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Review

Linking neocortical, cognitive, and genetic variability in autism with alterations of brain plasticity: The Trigger-Threshold-Target model

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ABSTRACT

The phenotype of autism involves heterogeneous adaptive traits (strengths vs. disabilities), different domains of alterations (social vs. non-social), and various associated genetic conditions (syndromic vs. nonsyndromic autism). Three observations suggest that alterations in experience-dependent plasticity are an etiological factor in autism: (1) the main cognitive domains enhanced in autism are controlled by the most plastic cortical brain regions, the multimodal association cortices; (2) autism and sensory deprivation share several features of cortical and functional reorganization; and (3) genetic mutations and/or environmental insults involved in autism all appear to affect developmental synaptic plasticity, and mostly lead to its upregulation. We present the Trigger-Threshold-Target (TTT) model of autism to organize these findings. In this model, genetic mutations trigger brain reorganization in individuals with a low plasticity threshold, mostly within regions sensitive to cortical reallocations. These changes account for the cognitive enhancements and reduced social expertise associated with autism. Enhanced but normal plasticity may underlie non-syndromic autism, whereas syndromic autism may occur when a triggering mutation or event produces an altered plastic reaction, also resulting in intellectual disability and dysmorphism in addition to autism. Differences in the target of brain reorganization (perceptual vs. language regions) account for the main autistic subgroups. In light of this model, future research should investigate how individual and sex-related differences in synaptic/regional brain plasticity influence the occurrence of autism.

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1. Introduction: Genetically determined high plasticity is associated with both the strengths of autistic people and variability in the autistic phenotype

Phenotypic, cognitive and genetic heterogeneity of autism has complicated the understanding of its causes, but may also have a heuristic value. Autistic people display cognitive strengths which may result from differences in the plasticity of brain functions at particular regions (Mottron et al., 2013). Brain imaging studies of autism have revealed a large-scale reorganization of the autistic brain which may reflect enhanced cortical plasticity. In parallel, genetic studies of autism have recently identified many de novo mutations (Gillis and Rouleau, 2011; Ronemus et al., 2014). Most of these mutations are implicated in synaptic plasticity (Kelleher et al., 2008; Baudouin et al., 2012), which is defined as the process of microstructural construction of synapses occurring during development and the remodeling of these synapses during learning. These findings suggest that enhanced synaptic plasticity triggers a regional reorganization of brain functions that account for both the unique aspects of autism and its variability. In this paper we will review the following: (1) the main sources of inter-individual variability of the autistic phenotype, with an emphasis on the domain-general strengths of autistic people; (2) how cortical reorganization, similar to that following sensory impairment, occurs within the most "plastic" regions of the human brain in autistic people; and (3) how mutations implicated in autism alter synaptic plasticity. In addition, we propose the Trigger-Threshold-Target model which describes how genetically triggered brain reorganization may account for autism and its cognitive, phenotypic and neurogenetic variability.

2. Main sources of inter-individual variability in the autistic phenotype

2.1. Phenotypic variability

Phenotypic variability is a key feature of autism (APA, 2013). Not all signs of autism are found in every autistic person, which means that diagnosis is based on polythetic criteria as opposed to a defined set of clinical features. For instance, speech abilities in autistic people can range from none to outstanding, and intelligence from intellectual disability to genius. Various approaches have been devised to categorize this variability. The DSM-IV (APA, 2013) proposed subtyping to account for variability in language development, and differentiated autism from Asperger syndrome. The DSM-5 proposed the use of clinical specifiers (language, intelligence, neurogenetic context, severity) to describe differences in cognitive, comorbid or adaptive characteristics within the autistic spectrum. The two approaches differ in that the categorical, subtyping approach clusters different values for each source of heterogeneity, whereas the dimensional, specifier approach allows an indefinite number of possible values and combinations (Szatmari, 2011) of heterogeneity. This symptomatic variability has been seen as an obstacle to the recognition and understanding of autism. The model we propose here suggests that the phenotypic, cognitive, but also genetic heterogeneity (Girirajan and Eichler, 2010) of autism is a fundamental feature that reflects its mechanistic causes.

2.2. Cognitive variability

2.2.1. Intelligence

One source of heterogeneity in the autistic phenotype is intelligence level. The prevalence of intellectual disability, epilepsy, microcephaly, and the female to male ratio is markedly higher in syndromic autism than in nonsyndromic autism (Amiet et al., 2008). However, there are also large differences in intelligence level amongst people with nonsyndromic autism. The reported incidence of intellectual disability in nonsyndromic autism has been in constant decline in the last few decades (Prevention CfDCa, 2013), from more than two-thirds of cases to less than one-third. Part of this previously reported intellectual disability resulted from the fragmented use of language by autistic patients, which impaired their capacity to perform well in standard intelligence tests. As a result, estimates of intellectual disability were strikingly lower when nonverbal tests were used (Dawson et al., 2007). The measurement of intelligence also reveals large intra-individual variability of performance depending on the task, with some tasks performed higher than expected according to the individual's predicted IQ score.

