Review

The phenotype and neural correlates of language in autism: An integrative review

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ABSTRACT

Although impaired communication is one of the defining criteria in autism, linguistic functioning is highly variable among people with this disorder. Accumulating evidence shows that language impairments in autism are more extensive than commonly assumed and described by formal diagnostic criteria and are apparent at various levels. Phenotypically, most people with autism have semantic, syntactic and pragmatic deficits, a smaller number are known to have phonological deficits. Neurophysiologically, abnormal processing of low-level linguistic information points to perceptual difficulties. Also, abnormal high-level linguistic processing of the frontal and temporal language association cortices indicates more self-reliant and less connected neural subsystems. Early sensory impairments and subsequent atypical neural connectivity are likely to play a part in abnormal language acquisition in autism. This paper aims to review the available data on the phenotype of language in autism as well as a number of structural, electrophysiological and functional brain-imaging studies to provide a more integrated view of the linguistic phenotype and its underlying neural deficits, and to provide new directions for research and therapeutic and experimental applications.

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Contents

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1. Introduction

Autism is a neurodevelopmental disorder associated with lifelong handicaps in social adaptation. The disorder is defined by a description of symptoms in three domains: social interaction, verbal and non-verbal communication and stereotyped behaviour (American Psychiatric Association, 1994). Autism is currently considered to be one of the autism spectrum disorders (ASD), which also include the Asperger syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD-NOS). The term *spectrum* refers both to the heterogeneity of the ASD disorders and the wide variety in functional ability. Although not universally agreed upon, the definition of AS provided in DSM-IV entails impaired social interaction and stereotyped behaviour in the absence of language and cognitive delay (Klin et al., 2005). Individuals with PDD-NOS fail to meet the full criteria for autism. This is the case when the number of criteria met is sub-threshold, or the onset occurs over the age of 3, or atypical symptoms are present, or a combination of the above (Buitelaar and van der Gaag, 1998; Buitelaar et al., 1999).

Linguists commonly describe language and language disorders in terms of phonology, semantics, syntax and pragmatics, and since the early seventies, researchers have been analysing linguistic deficits in autism using these categories (Cromer, 1981). Whereas phonology deals with the perception and production of sound units whose concatenation produces words, semantics deals with the meaning of lexical items, syntax with the structure of words in sentences, and pragmatics with the conventions and rules governing the use of language for communication (Boucher, 2003). From a neuroscientific perspective, however, there is no clear-cut relation between linguistic categories and cortical function. Recent functional imaging studies have furthered the idea that the language system is organised in a large number of small but tightly clustered modules in both the left and right hemisphere with unique contributions to language processing. There is also increasing evidence that cortical language regions are not specific to language, but involve more reductionist processes that give rise to language as well as non-linguistic functions (Bookheimer, 2002).

Given the absence of a clear-cut relation between the linguistic categories and cortical function, it is unfeasible to deduce neurobiological deficits in autism from the high-order language deficits characterising the disorder. Instead, several psychological theories, such as the weak central coherence (WCC) theory (Frith, 1996) and the impaired theory of mind (ToM) (Baron-Cohen et al., 1985), have attempted to explain the high-order language deficits in autism. The weak central coherence theory predicts that, since people with autism are biased towards local versus global processing, their ability to integrate contextual information into a composite whole is diminished. The high-order core deficit in central processing supposedly results in altered low-level processing. Several studies have indeed demonstrated a reduced ability to infer word-meaning from sentence context (Happe, 1997) or to infer global meaning from sentences (Jolliffe and Baron-Cohen, 2000), yielding empirical evidence for the WCC account for at least the semantic and pragmatic language deficits in autism. However, WCC would also predict a superior performance on single word tasks, as is the case in hyperlexia. Yet, hyperlexia is only rarely seen in autism. The majority of people with autism have difficulties with the meaning of isolated words as well as whole sentences.

ToM refers to the specific cognitive ability to infer other people's mental states and to understand that others have beliefs, desires and intentions that are different from our own. It has been argued that early stages of ToM are necessary for the ability to use symbols such as words (Tager-Flusberg, 2000), and that impair-

ment in ToM in autism therefore causes an inability to comprehend the meaning of words. Furthermore, acquisition of language may be mediated by shared or joined attention, which, in case of an impaired ToM, would be impaired as well (Kuhl et al., 2003). Semantic ability and false belief have indeed been found to correlate in children with autism (Tager-Flusberg, 2000).

The psychological framework provided by these top-down theories assumes that an impaired high-level cognitive function is causing the impairments in autism. This assumption has been criticised for several reasons. Firstly, converging evidence suggests that abnormalities of the processing of low-level sensory information may lead to impairments in higher-order cognitive functions, rather than the other way around (Happe and Frith, 2006; Bertone et al., 2005). That is to say, altered low-level perceptual processing in autism should not be considered a by-product of weak central coherence. Quite on the contrary, perceptual abnormalities give rise to weak central coherence. Secondly, these neuropsychological top-down theories are descriptive rather than explanatory, and finding the neural correlates of these theories has been proven difficult since their predictions of cortical functioning are too general to be falsifiable.

