be noted that in many of the above earlier human studies, important clinical variables such as lesion site and size, type of lesion, or epilepsy could not be controlled. Some more recent studies with relatively large patient samples tell a slightly different story. Above all, the effects of congenital brain damage (especially when not accompanied by seizure disorder) on verbal and nonverbal intelligence have been reported to be overall relatively mild (Bates *et al*., in press; Isaacs *et al*., 1996). Data on a sample of 161 children and adolescents with unilateral brain damage presented by Vargha-Khadem *et al*. (1999) suggest pronounced compensatory plasticity for language in children with congenital and perinatal lesions, but reduced plasticity and thus less long-term recovery in children with lesion onset between 6 months and 4 years of age (Fig. 1; cf. Bates *et al*., in press). This effect, which was observed only in seizure-free patients, is roughly consistent with the findings from a study on 149 hemiplegic children by Goodman and Yude (1996) that suggests a U-shaped relation between time at lesion onset and IQ outcome. According to the latter study, the period of relative vulnerability applies to lesions occurring between 1 month and 5 years of age.[3]

An additional aspect of maturational vulnerability is reflected in so-called *crowding effects* that may be observed after early left hemispherectomy and extensive left hemisphere lesion (Rudel *et al*., 1974; Strauss *et al*., 1990). Verbal sparing (i.e. higher VIQ than PIQ) in patients with early-onset lesion in either the right *or the left* hemisphere, has been observed in some studies (e.g., Goodman and Yude, 1996; Riva and Cazzaniga, 1986; cf. Nass and Stiles, 1996; Carlsson *et al*., 1994).[4] This phenomenon may be partly (and trivially) explained by a greater sensitivity of PIQ measures to brain damage in general. The theoretically more interesting hypothesis of 'crowding' pertains to a lesion-induced (re)organization of language in the right hemisphere *at the expense* of typical right-hemispheric functions (such as visuospatial processing). Thus, Strauss *et al*. (1995) observed a subtle but significant detrimental effect of atypical language laterality on PIQ in their extensive sample of patients whose hemispheric dominance was determined by means of the intracarotid amobarbital procedure (Wada and Rasmussen, 1960).

In the terms introduced above, crowding effects reflect *compensatory reorganization* for language and concurrent selective *vulnerability* for nonverbal functions. This suggests that differential effects of vulnerability and compensation are domain-specific (cf. Nass and Stiles, 1996). In this context, it is interesting that studies by Stiles and colleagues (Stiles and Nass, 1991; Stiles *et al*., 1997) of children with congenital or perinatal right hemisphere lesion show persistent deficits in the visuospatial domain – an outcome that contrasts with the typically good language development following congenital *left* hemisphere lesion. Judging from neuropsychological studies of children with early lesion, functions that predominantly involve the right-hemisphere (such as visuospatial, prosodic, and affective processes) appear to be organized in similar ways in children and adults (Stiles *et al*., in press; Vicari *et al*., 1998), whereas language organization may undergo fundamental changes in inter- and intrahemispheric organization during the first years of life (Bates *et al*., 1997; Bates *et al*., in press; Thal *et al*., 1991).[5] These changes may be related to an earlier maturation of the right hemisphere (as suggested by blood flow studies, cf. Chiron *et al*., 1997) possibly associated with an earlier establishment of a 'steady-state' functional organization. Domain-specific differences in schedules of postlesional vulnerability and compensation could thus be

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[2] *The possible confounds of seizure type and frequency were not addressed in this study.*

[3] *An early study including 40 patients with unilateral lesion (and diverse etiologies) by McFie (1961) presents compatible data, i.e., lower FSIQ outcome after lesion onset from 1-4 years than after onset from 5-9 years. Potentially consistent findings also come from studies on cranial irradiation effects in children with leukemia that show greater long-term intellectual deficits when treatment occurred before 4 years of age, compared to treatment later in childhood (Cousens* et al., *1988).*

[4] *Verbal sparing was not found in a recent study by Glass* et al. *(1998), who report a double dissociation of language versus visuospatial deficits in children with pre- or perinatal left versus right hemisphere damage, respectively. These findings may be explained by mild lesions in a majority of cases that presumably did not result in interhemispheric language reorganization.*

[5] *For example, Thal* et al. *(1991) found that pre- or early postnatal* right *hemisphere lesion resulted in reduced lexical comprehension in toddlers. Since lexicosemantic processing strongly lateralizes to the left hemisphere in adults (Binder* et al., *1997; Damasio* et al., *1996; Demb* et al., *1995), this would indicate developmental changes in hemispheric organization.*

explained on the basis of the visuospatial domain reaching quasi-adult organization earlier than language (possibly analogous to its earlier emergence in phylogeny; Stiles and Thal, 1993).

All in all, while there are obvious differences between functional domains, the data from human lesion studies and animal models contradict a simple 'Kennard principle' and instead indicate a *non*-monotonic relationship between lesion onset and the potential for compensatory plasticity (Fig. 1). Inconsistencies regarding the precise timing of periods of compensation and vulnerability may be explained in several ways: (a) neurodevelopmental stages can be compared across species only indirectly, (b) some animal studies apply symmetrical bilateral resections that do not correspond to naturally occurring lesions and the effects of which differ considerably from those of unilateral lesions (Kolb *et al*., 1989), (c) resections in animal studies are performed in diverse locations and differ etiologically from lesions in humans, and (d) tasks used to assess behavioral deficits in animal studies are qualitatively different from those used in human studies. With regard to point (d), part of the reason why the plasticity curve for human patients appears to be shifted forward on the temporal axis (in comparison with animal findings) may lie in the fact that human studies assess higher cognitive functions subserved by association cortices that mature later than sensorimotor regions (Huttenlocher and Dabholkar, 1997; Chugani *et al*., 1987).

Neuroimaging studies

The message from animal and human studies on the effects of early structural brain damage is thus more complex than a simple 'Kennard principle', due to an interaction of effects that appear to work in opposite directions with regard to behavioral outcome. This duality of effects is reflected in functional neuroimaging studies in patients recovering from brain damage. At this point, it should be noted that compensatory plasticity is by no means an exclusive prerogative of the maturing brain. In fact, the first neuroimaging studies on functional remapping following brain lesion were performed in adult patients. PET studies using oxygen-15 tracers have demonstrated enhanced right-hemisphere activations during language performance in patients recovering from aphasia following left hemisphere insult (Belin *et al*., 1996; Price *et al*., 1993; Weiller *et al*., 1995). Analogously, reorganization of motor functions into regions that are normally not robustly involved in motor performance (such as the inferior parietal, insular and prefrontal cortices and regions in the hemisphere ipsilateral to the movement) have been documented in adult patients suffering from stroke (Chollet *et al*., 1991; Seitz *et al*., 1998) and tumors (Seitz *et al*., 1995; Sabatini *et al*., 1995).

Neuroimaging studies examining postlesional functional reorganization in children and adolescents with early-onset lesion have been unavailable until recently (see review by Bookheimer and Dapretto, 1997). Using functional magnetic resonance imaging (fMRI), motor and language mapping was reported for a few pediatric cases with neoplasm (Chapman *et al*., 1995) and epilepsy (Benson *et al*., 1996; Hertz-Pannier *et al*., 1997; Zupanc, 1997). None of these patients showed clear evidence of lesion-induced regional or interhemispheric functional reorganization. Stapleton *et al*. (1997) examined the presurgical use of functional MRI in 16 pediatric cases, but did not address the question of postlesional or postsurgical reorganization.

In contrast, results from a series of [^{15}O]-water PET studies including patients with early- and late-onset unilateral lesions have overall supported the concept of greater reorganizational (presumably compensatory) plasticity in the developing as compared to the mature brain. In a study of regional cerebral blood flow (rCBF) changes associated with unilateral finger movement (Müller *et al*., 1997c), enhanced interhemispheric reorganization (i.e. activation in regions ipsilateral to the side of movement) was found in patients with unilateral lesion occurring before age 4 years as compared to patients with onset after age 10 years. These findings were robust for secondary motor cortices (premotor and supplementary motor areas), whereas a similar trend for the rolandic primary motor cortex was not significant (cf. Fig. 2). In other studies (Müller *et al*., 1998b, in press), stronger interhemispheric reorganization following early as compared to late-onset lesion was also found for the language domain, but here major interhemispheric reorganization was seen in the *primary* perisylvian language regions. This seems to indicate differences in interhemispheric reorganizational patterns between domains. While reorganization is predominantly

homotopic in language (i.e. reduced activation in left perisylvian regions is accompanied by a gain in right perisylvian activation), homotopic interhemispheric reorganization for the primary motor cortex appears to be limited (Müller *et al*., 1997a, 1998d,f,g; cf. Caramia *et al*., 1996; Pascual-Leone *et al*., 1992). As known from the study of congenital hemiplegia (or 'cerebral palsy'), pre- or perinatal lesions affecting the motor system are frequently associated with persistent motor impairment (Eicher and Batshaw, 1993; Stanley, 1994; Rudel *et al*., 1974). There is an interesting analogy here to the persistent visuospatial and visuoconstructive deficits following congenital right hemisphere lesion, as reported by (Stiles and Nass, 1991; Stiles *et al*., 1997, in press; Vicari *et al*., 1998). This again underscores domain-specific differences in the effects of lesion onset on compensatory plasticity, which are not expressed in the simplified diagram of Figure 1.

There are additional neuroimaging findings suggesting that developmental schedules of compensatory plasticity are more complex than assumed by the 'Kennard principle'. Regarding language reorganization following early left hemisphere damage, for example, it has become clear that the loss of functional participation in the lesioned hemisphere typically exceeds the complementary gain in the contralesional hemisphere. Thus, language-related activation in patients with early unilateral left hemisphere lesion was severely reduced in left perisylvian regions, whereas the complementary finding of enhanced activation in homotopic right hemisphere regions tended to be less pronounced (Müller *et al*., 1998b,e, in press). Analogous effects of loss in the lesioned hemisphere being greater than gain in the contralesional hemisphere have been observed for motor activations in the primary motor cortex (Müller *et al*., 1997c).[6] Such effects are in part and rather trivially explained by reduced activations in regions of structural brain damage. However, reduced activations were also observed in regions that appeared to be *unaffected* by structural damage. This phenomenon is akin to the classical finding of 'diaschisis', i.e. impaired function in brain regions distal from the site of structural brain damage (von Monakow, 1914; Feeney and Baron, 1986). While diaschisis is typically transient, it may persist. PET studies have demonstrated reduced glucose metabolism and blood flow in regions far removed from the site of structural damage, such as crossed cerebellar diaschisis in patients with cerebral infarct (Baron *et al*., 1980; Metter *et al*., 1987; Pantano *et al*., 1986; cf. Shamoto and Chugani, 1997).

In summary, functional neuroimaging is an important tool for the study of early structural lesion effects in at least two ways: First, it is uniquely suited to the identification of lesion-induced functional reorganization or atypical organization. Functional neuroimaging can thus detect hemodynamic correlates of events assumed to reflect functional compensation. Second, functional neuroimaging also sheds light on diaschisis effects, i.e. dampened function in regions distal from the site of a structural lesion. It therefore also serves as a tool for observing postlesional events that are assumed to be detrimental to cognitive behavioral outcome and that reflect maturational vulnerability.

What determines compensation and vulnerability?