2.2.2. Perception

Perceptual skills are the most documented cognitive strength in autistic people (Mottron et al., 2013). High perception of the surrounding environment appears to be present early in

development, with long visual fixations (Zwaigenbaum et al., 2005), early detection of audio-visual synchrony (Klin et al., 2009), interest in geometric shapes (Pierce et al., 2011) and periodic motion (Mottron et al., 2007), and superior visuo-spatial search (Kaldy et al., 2011). Perceptual strength, defined as a score superior to 1SD from the baseline IQ, is present in 30 (Howlin et al., 2009) to 50% (Caron et al., 2006) of autistic people, and is thereby a source of intra-individual heterogeneity. Perceptual strength cannot be easily classified according to perceptual levels or modalities. For instance, auditory processing is frequently altered in autism (O'Connor, 2012) and includes an enhanced ability to discriminate low level perceptual features such as pitch and loudness. Adept visual processing often involves mid-level perception, for instance the ability to detect patterns in embedded figures or visual search tasks (Mottron et al., 2012a) and more frequently involves extrastriate regions than primary regions (Schwarzkopf et al., 2014). Autistic people also have a high ability both to perceive details in compound visual stimuli (Wang et al., 2007), and to manipulate large-scale three dimensional figures (Soulieres et al., 2011). In addition, perceptual strengths in autism involve not only low or mid-level operations but also visuo-spatial reasoning (Stevenson and Gernsbacher, 2013).

2.2.3. Language

Language and speech function is another domain in which there is a striking range of strengths and deficits, both within and between individuals (Williams et al., 2008). Most autistic persons suffer from major speech onset delay (SOD), specific language impairment and/or particular deficits (deictic terms, pragmatics) early in development; however, some autistic people exhibit normal early language development. According to the DSM-IV criteria, early language impairment is associated with autism whereas individuals with Asperger Syndrome develop normal language skills. The DSM-5 no longer supports this distinction, partly due to its lack of reliability, and because features of the DSM-IV criteria of Asperger syndrome are inapplicable. Nonetheless, cognitive (Sahyoun et al., 2009; Bonnel et al., 2010; Jones et al., 2009a; Barbeau et al., 2013a) and brain imaging data (Yu et al., 2011; Sahyoun et al., 2010) of autistic spectrum (AS) people with (AS-SOD) or without (AS-NoSOD) speech onset delay and/or atypicalities, suggest that this distinction has some value.

Furthermore, there are major intra-individual variations in performance across different language functions, mostly in AS-SOD (Boucher, 2012). Despite speech onset delay, some language components are unimpaired, or even enhanced. An example of this is decoding, which is the ability to produce sounds corresponding to a graphic representation of speech (Jones et al., 2009b). This capacity has been associated with hyperlexia (Grigorenko et al., 2003), which is a precocious, transient nonlinguistic use of language. Most autistic strengths are related to pattern perception, reproduction and manipulation, for instance exceptional 3-D drawing or musical memory; however, others are not directly perceptual and are instead related to language (Klin et al., 2009) (e.g., calendar calculation, factorization, prime number detection, memory for proper names). Autistic people who possess proficient skills related to perception may show early speech alterations up to and including the absence of spontaneous speech, whereas hyperlexia or some hypermnesia imply the hyper-functioning of a component of language function (Mottron et al., 2013).

2.3. Differences in strengths according to Autism spectrum subgroups

Although autism spectrum appears as a heterogeneous condition with different patterns of enhanced or impaired perceptual and cognitive skills, patients can be divided into two main AS subgroups according to these strengths and deficits. Perceptual enhancement is largely associated with delay, deficits or abnormalities in speech (echolalia, pronoun reversal) (Caron et al., 2006). AS-SOD is characterized by strengths in reasoning (as measured with Raven matrices) and visuo-construction, combined with deficits in some, but not all, aspects of language (Dawson et al., 2007). Preserved language capacities are those that appear to involve the perceptual processing of language, for instance reading or reproducing a phonological sequence (Mottron et al., 2013). Similarly, in IQ tests, AS-SOD people perform well in visuo-spatial tasks such as the Block Design subtest, but poorly in the verbal Comprehension subtest (Stevenson and Gernsbacher, 2013). Perceptual capacity distinguishes AS-SOD from AS-NoSOD: the performance in visual inspection time tasks can correctly classify adults as AS-SOD or AS-NoSOD, because only adults with AS-SOD perform better than the comparison group (Barbeau et al., 2013a). Regarding auditory processing, AS-SOD but not AS-NoSOD is associated with an enhanced perception of low-level auditory dimensions of language such as pitch (Heaton et al., 2008a; Jarvinen-Pasley and Heaton, 2007; Eigsti and Fein, 2013).

Overall enhancement of language function, including speech, is found only in people with AS-NoSOD. These individuals develop language skills quickly with the use of polysyllabic words, exceptional mastering of syntax, and a special ability of abstract verbal reasoning as measured with the similarities subtest of the Wechsler scale. The overuse of language by AS-NoSOD people is also illustrated by occasional extreme verbosity (Adams et al., 2002), and by the "categorical", verbally defined nature of their restricted interests (Mottron et al., 2012b). These individuals do not display the visuo-spatial strengths that characterize patients with AS-SOD; they perform well in the Vocabulary and Similarities subtests of the WAIS (Nader et al., 2014) and perform poorly in the Comprehension and Coding subtests. In addition, motor clumsiness is a clinical sign associated with AS-NoSOD (Klin et al., 1995) but is rarely found in AS-SOD (Meilleur et al., 2014; Barbeau et al., 2013b). Thus, AS-NoSOD cannot simply be considered as "AS with language preserved", because these individuals display a specific pattern of enhancements in language combined with motor deficits. In contrast, perception in AS-SOD people is not only preserved, but is enhanced and is associated with speech and social alterations. This is coherent with a distinction between two AS subgroups based on their strengths, perception vs. language function, as well as their deficits, speech vs. motor function.

