In: ML Rice & SF Warren (eds.) *Developmental Language Disorders: From Phenotypes to Etiologies*.- Erlbaum, 2004, pp291-328.

Genes, language disorders, and developmental archaeology: What role can neuroimaging play?

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1 Grammar Modules and Language Genes

Historically, language has been often conceived as something "out there", in the outside world, rather than a system of mind or brain (Sampson, 1980). For a relatively recent example, Saussure (1915/1972) defined "langue" as a socially constituted system of signs. When B.F. Skinner (Skinner, 1957) adapted the behaviorist approach to the study of language, he described the rules of language in terms of reinforcement and conditioning, i.e. as fully determined by external parameters of stimulus and response. It was Chomsky's groundbreaking criticism of Skinner's book that launched the study of language as a mental system (Chomsky, 1959). Chomsky's early work on syntax as a mental system of quasi-mathematical rules (Chomsky, 1957; Chomsky, 1965) was an integral part of the newly developing "cognitive sciences" (Gardner, 1987). Later, Chomsky went a step further and reunited linguistics with biology. According to his views, language was a "mental organ" that would mature based on biological necessity (rather than environmental contingency) in the course of child development, in similar ways as a heart or a lung would mature (Chomsky, 1980). At the time, these views were radical compared to competing behaviorist and Piagetian views that granted experience an important role in language development (Piattelli-Palmarini, 1980). Chomsky's views were also radical with respect to the role they allotted genetic information. Chomsky believed that "universal grammar", a set of abstract principles determining acquisition of any possible human language, was fully specified in the human genome. Not only did this imply that homo sapiens was radically different from nonhuman primates with respect to linguistic capacities, but also that the core language system developed autonomously in mind/brain and that other domains of developing cognition (e.g., object recognition, visual spatial thinking, attention, memory) played no crucial role in language acquisition.

Since Chomsky first formulated this framework of ideas, the fields of psycho- and neurolinguistics have progressed dramatically. Nonetheless, his general ideas are still considered by many the most promising approach to the cognitive neuroscience of language. Traditional psycholinguistic arguments in favor of the Chomskian view relate to claims according to which, for example, language acquisition follows universal principles that cannot be inferred from typical language input children receive (Crain, 1991). More recent approaches, however, also include clinical and biological evidence. For instance, the existence of developmental disorders, such as 'specific language impairment' and Williams syndrome, is taken as evidence that language can be dissociated from other cognitive domains (Stromswold, 2000). As Pinker (1995) interprets such apparent modular dissociations in rather crude terms, there can be "intelligence without language" ('specific language impairment') and "language without intelligence" (Williams syndrome). In the following section, we will examine the former type of disorder in more detail.

1.1 Genotype-phenotype divergence: Developmental language disorders

One important set of evidence that has developed in the context of questions raised by Chomsky relates to developmental language disorders (DLDs), often referred to as "specific language impairments". A growing literature has related these disorders to identifiable neural features, such as atypical morphology and hemispheric asymmetry in perisylvian regions. In normal adults, postmortem and in vivo imaging studies indicate that asymmetries in posterior (Foundas et al., 1994; Tzourio et al., 1998; Witelson & Kigar, 1992) and anterior (Foundas

et al., 1996) perisylvian anatomy are related to language dominance. Even though there are some inconsistencies in findings regarding the planum temporale (Habib, 2000), most studies on DLD (Clark & Plante, 1998; Gauger et al., 1997; Jackson & Plante, 1996; Plante et al., 1991) and dyslexia (Eckert et al., 2003; Kushch et al., 1993; Leonard et al., 1993; Robichon et al., 2000) have identified some pattern of atypical morphology or asymmetry in or around perisylvian cortex. This is overall consistent with functional neuroimaging studies in children with DLD (Lou et al., 1990; Shaywitz et al., 2002; Tzourio et al., 1994) and in adults with a history of dyslexia (Horwitz et al., 1998; Paulesu et al., 2001; Rumsey et al., 1997; Shaywitz et al., 1998) showing various types of abnormalities in perisylvian regions.

Of particular interest here is the question whether brain-based DLDs can be traced back to genetics. The studies that probably received widest attention concern familial aggregation of 'specific language impairment' in family KE (Gopnik, 1990; Gopnik & Crago, 1991). Speech disorder in this family is an autosomal-dominant trait involving a single-gene on chromosome 7 (Fisher et al., 1998; Lai et al., 2001). Findings from family KE corroborate evidence for genetic factors in the DLD population at large (Bishop, 2002; Tomblin & Buckwalter, 1994). Initial studies in this family by Gopnik and colleagues also suggested a highly selective linguistic deficit restricted to certain aspects of morphosyntax (for example, past tense formation), compatible with the notion of modular linguistic subsystems and an autonomous neurofunctional organization of language vis-à-vis other cognitive domains (Chomsky, 1981; Pinker, 1991). However, more comprehensive testing by Vargha-Khadem and colleagues has shown that deficits in affected family members are not exclusively morphosyntactic. Not only did affected family members show significantly lower *performance* IQ scores than unaffected members, but also evidence of orofacial apraxia and impaired phonological working memory (Vargha-Khadem et al., 1995; Watkins et al., 2002). Voxel-based morphometry of structural MR images identified perirolandic sensorimotor cortex and the caudate nuclei as primary sites of gray matter reduction in affected members compared to normal controls (Watkins et al., 2002). The caudate nuclei are considered an "associative" region within the striatum, with multimodal connectivity from neocortex of all four lobes of the forebrain (Yelnik, 2002). There have been some reports of language-related impairments in basal ganglia patients (Wallesch et al., 1997; Wallesch & Wyke, 1985). However, Nadeau and Crosson (Nadeau & Crosson, 1997) concluded from a review of the clinical literature on patients with subcortical lesion that the basal ganglia do not play a specific linguistic role. The MRI findings in family KE are thus consistent with behavioral findings suggesting that basic impairments are probably non-linguistic and that morphosyntactic deficits are secondary to orofacial motor, phonemic, and other impairments.

The above evidence suggests that single-gene mutations can have detrimental effects on morphosyntactic aspects of language acquisition. However, these effects are *pleiotropic*, i.e. multiple other functional domains are also affected. Pleiotropy is a principle of *divergence* in genotype-phenotype relationships (Fig. 1A). A striking example of pleiotropy with neurological relevance is phenylketonuria (PKU), a single gene defect associated with a severe disorder of amino acid metabolism and toxic accumulation of phenylalanine. PKU is phenotypically characterized, not only by mental retardation and microcephaly, but also by social behavioral deficits, seizures, stunted bodily growth, and dermatological symptoms (Brenton & Pietz, 2000; Følling, 1994; Scriver & Waters, 1999). Another example is Rett syndrome, a disorder seen only in girls that is associated with apparently normal development up to age 6-18 months, followed by regression. In a large majority of cases, the disorder is caused by sporadic mutation of the *MECP2* gene on the X chromosome (Amir & Zoghbi, 2000). Females with Rett syndrome have been described as autistic-like. What is relevant in the present discussion, is the wide array of phenotypic traits associated with this single-gene mutation, including language and motor impairment, stereotypic behaviors, deficits in social interaction; disturbances of breathing, peripheral blood circulation, and sleep patterns; stunted growth and reduced head size; and widespread neuroanatomic and cellular abnormalities (Shahbazian & Zoghbi, 2002; Weaving et al., 2003). In both the examples of PKU and Rett syndrome, a single gene mutation results in phenotypic manifestations that are *pleiotropic*, affecting numerous biological systems.