We have thus far argued that the effects of early structural lesions should be understood in terms of both compensatory reorganization *and* maturational vulnerability. Simple affirmation of a duality of effects per se is, of course, not truly enlightening because it leaves open the question of what variables determine the kind of effects at work in a given clinical case with a given type of lesion. Figure 3 is an attempt to sketch some of the most probable causal relationships that determine outcome after prenatal or early postnatal lesions. It acknowledges a considerable potential for functional relocation. Realistically, what appears to be functional relocation will usually be reorganization *within* a

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[6] *The mentioned [^{15}O]-water PET studies on early lesion effects included mostly epileptic patients and general conclusions should therefore be drawn with caution. Long-standing seizures are associated with reduced IQ (Goodman and Yude, 1996; Muter* et al.*, 1997; Vargha-Khadem* et al.*, 1992), even though this effect may be due in part to larger lesions in seizure patients (Levine* et al.*, 1987). In patients with unilateral lesion, epilepsy and anti-epileptic drugs can functionally impair the contralesional hemisphere (Sankar* et al.*, 1995; Jibiki* et al.*, 1993), which could have a dampening effect on interhemispheric reorganization. It is conceivable that vulnerability effects after early structural lesion are less severe in the absence of seizure disorder.*

preexisting network. For example, we have discussed neuroimaging studies showing that the premotor and supplementary motor areas may become more prominently involved in movement when the primary motor cortex is damaged (cf. Fig. 2d&e). Language activations in patients with early lesion (and adult stroke) have been observed in right perisylvian regions that are probably involved in paralinguistic functions in the healthy brain (Ross, 1993) and that have been found to coactivate during language performance (Démonet *et al*., 1994; Herholz *et al*., 1994; Just *et al*., 1996; Mazoyer *et al*., 1993; Price *et al*., 1996; Cabeza and Nyberg, 1997; Lassen *et al*., 1978).

While the precise modes of network reorganization undoubtedly depend on the functional domain, i.e. on the way the particular network was organized premorbidly, such reorganization may reflect a 'reshuffling' of functional responsibilities within a network. However as indicated in Figure 3, the availability of intact *domain-compatible* tissue is a crucial variable that determines the degree to which reorganization is possible. This latter term conceptualizes the distinction between regions that are candidates for functional reallocation and those that are not. For example, there is no indication in the literature that early left perisylvian lesion could be compensated by reorganization of language functions into occipital or superior parietal cortices. These regions thus do not appear to be domain-compatible with language. Primary (and probably secondary) sensorimotor cortices exhibit very limited domain-compatibility across modalities, even though there are exceptions. Cross-modal plasticity is possible when subcortical afferents are experimentally rewired or when tissue is transplanted within protocortex in the immature animal brain (Schlaggar and O'Leary, 1991; Sur *et al*., 1990; O'Leary, 1989; O'Leary *et al*., 1994). In humans, early loss of one sensory modality also permits cross-modal plasticity. The best documented example here is tactile and Braille-reading related processing in occipital cortex in blind subjects, when blindness is congenital or occurs in childhood (Sadato *et al*., 1996; Sadato *et al*., 1998; Uhl *et al*., 1993).

Figure 3 indicates three major paths associated with vulnerability effects following early lesion. First, if little or no intact domain-compatible tissue is available, reorganization will be markedly limited since most postnatal brain tissue cannot regenerate neurons and neuronal loss at the site of a structural lesion can therefore not be fully compensated. An exception is early intrauterine lesion occurring before neuronal mitosis is terminated (cf. Kolb et al., 1998). Second, as seen in human imaging studies and in animal models, structural lesions may be associated with remote functional or structural impairment (diaschisis or remote degeneration). Third, reorganization may lead to (partial) recovery in one functional domain, but may be detrimental to another due to crowding. If domain-compatibility existed only within discrete or 'modular' functional networks that did not share neuronal resources, crowding would not be possible. However, there is little doubt that neuronal resources are shared among functional networks, especially in multimodal association cortex (Cabeza and Nyberg, 1997; Mesulam, 1990; Mesulam, 1998). For example, reorganization within the language network can lead to enhanced language involvement of parts of this network that are normally shared with some visuospatial functions, resulting in visuospatial impairment through crowding.

Neuroimaging and the study of developmental disorders

Turning to developmental disorders, we will now make a complementary argument. Our aim is to present developmental disorders both in terms of the obvious effects of maturational vulnerability *and* in terms of the typically more elusive effects of compensatory reorganization. The discussion will focus on autism and, to a lesser extent, on developmental disorders of language.

Autism and Asperger's syndrome

Until the mid 1990s, functional neuroimaging studies of autism have been generally limited to single conditions. In many studies, subjects were scanned at rest, sometimes with eyes closed (Rumsey *et al*., 1985; Horwitz *et al*., 1988), sometimes with eyes open (Sherman *et al*., 1984; George *et al*., 1992; Schifter *et al*., 1994; McKelvey *et al*., 1995; Mountz *et al*., 1995), or during sedation (De Volder *et al*., 1987; Chiron *et al*., 1995). Other investigators have attempted to control mental states by continuous performance (Heh *et al*., 1989; Buchsbaum *et al*., 1992;

Siegel *et al*., 1992) or verbal learning tasks (Haznedar *et al*., 1997). The diversity of experimental conditions may be one reason for the lack of overall consistency of findings across these studies (for detailed discussion, see chapter by D. Chugani in this book, and Rumsey, 1996b).

More recently, a few neuroimaging studies have attempted to map task-related activations in patients with pervasive developmental disorders. The techniques of [^{15}O]-water PET or fMRI systematically relate regional hemodynamic changes to differences in multiple task and control conditions by comparing scans for different conditions. These techniques make it possible to directly investigate the functional organization of cognitive or sensorimotor domains assumed to be impaired in a given disorder. The design of task paradigms is thus crucial for such studies.

In one approach, which we will call 'top-down', tasks are designed in accordance with a fully-fledged neuropsychiatric or cognitive model. Examples are the studies by Baron-Cohen *et al*. (1994), Fletcher *et al*. (1995), and Happé *et al*. (1996) applying 'theory of mind' tasks. The 'theory of mind' model is based on the hypothesis that autism involves a selective deficit in "the ability to impute mental states to oneself and to others" (Baron-Cohen *et al*., 1985: p. 39). This deficit is not attributed to *general* mental retardation, but rather to the impairment of a neurocognitive 'module' (Baron-Cohen *et al*., 1985; Baron-Cohen, 1991; Leslie and Thaiss, 1992), i.e. a genetically specified and functionally autonomous cognitive subsystem (Fodor, 1983; Shallice, 1988).

A single photon emission tomography (SPECT) study by Baron-Cohen *et al*. (1994) and a PET study by Fletcher *et al*. (1995) showed activation during performance on a 'theory of mind' task in prefrontal cortex (Brodmann areas [BAs] 10 and 8, respectively) in healthy adults. In the study by Happé and colleagues (1996), regional brain activations were additionally studied in a group of 5 adult men with a diagnosis of Asperger's syndrome, a pervasive developmental disorder similar to high-functioning autism, but without major delay in language acquisition (American Psychiatric Association, 1994; Ramberg *et al*., 1996; Szatmari *et al*., 1995; Volkmar *et al*., 1996). The task condition – comprehension of a 'theory of mind' story, which involved understanding of the mental states of characters – was compared to comprehension of a story that solely involved 'physical events'. The strongest activation peak for the patient group was in a more inferior location (BA 9) than for a normal control group (BA 8). However, it is unclear whether the differences in stereotactic peak localization (20mm on the superior-to-inferior z-axis; much less on the x- and y-axes) are meaningful in view of the limited spatial resolution of the [^{15}O]-water PET technique. An obvious hypothesis for this study would have been *reduction or absence* of activation in the putative neurocognitive 'theory of mind module' (presumed to be localized in prefrontal cortex; Fletcher *et al*., 1995) in subjects with Asperger's syndrome. Instead, the findings suggest *normal* magnitude of activation with differences in peak localizations that may well result from spatial normalization (see below), especially when performed in a small patient sample with potential neuroanatomic abnormalities (Minshew, 1994; Volkmar *et al*., 1996).[7]

Another [^{15}O]-water PET study of high-functioning autistic adults (Müller *et al*., 1998a) explored possible hemodynamic reflections of abnormalities previously proposed in autism research: atypical functional asymmetries (e.g., Chiron *et al*., 1995; Dawson *et al*., 1989), disturbances of auditory perception, and cerebellar impairment (see below). Despite the equally small patient sample (N=5), some of the expected differences between autistic and age- and gender-matched control subjects

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[7] *According to the atlas by Talairach and Tournoux (1988), the peak activation in BA 8 reported by Fletcher* et al. *(1995) for* normal *adults is not cortical, but located in white matter in the depth of the frontal lobe. This illustrates the potentially problematic effects of spatial normalization. RCBF changes identified by [^{15}O]-water PET are predominantly associated with synaptic function (Fox and Raichle, 1986; Jueptner and Weiller, 1995) and therefore occur almost exclusively in gray matter. Area 8 also incorporates the 'frontal eye field' (e.g. Nieuwenhuys* et al., *1988: p.373) and the activation focus reported by Fletcher* et al. *(1995) is located in the vicinity of the supplementary eye field (Goldberg* et al., *1991). Neither Fletcher* et al. *(1995) nor Happé* et al. *(1996) report recording of eye movements during task performance. Abnormalities of saccadic eye movements in autism have been reported (e.g., Kemner* et al., *1998). While abnormalities of eye movements and gaze in autism (Baron-Cohen* et al., *1997) are certainly of interest, it remains unclear whether the findings of the study by Happé and colleagues truly relate to 'theory of mind' processing rather than to oculomotor phenomena.*

(N=5) could be identified. For example, the leftward asymmetry of activations during verbal auditory stimulation (listening to sentences compared to rest) found in normal adults (Müller *et al*., 1997b) was significantly reduced or reversed in autistic adults. In the four male patients, activation in a left frontal region (BA 46) and in the left thalamus was significantly reduced (Müller *et al*., 1998c) for this condition. Cerebellar activations were also overall reduced in autistic subjects, especially during tonal stimulation. In addition, activation of the right-hemispheric deep cerebellar nuclei during verbal stimulation was also found to be significantly reduced in autistic as compared to normal men (N=5; Müller *et al*., 1998c). These results tentatively support the hypotheses of atypical functional asymmetry for language-related processing and of reduced cerebellar function in autism.

The studies by Happé *et al*. (1996) and Müller *et al*. (1998a) are exploratory and do not warrant any definitive conclusions. Their limitations highlight several general issues in the design of functional mapping in developmental disorders:

- Sample size: While it is difficult to collect functional imaging data from large samples of subjects with developmental disorders, in particular those typically associated with limited intelligence, hyperactivity, or hypersensitivity, a certain minimum size is required (probably on the order of N=8 per group) for the detection of subtle group differences in regional activations (Kapur *et al*., 1995). On the other hand, the potentially conflicting need for homogeneity of clinical samples suggests different solutions for PET and fMRI because the latter technique allows more extensive data acquisition in fewer subjects (for example, single-trial designs; Dale and Buckner, 1997) or multiple runs comparing task and control conditions in each subject).

- Undirected hypothesizing: Even when significance thresholds are corrected for multiple comparisons, the risk of false positive findings remains considerable in studies comparing patient and control groups with the 'blind' hypothesis that *some* brain regional measure will show *some* kind of group difference. Psychiatric patients are likely to respond differently to given stimuli or tasks, and atypical patterns of hemodynamic response may simply reflect differences in cognitive strategies or in affective and physiological states such as fear or arousal, rather than true neurofunctional abnormalities. Preferable are hypothesis-driven designs that specify a limited number of brain regions of interest on an a priori basis (see below). This can be complemented by an additional exploratory and undirected analysis of hemodynamic changes in the entire brain (or the entire image volume acquired), which may in turn generate specific hypotheses for future studies.