2.4. Variability of imaging findings in autism spectrum subgroups

In addition to differences in cognitive function, AS-SOD and AS-NoSOD markedly differ in brain reorganization. Several functional and structural Activation Likelihood Estimate (ALE) meta-analyses or systematic reviews on brain imaging in autism are now available. The analysis of functional neuroimaging data has revealed perturbations of task-related brain activity for both social and non-social tasks, and despite considerable methodological heterogeneity, main group differences can be extracted from these studies. In social tasks, these differences include greater activity in the post-central and superior temporal gyri in ASD individuals than in controls, whereas the opposite has been reported for the anterior and posterior cingulate cortex, the anterior insula and the amygdala (Di Martino et al., 2009). Also, differences between autistic individuals and nonautistic controls during task-related activity are often found in the fusiform area, with both hypo- and hyperactivation observed in the different fusiform sub-regions in autism (Di Martino et al., 2009; Samson et al., 2011a). In addition, children and adolescents within the ASD population show high activity in the post-central gyrus, with adults displaying greater superior temporal and hippocampal activity than children (Dickstein et al.,

2013). In non-social tasks, studies have consistently found that autistic individuals have greater activity in the precentral gyrus, in the fusiform gyrus and in the middle frontal cortex than nonautistic controls. In contrast, activity in the superior temporal gyrus, prefrontal cortex and cingulate cortex is frequently found to be higher in non-autistic than in autistic individuals (Di Martino et al., 2009; Samson et al., 2011a). Within ASD, activity in the insula and cingulate is stronger in children and adolescents than in adults, where as activity in the middle frontal cortex is greater in adults (Dickstein et al., 2013).

Ectopic activity in response to social and non-social information in autism is indicative of cortical reallocation. We conducted an ALE meta-analysis of 26 functional neuroimaging studies in which visual information was presented to a total of 370 controls and 357 ASD individuals. Despite similar performance levels for both groups, the activity of parietal and occipito-temporal regions associated with visual perception and expertise was higher in autistic individuals (mostly AS-SOD) than in non-autistic individuals (Samson et al., 2011a). Regarding connectivity, functional fMRI (Monk et al., 2009), EEG (Barttfeld et al., 2011; Murias et al., 2007), MEG (Kikuchi et al., 2013), and histological studies (Casanova et al., 2006; Hutsler and Zhang, 2010) have revealed limited long range connectivity between frontal and visual regions, as well as enhanced local connectivity within local cortical networks in autism. In particular, functional hyper connectivity (Khan et al., 2013) has been reported between the temporal and parietal lobe (Kikuchi et al., 2013), within the medial temporal lobe (Welchew et al., 2005), within the visual cortex (Turner et al., 2006; Noonan et al., 2009; Rudie et al., 2012; Keown et al., 2013), between the visual and frontal cortex (Leveille et al., 2010; Domínguez et al., 2013) and within the posterior cingulate cortex (Monk et al., 2009) in autism. This is indicative of highly autonomous functioning of the autistic visual cortex (see Fig. 1E).

AS-SOD individuals show reorganization of brain function during language tasks, including hyper-activation in the fusiform gyrus (Samson et al., 2011a) and atypical, strong (Leveille et al., 2010; Domínguez et al., 2013) functional connectivity between associative perceptual areas and other parts of the brain (Peters et al., 2013). This reorganization may explain why AS-SOD individuals use perception for typically nonperceptual, verbal tasks (Monk et al., 2009). However, in tasks involving the processing of non-social auditory information, AS-NoSOD individuals show greater activity in peri-auditory and language-related brain regions than AS-SOD individuals and non-autistic controls (Samson et al., 2009). This suggests that high activity and cortical reallocation in perceptual associative regions in AS-SOD individuals have an equivalent in AS-NoSOD individuals in the form of widespread allocation of auditory brain regions for language processing.

Alterations in gray and white matter have been reported in autistic persons, although there are some inconsistencies amongst studies regarding the location and direction of regional brain volume changes (Stanfield et al., 2008). Meta-analyses have established that overall brain growth is faster in the early years of life in autistic individuals than in age-matched controls (Stigler et al., 2011). Six clusters of alterations to brain structure were revealed by a recent structural meta-analysis. These structural alterations occur in the following regions (from the most to the least significantly affected): the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia, and the area proximate to the right parietal operculum. These regions contribute to the uni- and multi-modal perception of both social and non-social information (Nickl-Jockschat et al., 2012); no region is uniquely involved in the processing of social or emotional information. The analysis of combined alterations of gray and white matter (Cauda et al., 2014) has provided an additional source of information. Although autism is associated with hypertrophy of gray and white matter in the occipital regions, gray and white matter volume in the frontal and dorsal parietal brain cortices are smaller than in nonautistic controls. The most densely connected clusters of regions with volumetric variations in both directions are the left fusiform gyrus, the middle temporal gyrus, and the inferior occipital gyrus (Fig. 1C and D). A meta-analysis comparing AS-SOD and AS-NoSOD (Yu et al., 2011) has revealed structural differences between the two AS subgroups. AS-NoSOD have a reduced gray matter volume in the left occipital gyrus and enhanced volume in left fusiform than controls. AS-SOD individuals show clear structural alterations, including a lower gray matter volume than controls in the middle temporal gyrus and a larger gray matter volume in the left ventral temporal lobe.

Longitudinal studies and cross-sectional comparison of autistic children and adults indicate that the differences in overall brain volume between autistic and nonautistic individuals normalize at an adult age; however, local volumetric differences are maintained. Brain growth trajectories in autistic individuals depend on the region involved, and the growth of structures commonly affected in autism shows atypical synchronization in comparison with the rest of the cortex (Nickl-Jockschat et al., 2012). Interestingly, a longitudinal structural MRI study of ASD revealed that thickening of occipital gray matter is not present in children (Schumann et al., 2010), whereas in adults with ASD the volume of occipital regions is higher than in controls.