1.2 Genotype-phenotype convergence: Autism

Pleiotropy enhances the complexity of gene-behavior relationships. However, there is another, seemingly antagonistic principle that further complicates these relationships and is certainly also involved in developmental disorders of language. This is a principle of *convergence* in genotype-phenotype relationships (Fig. 1B). A prime example of a developmental disorder that appears to be governed by *polygenic* (or *multigenic*) principles of convergence is autism (Korvatska et al., 2002). Autism is a neurodevelopmental disorder with an estimated prevalence of 1-4 individuals in 1000 (Charman, 2002). The disorder is pervasive, affecting numerous domains of cognitive, sensorimotor, and sociobehavioral function (Tager-Flusberg et al., 2001). Delayed language acquisition is one of the diagnostic criteria autism (American Psychiatric Association, 2000). Twin studies demonstrate strong genetic factors (Bailey et al., 1995; Greenberg et al., 2001; Rutter, 2000). Recent evidence indicates potential links between genetic and cognitive subtypes in autism (Silverman et al., 2002) and heritability of general symptom severity (Spiker et al., 2002), as measured by the Autism Diagnostic Interview-Revised (Lord et al., 1994). Regarding language, genetic variation within the disorder may correlate with onset of phrase speech (Silverman et al., 2002), with a potential role of a site on chromosome 2 (Shao et al., 2002).

Despite such preliminary evidence, the current genetic linkage literature on autism appears confusing and fraught with inconsistencies. While there is partial convergence regarding chromosomes 7 (Folstein & Rosen-Sheidley, 2001; Hutcheson et al., 2003) and 15 (Shao et al., 2003; Sutcliffe et al., 2003), no sites of susceptibility for autism have been firmly established. In fact, the number of suspected genetic loci of susceptibility is extremely large (Folstein & Rosen-Sheidley, 2001; Shao et al., 2002; Veenstra-Vanderweele et al., 2003). Reviewing the impact of the human genome project on the study of autism and other psychiatric disorders, Cowan and colleagues (2002) acknowledge a "sense of disappointment and frustration" (p. 25) in view of the multitude of candidate sites and the inconsistencies across studies.

Further complicating the picture is the possibility that non-genetic events may, in some cases, mimic genetic effects in autistic pathogenesis. Claims implicating MMR vaccines in autism (Wakefield, 1999) are not supported by the bulk of available evidence (Korvatska et al., 2002). However, viral infections (Lotspeich & Ciaranello, 1993; Tanoue et al., 1988) or neurotoxic exposure in utero (Edelson & Cantor, 1998; Mason-Brothers et al., 1990; Rodier et al., 1997; Stromland et al., 1994) cannot be ruled out as risk factors in autism. Some studies also suggest links between perinatal risk factors and autism (Hultman et al., 2002), even though it remains unclear whether these factors are causative or secondary to autistic pathology.

Taking all the above together, it appears likely that numerous genes are involved in autism and that multiple genetic and environmental risk factors converge in autistic development (Jones & Szatmari, 2002). Language deficits in autism are unlikely to be linked to one or a few genes. There have been suggestions of involvement of common genetic sites in autism and DLD based on the proximity of susceptibility loci in region 7q31 for both disorders (Bradford, 2001; Folstein & Mankoski, 2000). This proposal is consistent with greater than expected comorbidity between autism and DLD and findings of symptom overlap between the two disorders (Bishop, 1989; Howlin et al., 2000; Mawhood et al., 2000). Folstein and Mankoski (2000) suggested there could be "a single gene on 7q31 that is involved in both autism and specific language impairment" (p.279). Despite initial excitement that one of the prime candidates, the *FOXP2* gene (Lai et al., 2001), "may have a causal role in the development of the normal brain circuitry that underlies language and speech" (Pinker, 2001) (p.465), recent studies have not yielded any evidence for involvement of this gene in either autism or DLD (Newbury et al., 2002; Wassink et al., 2002).

The discussion of this section should not create the impression that DLDs and autism are exclusively characterized by pleiotropic and polygenic principles, respectively. Divergent and convergent principles are at work in both types of disorder. For instance, even though one locus on chromosome 7 has been linked to language impairment in family KE and one unrelated case (Lai et al., 2001), a number of other loci have been identified for other DLD populations, including sites on chromosomes 16 and 19 (SLI-Consortium, 2002), as well as 13 and possibly 2 (Bartlett et al., 2002).

All in all, there is substantial evidence indicating the importance of genetic factors in language acquisition. As a first approximation, the Chomskian hypothesis of genetic foundations for the human languages capacity is

therefore correct. On closer examination, however, this hypothesis and its implications become more problematic. First, the study of DLDs shows that most likely a multitude of genes may be involved in such disorders. Second, genetic defects (and in particular, single-gene defects) do not result in "modular" or highly selective language deficits, but typically also affect non-linguistic cognitive and sensorimotor domains. The evidence on language impairments from behavior genetics may appear tantalizing because it indicates clear links between genes and language, but does not yield a true understanding of how exactly the two relate during development. Giving all this a more positive spin, the following conclusion can be drawn: A better understanding of the causal links between genes and language requires adequate consideration of developmental neuroscience. A brief discussion of some of the basic principles that may bridge genes and cognitive development will follow in section 2. The final sections will be dedicated to the role of functional neuroimaging in the study of these developmental neuroscientific principles.

2 INTRINSIC, ACTIVITY-DRIVEN, AND EXPERIENTIAL EFFECTS IN BRAIN DEVELOPMENT

The developing brain is shaped through interactions of constructive (Quartz & Sejnowski, 1997) and regressive (or selectional) events (Changeux, 1986; Pennington, 2001; Rakic, 1989). Early "exuberance" of neurons and synapses is followed by selective stabilization and loss. Whereas prenatal neuronal loss (apoptosis) is predominantly determined by endogenous neurotrophic factors (Jessell & Sanes, 2000), experience and environmental interaction play important roles in postnatal synaptic survival and loss (Katz & Shatz, 1996). Synaptic connectivity is overly abundant in the first years of life and is subject to subsequent pruning and selective stabilization (Caviness et al., 1997; Huttenlocher & Dabholkar, 1997; Pennington, 2001). Experiential and activity-dependent effects on the number and efficacy of synaptic connections have been shown in invertebrates (Kandel et al., 2000) and in mammals (Greenough & Bailey, 1988; Kleim et al., 1996).

Enriched environments have positive influence on cortical thickness, presumably because they are more stimulating and offer greater opportunities for interaction and manipulation (Kolb & Gibb, 2001). Increased cortical thickness has also been shown following motor skill learning in rats (Anderson et al., 2002). Besides synaptic effects mentioned above, gray matter thickness is probably affected by increase in glial cells, neuronal survival, and dendritic complexity due to environmental enrichment (van Praag et al., 2000). Although much of the supporting data come from animal studies, there is some evidence from research with human subjects. For instance, structural MRI has demonstrated greater depth of the central sulcus in professional musicians [compared to non-musicians (Amunts et al., 1997)]. This measure, which reflects the size of primary motor cortex, was significantly correlated with age at which musicians began keyboard or string instrument training. Human postmortem findings also suggest that laminar and cellular architecture in perisylvian language areas correlated with language experience and skills (Amunts et al., 2003) and educational level (Jacobs et al., 1993). Corroborating evidence from functional imaging will be discussed in the following section.

The generation and loss of neurons and synaptic connections is governed both by intrinsic mechanisms and environmental factors, although in different ways and at different stages of brain development. For example, early phases of synaptogenesis (gestational weeks 6-17 in humans) are probably driven by genetic factors, but environmental and activity-dependent mechanisms play important roles in later postnatal stages of synaptogenesis and selective loss (Pennington, 2001). Whereas plasticity may not be at work in early stages of neuronogenesis, apoptosis, and synaptogenesis, later stages are certainly affected by plasticity, which results in environmentally based variability of individuals, but also in resilience in the face of brain damage (see section 3).

Considering effects of early damage, a similar duality of genetic and environmental effects can be observed, albeit on a more macroscopic level. Recent studies have demonstrated the astounding genetic impact on brain morphology (Thompson et al., 2001) and cognitive abilities (Plomin & Kosslyn, 2001; Plomin et al., 1994). Nonetheless, it is also well established that neocortical differentiation into functionally specialized areas is not strictly predetermined genetically, but characterized by equally astounding malleability (O'Leary et al., 1994). In a recent review of experimental manipulations of early brain development in animals, Pallas (2001) distinguishes

between early *regionalization*, which is under relatively tight genetic control, and subsequent *arealization*, which is dependent on extrinsic and activity-driven factors. Knockout studies of regulatory genes provide evidence for the first part of the model. For example, *Emx2* expression shows a gradient in antero-posterior and lateral-medial directions in embryonic mice. *Emx2* knockout results in distorted regionalization, with more anterior (somatosensory, auditory) regions expanding at the expense of posterior visual regions (see reviews in (Cecchi, 2002; Pallas, 2001). However, the view of genetic and epigenetic influences on cortical differentiation occurring as a chronological sequence is probably overly simplified. More likely, they present interacting principles, in the sense that activity-dependent thalamo-cortical effects underlie genetic factors and may, in turn, influence cortical gene expression (O'Leary & Nakagawa, 2002).