- Studying outcome rather than pathogenesis: In principle, developmental disorders should be preferentially studied *during development*. Studies of younger patient groups and age-matched controls pose ethical problems when ionizing radiation is involved (as in PET or SPECT), even though there is little evidence for health hazards in studies limited to low-dose radiation (Ernst *et al*., 1998a). Functional mapping studies are, however, also feasible using functional MRI. Even though tasks compliance and head motion artifacts are problematic in young subjects, children under the age of 10 years (Casey *et al*., 1997; Kuppusami *et al*., 1997) and even as young as 4 years of age (Stapleton *et al*., 1997) have been successfully studied with functional MRI. However, since crucial pathogenic events will occur even much earlier in most developmental disorders, functional mapping studies remain inherently limited to the observation of outcome.

- Spatial normalization: Functional imaging data are most conveniently analyzed by first 'warping' image volumes for each individual subject to a standard space, typically Talairach space (Talairach and Tournoux, 1988), and then performing group statistical analyses. In view of normal individual anatomical variability, this approach is problematic in healthy adults (Steinmetz and Seitz, 1991; Rajkowska and Goldman-Rakic, 1995) and this is true a fortiori in *clinical* patients who may show anatomical abnormalities (and possibly *systematic* divergence from the model brain of a 60 year-old Caucasian female selected by Talairach and Tournoux). Analyzing spatially normalized image volumes in combination with undirected hypotheses is especially precarious, since subtle differences in activation

magnitude or peak stereotactic coordinates may be entirely due to group differences in the effects of spatial normalization. An alternative is the identification of regions or volumes of interest (ROIs or VOIs), based on specific hypotheses of regional brain abnormalities in a given clinical population. VOIs can be identified on coregistered high-resolution MRI in each individual subject and the mean signal change or the number of activated voxels within a VOI can be computed for statistical group comparisons.

Top-down and bottom-up approaches

As mentioned earlier, *top-down* approaches are defined as proceeding from a fully elaborated theoretical model of cognitive-behavioral outcome to the investigation of possible biological causes. 'Top-down' functional neuroimaging designs, as in the study on Asperger's syndrome by Happé *et al*. (1996), are thus critically dependent on the biological validity of the chosen theoretical model. While study designs will always be informed by preconceived theoretical ideas and empirical data will therefore always be theory-laden to some extent (Kuhn, 1962; Lakatos, 1970; Gregory, 1981; Sternberg, 1990), it is critically important whether a set of hypotheses remains falsifiable by empirical data produced within the given theoretical paradigm (Popper, 1965). Of course, top-down approaches may incorporate biological data or hypotheses about pathogenesis. The crucial characteristic of top-down approaches is, however, the attempt to *explain* available data in terms of a cognitive behavioral *outcome*. On the other hand, while bottom-up approaches ideally incorporate a maximum of behavioral outcome data, their objective will be to explain the latter in terms of biological *pathogenesis*.

With regard to the 'theory of mind' model, it is not established that the prefrontal activations observed by Baron-Cohen *et al*. (1994) and Fletcher *et al*. (1995) truly reflect the function of a 'theory of mind' module. The finding of a slightly atypical activation focus in patients with Asperger's syndrome by Happé *et al*. (1996) is therefore difficult to interpret. We believe that a 'theory of mind' model captures, at best, typical *indirect outcomes* of neurodevelopmental disturbances in autism as opposed to elementary cognitive-behavioral impairments that may reflect pathogenesis. From a biological point of view, it is highly unlikely that a 'theory of mind module' could be discretely 'programmed' in the human genome and 'hard-wired' into the brain during development (as seems to be suggested by Baron-Cohen, 1992). Most likely, the theoretical concept of 'theory of mind' relates to a set of higher cognitive processes involving complex and *non-localizing* neural networks that gradually emerge during brain maturation as a result of learning in many different cognitive and perceptuomotor domains (cf. Mesulam, 1990).

The issue of a 'theory of mind' module shows certain interesting parallels with the debate about the modularity of linguistic knowledge and the hypothesis of a genetically prespecified 'universal grammar' (Fodor, 1983; Chomsky, 1988; Pinker, 1995; Stromswold, 1995), which will be discussed later in this chapter. Baron-Cohen (1992) asserts that 'theory of mind' meets all the criteria of a Fodorian module.[8] However, this appears to be based on a misconception of Fodor's proposal. Even Fodor, who is perhaps the most outspoken proponent of the modularity concept in the cognitive sciences,[9] limits his strong hypotheses to *perceptual* 'input systems'. More complex cognitive processing, in his view, is carried out by *holistic* (and thus non-modular) 'central systems'. On a more general note, it is unfortunate that Fodor's treatise on the "modularity of mind", which incorporates neurobiological evidence only in a highly selective fashion and which Fodor himself (1985: p.33) later called a "potboiler", should be chosen as a theoretical reference point for a neuropsychiatric model (cf. Karmiloff-Smith, 1994; Müller, 1992). From an evolutionary, behavior genetic, and neurobiological perspective, complex multimodal cognitive domains (such as language or 'theory of mind') can only be understood as products of

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[8] *Modules are defined by Fodor (1983: p.37&47ff.) as: domain-specific (i.e. they do not cross stimulus or content domains), innate (i.e. genetically programmed), computationally specific (i.e. they do not rely on general elementary subprocesses), possessing hardwired (i.e. non-equipotential) neural mechanisms, computationally autonomous (i.e. they do not share resources, such as attention or memory, with other cognitive systems).*

[9] *For other modular models of neurofunctional organization, see for example Marr (1982), Gardner (1983), Gazzaniga (1985), and Minsky (1986).*

prolonged epigenesis and are thus unlikely to be neurally represented in terms of genetically prespecified 'modules' (cf. Gottlieb, 1995; O'Leary *et al*., 1994; Müller, 1996; Quartz and Sejnowski, 1997; Plomin *et al*., 1994). It appears therefore more commendable – given our as yet limited knowledge of neurofunctional abnormalities in autism – to first address more elementary cognitive deficits in a *bottom-up* approach.

One example of such an approach concerns auditory processing. In a single-case postmortem study of an autistic woman, Rodier *et al*. (1996) found severe neuronal dysgenesis in two brainstem structures, the facial nucleus and the superior olive. Since the superior olive is involved in sound localization (van Adel and Kelly, 1998; Kelly, 1991), dysgenesis of this structure would be expected to affect auditory function. There is indeed some evidence for auditory disturbances in autism, such as findings on abnormal listening preferences. For example, Klin (1991, 1992) found that a preference for maternal speech over multiple superimposed voices of strangers, as found in normal and non-autistic mentally retarded children, was absent in autistic children.[10] While there appears to be some confound with peripheral hearing loss (Klin, 1993; Gordon, 1993), electrophysiological studies also indicate auditory processing abnormalities of the central nervous system in some patients with autism. Abnormal auditory event-related potentials (ERPs) have been related to generators in the brainstem (Tanguay *et al*., 1982; Thivierge *et al*., 1990; Wong and Wong, 1991; but cf. Courchesne *et al*., 1985) and in cerebral cortex (Lincoln *et al*., 1995). Electrophysiological indications of auditory abnormalities in autism may be related to findings of a recent PET study reporting bilateral hypoperfusion in auditory cortex in autistic children under sedation (Zilbovicius *et al*., 1998; cf. also Bruneau *et al*., 1992). As mentioned above, Müller *et al*. (1998a) found significantly reduced activations in the bilateral cerebellum and the vermis during nonverbal auditory stimulation in a small sample of autistic adults. Reduced blood flow for this condition was also observed in lateral temporal cortex, including primary auditory cortex.

Our discussion is not meant to imply that the findings on auditory potentials in brainstem and cortex are specific to autism or apply to all variants of autism (Dunn, 1994; Grillon *et al*., 1989), nor do we wish to claim that there is any established etiologic link between auditory deficits and the multiple clinical symptoms in autism (cf. Gordon, 1993 vs. Gillberg and Steffenburg, 1993). What is of interest here are the conceptual merits of a bottom-up approach, i.e. the attempt to explain multiple neurofunctionally distributed deficits in the adult autistic brain in terms of discrete critical maturational events and identified neuropathological substrates. While the empirical validity of auditory abnormalities in autism is not fully established, this line of research has a bottom-up character in two ways: First, by considering the possibility of primary impairments in brainstem that may lead to secondary misdifferentiation in forebrain; second, by examining the role of elementary sensory processes in the development of socio-communicative impairment (Rodier *et al*., 1996; Tanguay and Edwards, 1982; Wong and Wong, 1991).

Another, in our view empirically more consistent, example of a bottom-up approach to autism relates to attentional functions. ERP studies showing reduced amplitude of endogenous potentials (N_c and auditory P3b) suggest attentional impairment in autism (Courchesne, 1987; Courchesne *et al*., 1989). Several convergent lines of evidence indicate that certain attentional deficits are linked to anatomical findings in the cerebellum and the parietal lobes. The cerebellum (especially neocerebellar regions of the hemispheres and the vermis) is a rather consistent locus of structural involvement in autism, both in terms of Purkinje cell loss as documented in postmortem studies (Bauman and Kemper, 1985; Bauman and Kemper, 1986; Arin *et al*., 1991; Bauman and Kemper, 1994; Ritvo *et al*., 1986; Williams *et al*., 1980; Bailey *et al*., 1998), and in terms of typical macroscopic hypoplasia (Hashimoto *et al*., 1995; Courchesne *et al*., 1988; Courchesne *et al*., 1994b; Murakami *et al*., 1989; Saitoh *et al*., 1995; Ciesielski *et al*., 1997). These structural findings have more recently been linked to behavioral data indicating selective deficits in the ability to shift attention in autism. For example, autistic patients showed deficits when required to quickly shift attention from the visual to the auditory domain and vice versa, whereas they performed normally when required to focus

[10] Another type of hearing abnormality in autism proposed by Rimland and Edelson (1995) is auditory hypersensitivity, which is less likely to be directly related to Rodier's finding in the superior olive.

attention within the auditory or visual domain, or when given more time (>2.5 seconds) for attention shifts between sensory modalities (Courchesne *et al*., 1994c). The rationale for relating these deficits to cerebellar impairments is twofold: First, patients with acquired cerebellar lesions show attentional deficits similar to those found in autistic subjects (Akshoomoff and Courchesne, 1992; Courchesne *et al*., 1994c). Second, functional MRI studies in healthy adults have demonstrated cerebellar involvement in nonmotor attentional processes (Allen *et al*., 1997), and specifically in shifts of attention within the visual domain (for example, between color and shape; Le *et al*., 1998). It appears that in autism reduced numbers of Purkinje cells are due to early disturbances in prenatal development (Courchesne, 1997). Attentional deficits could thus play a role in autistic ontogeny from very early on and contribute to an impairment of joint attention that interferes with normal mother-infant interaction (Courchesne *et al*., 1994c; Baron-Cohen *et al*., 1997; Voeller, 1996).

In addition to cerebellar anatomical and functional defects in autism, abnormalities in other brain systems are likely. However, as evidenced by the diversity of findings from structural imaging studies (for reviews, see Minshew, 1994; Rumsey, 1996b; Courchesne, 1997), involvement of non-cerebellar structures is probably more variable within the autistic spectrum. Volume loss in the parietal lobes has been found in a sizable subset of autistic subjects (Courchesne *et al*., 1993). Similar to patients with acquired parietal lesions (Posner *et al*., 1984), autistic subjects with parietal volume loss (but not those without) show deficits in redirecting attention in visual space, manifesting an abnormally narrow 'spotlight' of attention (Townsend and Courchesne, 1994; Townsend *et al*., 1996). This suggests that attentional deficits are not exclusively due to cerebellar malfunction, but rather to disturbances in cerebro-cerebellar networks (cf. Schmahmann, 1996; Akshoomoff *et al*., 1997).