Overall, these studies show that: (a) brain alterations occur in regions implicated in high and low level processing of both social and non-social information and are not limited to regions implicated in “superior” or “social” functions; (b) increases of brain volume and activity consistently involve associative perceptual regions, specifically areas devoted to perceptual expertise (e.g., fusiform gyrus and lateral occipital complex) in AS-SOD and involve language regions in AS-NoSOD; (c) there is a developmental shift with overall excess in brain volume in early years being replaced by a complex pattern of regional volumetric alterations in adulthood; and (d) large cortical volume of the perceptual area appears later in life. This pattern of alterations is consistent with genetic variation, which is responsible for altered, lifelong interaction with the environment, and affects cognitive, functional, and structural properties of either the perceptual associative regions or language regions according to the subgroup of the autism spectrum.

2.5. Syndromic and non-syndromic autism

A last, major source of heterogeneity in autism is neurogenetic and differentiates nonsyndromic autism from syndromic autism. Individuals with nonsyndromic autism have no recognizable syndrome associated with autism. Persons with this condition do not present morphological characteristics such as facial dimorphisms or neural tumors. In contrast, persons with syndromic autism present phenotypic manifestations of an additional syndrome including facial dimorphisms or alterations in brain structure. Fragile X, an inherited condition associated with atypical facial morphology and intellectual disability, is an example of syndromic autism when associated with an autistic-like phenotype. Similarly, tuberous sclerosis is a neurodevelopmental genetic condition characterized by brain tumors and epilepsy, and a high prevalence of autism. Both of these conditions, when associated with autism, meet the criteria for syndromic autism, despite the fact that they occur more frequently alone than with autism. Although useful from a clinical point of view, the distinction between nonsyndromic and syndromic autism has been blurred by the discovery of morphological variations (e.g., macrocephaly curves that peak in the first year (Redcay and Courchesne, 2005) in autistic people otherwise devoid of any recognizable neurological syndrome. Moreover, causative genetic alterations are found in nonsyndromic as well