Evidence for extrinsic effects on regionalization comes mostly from transplantation and rewiring studies. Schlaggar and colleagues (1991) transplanted embryonic occipital cortex into the postcentral region in neonatal rats and observed almost normal formation of barrelfields in transplanted cortex. This shows that occipital cortex, which assumes visual functions in normal development, has the capacity to develop somatosensory functions in response to somatosensory thalamo-cortical afferents (Schlaggar et al., 1993). Such *crossmodal plasticity* of developing cortical tissue has also been demonstrated in rewiring experiments by Sur and colleagues (1990). Inducing retinal afferents in newborn ferrets to connect to the medial geniculate nucleus (MGN, normally an auditory structure connecting to auditory cortex), they found that both MGN and primary auditory cortex responded to visual stimulation (Sur et al., 1988). More recent experiments with such rewired animals also show that this response is indeed functionally relevant and contributes to stimulus-appropriate behavior (von Melchner et al., 2000).

In sum, the functional architecture of the developing brain is probably subject to numerous interacting factors. Some of these are more directly related to genetic information, whereas others heavily involve activity of afferent connections, which in turn relates to (interaction with) the environment. This scenario greatly complicates the study of developmental disorders of language. First, it is unlikely that polymodal brain regions known to be important for language processing ("Broca's area", "Wernicke's area") achieve functional specialization based on one or a few genes alone. We can therefore not expect any simple links between gene defects and *specific* or "modular" language disorders. Second, any developmental abnormality is potentially compensated by developmental plasticity and reorganization, or possibly aggravated by developmental vulnerability and 'misconstruction' (see sections 3.2 and 4.1, respectively). Links between sites of brain abnormality and symptom complexes inferred from the study of adult lesion patients are thus unlikely to apply to developmental populations. Or in the words of Thomas and Karmiloff-Smith (2003), the assumption of "residual normality" – dubious even in adult patients – is clearly inadequate in developmental disorders (Müller, 2003).

3 INSIGHTS FROM FUNCTIONAL NEUROIMAGING

Functional neuroimaging techniques were first applied to developmental populations in the 1980s. Positron emission tomography (PET) and single photon emission tomography (SPECT) require radioactive tracers and their use in children is tightly restricted for ethical reasons (Morton et al., 1996). Nonetheless, these techniques have generated evidence that is relevant to the issues of brain developmental changes and plasticity discussed above. In the first systematic study of developmental changes in brain metabolism, Chugani and colleagues presented children that had received PET scans because neurological disorder was suspected (Chugani & Phelps, 1986; Chugani et al., 1987). Among a very large group of such children, 29 turned out to be neurologically normal. In these children, age-related changes in glucose metabolic rate could be identified that resembled synaptic density curves in animal and human postmortem studies (Huttenlocher & Dabholkar, 1997). Glucose metabolism showed a steep increase in the first two postnatal years, plateaued at 2-3 times higher than adult levels between age 3 and 8 years, and then slowly declined through the second decade of life (Fig. 2A). These findings were corroborated in later PET and SPECT studies of glucose metabolism (Bentourkia et al., 1998) and brain perfusion (Chiron et al., 1992). The dramatic changes in glucose metabolism and resting blood flow throughout childhood and adolescence predominantly reflect changes in synaptic density (Fig. 2B), which are in turn based on the constructive and regressive principles discussed in the

previous section. Functional neuroimaging has thus been able to confirm neurohistological evidence of changes in synaptic connectivity underlying developmental plasticity.

3.1 Experiential effects

More recently, neuroimaging studies have also been able to highlight such plasticity and the importance of experiential factors in studies of adults. One set of evidence comes from functional neuroimaging studies in adults with specific areas of expertise, such as professional musicians (Münte et al., 2002). Consistent with findings of structural effects related to musical expertise (Amunts et al., 1997; Schlaug et al., 1995), functional studies demonstrate more extensive functional representation of left-hand digits (Elbert et al., 1995) and greater motor learning-related short-term plasticity (Hund-Georgiadis & von Cramon, 1999) in primary motor cortex of professional musicians.

A second set of evidence highlighting experiential effects on neurofunctional organization concerns subjects with absence of peripheral sensory input in the auditory or visual modality. Grossly speaking, these studies have shown that in early-onset blindness or deafness, the functional representation of intact modalities expands into territory normally occupied by the missing modality. For instance, in congenitally deaf subjects the superior temporal cortex is activated during comprehension of sign language (Neville et al., 1995). This region also responds to nonverbal visual stimulation in early deaf subjects (Finney et al., 2001). Analogously, in early blind subjects, occipital cortex has been shown to participate in tactile Braille reading (Sadato et al., 1998). Occipital cortex in the congenitally blind also activates during auditory localization, in regions corresponding to those involved in visual localization in seeing subjects (Weeks et al., 2000). These studies of normal and clinical plasticity in humans therefore underline the effects of afferent information and experience on regional functional differentiation in cerebral cortex. Sadato and colleagues (2002) also showed more recently that such crossmodal plasticity effects are subject to critical periods. In their study, 'primary visual' cortex was activated during tactile discrimination only in subjects with blindness onset before age 16, but not with onset at a later age.

3.2 Plasticity caused by brain damage

Further evidence regarding neurofunctional development and its plasticity comes from imaging studies in children with brain damage. Brain damage in adults tends to result in persistent region-specific deficits (such as aphasia following left perisylvian lesion; (Caplan et al., 1996; Pedersen et al., 1995). In children however, early left lesion or left hemispherectomy is often associated with good long-term language outcome if the right hemisphere remains intact (Basser, 1962; Boatman et al., 1999; Curtiss et al., 2001; Vargha-Khadem et al., 1997; Vargha-Khadem & Mishkin, 1997). These differences may be related to critical periods of language plasticity and are thought to reflect an enhanced developmental potential for interhemispheric reorganization.

More recently, such effects have been demonstrated directly in imaging studies. In one PET study, 21 children with unilateral lesion and first risk within the first 6 years of life were examined (Müller et al., 1998). Left hemisphere patients showed robust right hemisphere involvement in simple language processes. In a follow-up study, effects of lesion onset were examined more directly in patients with unilateral left hemisphere lesion involving perisylvian language regions (Müller et al., 1999). When verbal auditory stimulation (listening to sentences) was compared to rest, perisylvian areas showed leftward asymmetry in healthy adults (Müller et al., 1997). This asymmetry was reduced in patients with late lesion and *reversed* in those with early lesion (Fig. 3). These findings were overall compatible with expected lesion onset effects, showing reduced left dominance for language-related processing in left lesion patients compared to normal adults, and overall greater interhemispheric reorganization in patients with *early* lesion compared to those with lesion acquired in adulthood. Concordant differences in perisylvian regions could also be shown for expressive language functions associated with sentence generation in a study that roughly matched small samples of early and late lesion patients for chronological age, lesion site, and VIQ (Müller et al., 1999). Nonetheless, inspection of rCBF changes in each patient showed considerable individual variation, most likely related to a host of clinical and demographic variables (such as underlying pathology, seizure disorder, and sex).