Nevertheless, there have been converging efforts from different disciplines to document the neural correlates underlying the symptoms of ASD (Volkmar et al., 2004). Although most of the research has focused on impairments in social cognition (mostly using visual stimuli such as faces), language impairments in autism are increasingly recognised. More and more findings on the clinical phenotype and the neural substrates of language and communication in autism are being added to the literature, but the broad field of autism research and the many different analytical approaches make it difficult to oversee the current literature. This paper therefore aims to review recent evidence from structural, electrophysiological and functional studies on the neural correlates of linguistic abnormalities in autism. Findings on the phenotype of language impairments in autism will also be addressed here. We will argue that the linguistic features in autism cover a wider range of impairments than described in the DSM-IV criteria for autistic disorder and are more linked to the neural architecture in autism than earlier behavioural studies have suggested. More specifically, language ability varies greatly among people with autism. Although most individuals with autism have semantic, syntactic and pragmatic language deficits, there is also a number that have phonological difficulties. Functional brain-imaging data show aberrant neural activation in semantic, syntactic and pragmatic tasks of higher-order language functions, as well as in low-level sensory processes. Furthermore, we will argue that the abnormalities of low-level sensory processing of linguistic stimuli can be interpreted in the light of connectivity models in autism. Finally, we will discuss the relationship between language impairments and the other functional impairments in autism (social interaction and stereotyped and rigid behaviour patterns), as well as the relationship between autism and specific language impairment (SLI), to provide a more integrated view of the linguistic phenotype and its underlying neural deficits. An integrated review may be useful for both clinicians and researchers, as it will allow further congruity between the observed language deficits and their putative causes and could lead to important therapeutic and experimental applications in the future.

2. Methods

We conducted an extensive internet search of the English literature published on the MEDLINE and PsycInfo databases in the past two decades, using the keywords (autism, autistic disorder, and Asperger syndrome) AND (language, language disorders,

language development disorders, language profile, communication, speech, voice, prosody, intonation, and auditory) AND (comprehension, brain, brain mapping, cerebral cortex, cortical, neural, hemisphere, functional, imaging, neuroimaging, magnetic resonance imaging (MRI), magnetoencephalography (MEG), electroencephalography (EEG), positron-emission tomography (PET)). As it is impossible to discuss all the publications here, we confined ourselves to reviewing the most recent representative papers in each area that were published in peer-reviewed journals.

3. The phenotype of language disorders in autism

Impaired language function is frequently observed in people with autism, often in combination with mental retardation. Language dysfunction in autism is, however, much more variable than the universal deficits in communication (Kjelgaard and Tager-Flusberg, 2001). At one end of the autism spectrum there are children whose verbal abilities are within the normal range of functioning, and at the other there are some who never start to speak (Lord and Paul, 1997). In those with sufficient language and cognitive abilities, i.e. people with high-functioning autism (HFA) and Asperger syndrome, social communicative abilities remain impaired. Language tends to be used one-sidedly, non-reciprocally and instrumentally rather than for social purposes (Fine et al., 1994). In their original descriptions of ASD, Kanner and Asperger both gave account of the typical language anomalies encountered in autism such as echolalia, pronoun reversal, utterances not related to the conversational context, and a lack of drive to engage in communication (Asperger, 1991; Kanner, 1943). Researchers have subsequently elaborated the phenotype of language impairment in autism, distinguishing phonological, syntactic, semantic and pragmatic deficits.

3.1. Phonology

It has been a widely held belief that the development of phonology progresses at a slower rate, but is not impaired in autism since phonologically correct echolalia is commonly found in low-functioning autism, suggesting that phonological perception and production is intact even in severely affected individuals (Tager Flusberg, 1996). However, there is converging evidence for an articulation deficit in a subgroup of autistic children. A delayed developmental trajectory of phonology has been reported (Bartolucci et al., 1976), as well as a greater number of articulation distortion errors in people with HFA and the Asperger group than in typically developing speakers (Shriberg et al., 2001). Recently, Kjelgaard and colleagues found phonological processing deficits (as measure by repeating non-sense words) in autistic children, although only in those with concurrent impaired vocabulary and higher-order semantic and syntax deficits (Kjelgaard and Tager-Flusberg, 2001). This language profile was also found by another group in half of the children with poor communicative abilities (Rapin and Dunn, 2003). It thus seems that, in a subgroup of autistic children, phonology is impaired along with language comprehension and production. This clustering of symptoms may suggest that common causes underlie phonology and syntactic abilities in autism and also in other disorders such as specific language impairment. This will be dealt with in more detail in Section 5.