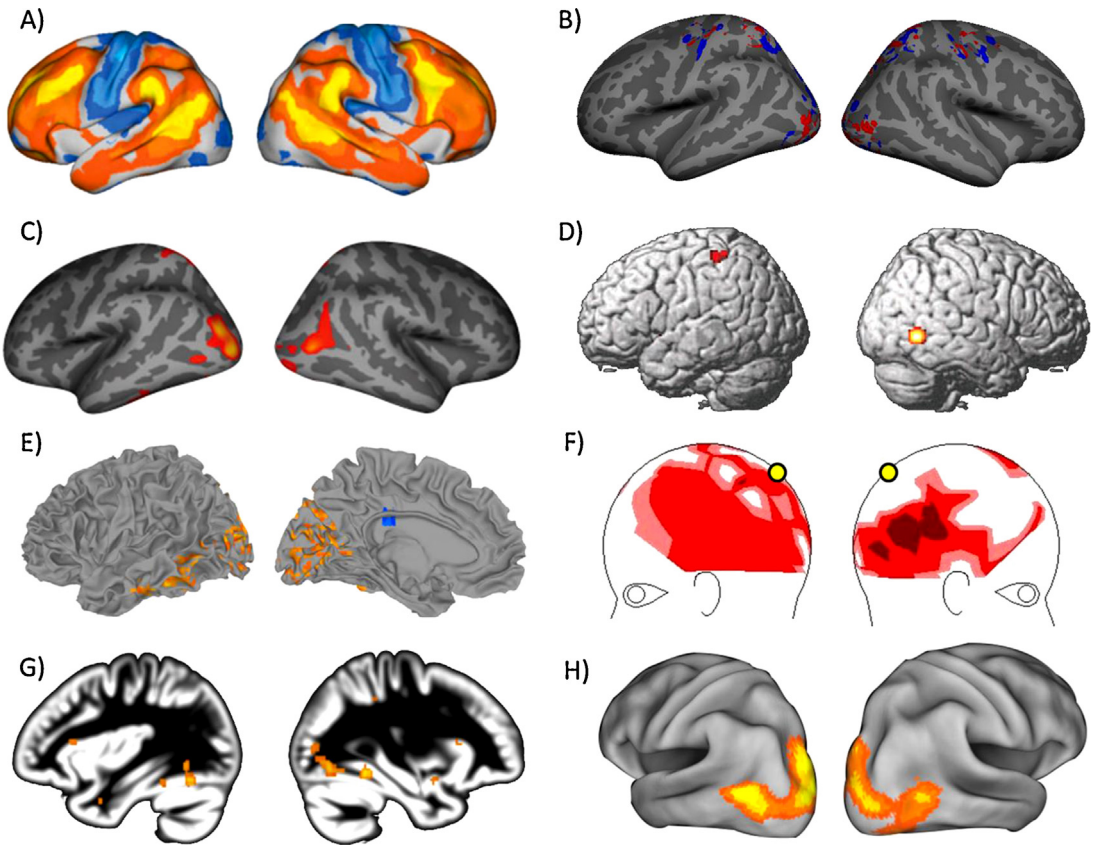

Fig. 1. Overlap between regions of: enhanced variability in non-autistic individuals (A), superior variability in autistic people (B), major gyrification (C), volumetric (D), connectivity (E, F) and functional (G) alteration in autistic people, and regions of cross modal plasticity in non-autistic, sensory-impaired people (H). (A) High inter-individual variability in resting-state functional connectivity in non-autistic individuals. Values above or below the global mean are displayed in warm and cool colors, respectively (Mueller et al., 2013); (B) The localization of the strongest peak of activity in autistic individuals (in blue) shows higher variability than in typical individuals (in red) (Poulin-Lord et al., 2014); (C) Regions showing greater cortical gyrification in autistic individuals than in non-autistic individuals. The warmer the color, the greater the significance of the group differences (Wallace et al., 2013); (D) Clusters of brain structure alterations (differences in gray matter or white matter) between autistic and non-autistic individuals (qualitative meta-analysis, whole brain FDR corrected) (Nickl-Jockschat et al., 2011); (E) Regions of enhanced resting-state local connectivity density in autistic individuals. Warm colors show the regions with greater connectivity in the autistic individuals than in non-autistic individuals, and cool colors regions of lower connectivity (Keown et al., 2013); (F) Regions where high connectivity with the right parietal region (yellow circle, MEG coherence analysis) is associated with high reading ability. The darker the color, the stronger the correlation (Kikuchi et al., 2013); (G) Regions showing more activity in autistic individuals than in non-autistic controls when processing visual information. Qualitative meta-analysis, whole brain FDR corrected (Samson et al., 2011a); (H) Regions of differences in activity between congenitally blind and sighted individuals when processing auditory information (whole brain FWE corrected; adapted from Collignon et al., 2011).

in syndromic autism. Thus, the definition of a "recognizable syndrome" (and hence the classification of syndromic autism) may be dependent on the progress of genetic knowledge.

3. Comparison between autism and cross-modal plasticity

Cognitive and imaging experiments have revealed that perceptual strengths and cortical reorganization develop during cross-modal plasticity following sensory deprivation. We will now discuss this condition in relation to autism.

3.1. Perceptual strengths in autism and cross modal plasticity

Like autistic individuals, people experiencing early and complete sensory loss (e.g., individuals born deaf or blind) have perceptual enhancements. Such enhancements involve the remaining senses (e.g., audition and smell in blind people) and are believed to be linked to the recruitment (Bavelier and Neville, 2002) of the brain areas deprived of their natural inputs to the remaining senses. This reorganization is termed cross-modal plasticity. Cross-modal plasticity in deaf or blind individuals is often considered as adaptive because it results in a more efficient interaction with the external environment. The magnitude of cross-modal recruitment may correlate with the level of performance enhancement reported in the blind (Amedi et al., 2003; Gougoux et al., 2005; Kupers et al., 2007), and with the contribution of the temporal cortex in mediating non-auditory processing in deaf adults (Bolognini et al., 2012). Cross-modal plasticity mechanisms are guided by the original computation style (Cardin et al., 2013) and/or connections (Collignon et al., 2011). Therefore, cross-modal plasticity is a particular case in which cortical recycling (Dehaene and Cohen, 2007) occurs within a sensory deprived region, with potentially beneficial effects for behaviors (Collignon et al., 2009a).

The perceptual enhancements observed in autism and sensory-deprived individuals exhibit striking similarities. For example, both blind and autistic individuals show superior pitch discrimination (Bonnel et al., 2010, 2003; Wan et al., 2010; Gougoux et al., 2004), spatial localization (Collignon et al., 2009a, 2006; Caron et al., 2004; Doucet et al., 2005), selective attention (Collignon et al., 2006, 2009b; O'Riordan et al., 2001; Plaisted et al., 1998; Collignon and De Volder, 2009; Kujala et al., 2000), tactile discrimination (Wong et al., 2011), verbal memory (Amedi et al., 2003; Mottron et al., 1996; Raz et al., 2007; Nakano et al., 2012), and an ability to quickly detect and discriminate auditory information (Hyde et al., 2011; Hertrich et al., 2013). Similarities also involve complex perceptual strategies: for instance, peripheral vision is enhanced in both autism (Mottron

et al., 2007) and early deafness (Voss et al., 2004; Chen et al., 2010; Frey et al., 2013). Parallel search, which is a widely accepted explanation for the enhanced visual search performance consistently found in autism, also occurs in deaf (Stivalet et al., 1998; Remington et al., 2012) individuals: both populations are less impaired by increasing number of visual distractors than typical individuals. People with intellectual disability plus deafness perform better in visual sorting tasks involving detailed visual information than intellectually disabled people, and autistic individuals also perform well in such tasks (Maljaars et al., 2011). Behavioral compensations in deaf individuals mostly involve inputs originating in the peripheral visual field (Neville and Lawson, 1987; Bavelier et al., 2000).

Modifications of visual strategies such as parallel search and enhanced peripheral vision that occur in deaf children strongly resemble the modification of visual attention that is beneficial to visual search in autism. These results reflect findings with congenitally blind individuals (or who became blind at a young age). Such individuals demonstrate supra-normal performances in tasks involving the localization of peripheral auditory sources, in which subtle auditory cues (i.e., spectral) have to be exploited to resolve the task efficiently (Voss et al., 2004; Röder et al., 1999; Fieger et al., 2006). Compensations involving peripheral stimuli occur preferentially in conditions where the task is difficult and where there is room for perceptual enhancement. It highlights the extreme precision of sight in deaf individuals and hearing in blind individuals (Voss et al., 2004; Röder et al., 1999; Lessard et al., 1998). Another example of similarities between AS and cross-modal plasticity is motion perception; despite some conflicting evidence, recent studies show that some aspects of visual motion perception may be enhanced in autism (Foss-Feig et al., 2013), as is the case for vision in congenitally deaf people (Hauthal et al., 2013) and for the audition of moving sounds in congenitally blind people (Lewald, 2013).