The use of PET in pediatric studies of reorganization is limited by the lack of age-appropriate normal control data (since healthy children are not usually studied with PET). FMRI studies, considered non-invasive and minimal-risk, do not underlie the same restrictions, but unfortunately only very few such studies on developmental plasticity for language have been published. One reason lies in the much greater motion sensitivity of fMRI compared to PET, which makes it difficult to acquire artifact-free fMRI data from young children (Eden & Zeffiro, 2000). A few studies examined the usefulness of fMRI for identification of eloquent language cortex in neurosurgery patients, but without directly addressing issues of reorganization (Benson et al., 1996; Hertz-Pannier et al., 1997; Lehericy et al., 2000; Stapleton et al., 1997). In one more recent study, language reorganization was assessed in a single child with Rasmussen's encephalitis (Hertz-Pannier et al., 2002). Word generation was associated with left frontal and inferior parietal activation before surgery, but with extensive right hemisphere activation after left hemispherotomy (extrathalamic white matter disconnection and callosotomy). Another study (Staudt et al., 2002) reported right hemisphere activations largely homotopic with left perisylvian language areas for silent word generation in a small sample of adult patients with a history of congenital left periventricular lesions.

The above neuroimaging studies of atypical language organization in patients with early onset left hemisphere lesion demonstrate plasticity guided by basic reorganizational principles. Even though premorbid and clinical variability is surely reflected in differences of neurofunctional outcome, certain types of postlesional reorganization appear common, whereas others are not seen. As discussed above, in studies of crossmodal plasticity of early deaf or blind subjects, one sensory modality can "invade" the territory of another modality that does not receive peripheral stimulation. Language reorganization even in cases of congenital or early postnatal lesion onset does not seem to include the potential for such invasion of unimodal sensorimotor cortex. In fact, the evidence for *intrahemispheric* reorganization into ipsilesional territory adjacent to the site of damage is inconsistent. On the other hand, evidence for a potential of *interhemispheric* reorganization is abundant. Here again the target sites of reorganization seem to be governed by strict principles and atypically strong activation is almost always seen in brain regions homotopic to those expected in healthy brains. Interestingly, these principles of language organization are different from those observed for the motor domain. In the latter, atypical ipsilateral activation of primary motor cortex is not as pronounced, whereas interhemispheric reorganization and lesion onset effects are mostly seen in secondary motor regions (Graveline et al., ; Müller et al., 1998; Müller et al., 1997).

Functional neuroimaging in pediatric patients thus supports the hypothesis of enhanced plasticity for language during the first decade of life. It also suggests that factors specific to each functional network affect the patterns of plasticity and postlesional reorganization. Thus, the differences observed between language and motor domains may be related to the earlier organization of motor circuits and the fact that humans start developing motor behaviors in utero (D'Elia et al., 2001), based on intrinsically driven processes that are much more directly under genetic control than is the case in language development. Motor circuitry becomes established relatively early in infants (Clearfield & Thelen, 2001), as opposed to language networks that develop much later and are characterized by a prolonged "critical period". However, the available functional imaging literature is suggestive rather than conclusive in all these respects.

One fundamental question remains to be addressed: How do different patterns of postlesional reorganization relate to cognitive compensation and long-term outcome for language? This question has only been examined in adult lesion patients recovering from aphasia. Greater than normal right perisylvian activations have been interpreted as beneficial (Calvert et al., 2000; Gold & Kertesz, ; Silvestrini et al., 1995; Thulborn et al., 1999; Weiller et al., 1995). However, none of the above studies directly compared patients with matched left hemisphere lesions that only differed in the degree of recovery. In a number of recent studies (Belin et al., 1996; Cao et al., 1999; Heiss et al., 1999; Rosen et al., 2000; Thomas et al., 1997; Warburton et al., 1999), good recovery from aphasia was found to be associated with reestablished activations in perilesional perisylvian cortex of the left hemisphere. The issue of how interhemispheric reorganization relates to language recovery is thus not fully resolved in adults. In children, this question has not yet been addressed in neuroimaging studies.

3.3 Neural underpinnings of developmental plasticity

A further question concerns the degree to which clinical studies of language plasticity can shed light on plasticity in *normal* development. Is malleability of functional organization a potential that is exclusively realized under abnormal circumstances (e.g., when crucial tissue substrates are damaged), or is this malleability a general characteristic of neurofunctional development? A simple but reasonable model of developmental language plasticity relates to the changes in synaptic density described above. Exuberant density in early development may imply excessive interregional and interhemispheric connectivity. This could be associated with a less distinctive or absent hemispheric asymmetry for language in the toddler (Fig. 5A).

Such an assumption would be overly simple because it is known that some potentially language-relevant asymmetries already exist in the neonate. These concern leftward asymmetries of the planum temporale (observed in the fetus), as well as auditory asymmetries detected in event-related potential (ERP) and dichotic listening studies of neonates and infants (Werker & Vouloumanos, 2001). Nonetheless, there is evidence pointing at greater right hemisphere language involvement during early stages of language acquisition. For instance, Mills and colleagues found that ERPs distinguishing known from unknown words were broadly distributed bilaterally in 13-17 month old infants, but more localized over left temporo-parietal sites in 20 month-olds (Mills et al., 1997). Neville & Mills (1997) further observed that a leftward asymmetry of ERPs to closed class (grammatical function) words, as found in adults, is absent or reversed in children under age 3 years. Studying children aged 5 years and older, Holcombe and colleagues (1992) found that ERP asymmetries observed in adults for semantic processing of sentence-final words are absent or inconsistent in children and become established only around age 13 years.

There is also limited neuroimaging evidence relevant to the question of right hemisphere language involvement in children. Balsamo and colleagues (2002) recently reported robust left dominance in lateral temporal areas for auditory response naming in children ages 7-9 years. However, this study did not directly compare children to adults. Gaillard et al. (2000), on the other hand, did find significantly greater overall right hemisphere involvement for verb generation in 8-13 year-old children, compared to young adults. Holland and coworkers (2001) studied subjects of a wider age range (7-18 years). They found a significant negative correlation between age and number of voxels activated in the right hemisphere overall. Laterality indices of activation were significantly correlated with age, indicating increasing left hemisphere dominance in older children and adolescents (for supportive evidence, see also Saccuman et al., 2002).

In agreement with these imaging studies, clinical evidence shows that in young children, lexical comprehension is more strongly affected by *right* (compared to left) hemisphere lesion (Bates, 1999; Thal et al., 1991; Vicari et al., 2000). Applying the above hypothesis of synaptic pruning and neurofunctional changes to lesion patients, loss of part of the initially rather distributed and bilateral network would results in stabilization of those parts of the network that remain intact. A left perisylvian lesion may thus result in suspended normal synaptic pruning and compensatory stabilization of synapses in right perisylvian regions (Fig. 5B).

The developing language network and in particular increasing left hemisphere lateralization for language in childhood may thus be considered a reflection of the general principle of synaptic pruning and stabilization. As discussed above, these synaptic changes are predominantly related to activity, stimulation, and interaction with environment, rather than being specified in the genome. Changes in the hemispheric organization for language, both in clinical lesion patients and in healthy children, thus epitomize the importance of epigenetic factors on neural and cognitive organization for language.

4 CAN DEVELOPMENTAL PATHOLOGY BE STUDIED WITH FMRI?

In the previous section, a number of imaging approaches were reviewed that elucidate neurofunctional development and the plasticity of the child brain. As mentioned, PET is hampered by ethical issues resulting in a lack of normative data. While PET continues to be of great promise for the study of brain biochemistry (Herscovitch & Ernst, 2000; Morris et al., 2000), its use in the imaging of task-related activation is limited by additional methodological disadvantages. In comparison with functional MRI, PET has a lower spatial and temporal resolution.

In particular, recent advances in event-related fMRI make it possible to study multiple conditions or trial types in randomized order with a temporal resolution of a few seconds (Miezin et al., 2000) or even less (Hernandez et al., 2002). Nonetheless, fMRI still has its limits in the study of developmental disorders. The mentioned sensitivity to motion artifacts makes it virtually impossible to study children under the age of 4 or 5 years during task performance in the awake state. MR imaging during natural sleep is possible (Courchesne et al.), but the range of cognitive processes that can be examined through passive stimulation is narrow.

