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Functional neuroimaging of developmental disorders: Lessons from autism research

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Any attempt to cover neuroimaging contributions to the large number of disorders that can be considered neurodevelopmental within a single chapter would be overly ambitious. Disturbances or defects can hit the developing nervous system in uncountable different sites and ways, and the resulting spectrum of impairments is vast. In a first approach, neurodevelopmental disorders can be grouped into three distinct classes: (i) Disorders that result from some kind of disturbance (e.g., neuromigrational) or lesion (e.g., stroke) during intrauterine or early postnatal phases; (ii) those caused by defects of a single gene or a well-defined chromosomal locus; and (iii) those known to be predominantly genetic in nature, but involving multiple different genetic (and epigenetic) risk factors.

Among the disorders of type (i), there are subtypes that demonstrate the astounding potential of the developing brain for compensatory reorganization. The most positive examples of developmental plasticity come from cases of perinatal or early postnatal stroke, or from neurodegenerative diseases such as Sturge-Weber syndrome or Rasmussen's encephalitis, which usually affect only one cerebral hemisphere, leaving the other intact. For instance, behavioral studies have documented the often surprisingly good language outcome in early left-hemisphere lesion patients (Nass & Stiles, 1996; Vicari et al., 2000), although etiology (Curtiss et al., 2001; Pulsifer et al., 2004) and presence or absence of seizures are important predictive variables (Isaacs et al., 1996; Muter et al., 1997). Similar positive outcomes have been reported for patients who underwent hemispherectomy following early onset left hemisphere disease (Curtiss & de Bode, 1999; Jonas et al., 2004; Vargha-Khadem et al., 1997; Vargha-Khadem & Mishkin, 1997). Functional neuroimaging studies in groups of early lesion patients (Müller et al., 1999b; Staudt et al., 2002) and in a single hemispherotomy patient (Hertz-Pannier et al., 2002) generally suggest that compensatory plasticity and good language outcome may be supported by neurofunctional reorganization, in particular atypical involvement of right hemisphere regions homotopic to the classical left perisylvian language areas (Broca's and Wernicke's). Although as mentioned the integrity of the right hemisphere is an important prognostic factor, it currently remains uncertain what other clinical variables drive or prevent interhemispheric reorganization for language (Liegeois et al., 2004).

There is additional evidence showing that not all neurodevelopmental disorders of type (i) will have relatively beneficial outcome. On the contrary, very early neurodevelopmental disturbances derailing basic organizational stages of brain development may result in severe brain malformations with negative prognosis. This has been shown through controlled lesion experiments in animals. For instance, Kolb and colleagues (1996) observed reduced functional sparing when bilateral frontal or parietal resections were performed at postnatal day 1 compared to day 10 in rats. These time points approximately correspond to human gestational month 5 and postnatal month 6, respectively. In cats, Villablanca and colleagues (1993a; , 1993b) showed good recovery after left frontal cortical ablation at postnatal days 8-14, whereas similar ablation during the third gestational trimester resulted in severe sensorimotor impairments. According to Kolb and Gibb (2001), animal lesion models overall suggest that "damage [at the] time of neural migration and the initiation of synaptic formation… is associated with dismal outcome" (ibid.: p179). In humans, neuromigrational disturbances, as seen in cortical dysplasia and heterotopia, are typically associated with epilepsy and cognitive impairment (Palmini et al., 1995; Raymond et al., 1995). Neurotoxins such as ethanol that are known to affect neuronal survival (Farber & Olney, 2003) and migration have profound and life-long effects on the CNS. Fetal exposure to alcohol is often associated with microcephaly, neuronal apoptosis (Farber & Olney, 2003), white matter reduction (especially in parietal lobes; Archibald et al., 2001), reduced size of the caudate nuclei (Chen et al., 2003; Mattson, 2000), and in severe cases with widespread cerebral dysgenesis and malformation (Coulter et al., 1993).

The catalogue of neurodevelopmental disorders of type (ii) has become longer in the past decade because for some disorders that had been previously described in clinical-behavioral terms relatively simple genetic causes have been identified. One such example is Williams syndrome, a disorder initially characterized based on a diverse set of features, such as atypical "elfin" faces, supravalvular aortic stenosis, deficient bodily growth, hypercalcemia, and severe visuospatial deficits in the context of often apparently good verbal abilities (Donnai & Karmiloff-Smith, 2000). In the early 1990s, the genetic cause of the disorder was identified as a microdeletion of the elastin gene and adjacent genes on chromosome 7 (Ewart et al., 1993; Morris, 2004). Another example is Rett syndrome, initially defined in clinical terms based on regressive loss of praxic and communicative abilities in young girls, with an outcome of severe retardation. In the late 1990s, it was discovered that up to 90% of sporadic (non-familial) cases of Rett syndrome presented with a mutation in the *MECP2* gene, a transcriptional repressor on the X chromosome (Shahbazian & Zoghbi, 2002).

Neurodevelopmental disorders of type (ii) are attractive because knowledge of affected genetic loci promises to open windows onto links between genes of phenotypes. However, even in single-gene disorders these links appear to be highly complex. Williams syndrome, for instance, affects numerous bodily and neural systems. Even when phenotypic traits are largely limited to the brain these traits affect a diversity of functional systems. An even more telling example comes from the recently described heritable disorder associated with language impairment that was identified in multiple members of family KE. This disorder was first described from a linguistic perspective as a selective impairment within the grammatical (more precisely: morpho-syntactic) domain (Gopnik & Crago, 1991). In 1998, it was linked to a locus on chromosome 7 (7q31), and the gene was suggestively labeled "SPCH1" (Fisher et al., 1998). The finding was greeted with enthusiasm by some in the linguistic community whose research had been based – following the groundbreaking work by Chomsky (1965) – on the theory of a genetically anchored language ability ("universal grammar") distinguishing humans from non-human primates. For instance, the most eloquent current spokesman for the Chomskian view, Steve Pinker (2001), saw the identified gene as playing "a causal role in the development of the normal brain circuitry that underlies language and speech" (p. 465).

Upon careful consideration, however, the disorder in family KE tells a very different story. First, more comprehensive clinical and neuropsychological evaluation of affected members was inconsistent with a selective morpho-syntactic deficit, demonstrating a broad picture of impairments including reduced non-verbal IQ, orofacial apraxia, and reduced phonological working memory (Vargha-Khadem et al., 1995; Watkins et al., 2002). Secondly, the gene initially called *SPCH1* was more accurately classified as a gene encoding forkhead transcription factors, therefore more aptly called *FOXP2* (Lai et al., 2001). Forkhead proteins are transcription factors that are involved in diverse very basic developmental events, such as cell differentiation and proliferation (Marcus & Fisher, 2003). Disappointingly for those who expect to have identified a "language gene", *FOXP2* is expressed during embryonic development, not only in the brain, but also in other organs such as the lungs and the heart. Recent findings of a cosegregation of one coding change of *FOXP2* with verbal apraxia could reflect a more specific link, but it remains clear that defects of the *FOXP2* gene will account for only a very small fraction of developmental language impairments (MacDermot et al., 2005). In conclusion, what appeared the most promising discovery in the study of the genetic origins of language turned out to be a tale of caution (for discussion, see Fisher, 2005; Müller, 2004, 2005).

The present chapter is dedicated to neuroimaging of developmental disorders of type (iii), which can be justly considered the most challenging type. One of the most puzzling of these disorders is autism, which will be the focus of the remainder of this chapter. Contrary to the disorders described above, autism is known to be strongly genetic, but probably involves many different genetic (in addition to epigenetic) risk factors located on several chromosomes. This developmental complexity raises special issues in the use of functional neuroimaging.

Autism

Autism is a neurodevelopmental disorder with a high prevalence of 2-4 in 1000 children (Baird et al., 2006; Fombonne et al., 2006). The disorder affects multiple domains of cognitive, perceptuomotor, and sociobehavioral function (Rapin, 1997; Tager-Flusberg et al., 2001). The rate of mental retardation in the autistic population is about

75%, and the vast majority of affected individuals requires lifelong institutional or therapeutic support (Rapin & Katzman, 1998).

By today's consensus, autism requires explanation in neurological terms. However, comprehensive models of neuropathological development in autism are not currently established. Diagnosis of autism is typically made relatively late (around age 3 years), whereas crucial etiological events may occur much earlier in postnatal or prenatal development. In addition, since many different etiological pathways (Trottier et al., 1999) may result in cognitive-behavioral phenotypes that fulfill diagnostic criteria for autism (American Psychiatric Association, 2000), the probability of identifying *consistent* abnormalities in brain imaging or event-related potential (ERP) studies is reduced (see below).