In summary, the particular aspects of perception which are enhanced following sensory deprivation (Cohen et al., 1997; Amedi et al., 2004; Collignon et al., 2007) are also commonly enhanced in individuals with autism. Adaptive value may decide what functions are enhanced in blind and deaf people. For instance, enhanced peripheral sound or visual localization in blind and deaf individuals, respectively, enables them to rapidly detect sources of danger. A similar adaptive benefit of enhanced perceptual functions is not so obvious in autism. However, the striking similarities between domains of enhanced perception in AS and sensory deprived people suggest that common mechanisms underlie the development of these supra-normal skills. Therefore, cross-modal plasticity may be a useful "model" for autistic enhanced perceptual functioning and may provide a mechanistic explanation for some characteristics of autism. The similarity between the two groups may result from neurobiological constraints, in particular from the superior plastic potential of particular perceptual functions.

3.2. Cortical reorganization in autism and cross modal plasticity

The comparison of brain imaging results in autism and in sensory-deprived individuals provides information about the cortical reorganization that underlies cognitive changes in these two conditions. Brain areas typically devoted to the de-afferented sensory modality are diverted from their original function by another intact sensory modality in blind or deaf individuals. However, not all regions associated with the impaired modality are affected by plastic reallocation and activated by sensory input of the intact modality. The associative/multimodal perceptual areas are among the regions the most commonly affected by these reallocations, in autism, blindness (Fig. 1G) and deafness.

An ALE meta-analysis of studies of autistic individuals indicated an atypical, strong activation of associative visual areas during multiple perceptual, language, semantic and problem solving tasks (Samson et al., 2011a; Cardin et al., 2013; Koshino et al., 2008; Soulières et al., 2009; Iuculano et al., 2014). This enhanced task-related activity in associative visual regions in autism is domain-specific. When studies included in the ALE meta-analysis were stratified according to broad categories of material presented (faces, objects, letters), differences between the groups of participants varied; nonetheless, regions of enhanced activity were notably seen in the fusiform gyrus, which is a region typically dedicated to experience-dependent expertise.

Cortical reorganization in autism may be associated with a gain of function, at least for situations where an additive processing of information by visual cortex is an advantage. A study involving fMRI showed that the activity of extrastriate areas (BA18) is higher in autistic than in non-autistic individuals during a task of non-verbal reasoning. However, the activity in the lateral prefrontal cortex (BA9) and the medial posterior parietal cortex (BA7) was lower in autistic individuals and they performed the task 40% faster than non-autistic individuals. The left middle occipital gyrus and the medial precuneus were significantly more activated in autistic individuals only during the most difficult items, consistent with the implication of the visual cortex in the autism-associated strength of non-verbal reasoning. In this case, cortical reorganization involves the enhanced contribution of a region important for a particular type of task (Soulières et al., 2009).

In individuals who become deaf or blind at an early age, cross-modal cortical reorganization are widespread in the sensory deprived regions but mainly involves the recruitment of de-afferented associative areas during the stimulation of the intact modality. Recent studies on cross-modal plasticity demonstrated that the cortical reallocation of a specific brain region may maintain the cognitive role of this region, despite the change in sensory input (Collignon et al., 2009a). For instance, in blind people, auditory spatial processing relies on parts of the occipital cortex typically involved in visual spatial processing (Collignon et al., 2011, 2007; Dormal and Collignon, 2011). Thus, blind persons use the same region as sighted persons for spatial processing, but blind people use it to derive space based on auditory cues, whereas sighted people use it to derive space based on visual ones. Similarly, inner connectivity within the "Visual Word Form Area", which is inactivated in illiterate, nonautistic people, is reinforced during reading in adults leading to its activation during the acquisition of literacy (Thiebaut de Schotten et al., 2014). This region is functionally recruited in congenitally blind people during Braille reading (Reich et al., 2011). Similar reorganization patterns are associated with higher level functions. For instance, the visual cortex is strongly involved in higher order speech operations in congenitally blind people (Amedi et al., 2003; Bedny et al., 2011). Overall, the cross-modal recruitment of the occipital region in the congenitally blind follows a division of computational labor (e.g., the "what" and "where" distinction) comparable to that observed in the sighted (Dormal and Collignon, 2011; Collignon et al., 2012).

Enhanced activation of auditory perceptual regions has also been reported in autism, although few studies have investigated this modality. Higher levels of spectral/temporal complexity in speech-like stimuli are associated with greater activity in the primary auditory cortex in AS-SOD individuals than in nonautistic individuals. In contrast, AS-SOD individuals showed low levels of activity related to temporal complexity in non-primary auditory regions within the superior temporal gyrus, which is a region linked with processing temporally complex sounds (Samson et al., 2011b).

Weak hemispheric asymmetry for functions that are typically lateralized is another indicator of functional reorganization in both autistic and sensory deprived persons. In autism, weak hemispheric

asymmetry was reported for language (Lo et al., 2011; Eyler et al., 2012), face perception (Dundas et al., 2012; Scherf et al., 2010) and perceptual response in general(Dinstein et al., 2012). A similar pattern is found in sensory-deprived individuals, since some aspects of language processing are less lateralized in deaf (Emmorey et al., 2010) and blind (Hugdahl et al., 2004) individuals than in perceptually unimpaired individuals. Face (Vargha-Khadem, 1983; McCullough et al., 2005) and motion (Bavelier et al., 2001) processing are more reliant on left brain regions in deaf people, whereas these functions are preferentially implemented by right-sided brain regions in hearing individuals.