As discussed above, child language disorders in DLD or autism are associated with strong genetic factors. It is likely that pathogenesis begins before birth in these disorders. Even if the age limit in fMRI can be lowered with more sophisticated head restraints and motion correction algorithms, imaging data will still primarily reflect *outcome* of initial pathogenic events. A pessimistic approach might discard functional neuroimaging in such genetically anchored disorders as irrelevant. However, the picture is much less bleak when the mechanisms that determine neurofunctional organization are taken into account. From the above discussion, it has become clear that functional organization in the mature brain largely reflects developmental processes (genetically driven regionalization, activity-driven arealization, fine-tuning through experience-driven synaptic pruning and stabilization). Any aberration of these normal developmental processes can therefore equally be expected to manifest itself in the more mature brain, in terms of atypical functional organization. The application of fMRI can then be considered "archaeological" because it may uncover developmental abnormalities that occurred long before the time of study.

4.1 Archaeological fMRI in the study of autism

This section will describe a hypothetical model of neurofunctional abnormalities in autism that illustrates how fMRI findings in older children and adults can shed light on pathological changes occurring much earlier in development, when functional maps first emerge. The hypothesis ties together structural and functional findings in the cerebellum with atypical functional maps seen in cerebral cortex.

Autism is most commonly thought of in terms of impairments of language and social communication. On the other hand, motor impairments have been observed by many investigators (Bauman, 1992; Eisenmajer et al., 1998; Ghaziuddin & Butler, 1998; Haas et al., 1996; Hughes, 1996; Jones & Prior, 1985; Rapin, 1997; Rinehart et al., 2001). Stereotypic behavior, which is a characteristic of autism, can be observed on the cognitive level (e.g., as obsessive interest in unusual objects), but also on a motor level, for instance in hand flapping seen in many patients. Interestingly, a study by Teitelbaum and colleagues (1998) suggests that abnormalities of elementary motor behaviors (e.g., righting, sitting, crawling) may be observed in the first months of life in children later diagnosed as autistic. A more recent retrospective study (Osterling et al., 2002) found additional behavioral markers (looking preferences, gestures etc.) that distinguished 1 year-old infants later diagnosed as autistic from those with mental retardation, but also identified repetitive motor behavior as one of the discriminating variables. Motor impairments thus emerge earlier or in parallel with socio-communicative, linguistic, and cognitive deficits, which may suggest an elementary role of motor impairments in autism. As mentioned, simple motor behavior normally begins in the fetus (D'Elia et al., 2001; Forssberg, 1999; Hepper, 1995). This indicates that neurofunctional organization of the motor system probably emerges early, during phases of development when autistic pathogenesis sets in.

Several fMRI studies looked at motor organization in autism from different angles. The first two examined extremely simple motor behavior (single finger movement). In one study (Allen & Courchesne, 2003), subjects performed button presses with the thumb. Only the cerebellum and posterior cerebrum were imaged. Cerebellar activity overall was greater in autistic patients. In particular, many patients showed activations scattered beyond the site of activation seen in normal adults (the anterior cerebellum ipsilateral to the movement). A second study (Müller et al., 2001) extended these observations to the cerebrum. Again, subjects performed simple finger movements (here: visually paced button presses with the index finger). When fMRI data were analyzed for whole groups of 8 normal and 8 autistic subjects each, few striking differences were apparent. Activations in typical motor regions (primary motor cortex, premotor cortex, supplementary motor area, basal ganglia) were simply less pronounced in the autism group. Such groupwise analyses in Talairach space are common procedure in studies of autism and

Asperger syndrome. Our study showed that this procedure might severely limit the ability to detect abnormalities in patients. When we analyzed imaging data on a subject-by-subject basis in native space (i.e., without warping to standardized space), we found that each control subject showed expected activation clusters along the central sulcus, in primary motor and somatosensory cortex. Autistic individuals also showed activation in this site, but most patients showed unusual additional activation outside typical motor areas, for example, in prefrontal cortex and in the superior parietal lobe (Fig. 6). The overall picture was thus highly similar to the scattered and unusually distributed activation patterns in the cerebellum, seen in the first motor study.

Similar analysis procedures were applied in a study on face perception (Pierce et al.). In groupwise analyses, normal activation in fusiform gyrus was absent in autistic patients. Inspection of single patient data in native space, however, demonstrated that loci around the fusiform gyrus (the site of main activation in normal adults) were activated in the majority of patients, even though these activations were scattered and individually highly variable.

A third motor study looked at more complex visually driven motor sequence learning. Again, we found unusual variability across autistic individuals with regard to the spatial loci of major activation foci in premotor and superior parietal lobes (the main sites of activation during early stages of digit sequence learning). In addition, groupwise abnormalities were also consistent with a general hypothesis of "hierarchical crowding" that was derived from the findings of the two motor studies described earlier. This hypothesis is based on the assumption that neural tissue has a generally reduced processing capacity in autism. (For supportive evidence, see Casanova et al., 2002, and the discussion below.) This impaired processing capacity would imply that early developing functional systems, for example, the visual and motor systems, require more processing territory than in the normal brain. Those additional territories will then be less available to later emerging higher polymodal cognition. The results from the study on simple finger movement (Müller et al., 2001) were consistent with this model because autistic individuals showed activation scattered beyond primary pericentral regions in frontal and parietal cortex (Fig. 7A). Findings on more complex visually driven motor learning (Müller et al., under review) were also consistent in that the autism group showed reduced activation in sites that were most robustly activated in normal adults (premotor and superior parietal cortex), but enhanced activation in prefrontal and more inferior parietal regions that are typically not involved in visuomotor coordination and digit sequence learning (Fig. 7B). These findings could explain why autistic patients show impairments of executive processing and delays of language acquisition (because prefrontal and inferior parietal lobes are partly "invaded" by simpler functional domains, such as visuomotor coordination).

The hypothesis of hierarchical crowding implies that abnormal emergence of functional maps early in development is reflected by persistent abnormalities in the adult autistic brain. This hypothesis is quite general and requires more specific neuroscientific support. One line of evidence relates to the parallel findings of activation scatter in autistic cerebellum and cerebrum described above. Even though there is much inconsistency regarding sites of volumetric abnormality in the autistic brain (reviewed in Cody et al., 2002), many studies have found evidence for cerebellar abnormalities (Courchesne et al., 2001; Courchesne et al., 1994; Courchesne et al., 1988; Gaffney et al., 1987; Hardan et al., 2001; Hashimoto et al., 1995; Murakami et al., 1989; Otsuka et al., 1999). Nonetheless, non-replications should be noted (Filipek, 1995; Holttum et al., 1992; Piven et al., 1997), as should be methodological issues regarding IQ matching that may confound cerebellar effects (Cody et al., 2002; Piven & Arndt, 1995; Yeung-Courchesne & Courchesne, 1997). In a postmortem study including 6 brains (Bailey et al., 1998), the most consistent finding was abnormality involving cerebellar Purkinje neurons. Reduced cerebellar measures in autism are associated with deficits of attention (Harris et al., 1999; Townsend et al., 1996) and reduced exploratory behavior (Pierce & Courchesne, 2001). Cerebellar hypoplasia presumably reflects reduced numbers of Purkinje neurons, which may set in prenatally (Courchesne, 1997) or in early postnatal stages (Bailey et al., 1998). PET studies have also identified abnormalities of serotonin synthesis in the cerebellar dentate nucleus in autistic boys (Chugani et al., 1997); see below).

As discussed above in section 2, animal work (O'Leary et al., 1994) has demonstrated the importance of thalamocortical afferents for neocortical differentiation and the development of adult maps of functional specialization. The cerebellum is heavily interconnected via the thalamus with almost all neocortical regions in

topographic and functionally specific ways (Schmahmann, 1996). Cerebello-thalamo-cortical fibers originate almost exclusively from deep cerebellar nuclei (in particular the dentate nuclei), which in turn receive synaptic inputs from inhibitory Purkinje cells in cerebellar cortex (Altman & Bayer, 1997). Cerebellar afferents to the thalamus terminate in ventrolateral "motor" nuclei (Altman & Bayer, 1997) p:71ff), but also in a variety of non-motor thalamic nuclei (Middleton & Strick, 1994; Schmahmann, 1996).