A final example of a bottom-up approach in autism research concerns the motor domain. In view of the evidence of structural and functional impairment of the cerebellum in autism, it is interesting to note that some motor functions activate the autistic cerebellum in seemingly normal ways. In the [^{15}O]-water PET studies mentioned earlier, cerebellar activations were reduced for all nonverbal and verbal auditory and expressive language conditions, but *not* for motor speech functions (i.e., repeating sentences compared to listening; Müller *et al*., 1998a,c). According to a series of PET studies in normal adults by Jueptner and Weiller (1998), cerebellar activity – apart from its known role in motor learning (Jenkins *et al*., 1994; Seitz *et al*., 1994) – reflects the processing of proprioceptive feedback during movement (rather than motor execution per se). In a recent functional MRI study, robust activation for finger movement was found in the anterior cerebellum of male autistic subjects (Allen *et al*., 1998, submitted). In fact, anterior cerebellar activation was more pronounced and bilateral in autistic compared to normal subjects. This finding is intriguing in view of motor coordination impairments (such as clumsiness and abnormalities of gait) that are often observed in autism and that resemble impairments observed in some patients with cerebellar lesion (Haas *et al*., 1996; Hallett *et al*., 1993).

An example of cerebellar activations for finger movement in an autistic subject with such motor deficits is shown in Figure 4. While cerebellar activation during movement is normally restricted to the ipsilateral anterior cerebellum and vermis (Desmond *et al*., 1997; Stephan *et al*., 1995), in this autistic subject activations are widespread throughout the bilateral cerebellum. Purkinje cell loss, as observed in postmortem studies (Bailey *et al*., 1998; Bauman and Kemper, 1985; Ritvo *et al*., 1986; Williams *et al*., 1980), could account for these findings in the sense that a partial loss of processing units in the ipsilateral anterior cerebellum could result in atypical spreading and fractionation of activations throughout the autistic cerebellum. This spreading would reflect a compensatory reorganization not unlike the functional reallocations within the forebrain observed in patients with early lesions. However, cerebellar reorganization (or atypical organization) appears to be more microscopic, affecting multiple cerebellar foci recruited for motor function from regions normally involved in higher cognitive processes (Schmahmann, 1996; Leiner *et al*., 1995; Courchesne and Allen, 1997). This reorganization may therefore be analogous to the 'crowding effects' discussed above in the context of early lesion studies (section 2.1). Though speculative, it could be hypothesized that an unusually wide distribution of motor processing throughout the cerebellum would render

neocerebellar regions less available for cognitive processing and thus contribute to reduced intelligence in autism.

This hypothetical scenario implies that autistic pathogenesis is not exclusively characterized by vulnerability effects, but also by compensatory plasticity. Differences in compensatory reorganization could explain some of the surprising variability in cognitive and neuroanatomic measures observed in autism studies on monozygotic twins, who are in fact sometimes discordant for autism (Le Couteur *et al*., 1996; Kates *et al*., 1998). Minor genetically or epigenetically based neurodevelopmental differences may lead to different reorganizational paths and different cognitive-affective profiles within a given developmental disorder. These issues will be discussed in detail in the final sections of this chapter.

The causal links established between the findings of auditory, attentional, or motor abnormalities and characteristic social, language, cognitive, and behavioral impairments in autism remain speculative. At early stages of research, bottom-up approaches may be insufficient to fully bridge the gap between biological and cognitive-behavioral findings. Nonetheless, bottom-up approaches provide a biologically solid platform for experimental design in the study of developmental disorders, in particular in neuroimaging studies. This contrasts with top-down approaches, which present with a complementary weakness (unestablished links between well-described phenotypic profiles and biological parameters) with fewer complementary strengths (cf. Rodier *et al*., 1997). In spite of this, top-down approaches can be appealing because they appear 'elegant', i.e. they seem to 'explain' a multitude of phenomena within a well-delineated and coherent theoretical framework. For example, a maximally 'elegant' version of the 'theory of mind' approach 'explains' autism by reference to a selective impairment of a 'theory of mind module' due to a defect in genes that normally encode for this module.

In the cognitive sciences, top-down approaches are often motivated by an 'engineering' logic, according to which a biological system can be 'explained' in terms of how one could best *construct a machine* that simulates relevant behavioral or output properties of the system (cf. Gardner, 1987; Jacob, 1977; Müller, 1992). Translated into the problem space of developmental neuropsychiatry, this engineering logic implies that an optimal *description* of outcome behavior (or impairment) is construed as an optimal *explanatory* model. Biological mechanisms are therefore investigated only *after* the outcome model has been fully designed and are understood as mere 'implementations' or 'substrates' of conceptual elements of the cognitive outcome model (cf. e.g., Fodor and Pylyshyn, 1988).

Bottom-up approaches, on the other hand, are more directly informed by biological and cognitive-behavioral data, even if these appear inconsistent, and can thus ultimately provide more powerful etiological explanations. The animal literature on early lesion effects shows that even when critical variables are experimentally controlled (which is much less possible in human studies), conclusions are hard to draw, most likely because additional neuromaturational and other unrecognized variables influence outcome through epigenetic mechanisms. These considerations apply even more to developmental disorders that cannot usually be defined in terms of a circumscribed anatomical lesion (for further discussion, see Courchesne *et al*., in press).

Developmental disorders of language

Even though our discussion focuses on pervasive developmental disorders, the conceptual and empirical divergence between bottom-up and top-down approaches can also be observed in the study of other developmental disorders. In this section, we will discuss some aspects of the debate about developmental disorders of spoken language and those of written language, which we will refer to as developmental language impairment (DLI)[11] and (developmental) dyslexia, respectively. There are fundamental differences between these disorders. DLI affects receptive and expressive language functions that develop much earlier than written language. The degree of continuity between dysphasia and dyslexia is not fully established (Catts, 1993; Wilson, 1996; Aram, 1993). Nonetheless, in the context of our present conceptual discussion of bottom-up and top-down approaches, there

[11] *We prefer this term to the more commonly used term* specific *language* impairment, *because the latter implies theoretical assumptions of linguistic specificity of the disorder that may be unjustified (for discussion, see below).*

are interesting parallels in the debates about developmental disorders of spoken and of written language.

The spectrum of neuroanatomical hypotheses regarding these disorders appears to be more restricted than is the case for autism (see reviews on DLI in Rapin and Allen, 1988, and on dyslexia in Rumsey, 1996a). This is in part due to the fact that developmental disorders of language predominantly affect a single cognitive domain ('language') for which adult brain regional specializations have been grossly established in the clinical and neuroimaging literature (e.g., Benson and Ardila, 1996; Cabeza and Nyberg, 1997). It is therefore not surprising that in spite of a considerable diversity of findings, there is some degree of convergence in the neuroimaging literature. Postmortem and MRI studies of normal adults have shown associations between asymmetries in posterior (Foundas *et al*., 1994; Witelson and Kigar, 1992) and anterior (Foundas *et al*., 1996) perisylvian anatomy and language dominance. Many studies on DLI (Clark and Plante, 1998; Gauger *et al*., 1997; Jackson and Plante, 1996; Plante *et al*., 1991) and dyslexia (Kushch *et al*., 1993; Leonard *et al*., 1993) have identified some pattern of atypical morphology or asymmetry in (the vicinity of) perisylvian regions, even though some dyslexia studies are non-confirmatory (Rumsey *et al*., 1997a) and suggest that age and sex may be major confounds (Schultz *et al*., 1994). Rare functional neuroimaging studies in children with DLI tentatively suggest perisylvian abnormalities (Lou *et al*., 1990; Tzourio *et al*., 1994). The more numerous studies in adults with a history of dyslexia have also mostly detected abnormalities in perisylvian regions (Flowers *et al*., 1991; Paulesu *et al*., 1996; Rumsey *et al*., 1992; Rumsey *et al*., 1997b; Shaywitz *et al*., 1998; Salmelin *et al*., 1996). While functional impairment of posterior perisylvian cortex in phonological and orthographic tasks appears to be a rather consistent finding, inferior frontal blood flow changes were normal (Rumsey *et al*., 1994b; Rumsey *et al*., 1997b) or even greater than normal (Shaywitz *et al*., 1998) in some dyslexia studies. However, Horwitz *et al*. (1998) recently reported reduced correlations of activation in the left angular gyrus with activations in frontotemporal language areas (including inferior frontal cortex) and in visual association cortex, suggesting functional disconnection within a reading network in dyslexia. Detailed critical review of the imaging findings on dyslexia is beyond the scope of this chapter (see chapter by F. Wood). Instead, we will focus on certain conceptual characteristics of the research on developmental disorders of language that spans an interesting spectrum of approaches primarily informed by linguistic theory, on the one hand, and by neurobiological evidence, on the other.

When 'specific language impairment' is approached from a theoretical linguistic perspective that assumes the genetically specified modularity of language knowledge (Chomsky, 1988; Pinker, 1995; Stromswold, 1995), the obvious question of a discrete deficit affecting only one or a limited number of linguistic 'modules' arises (for relevant discussions, see Clahsen, 1989; Rice, 1994; Curtiss and Tallal, 1991; Curtiss *et al*., 1992). An analogous debate in the research on developmental dyslexia concerns the question of an underlying *specifically linguistic* deficit (such as impaired phonological awareness; Shankweiler *et al*., 1995; Lyon and Chhabra, 1996; Vellutino, 1987) versus an underlying *nonlinguistic* sensory or perceptual impairment (Tallal *et al*., 1993). In the context of evidence for familial aggregation of 'specific language impairment', Gopnik and colleagues suggested a highly specific and modular deficit of certain syntactic and semantic features (such as tense or number; Gopnik, 1990) possibly caused by a single gene defect (Gopnik and Crago, 1991). At first glance, the attempt to relate DLI to gene defects may appear as a prime example of bottom-up theorizing. There is indeed irrefutable evidence from several research groups for the importance of genetic factors in DLI (Bishop *et al*., 1995; Tallal *et al*., 1989; Tallal *et al*., 1991; Tomblin, 1989; Tomblin and Buckwalter, 1994) and dyslexia (DeFries and Alarcón, 1996; Pennington *et al*., 1991; Pennington, 1995). However, the readiness to link an apparently 'modular' language deficit to gene defects is motivated by a theoretical approach to the cognitive organization of language (Chomsky, 1981; Fodor, 1983), which is itself little concerned with the empirical evidence on the linkage between genes and cognitive-behavioral variables (for discussion, see Bates, 1994; Müller, 1992; Müller, 1996).

Leaving aside programmatic statements from linguists regarding the genetic prespecification of 'universal grammar', it is unlikely that a complex and

phylogenetically recent cognitive domain such as language could be 'hard-wired' into the brain on the basis of a small and discrete set of genes. Instead, the typical scenario linking genome and higher cognitive function is *polygenic* and *pleiotropic*, which means that numerous genes, each influencing many phenotypic outcomes (pleiotropy), interact in the epigenesis of a cognitive domain (Pennington and Smith, 1983; Plomin *et al*., 1994; Gottlieb, 1995; Hay, 1985). Polygenic inheritance is by no means contradicted by the fact that in some instances single gene defects can lead to gross and specific abnormalities of phenotype. For instance, phenylketonuria (PKU), a single gene defect associated with a severe disorder of amino acid metabolism and toxic accumulation of phenylalanine, is phenotypically characterized, not only by mental retardation, but also by social behavioral deficits, seizures, stunted bodily growth and microcephaly, as well as dermatological symptoms (Blau, 1979; Allen *et al*., 1994; Hay, 1985; Spreen *et al*., 1995). Likewise, mutations of the L1 cell adhesion molecule (CAM) gene, which is involved in neuronal migration as well as axonal growth and myelination, are associated with a wide range of deficits (mental retardation, aphasia, gait abnormalities, spasticity) and neuroanatomical defects (callosal hypoplasia, hydrocephalus; Fransen *et al*., 1995) in humans. Pleiotropic effects of L1CAM gene mutation or knock out have been confirmed in animal models (Fransen *et al*., 1998). Note that even though these mutations affect only a single gene, phenotypic manifestations are not focal, but rather affect multiple, seemingly unrelated biological systems. Even these examples of well-established linkages between genetic and phenotypic defects therefore suggest that genetic influences are shared between neurocognitive and nonneural systems (Courchesne *et al*., in press). Interestingly, with respect to the findings of familial aggregation of DLI mentioned above, (Gopnik *et al*., 1996; Gopnik, 1996) has recently acknowledged that these do not imply the discovery of a 'gene for grammar'.