Perception of visual and auditory motion is a crucial perceptual skill for interacting with the environment. This ability relies on a set of highly specialized brain regions (Watson et al., 1993; Warren et al., 2002). Sensitivity to visual motion highly depends on early visual experience (Ellemberg et al., 2002), and is therefore a perceptual skill prone to reorganization. In deaf, visual motion relies on reorganized networks in temporal regions and in blind people the same is true for auditory motion in occipital regions (Neville and Lawson, 1987; Bosworth and Dobkins, 2002; Bedny et al., 2010; Noser and Byrne, 2007). Motion perception is also processed by modified neural networks in autism (McKay et al., 2012).

Regarding connectivity, sensory-deprived persons display alterations overlapping with those observed in autistic people. Blind people display an increase of intra-occipital and a decrease in long range resting state connectivity (Liu et al., 2011, 2007). Furthermore, task-dependent enhanced connectivity has been reported between the primary auditory and primary visual cortex (Klinge et al., 2010a; Leclerc et al., 2005; Collignon et al., 2013) in the blind, and between the parietal cortex and early visual areas in the deaf (Bavelier et al., 2001). Interestingly, absolute pitch and synesthesia, the prevalence of which is high in autism (Mottron et al., 2013), are both associated with enhanced local connectivity in the non-autistic population (Zamm et al., 2013; Loui et al., 2011), and can follow blindness (Steven and Blakemore, 2004; Pring et al., 2008) and brain damage (Bolognini et al., 2013).

In terms of the cellular mechanisms involved, both conditions are thought to be associated with disrupted pruning mechanisms. Disruption of pruning may explain high neural cell density in autism (Courchesne et al., 2011). Similarly, connections normally pruned away during development may be maintained following sensory loss due to lack of competitive perceptual input from the impaired sensory modality (Yaka et al., 1999; Berman, 1991). Studies of ocular dominance plasticity, a commonly used model to study synaptic and cortical reorganization following experience, in the fragile X mouse model revealed hyperplasticity involving an exaggerated response to visual deprivation (Dölen et al., 2007). Fragile X is a neurodevelopmental condition distinct but strongly associated with autism, for which the role of genetically-triggered enhanced plasticity is well established (see Section 4.1).

In summary, cortical reorganization in autism and in sensory-deprived individuals shares several characteristics. These include the identity of the reorganized areas, regional re-wiring of the regions affected by functional reallocation, alteration of lateralization, the reassignment of perceptual functions, and the gain of perceptual functions. Another important similarity is that the plastic modifications found in autism and sensory-deprived individuals mostly occur in specific brain regions, as will be described below.

3.3. *Regions of cortical reorganization in autism and cross-modal plasticity coincide with regions of maximal variability in humans*

Several reports suggest that the regions that are the most susceptible to reorganization in autism (the multimodal association regions) are also those that have the largest variability in terms of connectivity among non-autistic individuals (Mueller et al., 2013; Aichhorn et al., 2006) (Fig. 1A). The highest inter-individual differences in resting-state connectivity are in the multimodal association cortex and the lowest are in the unimodal sensory and motor cortices. Mueller et al. (2013) reported that regions of enhanced variability developed late during evolution, because they are the most divergent regions between monkeys and humans. They also demonstrated that cortical folding shows the highest degree of variability in these regions, and the slowest maturation. Thus, these regions appear to be highly susceptible to changes affecting ongoing learning and plasticity, and are therefore most likely subject to functional reallocation due to atypical experience (Barnes and Finnerty, 2010). These regions of maximum variability also show the largest functional activation differences between autistic individuals and non-autistic controls during the processing of visual information (Samson et al., 2011a) (Fig. 1F). In particular, the lateral occipital cortex (LOC) is a region that shows greater cortical gyrification (Wallace et al., 2013) and volumetry (Nickl-Jockschat et al., 2012) in the autistic individuals than in non-autistic individuals. This region is selectivity implicated in processing visual objects in sighted individuals (Martin, 2007) and is involved in cross-modal recruitment for auditory or tactile object processing in the congenitally blind (Amedi et al., 2007; Sathian, 2005).

For these reasons, high plasticity in autism should also be characterized by large inter-individual variability between autistic individuals in regions affected by plastic functional reallocation, with each reallocation in each individual being dependent on various environmental constraints. We scanned 23 overtly verbal autistic individuals and 22 non-autistic participants during a visuo-motor imitation task to test directly the hypothesis of high intra group variability in associative regions in autism (Poulin-Lord et al., 2014). We extracted the coordinates of the strongest activation peak in the primary and supplementary motor cortex, the visuo-motor superior parietal cortex, and the primary and associative visual areas. We then assessed the distance of each participant from their respective average group peak of activation to assess group differences in variability. The mean variability in the localization of activations in the associative visual or motor areas was higher than in the primary visual or motor areas for both groups. Importantly, we observed a greater variability in the left visuo-motor superior parietal cortex and in the left associative visual areas in the autistic group than in the control group (Fig. 1B). This indicates that the regions where autistic individuals display the maximum enhanced activity when exposed to visual information, and the regions where non-autistic individuals display the highest level of inter-subject variability are all included in the visual associative complex. Other autism studies have reported higher inter-individual variability of activation for faces than for objects, or an alteration of the typical distribution of allocation for faces vs. objects (Scherf et al., 2010; Schultz et al., 2000; Pierce et al., 2001) in the same regions.