As noted, postmortem histological studies of autistic brains show reduced numbers of Purkinje cells (Bailey et al., 1998; Bauman & Kemper, 1986). Reduced cerebellar levels of Reelin and Bcl-2, as observed in autistic postmortem brains, may be related to disturbances in migration, cortical lamination, and apoptosis (Fatemi et al., 2001) – although it must be noted that these findings from adult brains do not directly establish developmental abnormalities. Finally, absence of "empty" basket cells suggests that Purkinje cell reduction in adults is due to reduced neuronogenesis rather than subsequent loss (Bailey et al., 1998; Courchesne, 1997). Growth interaction between basket cells and Purkinje cells takes place before the differentiation of Purkinje cells is completed (around postnatal day 8 in the rat (Altman & Bayer, 1997), which roughly corresponds to the end of the second trimester in human gestation (Clancy et al., 2001)).

Early Purkinje cell loss may thus affect thalamocortical afferents from deep cerebellar nuclei. This could in turn have indirect effects on functional differentiation of cerebral cortex in autism ('misconstruction'). Inhibitory synapses of Purkinje cells in deep cerebellar nuclei probably form around the beginning of the third trimester in humans (Clancy et al., 2001; Garin & Escher, 2001). In the thalamus, afferents from deep cerebellar nuclei are present at birth in the rat, i.e. preceding the above events (Asanuma et al., 1988). Early Purkinje cell loss in autism may thus impair developing cerebello-thalamo-cortical connectivity and cerebral cortical functional differentiation, as reflected in abnormally scattered fMRI activation patterns.

Based on the hypothesis of aberrant cerebello-thalamo-cortical pathways in autism, one would have to expect evidence for thalamic abnormalities. Even though the evidence is limited to date, a few studies have reported reduced thalamic perfusion in autistic patients (Starkstein et al., 2000) reduced correlation of glucose metabolic rates between thalamus and fronto-parietal regions, which may be an index of impaired thalamocortical networks (Horwitz et al., 1988). A recent MR spectroscopy study found reductions of the neuronal marker *N*-acetylaspartate in the thalamus bilaterally in autistic children aged 3-4 years (Friedman et al., 2003). In a PET study using a serotonin precursor as tracer, Chugani et al. (1999; 1997) observed a characteristic pattern of increased serotonin synthesis in the cerebellar dentate nucleus, accompanied by decreases in contralateral thalamus and frontal cortex in autistic boys (but not girls). Serotonin plays an important role in neuronal differentiation and synaptogenesis. In particular, serotonin is crucially involved in the establishment of thalamo-cortical connectivity (Bennett-Clarke et al., 1996; D'Amato et al., 1987; Lauder, 1990; Lieske et al., 1999). The findings of the PET studies by Chugani and colleagues came from children aged 2 years and older and therefore do not conclusively demonstrate that serotonergic abnormalities are present when thalamocortical afferents are first established. Interestingly, a PET activation study in male autistic adults yielded some preliminary evidence for persistent functional impairments of dentato-thalamo-cortical pathways during language processing, albeit in a very small sample (Müller et al., 1998).

The above scenario would imply that developmental abnormalities of cerebello-thalamo-cortical afferents result in persistent neurofunctional abnormalities of autistic cerebral cortex. This scenario is not meant to be a comprehensive neurocognitive model of autism, but may account for some aspects of autistic pathogenesis. Other mechanisms are certainly involved. For example, a recent postmortem study suggests abnormal columnar architecture in frontal and temporal areas of the autistic brain (Casanova et al., 2002). These would probably require explanation in terms of neuromigrational disturbances. For another example, MR volumetric work (Courchesne et al., 2001) demonstrates rather diffuse brain growth disturbances in autism, with greater than normal growth up to age 2-4 years (as also reported by Sparks et al., 2002) and subsequent reduced or stunted growth especially in white matter. These results may be related to findings of abnormal brain growth factors in neonates later diagnosed as autistic, which were however not specific for autism in comparison with non-autistic mental retardation (Nelson et al., 2001). All in all, it is likely that potential cerebello-thalamo-cortical abnormalities are accompanied by more global neurodevelopmental disturbances.

It is unclear at this point how these different types of disturbances may interact in causing typical autistic impairments, such as language delays and deficits. In any case, the hypothesis of developmental cerebello-thalamo-cortical disturbances causing abnormalities in cerebral cortical functional maps serves, in the present context, as an illustration of how functional neuroimaging in older children and adults can shed light on much earlier occurring developmental events that are characteristic of an emerging language disorder. It also underlines that in autism, as in developmental language disorders (with the possible exception of rare cases, such as family KE), direct lines of causality between genes and language impairments are improbable (Gottlieb & Halpern, 2002; Pennington, 2001). Instead, the effects of suspected genetic risk factors and their interactions must be examined in the developing nervous system, in particular with regard to changes in normal activity-driven formation of the functional organization of cerebral cortex.

5 CONCLUSION

One of the goals of this review was to illuminate why relationships between genotypes and language-related phenotypic traits are unlikely to be simple and linear. This caveat applies to normal development as much as to developmental disorders. Divergence as well as convergence of genotype-phenotype links complicate the study of developmental disorders. We cannot expect simple genetic explanations for developmental disorders of language that are diagnosed with respect to diverse sets of consensus-based behavioral outcome criteria.

Without regard for the basic epigenetic principles of neurofunctional development, the search for one or a few genes that may "explain" language impairment in such disorders is almost certainly futile. While this may sound pessimistic, a realistic neurodevelopmental perspective, on the contrary, opens up experimental windows that have not previously been explored. One example is the use of functional neuroimaging in older children and adults with developmental disorders. The principles of activity-based neurofunctional organization of cerebral cortex allow us to interpret functional maps in patients as *reflections* of disturbances that occurred early in development. The traces of fetal and early postnatal abnormalities are therefore not entirely lost, but may be recovered even at later stages when patients become available for functional neuroimaging.

Acknowledgements

Supported by the National Institutes of Health (1R01-NS43999, 1R01-DC6155).

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Figure Legends

Figure 1. Schematic depiction of divergent and convergent principles in genotype-phenotype relations. (A) Divergence corresponds to pleiotropy in single-gene mutations, which have multiple effects in different (brain and non-brain) systems of the mature phenotype. (B) Convergence relates to phenotypically defined symptoms or disorders that may be caused by multiple different genetic alterations or by combinations of multiple genetic risk factors.

Figure 2. Developmental curves of glucose metabolism and synaptic density. (A) The top part of the figure (adapted from Chugani, 1991: p23-26) shows global glucose metabolism in a 6-year old child at levels 2-3 times higher than seen in adults. The period of elevated glucose metabolism is seen between about ages 2 and 10 years. This developmental curve corresponds well to changes in synaptic density during childhood. The lower part of the figure (B) shows synaptic density for primary visual, primary auditory, and prefrontal cortex (adapted from Huttenlocher & Dabholkar 1997).

Figure 3. Asymmetry regional blood flow changes (left minus right) in frontotemporal perisylvian cortex during verbal auditory stimulation (listening to sentences). Blood flow increases (activations) show leftward asymmetry in normal adults, bilaterality in patients with late onset left hemisphere lesion and reversed asymmetry (right hemisphere dominance) in patients with early onset left hemisphere lesion. The findings support the hypothesis of an overall greater potential for interhemispheric reorganization in the first years of life, compared adolescence and adulthood. Adapted from Müller et al. (1999).

Figure 4. Single-case examples of brain activations during an expressive language task (sentence generation), in which subjects create and overtly produce a sentence based on a stimulus sentence and a prompt word (e.g., "He listened to the radio – *television*", with expected response: "He watched television"). The control condition was sentence repetition. (A) An 8-year old male subject with a progressive calcification of congenital origin in the left hemisphere (Sturge-Weber syndrome) shows extensive right hemisphere frontal and parietal activation. (B) In contrast, a 17-year old female intractable epilepsy patient with seizure onset at age 10 and resection of left temporal epileptogenic tissue at age 13 years shows exclusively left hemispheric activation in fronto-temporal areas during sentence generation. These activations resemble those seen in a group of 9 healthy adults (C). Adapted from Müller et al. (1999; 1997).

Figure 5. Diagrammatic sketch of hypothesized links between synaptic pruning and regional and hemispheric organization for language. During synaptic abundance in early childhood, language processing involves numerous frontal, parietal and temporal regions in both hemispheres (A). Some of these interregional connections stabilize and strengthen during development, resulting in the typical left perisylvian organization for language in the mature brain. However, when left perisylvian regions are damaged early in life (B), some of the normal synaptic pruning is suspended and alternative connectivity, especially in homotopic right hemisphere regions, becomes selectively stabilized.