The studies on syntactic-semantic "feature blindness" by Gopnik and colleagues (Gopnik, 1990; Gopnik *et al*., 1996; Crago and Gopnik, 1994), which were described above, highlight a further characteristic of the top-down approach: empirical selectivity. Simply speaking, the chances of identifying a 'modular' deficit in a patient are inversely related to the breadth of neuropsychological and neurological examinations. The presentation of DLI-affected members of the family studied by Gopnik and colleagues suggested a highly selective linguistic deficit restricted to certain aspects of grammar, compatible with the notion of an autonomous neurofunctional organization of language vis-à-vis other cognitive domains (Fodor, 1983) and a modular organization of linguistic subsystems (Chomsky, 1981; Pinker, 1991). Yet broader testing of the same family members by a different group (Fletcher *et al*., 1990; Vargha-Khadem *et al*., 1995) subsequently showed that the deficits were by no means selective and discrete. Not only did affected family members have significantly lower *performance* IQ scores than unaffected members, but Vargha-Khadem *et al*. (1995) also found evidence of orofacial apraxia, further significantly distinguishing affected from unaffected members. Studying a different sample, Hill (1998) recently reported that children with specific language impairment had deficits in the production and imitation of meaningful gestures, similar to children with developmental dyspraxia (or 'developmental coordination disorder'; American Psychiatric Association, 1994). These findings suggest that linguistic deficits in some variants of DLI may be linked to underlying motor or praxic impairment (for related data on acquired aphasia, see Kimura and Watson, 1989). However, the notion that perceptuomotor functions could be instrumental in the ontogenesis of grammatical capacities is anathema to the linguistic theorizing of the Chomskian school (Chomsky, 1965; Newmeyer, 1986; cf. Piattelli-Palmarini, 1980), which may explain why impairments in these domains were neglected in reports by Gopnik and coworkers and, more generally, why studies of specific language impairment often fail to include measures of extralinguistic function (for discussion, see Johnston, 1994).

The innatist and modularist approach to DLI (or "intelligence without language", as it is labeled by Pinker, 1995: p.273) appears to be an extreme example of theory-driven top-down modeling and does not occupy a majority position in research of developmental disorders of language. At the other end of the spectrum of theoretical approaches, these disorders have been related to basic (i.e. non language-specific) perceptuomotor deficits. In a study of 15 dyslexic men, Rumsey *et al*. (1994a) found impaired performance on a nonverbal tone

discrimination and short-term memory task, which was associated with reduced right superior temporal and inferior frontal activations. Eden *et al*. (1996) studied 6 dyslexic men who showed normal activations in response to a stationary high-contrast visual pattern, but impaired stimulus *velocity* judgments and a failure to activate area V5/MT in bilateral occipito-temporal extrastriate cortex in response to a low-contrast, moving stimulus. Correlational PET activation analyses (Horwitz *et al*., 1998) suggest a disruption of normal connectivity between this visual area and the left temporoparietal cortex (known to be importantly involved in reading; Bavelier *et al*., 1997). These findings may suggest that underlying deficits in dyslexia are not specifically linguistic, but affect more basic sensory processing in the visual (cf. Cornelissen *et al*., 1991) or auditory domains (Kraft, 1993; Nicolson and Fawcett, 1993; for review, see Bishop, 1992). In particular, dyslexia has been related to disorders in the processing of rapidly changing stimuli in visual (May *et al*., 1988; Gross-Glenn *et al*., 1995) and auditory perception (Ribary *et al*., 1997), with possible analogous motor impairment (Heilman *et al*., 1996; Wolff, 1993). Some recent studies in children with DLI (Wright *et al*., 1997) and developmental dyslexia (McAnally and Stein, 1996) suggest that in addition to impaired perception of rapid auditory sequences, these disorders also affect the ability to distinguish subtle frequency differences between auditory stimuli.

The studies by Tallal and colleagues (Tallal and Piercy, 1973; Tallal *et al*., 1993, 1996), which are based on the assumption of a developmental continuity between DLI and dyslexia, support the notion of underlying auditory deficit, understood in the context of a general supramodal impairment in rapid perception (and possibly speech production). The findings of this group may be related to postmortem data from a small sample of subjects with history of developmental dyslexia reported by Galaburda and Livingstone (1993). These authors found evidence for anomalies (reduced cell size and abnormally shaped cells) in the magnocellular layers of the lateral geniculate nucleus, with sparing of the parvocellular layers. The magnocellular system is known to be important for the rapid processing of moving and low-contrast visual stimuli (Schiller *et al*., 1990; Livingstone and Hubel, 1988). FMRI findings by Eden *et al*. (1996), which were described above, and by Demb and colleagues (1997, 1998) are consistent with a selective impairment of the magnocellular system in dyslexia. Thus, Demb *et al*. (1997) found reduced activation in extrastriate area MT+ during low-luminance visual stimulation in dyslexic subjects – an area which is involved in motion perception and believed to receive strong input from magnocellular pathways. For their postmortem dyslexia sample, Galaburda *et al*. (1994) also report histological findings for the *medial* geniculate nucleus analogous to those for the lateral geniculate nucleus (reduced number of large neurons, increased number of small neurons), which could suggest that the auditory domain is affected in similar ways.

At the present time, there appears to be no consensus regarding the empirical evidence for specific hypotheses of the magnocellular theory (McAnally *et al*., 1997) and the efficacy of therapeutic interventions based on it (Merzenich *et al*., 1996; Tallal *et al*., 1996; for a recent review, see Stein and Walsh, 1997). For example, Borsting *et al*. (1996) report psychophysical data suggesting that magnocellular defect in the visual domain applies only to a subgroup of dyslexics, i.e. those with impaired grapheme-phoneme correspondence rules ('dysphoneidetics'), but not those with deficits in visual word gestalt perception ('dyseidetics'). Other studies altogether refute the notion of an underlying auditory temporal processing (as opposed to phonological) deficit (Mody *et al*., 1997). What is of sole interest here is the conceptual conflict between the linguistically informed top-down models that explain developmental disorders of language in terms of specific disruption of language modules and bottom-up approaches that account for such disorders in terms of more elementary sensorimotor disturbances and suspected neural pathology. This conflict is analogous to our earlier discussion of pervasive developmental disorders and the conflict between the 'theory of mind' model and bottom-up approaches pertaining to more elementary impairments in auditory, attentional, visuospatial, and motor domains.

Verbal sparing or verbal vulnerability?

Our discussion of developmental disorders indicates an interesting apparent conflict with findings from early lesion studies. If developmental brain impairments share the principles of compensation and vulnerability, then why would early structural lesions be often associated

with verbal sparing (at the expense of nonverbal functions), whereas language appears to be selectively vulnerable in developmental disorders – so much so that some researchers present language deficit as a central impairment in autism (Fay and Mermelstein, 1982; Baltaxe and Simmons, 1992), or view autism and the semantic-pragmatic of DLI as located on a single continuum of disorders (Bishop, 1989)? One explanation for this apparent paradox would relate to the fact that language involves multiple sensorimotor modalities and cognitive domains and therefore a great number of brain regions. This could account for enhanced vulnerability in the sense that a distributed system can be disrupted at more numerous neurofunctional loci than a focally organized system.

However, in the context of early structural lesions, this distributive organization appears to *enhance* rather than diminish the compensatory potential for language. An alternative explanation relates to the anatomically more diffuse nature of neuropathologies thought to underlie developmental disorders. While, for instance, structural lesions due to stroke are usually unilateral, developmental disorders are much less likely to be confined to one brain hemisphere. This is related to pleiotropic principles, which will be discussed in the following section. While neurofunctional disturbances in developmental disorders may thus be subtle, they tend to be widespread. The potential for language reorganization may therefore be reduced in developmental disorders due to a lack of intact domain-compatible tissue. Interestingly, language prognosis is equally poor when early *structural* lesion affects both hemispheres. For example, when hemispherectomy is performed within the first decade of life, cognitive and linguistic outcome tends to be good, if the preexisting lesion is confined to one hemisphere (Vargha-Khadem *et al*., 1997; Zupanc, 1997), as is often the case in Rasmussen's encephalitis or Sturge-Weber disease (Vining *et al*., 1993; Hoffman *et al*., 1979; Ogunmekan *et al*., 1989; Sujansky and Conradi, 1995). Conversely, hemispherectomy performed in patients with hemimegalencephaly is usually associated with less positive outcome, most likely due to preexisting impairment in the unresected hemisphere (Rintahaka *et al*., 1993).

Perspectives

Pleiotropy results in multiple brain-behavior impairments

Our discussion of bottom-up approaches in the study of developmental disorders does not imply that we believe primary causes or elementary impairments can be studied directly with behavioral, electrophysiological, neuroimaging or other techniques. In a trivial sense, this is so because affected subjects are not available for study when pathogenic events first occur.[12] Figure 5 is an attempt to grossly diagram possible epigenetic paths connecting biological etiologies with classes of developmental disorders. Initial pathogenic events will typically affect multiple brain regions, but may be in some cases limited to a single region. When a brain region is affected (for example, by reduced neurogenesis or early loss of neurons, as hypothesized for cerebellar Purkinje cells in autism), this may or may not have detrimental effects on the differentiation of other brain regions. For instance, recent volumetric evidence of inverse correlations between the sizes of the cerebellar vermis and the frontal lobes in autism (Carper and Courchesne, under review) might be explained by reduced inhibitory function of Purkinje cells, leading to remote overexcitation of the frontal lobes via dentato-thalamo-cortical pathways (Middleton and Strick, 1994) and to misdifferentiation of frontal cortex. Another region well-known for its differentiating role in brain development is the thalamus. Thalamocortical afferents are crucial for the functional differentiation of cerebral cortex (Shatz, 1992; O'Leary *et al*., 1994). In Figure 5, such regions that are important for the functional differentiation of other regions are characterized by the label 'remote differentiation'. When such regions are affected in a developmental disorder, the etiological course will result in *misconstruction* (for example, abnormalities of neuronal differentiation and connectivity or of gross morphological organization), in many regions besides the one originally affected by pathogenic events.

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[12] *This limitation can be potentially circumvented in genetic linkage studies (Schroer* et al.*, 1998; Cook* et al.*, 1998) and animal genetic knock-out models (Lipp and Wolfer, 1998; Fransen* et al.*, 1998).*

A developmental disorder can thus involve multiple neurofunctional systems at various hierarchical levels of brain organization (neocortical, subcortical, brainstem, cerebellar). Alternatively, it is theoretically possible that it remains confined to more circumscribed regions throughout development. The upper part of Figure 5 maps paths of potential compensatory reorganization in ways similar to those conceptualized in Figure 3 for early structural lesions (section 2.3). In multiple hierarchical system impairments, intact domain-compatible tissue will typically be unavailable, thus limiting the potential for reorganization. In the most severe case, a pervasive disorder such as autism will persist throughout development, i.e., show little cognitive-behavioral improvement. If there is more sparing or if partial reorganization is possible, high-functioning variants of a pervasive developmental disorder, such as Asperger's syndrome, may develop. With more confined impairments, affecting only a single region or only regions connected by a circumscribed corticosubcortical pathway ('single hierarchical system impairments'), domain-compatible tissue may be available to varying degrees. Accordingly, there will be varying degrees of cognitive-behavioral improvement over time in these cases and outcome may range from a persistent specific developmental disorder (such as DLI) to a residual and mild form of impairment that may be continuous with the normal spectrum. For example, as argued by Shaywitz *et al*. (1992), developmental dyslexia often resolves into very mild forms of the deficit that blend with the lower tail of the normal distribution of reading abilities.