From twin studies it is known that genetic factors are heavily involved in autism (Bailey et al., 1995). Linkage studies have further identified numerous potential genetic loci, but the current consensus on specific sites of susceptibility for autism remains limited (Folstein & Mankoski, 2000; Korvatska et al., 2002; Muhle et al., 2004). Furthermore, some studies suggest that non-genetic etiological mechanisms, such as viral infection (Lotspeich & Ciaranello, 1993; Tanoue et al., 1988) or neurotoxic exposure in utero (Edelson & Cantor, 1998; Rodier et al., 1997; Stromland et al., 1994) may increase the risk of autism. Finally, autism spectrum disorders are often associated with other medical disorders (Gillberg & Coleman, 1996; Miller et al., 2005) – such as tuberous sclerosis (Gillberg et al., 1994) – even though it is unclear whether such associations relate to mental retardation rather than autism per se (Barton & Volkmar, 1998).

A unique genetic or epigenetic cause of autism is therefore unlikely. Consequently, we have to expect that there are multiple etiological pathways and patterns of neurodevelopmental disturbances that ultimately result in a cognitive-behavioral phenotype fulfilling diagnostic criteria for autism. From this perspective, it is not surprising that numerous brain regions have been reported as affected in diverse neuroanatomical studies, sometimes without replication (reviewed in Akshoomoff et al., 2002; Brambilla et al., 2003). Findings of abnormality have been reported for the frontal (Carper & Courchesne, 2005; Herbert et al., 2004), parietal (Courchesne et al., 1993), and lateral temporal lobes (Rojas et al., 2005; Zilbovicius et al., 2000), the cingulate region (Abell et al., 1999; Haznedar et al., 1997), the corpus callosum (Egaas et al., 1995; Piven et al., 1997; Waiter et al., 2005), the hippocampal formation and amygdala (Bauman & Kemper, 1994; Otsuka et al., 1999; Raymond et al., 1996; Saitoh et al., 2001; Schumann et al., 2004), as well as the basal ganglia (Hollander et al., 2005; Sears et al., 1999), the thalamus (Tsatsanis et al., 2003), and the brainstem (Hashimoto et al., 1995a; Rodier, 2002). Besides these, the brain region that has received most attention is the cerebellum. Cerebellar abnormalities have been identified in a number of studies (Courchesne et al., 1994a; Courchesne et al., 1988; Gaffney et al., 1987; Hashimoto et al., 1995b; Murakami et al., 1989; Otsuka et al., 1999), some of which indicated specifically reduced size of the posterior vermis (lobules VI-VII`; Courchesne et al., 2001; Courchesne et al., 1988; Murakami et al., 1989). In postmortem studies, the most consistent finding has been reduced numbers or size of cerebellar Purkinje neurons (Bailey et al., 1998; Palmen et al., 2004). However, cerebellar findings have not been replicated in an equally large number of MR volumetric studies (reviewed in Brambilla et al., 2003). The degree to which cerebellar findings are specific to autism has thus not been definitively established.

Functional neuroimaging in autism

Starting in the mid 1980s, functional imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) began to be applied to the study of autism. These studies were usually limited to single conditions, with subjects being scanned at rest, with eyes closed (Horwitz et al., 1988; Rumsey et al., 1985) or open (George et al., 1992; McKelvey et al., 1995; Mountz et al., 1995; Schifter et al., 1994; Sherman et al., 1984), or during sedation (Chiron et al., 1995; De Volder et al., 1987; Ohnishi et al., 2000; Zilbovicius et al., 2000). Only in a few studies, cognitive conditions were controlled through experimental conditions, such as verbal learning (Haznedar et al., 1997) and continuous performance tasks (Buchsbaum et al., 1992; Heh et al., 1989; Siegel et al., 1992). Some of these early studies yielded intriguing results. For instance, Horwitz and colleagues (1988) found reduced correlation in regional glucose metabolism between frontal, parietal, thalamic and neostriatal regions in young autistic men, suggesting disruptions of functional networks. As I will describe below, this

study anticipates some of the promising approaches in current functional neuroimaging research on autism. All in all, however, it is hard to draw conclusions from the single-condition PET and SPECT studies listed above because of the diversity and even inconsistency of many findings. For one example, in the very first such study, Rumsey and colleagues (1985) observed widespread hypermetabolism in young autistic men. Contrary to this, Herold and colleagues (1988) reported normal rates of glucose metabolism and regional cerebral blood flow in a small sample of young autistic men. De Volder et al. (1987) also found normal rates of glucose metabolism in autistic children and adolescents (including females).

The literature on single-condition functional imaging studies, is reviewed in detail by Chugani (2000). Inconsistencies in this literature can be attributed to several factors: Differences in mental condition (task performance, rest, sedation); differences in inclusionary criteria (age, gender) as well as in diagnostic criteria for autism; and differences in the selection of control groups (e.g., healthy controls, siblings, mentally retarded controls). Some of the shortcomings in early studies have been overcome in more recent functional neuroimaging work of a different type, i.e., task-induced activation studies. Further progress has been driven by the need in the autism field in general to tighten diagnostic criteria. Thus, it has become standard to include only subjects who fulfill criteria on the retrospective Autism Diagnostic Interview (ADI-R; Rutter et al., 1995) and the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2001) in addition to those of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 2000). Whether this truly eliminates sample heterogeneity is in doubt, as discussed above; but diagnostic progress in the past decade or two has certainly added to the replicability of findings.

Task-induced activation studies differ from earlier PET and SPECT studies described above in that they do not assess absolute levels of activity in a single state (e.g., regional glucose metabolic rate at rest), but *compare* relative levels of activity between two or more different cognitive states. Task-induced studies are therefore, at least in theory, more controlled, avoiding such ill-defined conditions as so-called rest. There is good reason to assume that for a healthy adult the "resting state" is one of potentially intense mental activity (Binder et al., 1999; Raichle et al., 2001). There is also little confidence that every healthy adult will respond in identical ways to an unfamiliar setting in a scanner, which in functional MRI is also restrained and noisy. In other words, the resting state invites uncontrolled mental function as well as individual variability of such function. It is reasonable to expect that such variability is even greater in clinical populations, as for instance in autistic subjects. Keeping subjects on task continuously while monitoring behavior (using button press responses, for example) is probably the best available method to control effects of experimental setting.

Cognitive specificity in task-induced studies has enabled autism researchers to target functional domains of interest in much more direct ways than was previously possible. For example, a structural imaging study may target the amygdala because this structure is known for its involvement in socio-emotional functions that are impaired in autism (Schumann et al., 2004); or a single-state PET study may target the superior temporal lobe based on hypotheses of auditory dysfunction in autism (Zilbovicius et al., 2000). In these cases, functional specificity is indirectly attained through selection of an anatomical region of interest based on assumed function of this region in the healthy brain. In task-induced studies, on the other hand, specificity is directly attained by selection of a cognitive or sensorimotor task paradigm tapping into domains of known or expected impairments in autism. The rationale for this approach is very straightforward. For instance, in the very first task-induced study of autism by Happé and colleagues (1996), comprehension of narratives requiring 'theory-of-mind' or mentalizing – known to be impaired in autism (Baron-Cohen et al., 1985; Happé & Frith, 1996) – was compared to comprehension of physical stories (assumed unaffected in autism) during PET scanning, which showed differentially localized activity in medial frontal cortex in participants with autism spectrum disorders, compared to control subjects.

Imaging studies of social cognition

Given the salience of socio-communicative deficits among the diagnostic criteria for autism (American Psychiatric Association, 2000), it will come as no surprise that the bulk of currently available task-induced neuroimaging studies have focused on functions related to social cognition. Among these, the largest set has been dedicated to face processing. For instance, a study by Schultz and colleagues (2000) suggested that face perception in autism was associated with activity patterns in lateral portions of the inferior temporal lobe typically found for non-face object

perception in healthy controls. A study by Pierce et al. (2001) supported reduced activity in the 'fusiform face area' (FFA) in autism during face perception, but not the complementary activity in lateral inferior temporal gyrus. Hubl and colleagues (2003) also observed reduced FFA activity in 10 autistic subjects during face processing, but found enhanced activation in the medial occipital lobe in their autism group, compared to controls.