3.2. Semantics

Difficulties in both understanding and expressing lexicon are the most widely recognised linguistic impairments in autism. Semantic impairments are most severe in people with low-functioning autism (LFA) and least severe in those with HFA and AS (Boucher, 2003). Delay in speech acquisition is one of the primary diagnostic characteristics and the degree of language impairment is a key prognostic factor (Lord and Paul, 1997; Venter et al., 1992). Yet, the course and development of semantic difficulties is an under-researched area in autism. One comprehensive study revealed marked difficulties in lexical comprehension and expressive vocabulary in the majority of children with autism (Kjelgaard and Tager-Flusberg, 2001). Furthermore, a strong correlation was found between full-scale IQ and performance on tests for comprehension (Peabody Picture Vocabulary Test) and expression (Expressive Vocabulary Test) (Dunn and Dunn, 1997; Williams, 1997). This correlation suggests that semantic comprehension and expression are unimpaired in the most able people with autism, and especially in those with Asperger syndrome. Subtle semantic impairments are however also present in HFA and AS. Howlin et al. found a poor performance on tests for productive (British Picture Vocabulary Scale) and receptive (Expressive One Word Picture Vocabulary Test) semantic abilities for both AS and HFA (Gardner, 1982; Howlin, 2003; Dunn et al., 1997). While there was no significant difference for language comprehension between HFA and AS, ratings for language expression revealed a small but significant difference favouring the AS group. Thus, in accordance with clinical experience and anecdotal evidence, language abilities in people with HFA and AS differ mainly with respect to expressive abilities.

It has been suggested that the semantic difficulties in autism are a consequence of deficits in advanced conceptualisation, since simple concepts referred to by lexical items are not affected in autism (Tager Flusberg, 1981) and comprehension of terms referring to emotional states (Tager Flusberg and Sullivan, 1995; Hobson and Lee, 1989) or abstract terms (Frith and Snowling, 1983) is more affected than comprehension of concrete words. Other studies, however, do not support this finding. Interference during a reading task was not different for concrete and abstract words (Eskes et al., 1990), and abstract terms that exist through human agency such as 'war' and 'peace' were not found to be used anomalously in autism (Perkins et al., 2006). Thus, the exact nature of the semantic deficits in autism remains to be established.

3.3. Syntax

As with the phonological properties of language in autism, syntactic impairments have not been well researched. Recent findings, however, do provide evidence for distinct and specific syntactic deficits in autistic children who acquire spoken language, and more noteworthy, they also show that, in those who do not acquire speech, the ability to acquire the grammar (and vocabulary) of signed language is impaired as well (Boucher, 2003). The distinct syntactic deficits in autism entail reduced expressive and receptive syntactic abilities, which have been found using the Clinical Evaluation of Language Fundamentals (CELF) (Kjelgaard and Tager-Flusberg, 2001) and mean utterance length in free play sessions (Eigsti et al., 2007). Contrary to the consistent findings on the length of syntactically complex utterances, the findings on grammatical morphemes such as verb tense markers and articles are inconsistent. Whereas earlier studies found more grammatical errors (Bartolucci and Albers, 1974; Bartolucci et al., 1980), a more recent well-matched study found no such errors in spontaneous autistic speech (Eigsti et al., 2007). Yet, Roberts et al. did find high rates of omissions of tense marking in a subgroup of children who were language impaired (Roberts et al., 2004). The inconsistency of findings on grammatical morphemes probably reflects the fact that subgroups are affected rather than all autistic people, so that sufficiently large subject groups are needed.

It has been a long-held belief that people with autism are better at language production than at language comprehension. The main reason for this assumption was a series of studies conducted in the seventies that compared autistic children with children with severe receptive language disorder. These studies revealed significant differences in comprehension of vocabulary and the production of syntactically complex utterances, favouring the children with receptive language disorder (Bartak et al., 1975; Cox et al., 1975; Cantwell et al., 1978). It was therefore argued that syntactic comprehension was more affected than production. However, in contrast with the above finding for syntax, a more recent study did not replicate a difference between *semantic* comprehension and expression (Kjelgaard and Tager-Flusberg, 2001). A language profile in autism with better production than comprehension could thus not be replicated. Nevertheless, evidence was found for two distinct language profiles in autism. The language profile in one subgroup entailed worse performance on tests of grammatical ability than vocabulary (Kjelgaard and Tager-Flusberg, 2001), possibly clustering with phonological impairments (Rapin and Dunn, 2003) (see also Section 3.1). The language profile in the other subgroup entailed impaired semantics and pragmatics (Rapin and Dunn, 2003). These subtypes suggest that syntactic and phonological deficits have a common cause, as have semantic and pragmatic deficits in autism. However, the distinction of subtypes was based on a number of studies with an autistic sample that was pre-selected for the presence of difficulties in language comprehension, so the extent to which these findings can be generalised to the broad autism spectrum remains to be established.

In summary, syntactic abilities in autism are characterised by sparse expressive language with immature syntax in a majority of children. There is some evidence for a clustering of syntactic/phonological deficits in a subgroup of children and a clustering of semantic/pragmatic deficits in a subgroup, but this will require confirmation in an unselected autistic population.

3.4. Pragmatics and prosody

Pragmatics entails both the linguistic and non-linguistic items that are covered by the defining criteria of autism. Linguistic pragmatics implies difficulties in the ability to disambiguate meaning, the ability to structure coherent discourse and to understand irony and implied meaning. The ability to understand other people's intentions, social rules of conduct and non-verbal communication gestures are regarded as non-linguistic pragmatics. Deficits in pragmatic functioning are evident at all developmental stages, even in highly verbal adults with autism (Lord and Paul, 1997; Tantam et al., 1993; Happe, 1993; Martin and McDonald, 2004; Baron-Cohen, 1997).