Figure 6. Typical examples of activations seen during visually prompted index finger movement. (A) In normal controls, focal activations are seen (primary motor and somatosensory cortex) along the central sulcus (green lines) with some additional activity in mediofrontal supplementary motor area (subject upper row, center). (B) Autistic individuals also show activations in these areas, but their activation patterns are more scattered, with distributed activation in parietal and prefrontal areas.

Figure 7. Schematic diagram of hypothesized effects of scattered functional maps in autism. (A) Simple motor execution scenario (corresponding to the findings in Müller et al. 2001). (B) Motor learning scenario corresponding to findings of Müller et al. (under review). Dark shaded circles indicate regions of stronger activation in normal adults, light shaded circles those of stronger activation in autistic patients. Dotted arrows indicate direction of scatter

beyond regions of normal primary activations observed in autistic patients. Adapted from Müller et al. (under review).

Fig. 1

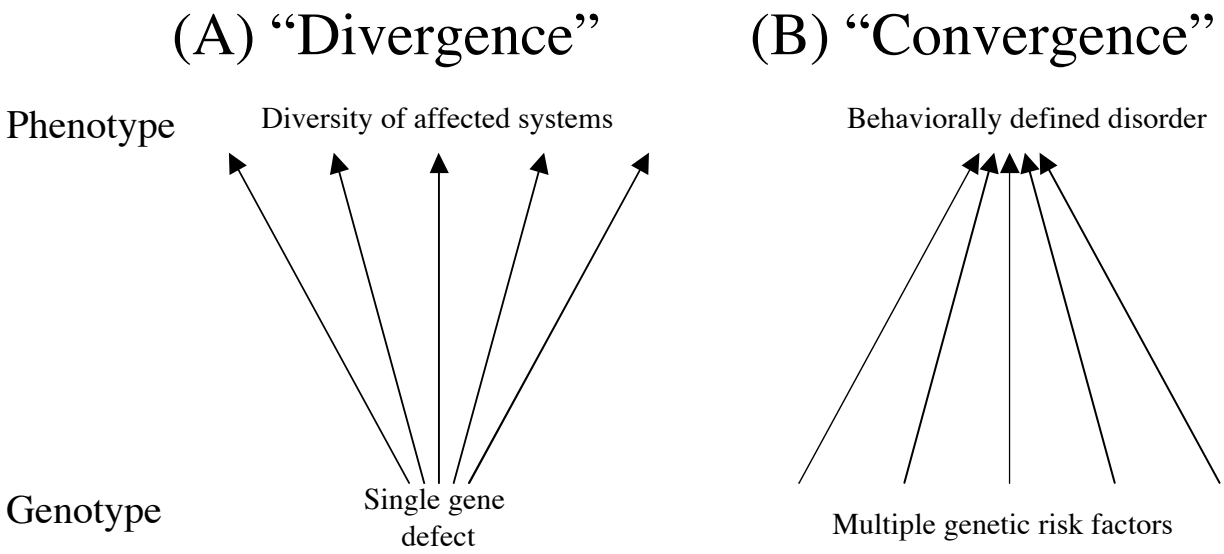
(A) "Divergence"
(B) "Convergence"
Phenotype
Diversity of affected systems
Behaviorally defined disorder
Genotype
Single gene defect
Multiple genetic risk factors

Fig. 2

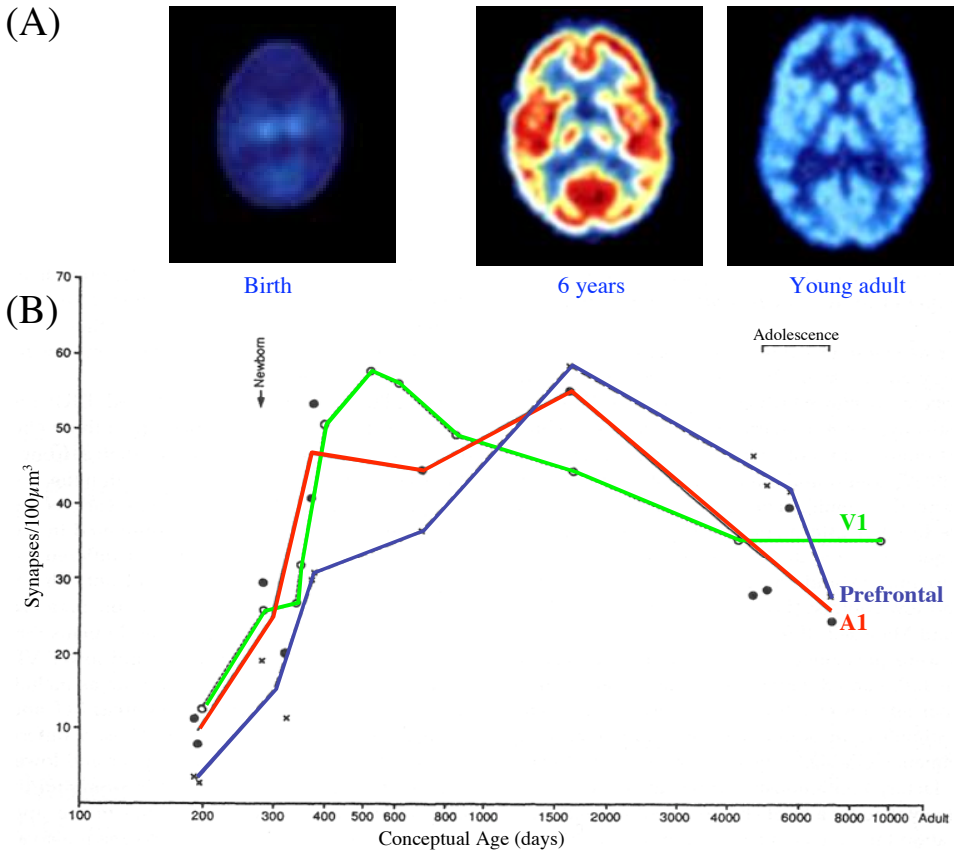
(A)
Birth
6 years
Young adult
(B)
Adolescence
Newborn
Synapses/100μm^3
V1
Prefrontal
A1
Conceptual Age (days)
Adult

Fig. 3

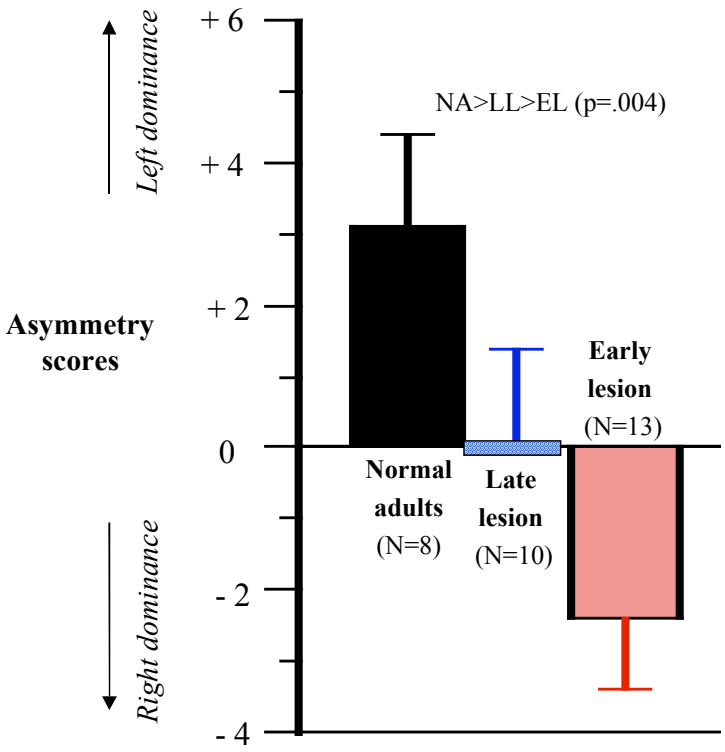
+ 6
+ 4
+ 2
0
- 2
- 4
Left dominance
Right dominance
Asymmetry scores
NA>LL>EL (p=.004)
Normal adults (N=8)
Late lesion (N=10)
Early lesion (N=13)