More recently, it has become clear that the results from these earlier studies cannot be simply construed as the reflection of a defective FFA in autism. Hadjikhani and colleagues (2004) partially replicated the design of the study by Schultz et al., but had subjects passively view faces, objects, and scrambled faces. In their study, activity in the fusiform face area was clearly present in autistic subjects during face viewing. It is therefore possible that the nature of the task and the response modality (passive viewing versus sameness judgments by button press of two simultaneously shown stimuli in the study by Schultz et al.) may affect presence or absence of FFA activation in autism. A recent follow-up study by Pierce and colleagues (2004) supports the conclusion that the FFA is not simply defective in autism, but modulated in atypical ways in certain task settings. In this study, autistic subjects passively viewed familiar faces (family and friends) and strange faces. Contrary to their earlier study (Pierce et al., 2001), which involved gender discrimination via button press, FFA activity was present in autistic subjects for faces of strangers and even more robustly for familiar faces.

At least two general lessons can be drawn from face perception studies in autism. First, they show that results from a single task paradigm may erroneously suggest some localized neurofunctional defect, whereas reduced activity may be more reasonably explained by an unusual response to a particular type of task and by atypical ways in which functional systems in the autistic brain cooperate. For instance, absence or presence of FFA activity in the studies reviewed above could be explained by use of an orthogonal task (gender discrimination, sameness judgments), which may have reduced attentional upregulation of FFA activity in autistic, but not in control subjects. If so, the true underlying abnormality would be related to attentional functions (see below).

To appreciate the second more general lesson from the face perception studies, let us assume (counterfactually) that absence of FFA activity in response to faces in autism had been definitively replicated in a number of studies. What would such a finding actually explain? Avoidance of eye contact is one of the core diagnostic criteria for autism (American Psychiatric Association, 2000; Baird et al., 2000). This implies that subjects with autism look at faces much less frequently than typically developing children (Klin et al., 2002). In other words, domain-specific stimulation is strongly reduced in autism. It is further well known that experience and activity are important factors that shape the neurofunctional organization of cerebral cortex during development. Animal studies, for example, show that a prospective "auditory cortex" in superior temporal lobe will assume visual function if afferent information from the retina is rerouted via the thalamic medial geniculate nucleus (Sur & Leamey, 2001). Human studies show that congenitally blind subjects, who process tactile information much more intensely than seeing subjects (e.g., in Braille reading), "use" their occipital cortex for tactile functions (Sadato et al., 2002). Professional musicians, who have engaged in intense sensorimotor practice on their instruments over many years, show respective expansions of perirolandic sensorimotor maps (Elbert et al., 1995). On this background, even if neuroimaging could demonstrate reduced FFA involvement during face perception in autism, it would be reasonable to explain such reduction as a reflection of normal experience-based neurofunctional plasticity. This underscores the need for caution when it comes to interpreting unusual regional activation patterns in autism as reflections of brain defects. At the same time, if it is true that atypical response in FFA to faces is a result of atypical experience with faces in autism, a deeper question still remains: What elementary early-onset neurofunctional abnormalities may explain reduced face perception experience in autism? This need for answering elementary questions first in autism research will be discussed in more detail below.

A few functional imaging studies have examined responses in the autistic brain specifically to emotional expression of faces. Critchley and colleagues (2000) presented subjects with happy or angry faces (versus neutral faces in a control condition) in an implicit passive viewing and an explicit judgment task. Overall autistic subjects showed lower than normal activity in right FFA. A site close to the left amygdala was active during the implicit condition in controls, but only activated during the explicit task in autistic subjects. This specific finding could suggest that passive viewing of faces may not be as automatically engaging for autistic individuals as it is for healthy control subjects. Such an interpretation would contrast in interesting ways with the results of non-emotional face processing studies discussed above, which suggested that an explicit task that is unrelated or orthogonal to face processing per se may

reduce FFA activity in autism. Taken together, the findings may imply that FFA will activate in autism in the context of explicit processing of facial emotion, but not when an additional task (e.g., gender discrimination) is given. A study by Piggot (2004) further implies that FFA activity in high-functioning autism may be normal for verbal labeling of emotional face expressions, but slightly reduced for nonverbal matching of such expressions.

In a more recent study, Hall and coworkers (2003) tested autistic men on emotional matching of facial expressions with voices, comparing this to a gender-matching condition. Even though this task design was thus very different from the one used by Critchley and colleagues, Hall et al. also observed diminished activity in right FFA in their autism group. Baron-Cohen and colleagues (1999) presented only parts of facial stimuli containing eyes and brows to young adults with autism. The task was to select the emotional state of a pair of eyes from two words (e.g., "unconcerned" vs. "concerned") presented at the bottom of a screen. This task was considered to tap into theory-of-mind because it required empathizing. In the control condition, subjects had to make gender decision in an analogous design. Controls showed highly distributed activation in bilateral frontal, temporal, and parietal lobes, whereas much less significant activation was seen in autistic subjects, mostly in the right hemisphere. Although an expected group difference was found in the left amygdala, where autistic subjects showed less activation than controls, a number of significant group effects in perisylvian cortices could probably be attributed to differential response to verbal components of the task. Welchew and colleagues (2005) recently examined functional connectivity during viewing of facial expressions and found that medial temporal structures, such as amygdala and parahippocampal gyrus, were affected by "disconnectivity" in men with autism or Asperger's syndrome.

One further neuroimaging study examined theory-of-mind in autism. In this PET study, Castelli and colleagues (2002) showed subjects triangles moving around on a screen. In one condition, the movement was random, whereas in a theory-of-mind condition, triangles appeared to mentalize, i.e. anticipate or manipulate the other triangle's mental state. A group of autistic adults showed normal levels of activation for the theory-of-mind (compared to the random) condition in extrastriate visual cortex, but significantly less activation than normal controls in three other regions of the right hemisphere: a basal temporal region close to the amygdala, the superior temporal sulcus, and medial prefrontal area 9.

These results are important because they highlight the more consistent findings (among a wealth of non-replicated results) in studies of social cognition and face processing in autism. First, atypical activity in the amygdala or its vicinity is a relatively consistent finding (but see Piggot et al., 2004 for a counterexample). It is also supported by evidence from other experimental techniques, such as postmortem cellular examination and structural imaging (Baron-Cohen et al., 2000; Sweeten et al., 2002). However, it clearly does not imply total absence of function in the autistic amygdala (Pierce et al., 2004). Secondly, the superior temporal sulcus is known for its involvement in the perception of biological motion (Puce & Perrett, 2003). Lack of activity in this area may reflect a reduced ability in autism to perceive visual stimuli as biological motion – even when such a perception is factually an illusion (as in the triangle study by Castelli and colleagues). One other functional neuroimaging study on voice processing (compared to non-biological tones) supports the finding of reduced activity in the superior temporal sulcus in autism (Gervais et al., 2004). Thirdly, beginning with early imaging studies (Baron-Cohen et al., 1994; Happé et al., 1996), the role of medial prefrontal cortex in social cognition has been documented (Ramnani & Miall, 2004). Both the studies by Happé et al. (1996) and Castelli et al. (2002) did indeed report atypical activation in this region for autistic participants. However, the specific findings were quite different. Happé and colleagues found that normal activity for a theory-of-mind task located in Brodmann area 8 was displaced and located more inferior and anterior in area 9 in a group of 5 subjects with Asperger's disorder. Contrary to this, Castelli and colleagues saw an absence of normal activation in area 9 in autistic adults for their version of a theory-of-mind task. Strictly speaking these results are contradictory, but it remains likely that social cognition impairments in autism involve atypical medial prefrontal function, in addition to abnormalities in the amygdala and the superior temporal sulcus.

Imaging studies of language

Bearing in mind that language acquisition is commonly delayed in autism and that many lower functioning autistic individuals never acquire phrase speech (Lord et al., 2004), the number of functional imaging studies of language in autism is surprisingly small. In an early small-sample PET study (Müller et al., 1999a), autistic adults – when listening to short sentences – showed blood flow increases in perisylvian cortex that lacked the leftward asymmetry

seen in a normal control group (Figure 1). However, when autistic subjects had to generate their own sentences, prompted by sentences and cue words (e.g., "He was listening to the radio. – *Television*"), normal perisylvian leftward asymmetry was found and left inferior frontal activation appeared normal. A number of results from techniques other than task-related neuroimaging have suggested atypical hemispheric asymmetries in language-related areas (Chiron et al., 1995; Gendry Meresse et al., 2005; Herbert et al., 2002; Rojas et al., 2005). The results of our PET study (Müller et al., 1999a) may indicate that atypical language-related asymmetries are task-dependent in high-functioning autistic subjects, i.e., affect only subcomponents of the language system (e.g., receptive functions). A follow-up analysis (Müller et al., 1998) limited to four autistic males, however, did suggest reduced left dorsolateral prefrontal activity, as well as atypical rightward asymmetry of thalamic activation during sentence generation. A more recent PET study by Boddaert et al. (2003), again in a small sample of 5 autistic adults, yielded evidence consistent with atypical receptive asymmetries. This study used synthetic speech-like stimuli for passive listening (compared to rest). Leftward asymmetry of activation in superior temporal cortex, as observed in healthy controls, was reversed in the autism group.