It should be noted that most research in autism on non-linguistic pragmatic abilities, such as the ability to understand other people intentions, as measured by ToM tests, involve language. Data on whether the deficit in ToM extends to people with autism with little or no language is sparse, making it difficult to disentangle the relative contributions of linguistic and non-linguistic deficits in the socio-communicative deficits in autism. Moreover, it has been argued that the syntactic ability to build subordinate clauses allow children to reason about mental states that are at odds with reality (e.g. "Jane *thinks* the cookies are in the cabinet") (De Villiers and De Villiers, 1995). Syntax mastery has indeed been found to correlate with performance on ToM tasks. However, using a non-verbal ToM test, Colle et al. found that children with autism selectively failed false-belief tasks, whereas children with SLI or typically developing children did not (Colle et al., 2007), indicating dissociation between verbal and pragmatic abilities.

A pragmatic ability closely related to language comprehension is the ability to perceive and use intonation, rhythm, tone of voice and stress, referred to as prosody. The use of aberrant prosody is mentioned in the DSM-IV description of autism, and the perception of prosody in autism has been investigated by several authors. Rutherford et al., for example, compared the ability of adults with ASD to attribute emotions to sentences spoken with an emotional tone of voice, and found that individuals with the HFA or Asperger syndrome have difficulties extracting mental state information from vocalisations (Rutherford et al., 2002). Researchers found deficits in the perception and production of stress, intonation and phrasing (Paul et al., 2005), as well as a preference for non-verbal sounds and an indifference to the mother's voice in children with autism (Dawson et al., 1998; Klin, 1991). The latter finding seems to indicate that deficits in the perception of prosody do not reflect an innate inability, but arise as a consequence of non-social orientation. However, the direction of causality may also be the other way around, or even be bidirectional. The contribution of low-level deficits to high-level deficits will be dealt with in greater detail in Section 5.

In summary, linguistic and non-linguistic pragmatic deficits and prosodic deficits are part of the most commonly affected domains of functioning measured across the spectrum of autism disorders. It appears that linguistic abilities do indeed facilitate pragmatic abilities, although they are not necessary per se for pragmatic competence.

4. The neural correlates of language disorders in autism

Although autism is a heterogeneous disorder that includes many contradictory neurophysiological findings, several neural correlates underlying the linguistic deficits of autism have been reproduced in different investigative modalities. Some researchers focused on structural abnormalities (Herbert et al., 2002), while others addressed the perception of simple linguistic stimuli (Boddaert et al., 2003; Ceponiene et al., 2003) and higher-level linguistic functions (Harris et al., 2006; Kana et al., 2006). The results indicate that individuals with autism activate alternative and possibly less flexible networks during phonetic, semantic, syntactic and pragmatic language processing. Abnormalities at an early level of information processing contribute to the hypothesis of a bottom-up aetiology in which, for example, an alteration of auditory cortical processing leads to abnormal language development in early childhood.

4.1. Structural abnormalities

After a long period of inconsistent findings in structural neuroimaging studies, data of recent studies converge to elucidate the underlying abnormalities in autism (see Palmen and van Engeland, 2004 for a review). Using MRI, an abnormal developmental trajectory of the cerebral cortex in autism was found, in which autistic children had normal head circumference at birth, and increased grey and white matter volume at 2–3 years of age, which normalised again in later years (Courchesne et al., 2001). Particularly the frontal lobes were abnormally enlarged (Carper et al., 2002). The abnormal developmental trajectory was confirmed in a meta-analysis of head circumferences, post-mortem findings and MRI measurements (Redcay and Courchesne, 2005), which led the authors to argue that the early overgrowth interferes with the normal developmental trajectory of cortical connectivity. Cellular abnormalities such as neuroinflammatory processes (Vargas et al., 2005) and supernumerary neurons (Smitz, 2005) that are predominantly present in the frontal, temporal and cerebellar structures (Courchesne et al., 2005) may lead to an

impairment in the information transfer between the frontal cortex and other systems (Courchesne and Pierce, 2005). The hypothesis of aberrant collaboration between cortical areas or abnormal cortical connectivity in autism is a scientific area that is currently receiving much attention. In Section 5, we will go deeper into its implications for language in autism.

More importantly, the areas associated with cellular abnormalities in autism (the frontal, temporal and cerebellar structures) all subserve language functions, although the cerebellum is only considered to play a facilitating role (Allen et al., 2004). Consequently, morphometric findings on the frontal and temporal language areas have been associated with language impairments in autism. Asymmetry reversal of the frontal language-related cortex was found (DeFosse et al., 2004; Herbert et al., 2002; Abell et al., 1999), as well as anterior and superior shifting of the left inferior frontal sulcus and superior temporal sulcus bilaterally (Levitt et al., 2003) and decreases of grey matter concentration bilaterally in the superior temporal sulcus (Boddaert et al., 2004b). Although cognitive functions are difficult to relate to morphometric findings in a one-to-one manner, the main conclusion of these studies is that the cortical development of language-related areas follows a different trajectory in autism, possibly in the context of a reduced left-lateralised hemispheric dominance. Whether these findings of aberrant development and collaboration between cortical areas are specific for autism is, however, not clear. As a consequence, there is a need to directly compare the neurobiological development and functioning in autism with other disorders of language such as SLI and dyslexia.