The above considerations focus on pleiotropic effects in the pathogenesis of developmental disorders.[13] With regard to spectrum disorders such as autism however, it is likely that different etiological pathways can lead to a phenotype that will meet diagnostic criteria (Yeung-Courchesne and Courchesne, 1997). This insight highlights the fundamental limitations of pure top-down approaches because an outcome disorder is equivocal with regard to multiple potential etiologies. Thus, regardless of the empirical validity of findings on 'theory of mind' deficit in autism, such findings cannot elucidate the pathogenesis of autism *unless* there is *independent biological* evidence supporting the model (see (Courchesne *et al*., in press) for further discussion).

As Figure 5 indicates, developmental disorders will likely affect multiple brain regions. For instance, regarding our exemplary discussion of autism we do not assume that cerebellum-based attentional deficits represent a singular impairment underlying all other abnormalities observed within the autistic spectrum. This would be unexpected in view of our understanding that gene defects (which play a major role in autism; Bailey *et al*., 1995; Plomin *et al*., 1994) act *pleiotropically*, i.e. result in widespread disturbances throughout the brain (Courchesne *et al*., in press; Yeung-Courchesne and Courchesne, 1997). We therefore hypothesize that certain attentional functions are *specifically vulnerable* to the type of neurodevelopmental disturbance and misconstruction found in autism. Attentional impairment is not expected to be modality- or stimulus-specific nor is it expected to be tied to the exclusive dysfunction of a single anatomic structure. In view of its widely distributed connectivity and its potential participation in numerous cortico-subcortical networks (Schmahmann, 1996) and in view of the evidence for dysgenesis or early loss of Purkinje neurons (Courchesne, 1997; Bailey *et al*., 1998), the cerebellum could play a pivotal role as 'mediator of neurogenetic misconstruction' in multiple neocortical, limbic, and subcortical regions. We have discussed evidence for parietal lobe dysfunction above, but involvement of other brain regions can be additionally expected in autism, though possibly in more subtle ways or only in portions of the autistic population. This expectation is supported by the multitude of brain structures for which some degree of abnormality has been found in previously studied samples (see reviews in Bailey *et al*., 1996; Ciaranello and Ciaranello, 1995; Rumsey, 1996b; Minshew, 1994; Courchesne, 1997).

One example are the frontal lobes. Involvement of the frontal lobes has been suggested in earlier studies based on clinical symptomatology (Damasio and Maurer, 1978) and attention-related ERP data (Courchesne *et al*., 1984; Ciesielski *et al*., 1990), as well as in developmental studies on cerebral blood flow (Zilbovicius *et al*., 1995) and serotonin synthesis capacity (Chugani *et al*., 1997;

[13] *Our use of the term* pleiotropy *is broader than its definition in behavior genetics and includes the spreading of detrimental effects over multiple biological subsystems following* nongenetic *pathogenic events (such as viral infection or neurotoxic exposure).*

see chapter by D. Chugani). As mentioned above, Carper and Courchesne (under review) found that the size of vermal lobules VI and VII (typically hypoplastic in autism) was inversely correlated with frontal lobe volume, possibly suggesting a pathogenic link between cerebellar and frontal findings. Deficits on putative 'frontal-lobe tests' of executive function and problem solving have been identified in autism (McEvoy *et al*., 1993; Prior and Hoffman, 1990; Rumsey, 1985). According to Ciesielski and Harris (1997), high-functioning autistic subjects appear to be "stuck-in-set", i.e. impaired in switching between problem-solving strategies. This is reminiscent of the attention shifting deficits discussed above, but an 'executive shifting' deficit suggests predominantly prefrontal involvement (Alexander *et al*., 1989; Dias *et al*., 1996).[14]

Studies combining neuropsychological, structural imaging, electrophysiological, and functional mapping techniques can be directed at investigating brain-behavior relationships analogous to those demonstrated for the parietal lobe and the cerebellum (Akshoomoff and Courchesne, 1992; Townsend and Courchesne, 1994; Townsend *et al*., 1996). A catalogue of brain-behavior links for cognitive networks involving various cortical-hemispheric, subcortical, and cerebellar systems that may be impaired in autism could help to identify neurofunctionally based variants within the autistic spectrum from an outcome perspective.[15] In a further step, such taxonomies may be linked to genetically defined variants of each developmental disorder. While a direct mapping from genetically to brain-behaviorally defined variants is unlikely, only a bidirectional approach, integrating ontogenetic with outcome data promises an eventual biological understanding of autistic and other psychopathological spectra and the development of therapies adequate for given variants of each disorder.

Is there compensation in developmental disorders?

As argued above, functional neuroimaging can be an empirical tool for addressing vulnerability and compensation in the study of developmental disorders and early structural lesion effects. As a first approximation and assuming a simple dichotomy, developmental disorders may be viewed as predominantly characterized by vulnerability. Neuroimaging can thus serve to identify the multitude of anatomically and functionally distributed outcome impairments caused by some putative genetic defect or early pathogenic event (indicated by a "V" in Fig. 6). From this perspective, pleiotropic effects of gene defects reduce the potential for compensatory reorganization because these effects may not respect the boundaries of neurofunctional organization (and may in the worst case affect the entirety of neurofunctional circuits). Inversely, in patients with early structural lesion, functional imaging can focus on loci of compensatory reorganization (indicated by a "C" in Fig. 6). The potential for compensatory reorganization may be pronounced because a structural lesion may be confined to one or a few brain regions and thus may leave other domain-compatible tissue intact.

These fundamental differences between the effects early structural lesion and developmental disorders are related to the fact that initial pathogenic events tend to occur earlier in developmental disorders (in which genetic factors have been established or are suspected). The time-plasticity curves in Figure 1 may be misunderstood as reflecting a purely quantitative effect of time at lesion onset. However, as discussed earlier, findings in animals can be applied only with difficulty to the human species because conceptual and postnatal ages and corresponding maturational states cannot be linearly translated across species. Since ontogenetic time is linked to certain sets of neurodevelopmental events, it is inherently *qualitative* (Rodier, 1980; Kolb, 1995). For example, an intrauterine infarct occurring before neuronal migration and destroying neuroblasts in the germinal matrix will have

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[14] *Evidence for cerebellar participation in multiple neurocognitive networks (Leiner* et al.*, 1995; Schmahmann, 1996; Courchesne and Allen, 1997) and for massive connectivity between deep cerebellar output nuclei and the dorsolateral prefrontal cortex (Middleton and Strick, 1994; Schmahmann, 1996) suggests that the cerebellum may be additionally involved to an unknown degree in these 'executive shifting' functions (cf. Hallett and Grafman, 1997).*

[15] *Analogous considerations apply to other forms of developmental psychopathology (cf. Weinberg* et al.*, 1995). However, brain-behavior relationships in developmental disorders cannot be based on the adult acquired lesion literature, since it is unlikely that lesion locality and outcome impairment are linked by the same rules in the developing as in the mature brain. Brain-behavior links therefore need to be independently established for each developmental disorder in affected populations.*

qualitatively different effects from an infarct destroying an area of cortex post migration (cf. Kolb *et al*., 1996). The first type of structural lesion shares some pleiotropic features with developmental disorders in that a focal insult in the germinal matrix may have widespread effect on developing cortex (cf. Walsh and Cepko, 1992).

As discussed in the previous sections, a simple and discrete dichotomy between developmental disorders and early structural lesion effects, even though plausible as a first approach, represents an oversimplification. This is well documented for early structural lesions that often result in compensatory reorganization accompanied by functional diaschisis in remote regions and that appear to be extremely detrimental at some stages of early development. Regarding developmental disorders, there is an obvious rationale for neuroimaging studies that examine multiple neurofunctional impairments (i.e. functionally and spatially distributed effects of vulnerability). On the other hand, it is less obvious how compensatory reorganization may be identified. It may well be that some variants of developmental disorders exclusively reflect vulnerability, in the sense that a singular early disturbance (e.g., gene defect) leads to widespread misconstruction of brain circuits without significant potential for functional compensation (cf. the path on the left in Fig. 5). A case in point might be autism with severe mental retardation.

Nonetheless, autistic patients often show obsessive activity limited to certain kinds of objects or events, which in its extreme form may develop into so-called 'savantism' (Casey *et al*., 1993; Treffert, 1988). Or, for another example, Williams syndrome (a genetic disorder of calcium metabolism) is characterized by a highly uneven cognitive profile of low overall intelligence and severely impaired visuospatial and visuoconstructive functions, but in part highly developed socio-communicative functions (including some components of language; Bellugi *et al*., 1994; Singer *et al*., 1994; Tager-Flusberg *et al*., 1998; Reilly *et al*., 1990; Karmiloff-Smith *et al*., 1995; Udwin and Yule, 1991; Barisnikov *et al*., 1996). Thus, when asked about elephants a patient with Williams syndrome will be able to provide an elaborate verbal description, but will be unable to produce a coherent drawing (Bellugi *et al*., 1992). The obsessive specializations in 'savants' or the overdeveloped sociocommunicative functions in patients with Williams syndrome can be conceptualized as reflections of compensatory neurofunctional reorganization, with cognitive processing being rechannelled into domains of relative sparing. While such reorganization has yet to be definitively demonstrated in neuroimaging studies, it is likely that narrow specializations in the context of general intellectual deficit will be reflected by recruitment of atypical brain circuits. In Williams syndrome, for example, the cerebellar tonsils (Wang *et al*., 1992) and lobules VI and VII of the cerebellar vermis (Jernigan and Bellugi, 1990) as well as temporal limbic regions (Jernigan and Bellugi, 1994) have been found to be of normal size or hyperplastic in the context of overall cerebral hypoplasia. Such regions could conceivably participate in neurofunctional circuits involved in these subjects' hypercommunicative behavior.

The notion of compensatory events (interacting with effects of vulnerability) is even easier to grasp with regard to developmental disorders that do *not* involve general intellectual impairment. High-functioning autism and Asperger's syndrome are likely to reflect some degree of neurofunctional reorganization that allows some individuals to lead independent or semi-independent lives and, in rare instances, to function in intellectually challenging professions in spite of sensorimotor and sociocommunicative impairments (Carpenter *et al*., 1992; Grandin, 1992). Such compensatory effects can be addressed in longitudinal functional neuroimaging studies that could also investigate neurofunctional changes associated with therapeutic intervention. Compensatory reorganization may be reflected in improved cognitive-behavioral functioning following behavioral intervention, especially in young autistic children (Lovaas, 1987; McEachin *et al*., 1993; Burke and Cerniglia, 1990). The overall balance of vulnerability and compensation will vary between disorders and individuals, and plasticity may be 'successful' to differing degrees, ranging from almost complete compensatory reorganization (possibly exemplified in the 'broader phenotype' of pervasive developmental disorders; Le Couteur *et al*., 1996; Baron-Cohen and Hammer, 1997) to widespread misconstruction of neurofunctional networks (as in low-functioning autism; cf. Courchesne *et al*., 1994a; Courchesne, 1997). Monitoring treatment effects with functional neuroimaging implies that, in addition to the typical focus on loss and anomaly of activations, imaging studies could

aim at identifying the neural bases of *spared* functions in a given developmental disorder and thus explore optimal windows for therapeutic intervention.