In an fMRI study, Just and colleagues (2004a) applied a sentence comprehension paradigm in a comparatively large sample of 17 high-functioning autistic individuals. In comparison with a low-level baseline task (visual fixation), both autism and control groups showed extensive activation in occipito-parietal, lateral temporal, premotor, and inferior frontal areas. Direct statistical group comparisons for identifying activation differences were not reported. However, the study also included functional connectivity analyses, suggesting generally reduced interregional cooperation during language processing in the autism group (for discussion, see below). More recently, Gaffrey and coworkers (under review) studied semantic category decisions in 10 adolescents and young adults with autism spectrum disorder, also using fMRI. A matched control group showed extensive left inferior frontal activation, which was also seen – though less robustly – in the autism group. The main finding on direct group comparisons was much stronger activation in extrastriate cortex in autistic subjects, suggesting that semantic organization in autism may rely heavily on visual imagery. This is consistent with a study by Kana and colleagues (2006), who found greater than normal activity in visual cortex in autistic adolescents and adults for sentence comprehension, especially for low-imagery sentences. Enhanced extrastriate activation in autistic adults has also been reported by Koshino et al. (2005) for an n-back verbal working memory task, which again would indicate an unusual visual strategy for processing linguistic stimuli (here: letters).

Imaging studies of attention and sensorimotor functions

Although not included among the diagnostic criteria, attentional impairments have been for a long time considered an elementary disturbance in autism, potentially accounting for higher cognitive deficits. In early electrophysiological studies, reduced amplitude of endogenous event-related potentials (N_c and auditory P3b) was considered evidence for attentional dysfunction (Courchesne, 1987; Courchesne et al., 1989). More recent behavioral data indicate selective deficits in the ability to shift attention in autism. In one study, autistic patients had problems quickly shifting attention from the visual to the auditory domain and vice versa, whereas they performed normally when required to focus attention within the auditory or visual domain, or when given more time (>2.5 seconds) for attention shifts between sensory modalities (Courchesne et al., 1994b). These deficits could be related to cerebellar pathology in autism, given that patients with acquired cerebellar lesions show attentional deficits similar to those found in autistic subjects (Akshoomoff & Courchesne, 1992; Courchesne et al., 1994b) and that functional MRI studies in healthy adults have demonstrated cerebellar involvement in nonmotor attentional processes (Allen et al., 1997; Le et al., 1998). Another neuroanatomical site of interest with regard to attentional impairments are the parietal lobes. Volume loss in the parietal lobes has been found in a 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 & Courchesne, 1994; Townsend et al., 1996).

More recently, the indirect evidence for links between cerebellar and parietal anatomical involvement and attentional deficits in autism has been complemented by functional neuroimaging results. In a study by Belmonte and colleagues (2003), six subjects with autism spectrum disorders performed a visuospatial covert attention shifting task, in which detection of an oddball target in one location shifted covert attention to the opposite location. The

autism group showed unusual ventral occipital activity, whereas activation in superior parietal lobes that was prominent in healthy controls was absent. Haist and coworkers (2005) found reduced inferior parietal activity in autistic adolescents and adults during spatial attention shifting when intervals between cues and response were short (100 msec). Allen and Courchesne (2003) focused on the cerebellum in a study of visual attention in 8 autistic individuals. Subjects selectively attended and responded to either a shape or a color in any given task block. A parametric design allowed the authors to examine effects of task difficulty, with stimuli presented at three different interstimulus intervals. Activation in several regions of the posterior cerebellum tended to be reduced in the autism group (compared with matched controls) even when subjects were matched for performance. The study by Allen and Courchesne had a limited field of view, with only 4 coronal slices through the cerebellum. Although parietal effects were not statistically examined, attention-related parietal activity appeared bilaterally reduced in the autism group, compared to controls.

A few studies have investigated basic sensorimotor functions in autism. Gomot and colleagues (2005) observed reduced activity in left anterior cingulate cortex in a group of autistic children during detection of novel and deviant tones in an auditory oddball paradigm. Allen and colleagues (2003; , 2004) contrasted their attentional findings in the cerebellum with those for simple thumb movement. The results suggested that the cerebellum showed specific activational reduction associated with attention, whereas activity related to movement was actually greater than normal. In particular, motor-related activation in autistic subjects extended into posterior cerebellar regions that were involved in attentional functions in healthy controls. Allen et al. (2004) also observed that reduced anatomical size of the anterior cerebellum and the posterior lobule VII correlated with enhanced activation extent (volume of activation) during thumb movement. As mentioned above, reduced cerebellar volume has been hypothesized to be developmentally related to autistic pathology (Courchesne, 1997; Courchesne et al., 1988). The finding of correlated overactivation for simple motor functions in cerebellar regions of volume loss may indicate neurofunctional sequelae of cerebellar pathology in autism.

A further study (Müller et al., 2001), also on simple finger movement (visually prompted button pressing with the index finger of the preferred hand), yielded information on cerebral activation patterns consistent with those of the above studies by Allen and colleagues. Even though groupwise activation analyses for a sample of 8 autistic men showed only a slight reduction of normal activation in motor, premotor, and supplementary motor cortices, inspection of data in individual subjects revealed that these differences were due to unusual scattering of motor-related activation into parietal and prefrontal brain areas in a number of autistic individuals – a pattern not seen in a single control subject (Figure 2). This observation, together with the results from Allen et al. (2004), could reflect elementary disturbances in neurofunctional organization in autism, potentially related to the finding of abnormal brain growth curves in early autistic development (Carper et al., 2002; Courchesne et al., 2001). According to a very simple hypothesis, early developing functions (e.g., simple motor control) require greater than normal processing territory in cerebral cortex (presumably due to reduced processing efficiency of autistic cortex`; Casanova et al., 2002) at the expense of later developing higher cognitive functional systems. A further fMRI study examining slightly more complex visuomotor coordination, in which subjects had to perform button press sequences prompted by visual cues, yielded results consistent with this model, i.e., spread of activation in autistic subjects beyond normal premotor and superior parietal sites into prefrontal and inferior parietal cortex (Müller et al., 2003).

Task-induced neuroimaging studies of learning in autism are currently not available, except for one study on procedural digit sequence learning (Müller et al., 2004). This experiment used the visuomotor design of a previous study mentioned above (Müller et al., 2003), but examined changes over time associated with learning. Both an autism group (consisting of 8 men) and a matched control group relied heavily on premotor and superior parietal activity during early stages of performing a repeating 8-digit sequence. Reduced reaction times in the later phases of the experiment indicated learning effects, which were associated with overall decreased premotor activity in controls, but increased premotor involvement in the autism group. Although this was not predicted based on the hypothesis of early-developing functions 'invading' what is normally polymodal association cortex, it may be considered a complementary finding, adding up to a more general hypothesis of neurofunctional organization in autism. This hypothesis implies that (a) early emerging sensorimotor functions require too much cortical processing territory and therefore spread into adjacent cortices that are normally involved in complex polymodal processing; and (b) high-functioning autistic individual develop strategies for solving more complex tasks that rely heavily on

sensorimotor components. This latter hypothesis is supported by abnormal premotor cortex involvement in learning, but also by the finding of atypical activation in extrastriate visual cortex during semantic decision and verbal working memory, as described above.

Limits and promises of functional neuroimaging in autism

Functional neuroimaging has experienced an astounding rise in the past two decades. When in the early 1990s, fMRI was established as an alternative to PET in its ability to map out regional brain activation (Belliveau et al., 1991), this rise became exponential because widely available clinical MRI scanners could be easily upgraded for echo-planar imaging and fMRI use. Today, several thousand fMRI studies are published every year, and even for the study of developmental disorders, such as attention deficit disorder or autism, which pose extreme problems of subject cooperation regarding head motion and task compliance, fMRI has become an important source of evidence. However, enthusiasm about functional neuroimaging techniques needs to be viewed in context, with its historical baggage and future promises.