4.2. Auditory perception and lower-level language paradigms

Several authors have focused on clarifying two main questions in the field of language in autism: whether or not early sensory processes are deficient in autism and whether or not these early sensory processes are speech-specific. These questions are highly relevant to better understand the nature of language deficits in autism, since they allow inferences on the contribution of top-down versus bottom up-processes in the functional impairments in autism. Basically, bottom-up theories assume that early sensory deficits give rise to deficient high-level operations such as language and social behaviour (cf. the inability to speak in deaf people). Alternatively, top-down theories assume that the ability to perceive stimuli is not impaired. Yet, deficits in high-level processes such as social behaviour could give rise to undirected attention, or attention directed to non-socially relevant clues, so that word-object associations do not develop efficiently in autistic children. In healthy children, joint attention has indeed been shown to be a prerequisite for acquiring language (Kuhl et al., 2003), suggesting a role for top-down influences in autism. Yet, it is still possible that sensory deficits give rise to deficits in joint attention. To shed light on this chicken-and-egg problem, much data has been collected using neurophysiological experiments that measure neural responses to stimuli at a millisecond scale.

Čeponienè et al. used an ERP oddball paradigm to examine the sensory and early attentional processing of speech and non-speech sounds in children with HFA (Ceponiene et al., 2003). They found no differences in mismatch negativity (MMN, an index of automatic sound change detection, situated in time after the N1c wave and before the P3a wave), which suggests intact early perceptual abilities in autism. However, involuntary orienting (P3a) was different for speech sounds but not for non-speech sounds in the HFA group. This finding supports the hypothesis of a speech-specific *post*-sensory auditory impairment, suggesting that people with autism may perceive but not attend to linguistic stimuli. Contrary to Čeponienè's findings, Kasai et al. did find a delayed magnetic mismatch field for vowels (but not for tones) by using magnetoencephalography (Kasai et al., 2005). Thus, early perceptual processing in autism appeared to be deficient and speech-specific. Others studies have confirmed the early perceptual processing deficits, but the speech specificity was not replicated: they reported smaller N1c waves in children with autism in an event-related paradigm with simple tones (Bruneau et al., 1999) and delayed MMN for both speech and non-speech sounds (Oram Cardy et al., 2005). Whether or not cortical sound processing impairments are speech-specific, sound processing impairments may be fundamentally associated with language impairments.

In an fMRI study that contrasted voices with environmental sounds, no differential activation between the two conditions was found in the autism group, suggesting that speech was not processed by a speech-specific cortical region (Gervais et al., 2004). The control group, on the other hand, showed greater activation for voices along the upper bank of the superior temporal sulcus bilaterally. The abnormal pattern of cortical activation in the autism group might reflect a bottom-up sensory impairment, or alternatively, it may be caused by an attention bias towards non-vocal sounds, which in turn may lead to the development of linguistic deficits in autistic children. This problem was tackled by a positron emission tomography (PET) study that investigated the auditory cortical processing of pre-linguistic speech-like sounds that have an acoustic structure similar to speech (Boddaert et al., 2003; Boddaert et al., 2004a). The study reported a reversed hemispheric dominance in the autism group and, compared with controls, less left-temporal activation and greater right middle frontal gyrus activation. The elegance of the study design was that top-down processing of language was less likely because the sounds were not perceived as language but rather as strange electronic tones. The acoustic structure was made to resemble speech sounds, such that any cortical processing differences reflected bottom-up linguistic abnormalities. The authors therefore speculated that the observed abnormal auditory processing led to an abnormal early stage of language development rather than that it reflects the consequences of abnormal language development.

The above-mentioned studies converge to the idea that impairments of information processing may lead to an abnormal developmental trajectory of language in autism. Studies of the maturational path of cortical language processing do indeed indicate an abnormal developmental trajectory in the form of reversed hemispheric dominance. Dawson et al. reported a strong relationship between language ability and hemispheric asymmetry in ERP, on the one hand, and vowel stimuli in autism, on the other (Dawson et al., 1989). Furthermore, in a MEG study using simple vowel stimuli, Flagg et al. found rightward instead of typical leftward hemispheric lateralisation (Flagg et al., 2005). Reduced leftward hemispheric activation was also found in non-linguistic neuroimaging studies (Gendry-Meresse et al., 2005; Chiron et al., 1995). Yet, the association of cortical processing impairments and impaired language in autism does not per se imply causality. That is, cortical sound processing impairments may cause language deficits, but language deficits may also cause cortical sound processing impairments. Alternatively, another factor such as a genetically programmed maldevelopment of neuroarchitecture in autism may give rise to both cortical sound processing impairments and language deficits.

In short, impaired cortical sound processing is reproduced reliably in autism. Whether or not the auditory processing abnormalities are speech-specific is still unclear, but early sensory impairments and their interplay with the maturational path of the cerebral cortex are likely to play a part in the abnormal language acquisition in autism.