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Figures

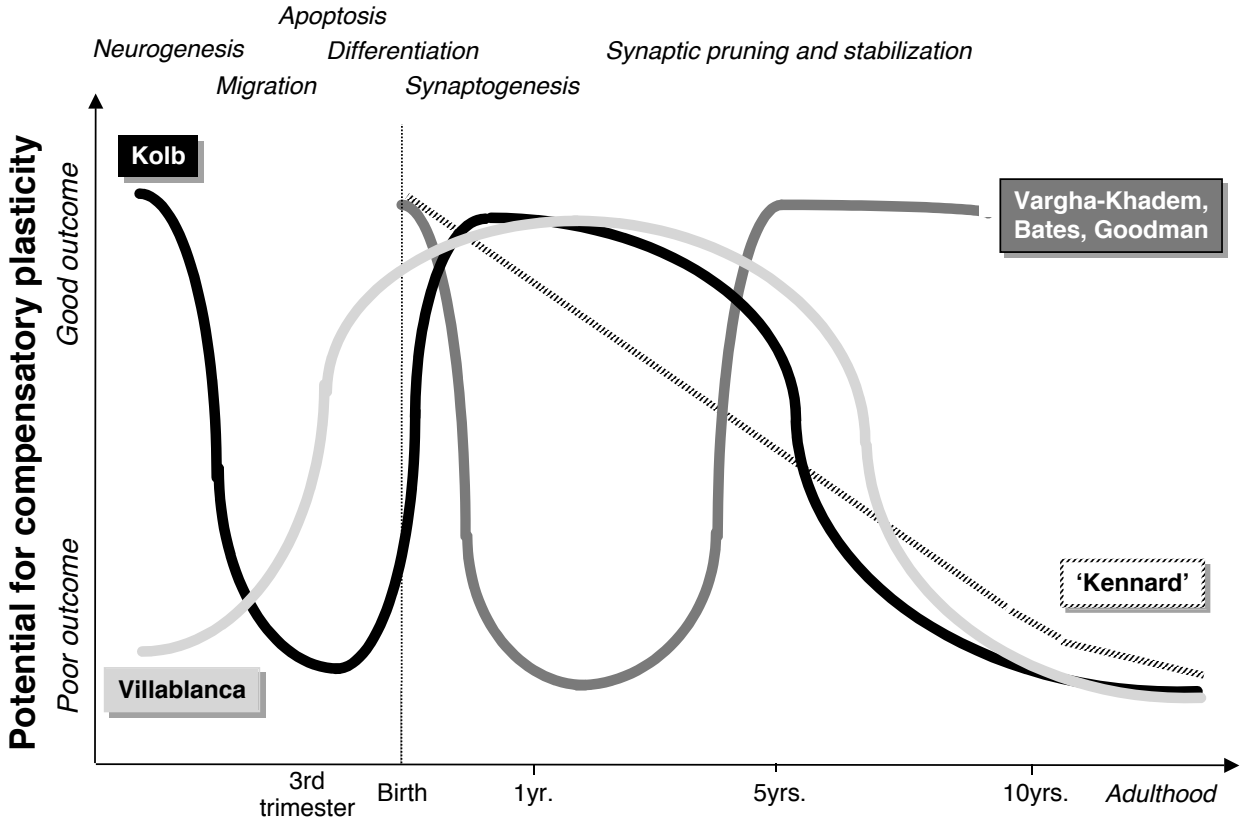


Fig. 1. Effect of age at lesion onset on the potential for compensatory reorganization. The position of neurodevelopmental stages at the top is approximate. Age at lesion onset refers to human developmental time. Findings from animal studies are converted to roughly equivalent human time. The dotted line indicates a linear decrease in plasticity after birth until adulthood, which is a simple rendering of the 'Kennard principle' (e.g., Teuber, 1974). The black line is based on animal studies reviewed in Kolb (1995) and Kolb *et al*. (1998). The light gray line reflects the conclusions of Villablanca *et al*. (1993a,b) based on experiments in cats. The dark gray line is based on human lesion studies, i.e. the sample of Vargha-Khadem *et al*. (1999), the congenital lesion sample of Bates *et al*. (in press), and the sample presented by Goodman and Yude (1996)

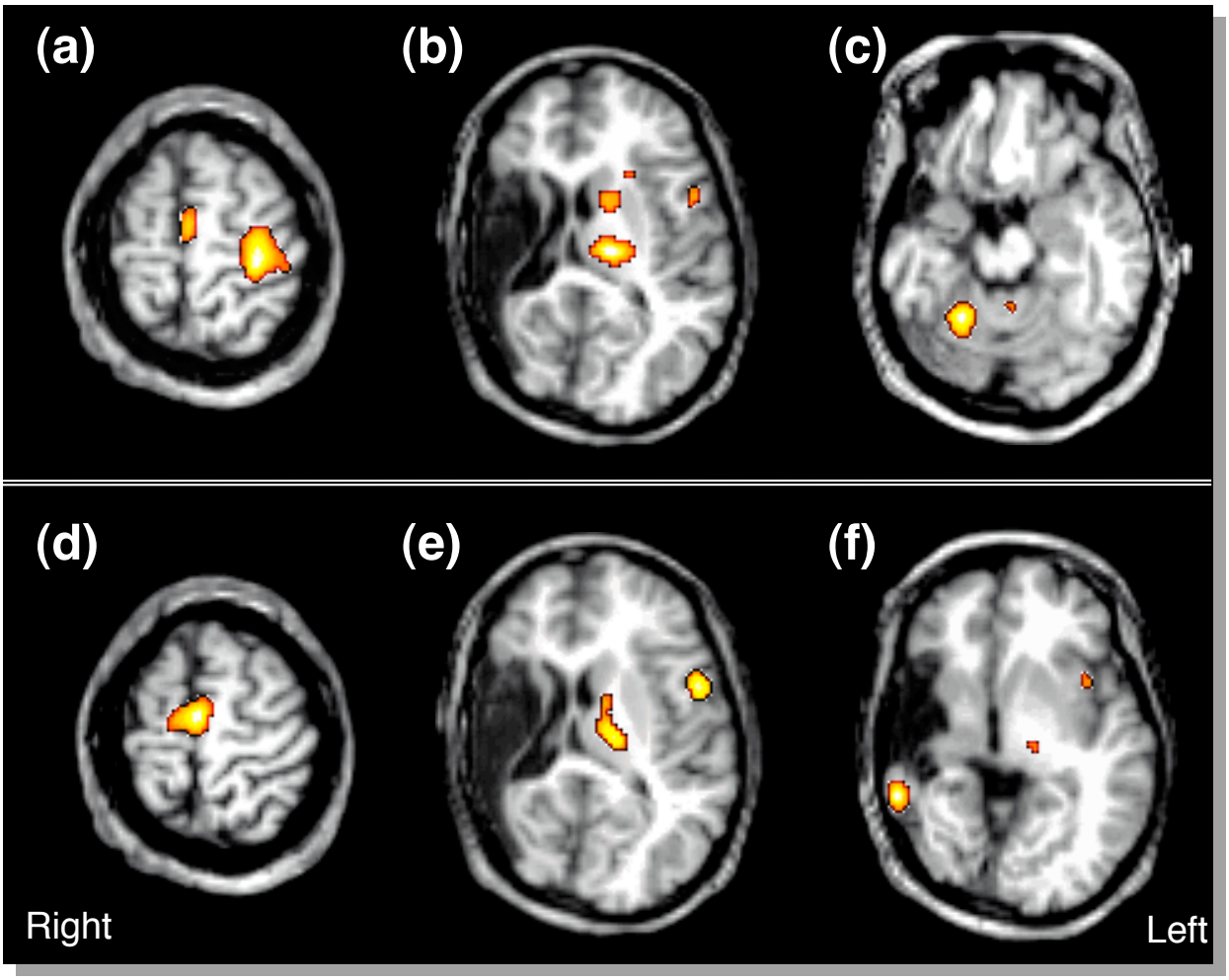


Fig. 2. Regional cerebral blood flow (rCBF) increases > 20% ($p<.001$; uncorr.) for unilateral finger movement in a 20 year-old patient with history of intrauterine or perinatal middle cerebral artery infarction in the right hemisphere (from Müller *et al*., 1998g). The activations from the [^{15}O]-water PET subtraction images are superimposed onto the patient's structural MRI. In the upper row, a normal pattern of activations for finger movement of the unaffected right hand is seen in primary motor cortex and the supplementary motor area (a), as well as in the thalamus, basal ganglia, and premotor cortex of the left hemisphere (b), and in the right anterior cerebellum (c). The lower row shows activations for movement of the hemiparetic left hand. Activations in the supplementary motor area (d) are enhanced and more bilateral compared to movement of the unaffected hand, but there is no activation in primary motor cortex. Atypical activations are also seen in the hemisphere *ipsilateral* to the side of movement in premotor cortex and in the thalamus (e). Finally, an unexpected activation is found in residual temporal cortex of the lesioned hemisphere (f). The activations for movement of the hemiparetic hand suggest that multiple regions are involved in reorganization, with the *exception* of the primary motor cortex.

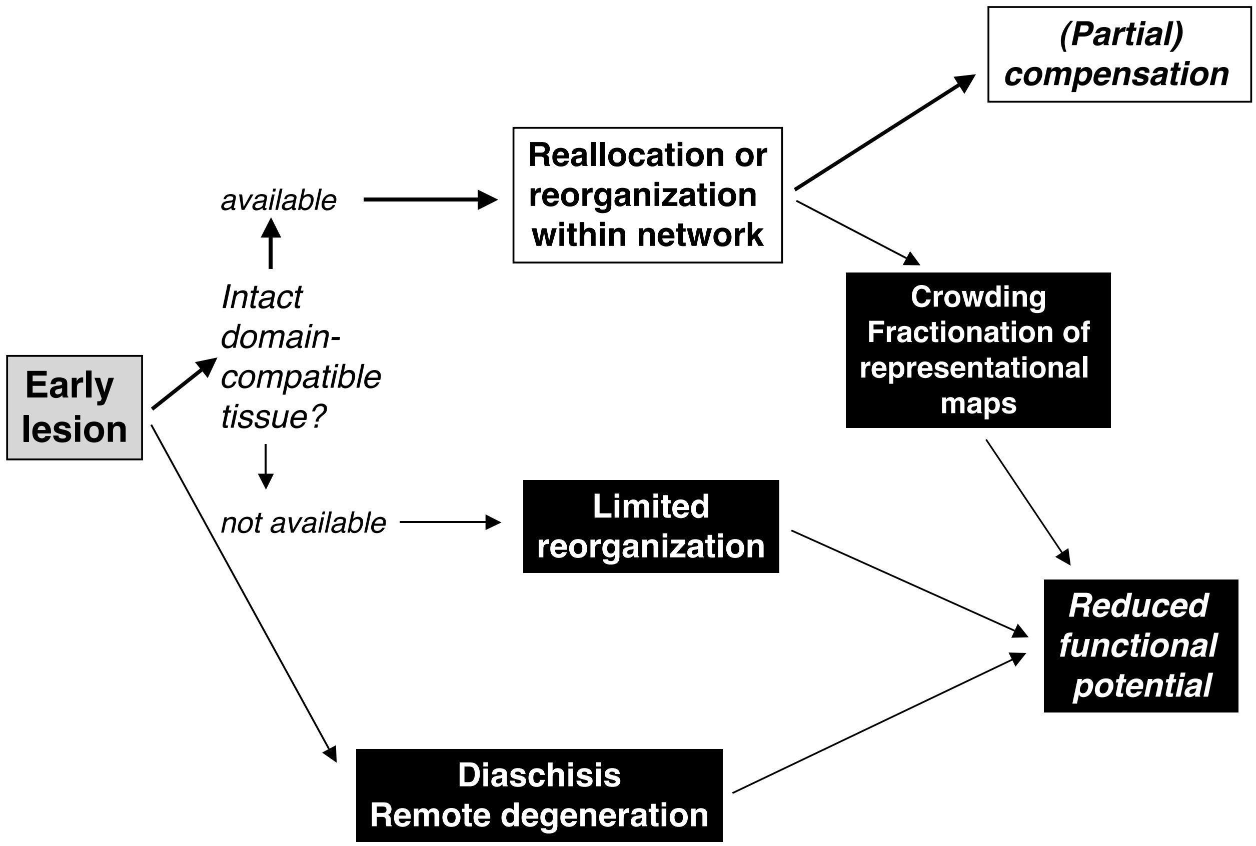
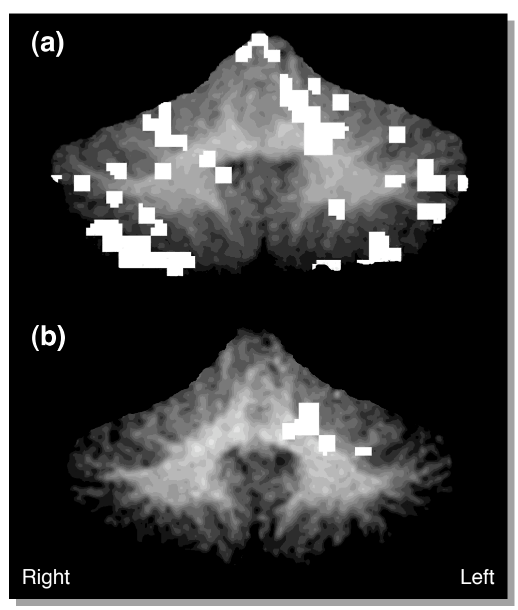