Past: The brain as a map

Many basic assumptions of modern functional neuroimaging have a long history in the prescientific study of the brain and in early neurology, which was dominated by the idea of brain organization as a functional landscape or "map" (Clarke & Dewhurst, 1972). Interestingly, today's most important professional organization representing functional neuroimaging research still abides by this metaphor, calling itself the Organization for Human Brain Mapping (www.humanbrainmapping.org). An exhaustive discussion of the roots and limitations of this metaphor in neurology and cognitive neuroscience is beyond the scope of this chapter (see, for example, Müller, 1992; Sternberg, 1990). Suffice it to state here that there is a growing awareness in cognitive and clinical neuroscience that localization of function (or dysfunction) per se may not be explanatory (e.g., Mesulam, 1998). Some conceptual elements of this awareness have a long history. For instance, the notion of functional systems being organized, not as serially lined up 'centers' (Lichtheim, 1885), but as distributed networks can be traced back at least to the work of Pierre Flourens in the early 19th century. Directly relevant to the study of clinical disorders, neurologists of the late 19th and early 20th centuries, such as Hughlings-Jackson (1878) and Head (1926), explained behavioral changes in lesion patients as resulting from brain systems that remain *intact* following brain damage – contrary to the conventional focus on links between lesion site and behavioral impairment, which is still dominant in today's cognitive neuropsychology. Animal work by Lashley (1950) following this 'holistic' tradition in neurology had groundbreaking impact on emerging modern concepts of distributed neuronal representations and the developmental plasticity of multipotential cortex (cf. O'Leary & Nakagawa, 2002).

Present: The limits of deficit "blobology"

The traditional metaphor of the brain as a functional map, which today continues to dominate cognitive neuroscience, has direct repercussions for neuroimaging studies of developmental disorders. Adopting the terminology of Thomas Kuhn (1962), the 'dominant paradigm' of imaging research in healthy adults has been to localize cognitive components of function to one or a few brain regions, typically presented as colorful blobs on standardized brain anatomy that reflect clusters of voxels (image volume elements) that survive corrected significance thresholds for an activation statistic. The obvious adaptation of this paradigm to the clinical realm and to developmental disorders is to localize components of impairment to specific brain regions in similar ways. As discussed above, the literature on face processing in autism initially took this approach. However, this view is questionable because it is unlikely that brain regions, such as the fusiform gyrus, work independently to fulfill a specific function such as face perception. To anyone familiar with the relative homogeneity of cortical architecture across different regions and the density of connections between cortical regions and between subcortex, cerebellum, and cerebral cortex, this modular idea of autonomous and 'encapsulated' function of a brain region will appear highly unlikely. The idea was formulated in its purest form by Fodor (1983), who postulated that perceptual systems were modular, i.e., domain specific, informationally encapsulated (without access to processing in other modules), innate, and associated with a fixed neural architecture. Given that Fodor's book was primarily meant as a

provocation (a "potboiler" as pointed out by Fodor, 1985: p33) and that from a neuroscientific view his ideas appear mostly unfounded (Müller, 1996), the impact of his book on the cognitive sciences has been surprisingly deep. For an example relevant to the clinical discussion of this chapter, Baron-Cohen (1992) and more recently Scholl and Leslie (2001) have argued for a modular status of 'theory of mind', referring to Fodor's above mentioned criteria. The claim implies that autism may be explained in terms of a 'broken module'. The more general assumption for developmental disorders is that certain modules may be selectively affected in certain disorders, presumably due to specific genetic defects, whereas for the remainder of the developing neurocognitive systems 'residual normality' can be assumed (for a critique, see Thomas & Karmiloff-Smith, 2002).

The issue of 'residual normality' has been debated in neurology for centuries. It is not limited to the developmental setting, but it arises in analogous ways in the study of adult patients with brain damage, as mentioned in the previous section. Following in the footsteps of Hughlings-Jackson (1878) and Head (1926), modern clinical neuroscience has begun to understand that an acquired brain damage, even when it appears focal on a CT or MRI scan, can only be fully understood if reorganizational changes in the remainder of the brain are taken into account. The brain outside the lesion may appear structurally intact, but may not be functionally "normal", either in a positive or a negative sense. For example, studies in adults with left perisylvian stroke have shown that right hemisphere brain regions homotopic to the classical language areas become more involved in language processing than they are in the 'normal' adult brain (Leff et al., 2002; Ohyama et al., 1996; Thulborn et al., 1999). Recent animal stroke models also demonstrate enhanced neurogenesis in the hippocampal dentate gyrus following middle cerebral artery ischemia, which may support postlesional compensatory changes (Tureyen et al., 2004). From these perspectives, the residual brain could be considered *supernormal* because it compensates for the loss of tissue in a variety of ways. In other respects, postlesional changes in the residual brain may imply *subnormality*, i.e., additional loss of function. A good example is the reduced function of the contralateral cerebellum in patients with unilateral cerebral stroke, a phenomenon called crossed cerebellar diaschisis (Gold & Lauritzen, 2002; Pantano et al., 1986).

'Residual normality' is thus clearly not present in adult patients with acquired focal lesion. Much less so can we expect it in developmental disorders, for at least two reasons. First, developmental brain impairments are usually not focal. Among the types of neurodevelopmental disorders discussed at the beginning of this chapter, cases of type (i) in which brain lesion is truly focal are probably quite rare. Among types (ii) and (iii), i.e., disorders that are predominantly caused by genetic risk, focal brain impairment is highly improbably, as discussed above. Second, damage to a functional region or system is likely to have different consequences depending on developmental stage. A striking illustration of this was already discussed at the beginning of this chapter. Children with early-onset damage to the left hemisphere show usually much better language outcome than adults with comparable left-hemisphere damage. This can be attributed to greater plasticity of the developing brain and it is likely that greater synaptic density in the child brain is one of the parameters related to this plasticity.

Another, more specific example of the differential roles of functional systems across development relates to the neurotransmitter serotonin (5-HT) and autism. There is some evidence from neuroimaging (Chugani, 2002; Chugani et al., 1999), as well as from blood plasma and pharmacological studies (Buitelaar & Willemsen-Swinkels, 2000) for serotonergic abnormalities in autism. Although the precise roles of serotonin transporter and serotonin receptor genes in autism have not been fully elucidated, their involvement in this disorder appears probable (Veenstra-VanderWeele & Cook, 2004). Interestingly, the role of serotonin changes dramatically during development. In the mature brain, serotonin functions as a neurotransmitter active in widely distributed projections from the raphe nuclei in the brainstem and is considered important for attentional regulation (Schwartz, 2000), as well as sensory gating, inhibition, and a variety of affective and endocrine functions (Anderson & Lombroso, 2002). During development, however, serotonin plays neurotrophic roles with an impact on neuronal differentiation, myelination, synaptogenesis, and dendritic development (Whitaker-Azmitia, 2001). Abnormal serotonin metabolism at critical developmental stages may affect thalamocortical afferents (Chugani, 2004) as well as laminar and columnar cortical organization (Janusonis et al., 2004). Therefore, even if autism could be explained solely on the basis of serotonergic abnormalities, these would still imply a variety of effects, others resulting from disturbances of early cortical organization, some involving functional systems, such as attention, sensory gating, or inhibition, for which serotonin plays an important role in the mature nervous system.

The above example underscores that 'residual normality' cannot be expected in developmental disorders (for detailed argument and peer discussion, see Thomas & Karmiloff-Smith, 2002). This conclusion has repercussions for functional neuroimaging in these disorders. While the metaphor of 'functional mapping' may be a useful paradigm in adult neuroimaging (though it will certainly come to be considered crude and misleading in the future), it is to be treated with utmost caution in developmental disorders. From all that we know today, it is unrealistic to expect that the phenotype of a developmental disorder – even if it caused by a single-gene defect – could be explained by a focal brain regional abnormality (Fisher, 2005; Müller, 2005). This implies that the conventional lesion approach of adult cognitive neuropsychology, according to which damage to a brain area with resulting specific impairment indicates that the impaired function was localized to the damaged site premorbidly (and is analogously localized in the healthy brain), is questionable in developmental disorders. An example regarding abnormal activity patterns in the fusiform gyrus during face perception in autism was discussed above. Similar considerations concern the possibility of atypical perisylvian asymmetries for language in autism.