4.3. Higher-level language paradigms

Given the neuroimaging data found so far, it is unlikely that a deficit in a single cortical area can account for the phenotypic language deficits in autism, as is the case in post-stroke aphasia. In the autistic brain, cortical regions seem to collaborate in a different fashion, and cortical areas that show hypoactivation or hyper-activation for one task may show normal activation for another task.

The first functional imaging study of higher-level language perception and generation in autism was a small exploratory PET study conducted in 1999 (Muller et al., 1999). In five autistic participants, sentence perception was associated with the reversal of normal left-hemisphere dominance, while sentence generation showed normal left inferior frontal activation. In a re-analysis of the data on the same subjects, which focused on three regions of interest, participants with autism had a reduced Broca's area (Broca's area is situated in the opercular and triangular sections of the inferior frontal gyrus) activation during language perception and production (Muller et al., 1998). A more recent fMRI study, using a reading paradigm that required the attribution of complex mental states contrasted with rest states, demonstrated more right frontal activation in the autism group, also indicating a reversal of hemisphere dominance (Takeuchi et al., 2004). These studies should, however, be considered exploratory because of their small sample sizes and multiple comparisons.

In an fMRI study by Harris et al., the semantic and perceptual processing of single words was assessed (Harris et al., 2006). Semantic processing (evaluate words as positive or negative) and perceptual processing (lower or UPPER case) were contrasted as well as processing of concrete and abstract words. The participants with autism had weaker left and right frontal activation, but greater temporal activation for semantic processing, relative to perceptual task conditions. More importantly, compared with the control group, there was little differential activation between semantic and perceptual processing in the autism group. The concrete versus abstract contrast also demonstrated less activation differences between the two conditions in the autism group.

In another fMRI study, abnormal Broca's and Wernicke's area (Wernicke's area is situated in the posterior section of the superior temporal gyrus and the Sylvian fissure) activation in autism was also demonstrated using a sentence comprehension task with syntactically demanding probes (Just et al., 2004). The autism group had less activation of Broca's area and adjacent areas and more Wernicke's area activation. Furthermore, the study showed a reduced synchronisation of neural activation across the large-scale cortical network for language processing. The greater Wernicke's area activation was interpreted as a tendency for more extensive processing of the meanings of the individual words that make up a sentence in autism. The authors hypothesised that the reduced Broca's area activation may reflect a reduced ability to integrate the meaning of individual words into a coherent conceptual and syntactic structure. This may still hold, but Harris's study showed that Broca's area and Wernicke's area are also abnormally activated during the processing of single words when no syntactic demands are made (Harris et al., 2006).

The findings on underconnectivity were elaborated in an fMRI study in which autistic participants processed sentences with a high-imagery or low-imagery content (Kana et al., 2006). Measures of functional connectivity showed a reduced functional synchro-nisation between the frontal and parietal areas. Again, the controls had greater Broca's area and adjacent area activation. In contrast to the control group, there were little activation differences between the two conditions in the autism group: the autism group seemed to process high- and low-imagery sentences similarly.

Thus, the neuroimaging data give rise to four main conclusions. Firstly, the data indicate that people with autism tend to rely more on Wernicke's area (temporal region) and less on Broca's area (frontal region) for processing sentences and single words. Since Broca's area subserves integration processes (Hagoort et al., 2004) and Wernicke's area is more associated with semantic retrieval, the neuroimaging data present an intriguing parallel between the WCC's piecemeal processing style and the greater reliance on Wernicke's area neurally. It might thus well be that early sensory processes that highlight individual components in a composite whole give rise to the greater Wernicke's area activation rather than that Wernicke's area itself is malfunctioning.

Secondly, the neuroimaging data suggest that, during high-level processing in autism, cortical areas are used in a different manner and in reaction to other stimuli rather than that certain cortical areas are malfunctioning per se. An elegant example of this are two studies by the same group that assessed the neural basis of irony comprehension in autism. One study found hypoactivation of prefrontal and temporal regions during judgment of scenarios that involved irony (Wang et al., 2007). However, the other study, in which also scenarios that involved irony were presented, used a paradigm that demanded explicit attention to socially relevant clues, and found greater activation of the prefrontal and temporal regions (Wang et al., 2006).

Thirdly, the task indifferent pattern of activation during language tasks in autism supports the idea that the neural networks that are temporarily recruited for a cognitive task cannot be reset as easily as in controls when the task is changed. There is theoretical evidence that suggests that less flexible network regrouping could be the result of abnormalities in low-level sensory processing (Gustafsson, 1997) in the sense that high-level processes are flooded with irrelevant information from low-level centres and the extra processing demand impedes the flexibility required for neural assemblies to form (Belmonte et al., 2004b). As such, less flexible network regrouping has been associated with models of aberrant connectivity in autism. This matter will be further discussed below. Interestingly, less flexible network regrouping might also be involved in the part of the triad of symptoms that involves rigidness and repetitive/restricted beha-viour. The correspondence between the triad of symptoms in relation to their putative causes will be also addressed below.