Fig. 3. Possible event paths determining compensation and vulnerability after prenatal or early postnatal lesion. White boxes indicate events reflecting compensation (i.e. events that benefit cognitive-behavioral outcome), black boxes indicate detrimental events that reflect vulnerability. For details, see text.

Fig. 4. Coronal slices through the cerebellum showing activations (superimposed in white onto structural MRI) for repetitive thumb movements of the dominant left hand in a 21year-old autistic subject (a), who demonstrated no motor deficit on neurological examination typically observed in patients with cerebellar damage (impairment of fine motor coordination and gait; Haas *et al*. 1996; Hallett *et al*. 1993). While an age-, sex-, and handedness-matched normal control subject (b) shows circumscribed activation in the ipsilateral anterior cerebellum, activations are scattered across the cerebellum bilaterally in the autistic subject. The statistical map is based on a correlational analysis of the time course of each voxel compared to a hemodynamic model curve (Bandettini *et al*. 1993), a statistic with relatively low risk of Type I errors due to movement artifacts. Adapted from Allen *et al*. (submitted).



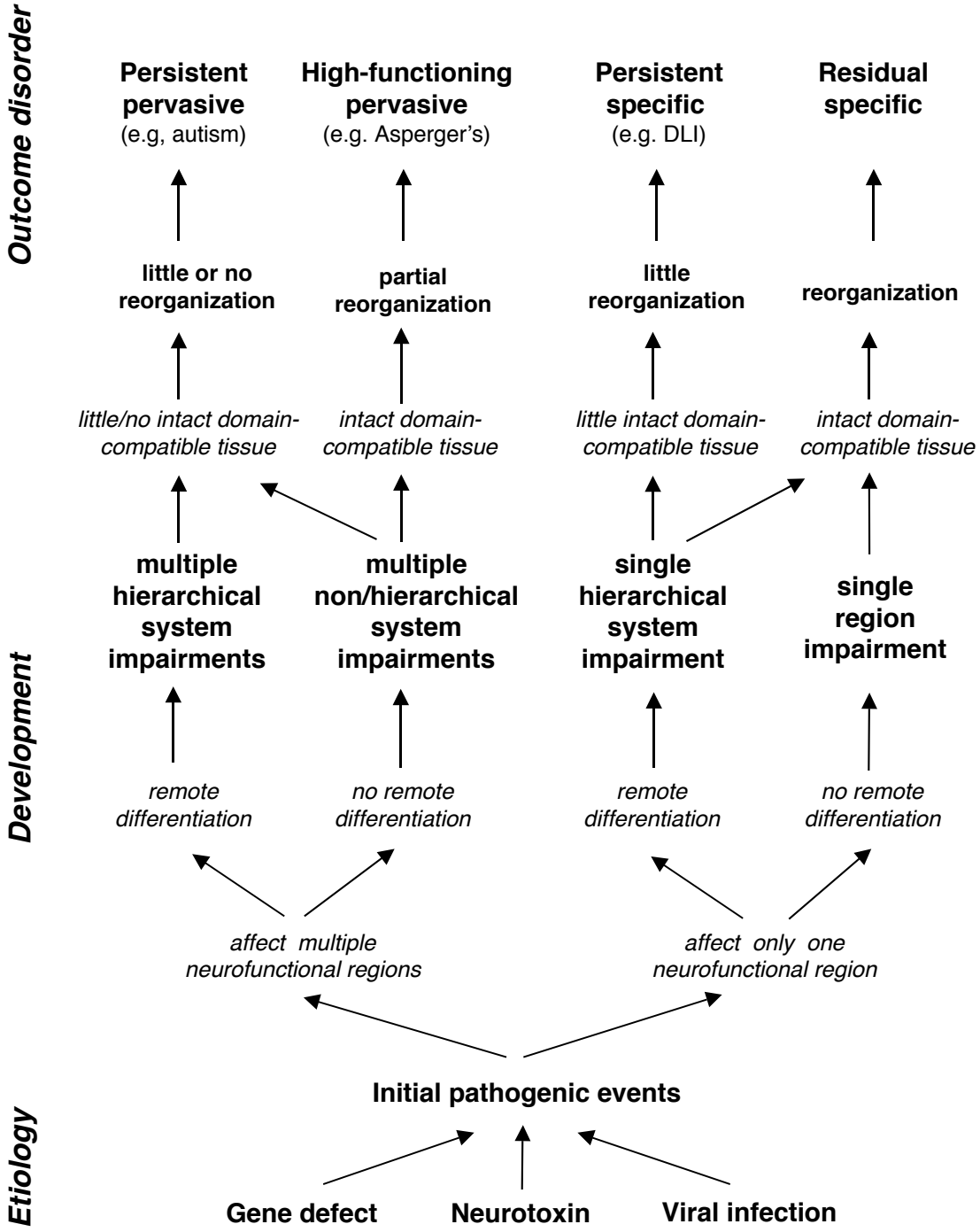


Fig. 5. Possible neurodevelopmental paths determining vulnerability and compensation in developmental disorders. For explanation of terms such as 'remote differentiation' and 'domain-compatibility', see main text. The linearity of events indicated by the arrows constitutes a simplification. For example, a genetic deficit may cause persistent pathogenic states (rather than only one initial pathogenic event) and will thus be associated with persistent vulnerability, reducing the potential for compensatory reorganization. A further limitation of the figure is its emphasis of structure-function relationships. *Qualitative* differences between diffuse disturbances of different neurotransmitter systems – for instance, of serotonin in autism (McDougle *et al*., 1996b; McDougle *et al*., 1996a) or of dopamine in attention deficit hyperactivity disorder (Ernst *et al*., 1998b) – are not taken into account.

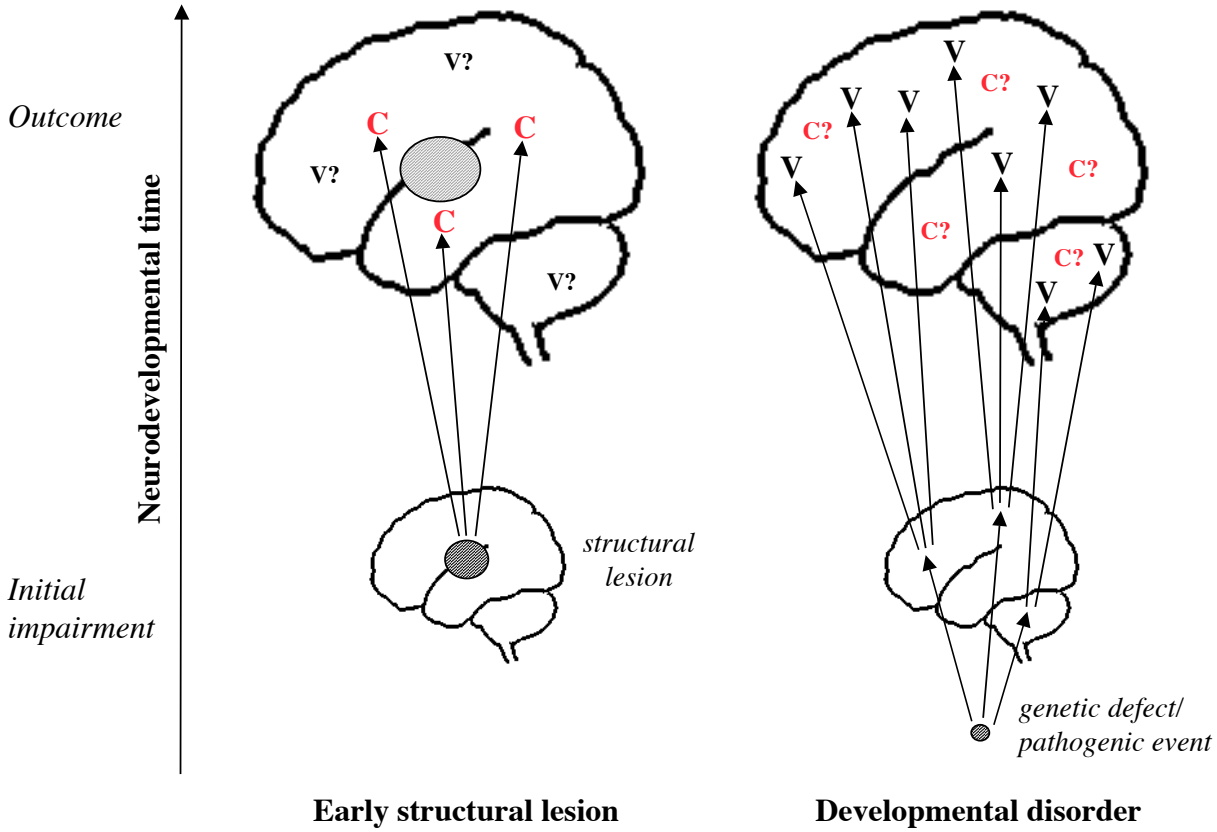


Fig. 6. Contrasting effects of developmental disorders and early structural lesions across neurodevelopmental time. The location of symbols is arbitrary and does not refer to actual brain regions. The prototypical early structural lesion results in an area of dysfunctional brain tissue (or encephalomalacia) at the outcome stage. Some of the functions typically assumed by the lesioned area will be reallocated to others, for example, to surrounding brain regions that perform compensatory functions (C). However, structural damage may also trigger vulnerability effects (V), such as functional diaschisis or remote degeneration. On the other hand, the prototypical developmental disorder is characterized by a focal early defect that has pleiotropic effects on various distributed neurofunctional circuits over time. Depending on the availability of domain-compatible tissue, these multiple impairments due to vulnerability (V) may be accompanied by compensatory reorganization (C).