Recent MR volumetric work by Herbert and colleagues (2002) showed that leftward volumetric asymmetries commonly seen in typically developing children were reversed in autistic children when large brain regions are measured, whereas examination of small subregions (Herbert et al., 2005) revealed complex patterns of partially exaggerated leftward asymmetry (as in the planum temporale) and partially reversed asymmetry (as in the frontal operculum). As mentioned above, there are only few functional neuroimaging studies of language in autism. Some of these are consistent with the hypothesis of atypical asymmetries in autism (Boddaert et al., 2003; Müller et al., 1999a; Müller et al., 1998), whereas others have yielded evidence for apparently typical leftward asymmetry in inferior frontal cortex ('Broca's area') in autism during sentence comprehension (Just et al., 2004b) and semantic category decision (Gaffrey et al., under review). The question of atypical asymmetries in autism may have to be raised in much more specific ways. For example, it may depend on the nature of the task (e.g., passive stimulation with verbal material versus active production or judgment); and there may be greater individual variability within the autistic population, with the possibility of atypical language asymmetries being related to atypical hand preferences (Escalante-Mead et al., 2003; Soper et al., 1986). A deeper issue is our limited understanding of the developmental causes for functional brain asymmetries, i.e., it is not fully understood why typically developing young children begin to prefer one hand over the other, why they typically use predominantly the left hemisphere for language-related functions, and how these two developmental processes relate to each other. I will not discuss the evidence relevant to the above questions in this chapter because it would lead too far away from the topic of functional neuroimaging. However, the issue highlights the importance of a developmental perspective. Such a perspective should be the obvious choice in the study of developmental disorders. However, since subjects can usually be included in functional neuroimaging studies only as adults or adolescents, given the high demands on cooperation, the evidence provided by most such studies is not developmental per se, but requires a conceptual effort developmental interpretation.

A straightforward, but potentially non-developmental interpretation of imaging findings in autism would be to say, for example: "Autistic individuals have problems perceiving faces because the fusiform face area does not function normally" (as debunked above); or: "Children with autism have language delays because language asymmetries (structural or functional) are abnormal." Such interpretations are as tempting as they are misleading. As argued earlier, it is very likely that effects of experience and activity (interaction with the environment) continuously alter neurofunctional organization in autism throughout childhood. Therefore abnormalities observed in older children or adults are at least in part a reflection of atypical experience rather than an indication of a *cause* of impairment. This raises the issue of belated study in neuroimaging, i.e., the study of a disorder long after the onset of pathogenesis.

Future: Development and integration

Technical advances. There are two possible technical solutions to the problem of belated study. The first one is to adapt neuroimaging techniques such as fMRI that are typically used in older children and adults to the study of infants and young children. Some pioneering work suggests that this is indeed possible. Dehaene-Lambertz and colleagues (2002) studied 20 non-sedated infants, ages 2-3 months, during speech stimulation and found evidence for leftward asymmetry of temporal lobe activation. Interestingly, this group of researchers could even obtain usable

data from five infants who remained awake throughout the procedure. Temporal activation associated with speech stimuli was found in sleeping as well as in awake subjects. A similar study using nonverbal auditory stimuli found effects in superior temporal cortex in neonates (Anderson et al., 2001), including preterm babies as young as 25 weeks of gestation. Notably, blood oxygenation level dependent (BOLD) effects were positive in some, but negative in the majority of the neonates, with no obvious correlation between gestational or postnatal age and BOLD polarity.

This highlights the unresolved issue of maturational changes in the physiology underlying the BOLD response in fMRI studies of young children. In one study, an abrupt shift at about 8 weeks of age from positive to negative BOLD response associated with visual stimulation was reported (Yamada et al., 2000). Born and colleagues (2002a; , 1998) reported BOLD inversion even in older children up to the age of 71 months. However, these results may have been affected by the use of sedatives, given that Dehaene-Lambertz and colleagues (2002) found consistently positive BOLD responses in the study of unsedated 2-3 month-olds. Alternatively or additionally, polarity of BOLD response may interact with the functional system examined. Most reports of BOLD negativity come from visual studies (2002b; Born et al., 1998; Meek et al., 1998; Muramoto et al., 2002; Yamada et al., 2000), whereas auditory studies of infants and neonates (Anderson et al., 2001; Dehaene-Lambertz et al., 2002) and even of the fetus in utero (Moore et al., 2001) have shown mostly positive BOLD responses. Based on the limited available evidence, factors such as age, physiological state (awake, natural sleep, sedated), and functional system may interact in determining polarity of the BOLD response. This complicates the prospect of neuroimaging studies in developmental disorders at ages that promise minimal effects of postnatal plasticity and reorganization and therefore a clearer picture of the primary pathological effects on functional brain organization.

A second solution to the problem of belated study is the use of techniques that can be better adapted to the study of young children. Positron emission tomography (PET) has the advantage of a quiet experimental setting, compared to noisy fMRI data acquisition, but is considered unethical in children except for those with severe neurological conditions (Morton et al., 1996). Event-related potential (ERP) and magnetoencephalographic (MEG) studies are also performed in relatively non-distracting environments, although they are sensitive to head motion, which is hard to prevent in young children. Besides a number of ERP studies in autistic children below age 8 years (Bruneau et al., 1999; Dawson, 1986; Dawson et al., 1995; Martineau et al., 1992; Ogawa et al., 1982; Roux et al., 1997) there have been some recent promising applications of MEG in the study of the auditory system in autistic children ages 8 years and older (Gage et al., 2003a; , 2003b). While temporal resolution of ERP and MEG is greatly superior to fMRI and PET, spatial resolution is inferior. Near-infrared spectroscopy (NIRS) is a technique that relies on effects of blood oxygenation on tissue absorption of near-infrared light. This completely non-invasive technique has been used extensively for clinical purposes in neonates (Nicklin et al., 2003). A few studies have applied this technique in neurologically healthy neonates and infants and were able to show expected oxygenation effects over occipital and temporal sites during visual (Meek et al., 1998) and auditory stimulation (Zaramella et al., 2001), respectively. However, the spatial resolution of NIRS is low and its application has been mostly limited to gross examination of basic sensorimotor functions, despite a few attempts to study more complex affective (Hoshi & Chen, 2002) and executive functions (Hoshi, 2003; Schroeter et al., 2004).

A developmental understanding of cognitive outcome. Technical progress may certainly contribute to solving the problem of belated study in the coming years, but the more fundamental challenge for the study of developmental disorders is a change in perspective – away from the common adultocentrist view of children as little adults on their way to completion and towards a constructivist understanding of development, i.e., one that views the cognitive system at any stage as erected on the building blocks of previous stages. This perspective, of course, belongs to the Swiss psychologist Jean Piaget and his school (Piaget, 1979), which in the context of the 'cognitive revolution' of the 1960s (Gardner, 1987) became considered quasi-empiricist and incompatible with the radical anti-behaviorism of Chomsky and his followers (Piattelli-Palmarini, 1980). Piaget's biggest 'sin' in this historical context was to deny language the innate and autonomous status on which Chomskian generative grammar and its offshoots in psycholinguistics were founded. As discussed above, the repercussions of this Chomskian view can still be felt in the study of developmental disorders, in particular when it comes to defining language impairments in disorders such as specific language impairment, Williams syndrome, or autism.

Alternative views of language acquisition, which take into account developmental precursors, are however gaining more ground (Bates et al., 2003; Carpenter et al., 1998). These have important implications for developmental disorders. For example, the question of whether language capacity is compromised in autism can be reformulated: Are any of the precursor or ingredient functions of language acquisition impaired and may this be the cause of delays in language acquisition? 'Ingredients' of language can be defined as neurocognitive functions that emerge before the onset or during the course of language acquisition and that are prerequisites for normal language development (Müller, 2005). As already discussed, interactive mechanisms of language acquisition are likely to be compromised in autism (Baltaxe & Simmons, 1975). For a specific example, there is overall consensus that imitation is delayed in autism (Williams et al., 2004). This may reflect more general delays in sensorimotor integration. Imitation deficits have been shown correlate with impaired social cooperation in young children with autism (Rogers et al., 2003). Furthermore, joint attention, which is intimately related with and probably a predictor for language acquisition (Bates et al., 2003; Markus et al., 2000), is impaired in autism (Bruinsma et al., 2004; Charman, 2003). Baron-Cohen et al. (1997) observed that autistic children, when presented with a novel object in combination with a novel word, followed a speaker's direction of gaze much less often than typically developing and non-autistic mentally retarded children. Joint attention deficits in autism have been found to correlate with delays in language acquisition (Bono et al., 2004; Mundy et al., 1990), which suggests that reduced joint attention undermines normal strategies for lexical learning. What appears as a language disorder may thus be developmentally explained based on more elementary impairments.