Fourthly, autism is a heterogeneous disorder and the same can be said about the neuroimaging results on language in autism. Some of the conflicting findings can be explained by the wide range of phenotypic variation with different intellectual levels and age groups studied. As a consequence of the difficulty to obtain large enough sample sizes, only a minority of the neuroimaging studies have evaluated the results at a search volume correct *p*-value and have used a random effects analysis and a direct group comparison.

5. Discussion

Over two decades of research have shown that linguistic deficits are present in the majority of individuals with autism. Neurophy-siological studies that sought the neural basis of these deficits have shown abnormalities at a basic, early level of sensory information processing in autism (Boddaert et al., 2003; Ceponiene et al., 2003). Quite likely, these findings reflect developmental abnormalities, and as such, they are in accordance with hypotheses on impaired integration of cortical information in autism. Basically, these theories state that cortical regions do not operate in synchrony, but show disorganised and inadequately selective development of connectivity (Rippon et al., 2007; Just et al., 2004; Belmonte et al., 2004a). Especially impaired connectivity between the frontal lobe and other systems has been implicated in autism (Courchesne

et al., 2005). A growing body of evidence lends support for aberrant connectivity in autism, including deficits in physical connectivity, such as histopathology findings of neuroinflammatory microglial activation (Vargas et al., 2005), the abnormal developmental trajectory of brain size (Redcay and Courchesne, 2005), decreases in white matter structure integrity measured with DTI (Keller et al., 2007; Barnea-Goraly et al., 2004; Alexander et al., 2007) and deficits in computative connectivity measured as the synchrony of time series of activation of cortical regions (Kana et al., 2006; Wilson et al., 2006). Although it is tempting to ascribe a unidirectional causal relation to deficits in connectivity and impairments in autism such as abnormal language development, a bi-directional relation between connectivity and functional impairments in autism is more likely. In healthy adults, white matter integrity changes over time (Snook et al., 2005), suggesting that experiences influence neural connectivity. The socio-communicative deficits in autism could likewise give rise to abnormal connectivity.

Yet, it has been argued that, in autism, genetic factors in interaction with environmental influences lead to an abnormal neural architecture that causes either increased or reduced neural connectivity, or both (Belmonte et al., 2004b). Both conditions could cause an abnormally low signal-to-noise ratio in developing neural assemblies, given the fact that there is excess noise in hyperconnected systems and the signal gets lost in the noise in hypoconnected systems. This may result in a failure to delimit activation in perceptual processing centres, forcing higher processing mechanisms to actively suppress irrelevant sensory information at a later, less efficient stage. These compensatory mechanisms can presumably not be reset as quickly as the normal mechanisms of selective attention. Empirically, the allocation of neural resources during higher-order language tasks does indeed seem to be more task-indifferent in autistic individuals than in controls. The observation of less flexible network regrouping in autism during different language task conditions (see also Section 4.3) can possibly be explained by the high neural demands that active filtering of relevant stimuli imposes (Belmonte et al., 2004b).

More direct evidence suggesting reduced cortico–cortico connectivity during language tasks in collaborating cortical areas has been provided as well (Just et al., 2004; Kana et al., 2006). Intraregional underconnectivity during a simple auditory task has also been reported (Wilson et al., 2006). The high-level processing deficits of linguistic stimuli might arise when an unfiltered flood of linguistic information reaches higher information processing units that have to evaluate and actively suppress irrelevant sensory inputs. The greater reliance on Wernicke's area for linguistic processing in autism (Just et al., 2004) might thus result from compensatory developmental processes that lead to a more self-reliant Wernicke's area.

Additional empirical findings from a number of histopathology studies of autistic brains that have shown an atypical distribution of interneurons suggest that lateral inhibition may be involved in the abnormal neural architecture in autism (Casanova et al., 2003; Casanova, 2006). Lateral inhibition refers to a physiological process in which neurons of one neuronal layer make inhibitory synaptic connections through interneurons in minicolumns. Based on computer simulations, it has been predicted that alterations in the strength of lateral inhibition can have a positive effect on perceptual discrimination abilities but have a detrimental effect on more global perception, exactly as is the case in autism (Gustafsson, 1997). This hypothesis is however arguably speculative and further research into this matter is required.

It should be noted that linguistic and communicative impairments comprise only one-third of the triad of impairments in autism. Whether or not abnormal connectivity and the genetic constellation associated with communicative abilities contribute to the other behavioural domains in autism (social interaction and restricted and repetitive behaviours and interests) has been the topic of an ongoing debate. This issue will be further discussed below.

5.1. The relationship between linguistic impairments and social and restricted/repetitive impairments in autism

The core deficits in autism are traditionally viewed as inherently intertwined, i.e. communicative, social and restricted/repetitive difficulties influence each other and are highly interdependent. Indeed, the acquisition of language is one of the strongest predictors of long-term positive academic and social outcome in children with autism (Gillberg, 1991). Conversely, joint attention and immediate imitation predict language ability at ages 3–4, and toy play and deferred imitation predict communication development at ages 4–6 (Toth et al., 2006). However, recent behavioural-genetic data from a large general population-based twin-pair study indicate that phenotypic correlations between traits usually associated with autism (social interaction, repetitive-restrictive behaviours and communication) are low (Ronald et al., 2006). Even social interaction and communicative abilities were only modestly clustered with correlations of 0.2–0.4 (Happe et al., 2006). Furthermore, although each aspect of the triad of impairments was found to be highly heritable, cross-trait, cross-twin correlations were low, suggesting that most genetic effects are specific to one of the core symptoms.