Fig. 4

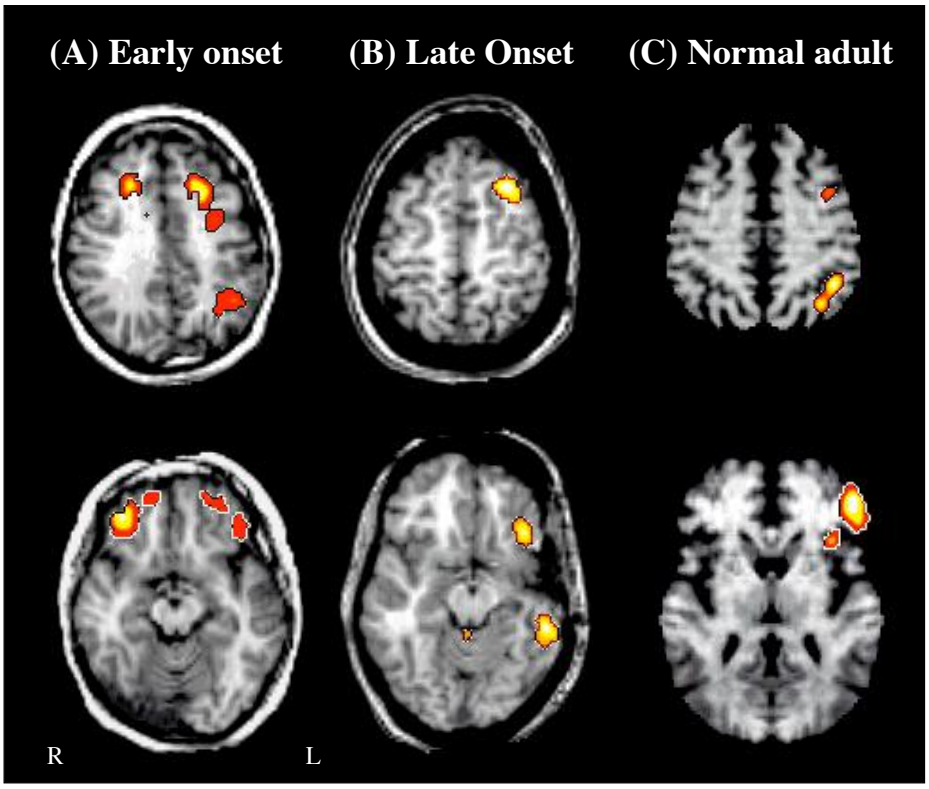
(A) Early onset
(B) Late Onset
(C) Normal adult
R
L

Fig. 5

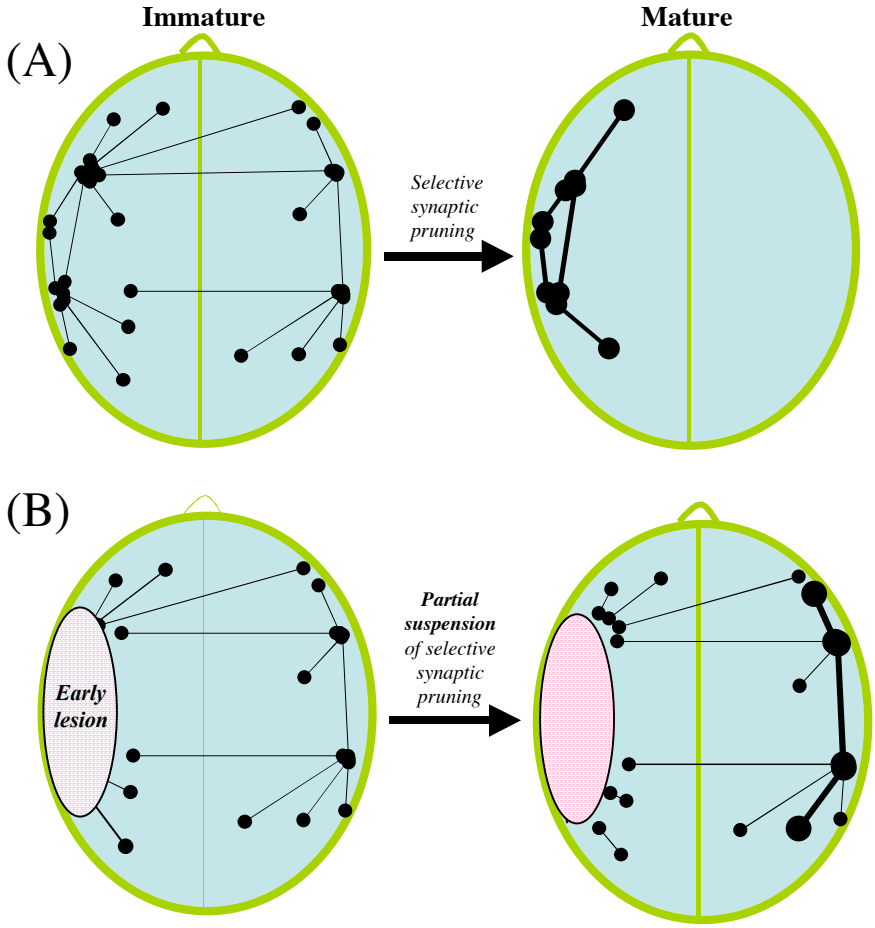
Immature
Mature
(A)
Selective
synaptic
pruning
(B)
Early
lesion
Partial
suspension
of selective
synaptic
pruning

Fig. 6

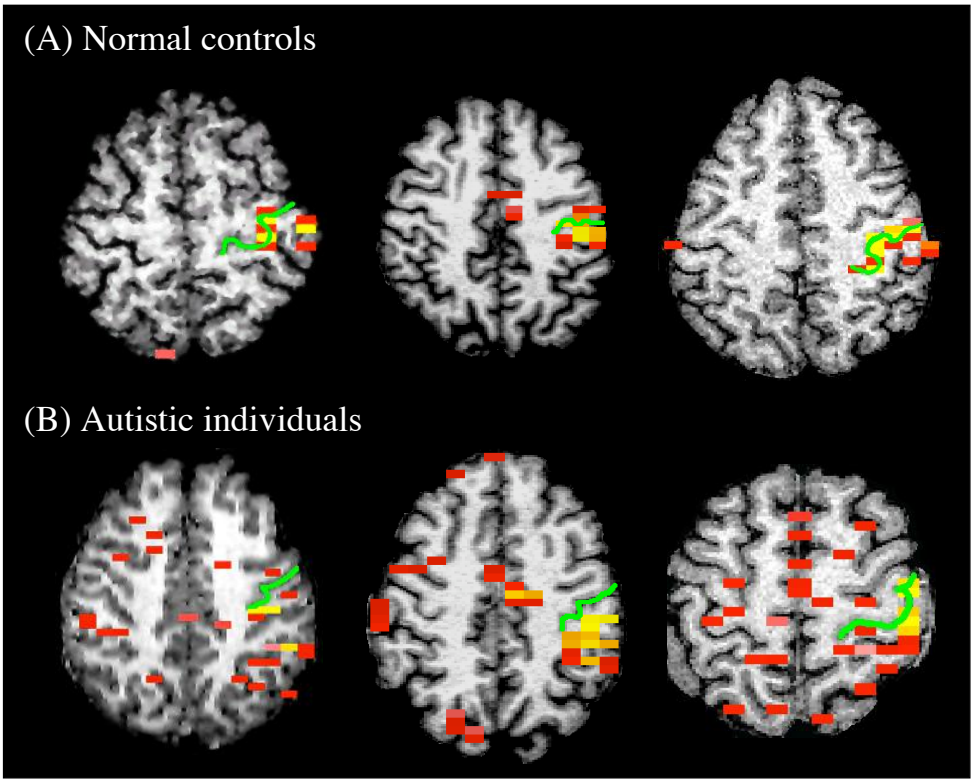

Fig. 7