Support for the model of language ingredients comes from neuroimaging evidence, which has demonstrated participation of left inferior frontal cortex ("Broca's area") in many seemingly nonlinguistic functions. Among these are imitation (Buccino et al., 2004; Iacoboni et al., 1999), motor preparation (Krams et al., 1998) and complex motor planning (Fincham et al., 2002), sequence learning (Haslinger et al., 2002), action imagery (Binkofski et al., 2000) and observation (Buccino et al., 2001), rule shifting (Konishi et al., 1998), response selection (Thompson-Schill et al., 1997), response inhibition (Kemmotsu et al., 2005; Rubia et al., 2001), and working memory (Chen & Desmond, 2005). Adult cognitive neuroscience tends to be agnostic with regard to the unexpected apparent overlap of functional specializations in Broca's area. A developmental perspective, however, offers clues. Rather than asking why in adults all those non-linguistic functions *also* populate a relatively small piece of cortical tissue in inferior frontal cortex, a developmental perspective considers many of those nonlinguistic functions as language ingredients. From this perspective, Broca's area is pivotal for language learning because a number of functional pathways providing crucial components for language learning converge in this brain area by the second year of life (Müller & Basho, 2004). This argument has been partially made previously with regard to the mirror neuron system (Rizzolatti & Arbib, 1998), but it should be additionally noted that convergence of the dorsal visual stream (grossly related to the mirror neuron system) with afferents from the ventral visual stream (Di Virgilio & Clarke, 1997; Petrides & Pandya, 2002) providing information about objects in the world is equally important for an understanding of the role of Broca's area.

Network impairments. A model of language development emerging from language ingredient functions is important for the study of developmental disorders such as autism or specific language impairment because it acknowledges that atypical language organization may be a secondary outcome of impaired development of ingredient functions, such as imitation, joint attention, or complex motor planning. On the neurofunctional level, an understanding of cognitive impairment as emerging from more elementary sensorimotor impairments translates into a focus on distributed networks, as opposed to localized modules. Staying with the example of language impairment, a developmental neurofunctional approach has to consider all systems that may function as language precursors or ingredients. Disturbances in any of these systems may result in secondary language deficits. Therefore, developmental cognitive neuroscience needs to examine the integrity of the neural systems involved in potential ingredient functions. It becomes clear that an exclusive focus on what are considered left perisylvian 'language areas' in the adult brain is insufficient. Instead, extensive regions outside left perisylvian cortex are likely to cooperate in enabling the young child to begin acquiring words and grammar. The developmental and constructivist perspective therefore highlights the distributed organization of emerging cognitive systems. This in turn means that impairments in a given domain such as language can be explained as a result of either (a) damage to one or several regions in a

distributed system, or (b) as an abnormality in the way multiple regions cooperate. In other words, issues of brain connectivity and the integrity of white matter come to the forefront.

One promising bottom-up approach relates to the role of the dorsal visual stream and the mirror neuron system – a system first described in monkeys that includes neurons with increased firing during action planning *and* action observation (Fadiga et al., 2000; Rizzolatti et al., 2002). It has been argued that this system plays a pivotal role in the phylogenetic emergence of language and in child language acquisition (Rizzolatti & Arbib, 1998), and that defects in the mirror neuron system may explain joint attention deficits and language delays in autism (Williams et al., 2001). FMRI studies of visuomotor functions (Müller et al., 2004; , 2003; , 2001) have documented atypical patterns of parietal and frontal activity, which suggest that the dorsal stream in autism is atypically organized. This view of the dorsal stream follows recent evidence of this pathway being a system of "vision for action" (rather than solely a system supporting visuospatial functions), which incorporates portions of prefrontal cortex (Goodale & Westwood, 2004).

The study of functional networks and pathways, such as the mirror neuron system, requires imaging techniques that go beyond the detection of local activation and towards the measurement of interregional cooperation. Recent structural MRI studies have documented abnormal growth patterns of white matter in autistic children, with atypical overgrowth in the first years of life followed by lack of normal growth (Carper & Courchesne, 2005; Carper et al., 2002; Courchesne et al., 2001). Herbert and colleagues (2004) showed that white matter increases in autism are region-specific, with prominent involvement of the frontal lobes, and strongly affect late-myelinating radiate components of white matter. A technique that directly assesses white matter integrity is diffusion-tensor MRI (DTI). Very little DTI evidence is currently available for autism. One study (Barnea-Goraly et al., 2004) found reduced diffusion anisotropy, which is considered a measure of white matter integrity, in a large number of regions across all four forebrain lobes in boys with autism.

An alternative approach to the study of neural network organization is functional connectivity MRI (fcMRI), which is based on interregional low-frequency correlations of the blood oxygenation level dependent (BOLD) signal in fMRI. Although their precise underlying physiology remains to be fully elucidated (cf. Obrig et al., 2000), such BOLD cross-correlations have been shown to reflect functional connectivity in numerous previous studies (Allen et al., 2005; Biswal et al., 1995; Cordes et al., 2000; Greicius et al., 2003; Hampson et al., 2004; Jiang et al., 2004; Koch et al., 2002; Koechlin et al., 2003; Lowe et al., 2000; Stamatakis et al., 2005; Stein et al., 2000; Xiong et al., 1999). In a clinical study, Quigley and colleagues (2003) found that the robust fcMRI effects between homotopic sensorimotor regions seen in healthy subjects were absent in patients with callosal agenesis. While fcMRI approaches probably do not exclusively reflect monosynaptic axonal connections, they are likely to relate (at least indirectly) to anatomical connectivity and white matter integrity.

In one recent study (Villalobos et al., 2005), functional connectivity along the dorsal stream was examined in autistic individuals and matched control subjects during visuomotor coordination. The main result was that functional connectivity between primary visual cortex and bilateral inferior frontal area 44 was significantly reduced in autism (Figure 3) – a result that is consistent with the hypothesis of mirror neuron defects (see above). Just and colleagues (Just et al., 2004a), examining interregional BOLD covariance associated with language processing, reported across-the-board reductions of functional connectivity within cerebral cortex and hypothesized that the autistic brain is generally characterized by underconnectivity. Additional studies from the same group of researchers on sentence comprehension (Kana et al., 2006) and an executive (Tower of London) task (Just et al., 2006) largely support generalized underconnectivity. However, the findings by Villalobos and colleagues (Villalobos et al., 2005) – showing partly intact occipito-parietal functional connectivity – as well as recent results suggesting partial *overconnectivity* between subcortex (thalamus, caudate nuclei) and some cerebral cortical regions (Mizuno et al., 2006; Turner et al., in revision) imply that regionally specific models of connectivity in autism may be more promising than one of overall underconnectivity (see also Koshino et al., 2005).

Conclusion

The wide availability of non-invasive functional neuroimaging techniques, in particular fMRI, has in the past few years greatly boosted the role of neuroimaging and activation mapping in the study of developmental disorders.

Task-induced neuroimaging affords twofold specificity because it permits the investigator to examine specific *anatomical* loci under well-controlled *functional* conditions. When using fMRI in the study of developmental disorders, such as autism, it is tempting to focus on functional domains of impaired outcome. However, since functional neuroimaging techniques are today largely limited to application in older children and adults, it is hard to distinguish apparent abnormalities of activation patterns that are direct reflections of the disorder itself from effects of abnormal experience or compensatory plasticity. One has to be therefore wary of interpreting atypical activation patterns (for example, absence of activation in the fusiform face area) as *explanations* of functional deficits (e.g., impaired face perception). The need for developmental disorders to be studied from a developmental perspective – self-explanatory as it may sound – is not always evident in the neuroimaging literature. From a developmental perspective, it is highly unlikely that neurodevelopmental disorders can be accounted for in terms of modular and localized defects, with one functional system being impaired and the remaining functional systems unaffected. Instead, a developmental perspective requires an understanding of how elementary functional systems interact in the emergence of more complex functional systems. For neuroimaging, this implies that we have to go beyond simply mapping out differences and towards models of network cooperation. In this context, recent technical advances in diffusion-tensor imaging and functional connectivity MRI are promising.