One might argue that these behavioural-genetic findings suggest that the neural underpinning of the separate parts of the triad of symptoms is trait-specific as well. However, a different pattern of genetic and environmental causal factors for each of the symptom domains of autism does not preclude the possibility of a common neural deficit. In fact, each of these causal patterns may lead to a common neural deficit which further compromises other neural functions and give rise to the triad of symptoms in various degrees. The neural circuitry that makes up the social brain consists of a specific network comprising the amygdala, medial prefrontal cortex, cingulate cortex, right somatosensory-related cortex and temporal lobe structures, including the superior temporal sulcus and fusiform gyrus (Adolphs, 2001). The language brain, on the other hand, comprises the superior temporal lobe, inferior parietal, temporal-parietal-occipital junction and inferior frontal areas (Hickok, 2001; Vigneau et al., 2006). Thus, the speech-specific superior temporal areas are the main link between the social and language networks. The triad of symptoms may not only share anatomical characteristics, but have neurophysiological characteristics such as impaired connectivity in common as well. Further genetic and neurophysiological studies will need to address the attributions and, if possible, the direction of causality of impaired connectivity for the separate parts of the triad.

5.2. Genetic, endophenotypical and behavioural correspondence between autism and language impairments

In DSM-IV, there is an explicit contrast between autism and specific language impairment. Children with SLI have a specific disability to acquire age-appropriate language, while development in all other domains is normal (American Psychiatric Association, 1994). Children with autism, by contrast, may not only have a delay in language development, other developmental domains are affected as well and there are also linguistic deviations that are not normal for any stage of development (Bishop, 2002). Nevertheless, the linguistic deficits observed in specific language impairment resemble the language impairment in autism. Children with SLI

usually have limited vocabularies, produce immature speech sounds and use basic grammatical structures (Newbury et al., 2005). The profile of language performance among a subgroup of children with autism mirrors the profile of SLI: poorer performance on tests of grammatical ability than vocabulary, and difficulties with non-word repetition (Tomblin and Zhang, 1999; Dollaghan and Campbell, 1998; Kjelgaard and Tager-Flusberg, 2001).

The overlap in both disorders suggests that autism and SLI involve a shared neural substrate and one or more shared genes (Kjelgaard and Tager-Flusberg, 2001). Regarding the possibility of a shared genetic aetiology, family members of probands with autism have a higher than chance rate of language impairments, and family members of probands with SLI are at risk for autism (Piven and Palmer, 1997; Tomblin et al., 2003). Several genome-wide screens have been undertaken to find susceptibility loci for autism, providing the most significant findings on 7q31 (International Molecular Genetic Study of Autism Consortium, 1998) (but for a review see Klauck, 2006).

Given the similar phenotype and genetic overlap between autism and SLI, the issue of to what extent underconnectivity is involved in the emergence of SLI needs to be addressed. Interestingly, phenotypic similarity at a neural level has been found between language impaired boys with autism and boys with SLI (DeFosse et al., 2004). Segmented MRI scans showed larger right than left frontal language association cortexes in both groups. Since the inversed asymmetry was not present in the autism group that was linguistically unimpaired, these results suggest that there is a common underlying (genetic) cause for the language impairments in autism and SLI.

5.3. Implications for therapies and directions for future research

There is a pressing need for further research into functional and structural connectivity in autism. The coarse current knowledge on neural connectivity could be refined by combining measures of connectivity such as DTI, MEG and fMRI and genotyping (imaging genomics), so that genes associated with connectivity can be found. Also, if reliable and valid subgroups can be formed based on neuroimaging measures, the power of whole genome screens would increase considerably. Imaging should also be combined with administration of pharmacologic agents to allow for inferences on the biochemical basis of autism. Apart from combining investigative modalities, research on autism will also benefit from using well-selected subject groups. Knowledge on the developmental trajectory of connectivity in autism could be gained by using different age groups (cross sectional studies) or better, by employing longitudinal imaging study designs. Comparison between people with HFA, Asperger syndrome and SLI will allow for inferences on language deficits compared to social deficits, and the influence of symptom severity on micro architectural measures could come from contrasting people with autism and PDD-NOS.

There is furthermore a need for biological markers of autism, since early diagnosis based solely on observation of behavioural symptoms has been proven difficult and inefficient (Groen et al., 2007). Other psychiatric disorders with an onset in early childhood, such as attention deficit hyperactivity disorder (Murias et al., 2007) have also been associated with aberrant connectivity. Therefore, the specificity and extent of abnormal connectivity in autism should be addressed, so that the possibility of a connectivity-based biomarker can be explored. Diffusion weighted imaging might facilitate early diagnosis if a sufficiently sensitive and specific acquisition procedure can be developed. Early diagnosis may be one way of opening the door for effective therapies.

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