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Figures

Figure 1. Regional cerebral blood flow increases associated with passive verbal stimulation (listening to sentences compared to rest) in a group of 5 autistic adults (top row) and 5 matched normal controls (bottom row). Activation clusters are superimposed onto standard MRI in Talairach space. The autism group shows activation in right middle frontal (A), bilateral superior temporal (B), and right inferior frontal gyri (C), which contrasts with predominantly left-lateralizing temporal activation seen in the control group (D-E). Adapted from Müller et al. (1999a).

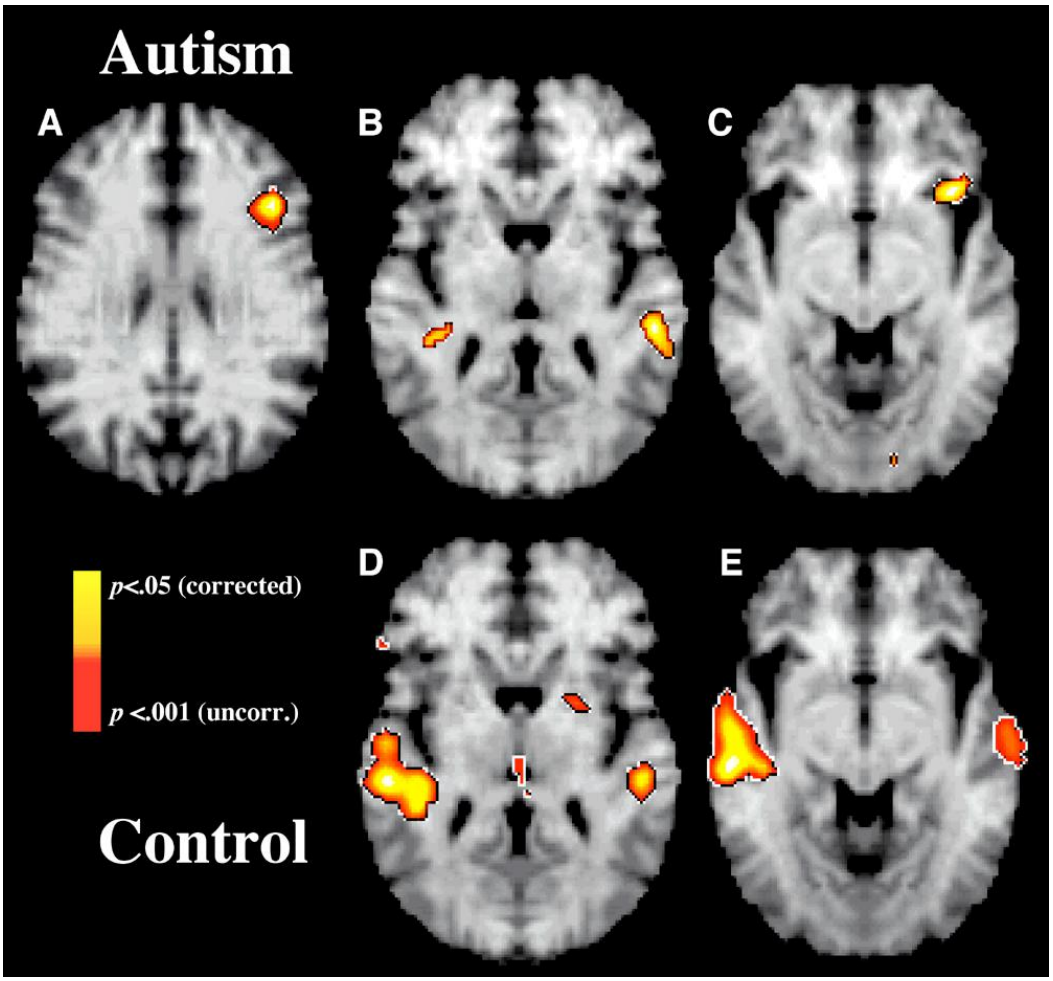

Figure 2. Number of subjects per group (autism versus normal control) showing activation ($p<.05$; corr.) in regions of interest during unilateral finger tapping. Bars on the left ("canonical sensorimotor regions") indicate activations in contralateral regions expected to activate in a simple motor task, bars on the right show activation in other regions of the hemisphere contralateral to the movement. The prefrontal region includes all portions of the superior, middle and inferior frontal gyri not included in the sensorimotor regions. Whereas fewer autistic than control subjects show activations in canonical sensorimotor regions, the inverse is seen for other regions in the frontal, parietal, and temporal lobes. Based on data published in Müller et al. (2001).

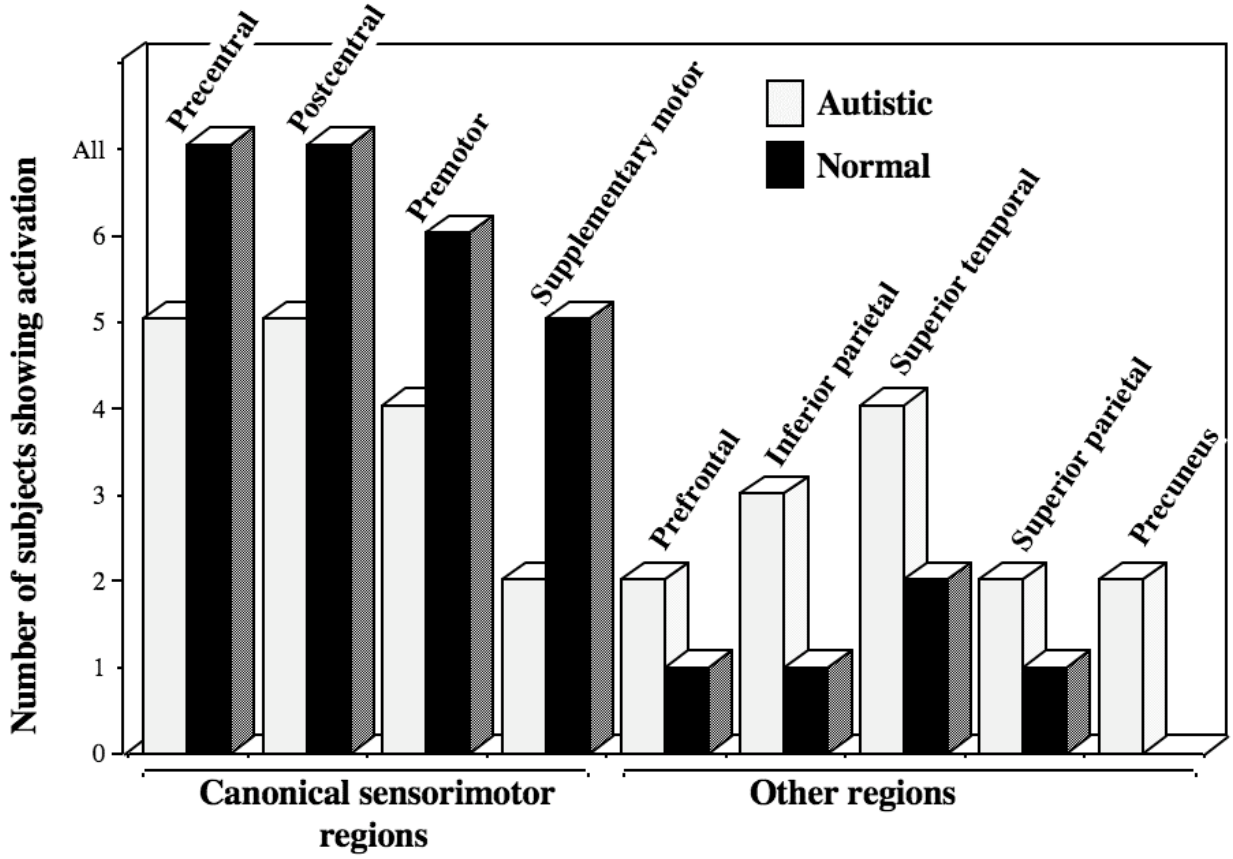

Figure 3. Clusters of significant functional connectivity (p<.05; corr.) with area 17 (primary visual cortex) for autism (A) and normal control groups (B). Extensive connectivity in superior parietal, superior frontal, and thalamic regions seen for the control group (B) are reduced in the autism group (A). Direct group comparisons show significantly reduced functional connectivity in bilateral inferior and superior frontal gyri (C-D). Adapted from Villalobos et al. (2005).