In summary, the regions of major differences in perceptual brain activation between autistic and non-autistic individuals, as well as regions displaying the largest cross-modal plasticity in sensory-deprived individuals, overlap with regions that are the most variable and most plastic in neurotypical individuals. This overlap suggests a general mechanism for neuroplasticity, which mostly involves brain regions that are highly susceptible to reorganization. In contrast, primary sensory regions which probably require a high degree of neural constraints due to their topographic (e.g., retinotopic/tonotopic) organization may require a more hard-wired rigid organization and connectivity.

4. Genetic or prenatal risks predisposing to autism

We have presented how autistic strengths and cortical reallocations may be the result of enhanced cortical plasticity. We will now

discuss the genetic and molecular mechanisms that may explain these alterations.

4.1. Upregulation of synaptic plasticity

Due to recent advances in high throughput genomic technologies, deleterious mutations, including de novo copy number variants (CNVs) (Levy et al., 2011; Sanders et al., 2011; Marshall et al., 2008; Sebat et al., 2007), and de novo point mutations (Iossifov et al., 2012; O'Roak et al., 2012, 2011; Sanders et al., 2012; Neale et al., 2012), have been recently identified. These alterations involve a large number of genes in nonsyndromic autism and its related phenotypes, in addition to over 100 genes implicated in inherited monogenic syndromic autism (Betancur, 2011; Lim et al., 2013; Chahrour et al., 2012; Yu et al., 2013). "Animal models" (Chung et al., 2012; Shinoda et al., 2013) and neuronal cell cultures make it possible to study in vivo micro-structural modifications resulting from mutated neuroplastic genes or in utero toxic exposure. However, these are not "true" animal models of autism. Such models do not exist and may never exist. They are nonetheless experimental models of neuroplastic disruptions, which in humans, mostly result in neurodevelopmental dysmorphic syndromes with intellectual disability and a phenotype corresponding to current autism criteria in a substantial proportion of cases. They can thus contribute to understanding the mechanisms of syndromic autism, and, by extension, to autism per se. These animal models have revealed that most genes with strong effects and in utero toxic exposure implicated in autism and autistic-like phenotypes act upon a relatively small number of key biological processes affecting the structure and function of the synapses (Gillis and Rouleau, 2011).

Cascades of neuroplastic proteins control the formation of neural microcircuits between cells. This includes synaptogenesis, axonal guidance and growth, as well as synaptic plasticity, i.e., the ability of synapses to strengthen or weaken over time, in response to increased or decreased activity. Moreover, the timing of microcircuit construction follows developmental milestones, with a period of pruning starting in the second year of life, which is when most cases of autism are detected. In turn, pruning is stimulated by enriched environments (Sale et al., 2011), and coincides with learning and the formation of memory. Genes encoding many of these neuroplastic proteins have been implicated in autism, including: (1) cell adhesion molecules, e.g., neuroligin-3 (*NLGN3*) and neuroligin 4 X-linked (*NLGN4X*), mutations of which lead to high or ectopic GABAergic synapse formation (Tabuchi et al., 2007; Hoy et al., 2013); (2) postsynaptic "scaffolding" proteins, e.g., SHANK genes (i.e., *SHANK1*, *SHANK2* and *SHANK3*) which connect glutamate receptors to the actin in cytoskeleton via various intermediary elements and are a binding partner of neuroligins (Arons et al., 2012); (3) ionotropic (*AMPAR* and *NMDAR*) and metabotropic glutamate receptors (mGluR) at synapses (Chiocchetti et al., 2014); (4) transcriptional regulators of these synaptic proteins; and (5) signal transduction and tumor suppressor genes (Rinaldi et al., 2008) such as *TSC1* and *TSC2*, *NF1* and *PTEN*, involved in syndromic autism. The production of the synaptic proteins listed in (2) is controlled by genes that are in turn transcriptionally regulated by factors such as *MECP2*, a transcriptional repressor of brain-derived neurotropic factor (*BDNF*) and neuronal transcriptional regulators such as *DLX5*. Their production is also controlled by the fragile X mental retardation protein (*FMRP*) which binds mRNA transcripts in dendritic spines, exerts control over protein translation and regulates several families of synaptic proteins. Mutations of *TSC1* and *TSC2* are associated with Tuberous Sclerosis, and mutations of *NF1* and *PTEN* are associated with Neurofibromatosis and Cowden syndrome, respectively. The prevalence of autism is high in these disorders, and these mutations deregulate the production of neuroplastic proteins and modify the synaptic excitation/inhibition ratio (Bateup et al., 2013). In these cases, altered mechanisms of molecular plasticity also lead to tumors. These neuroplastic proteins regulate the production and balance of excitatory and inhibitory GABAergic synapses (Desgent and Ptito, 2012), and that of long term potentiation and depression (LTP/LTD) proteins that stabilize and remodel new circuits. Mutations in these genes cause dysregulation of activity-dependent signaling networks that control synapse development, function and plasticity (Ebert and Greenberg, 2013).

Mutations predisposing to autism appear to affect microstructural proteins and regulators. This alteration is mostly in the direction of hyper microstructural connectivity and hyper excitability (Arons et al., 2012), or more generally, the upregulation of the local plasticity (Kelleher et al., 2008; Zuko et al., 2013; Zoghbi and Bear, 2012). Disturbance of the regulation of gene expression following neural activity, or activity-dependent signaling, is among the most common functional effects of causative mutations involved in autism (see Ebert and Greenberg, 2013 for a review). Mice models have revealed that the four main mutations predisposing to autism, Nlgn3, Fmr1, Tsc2 and Shank3, produce similar physiological effects, involving the upregulation of typical synaptic plasticity mechanisms (Baudouin et al., 2012), specifically a deregulation of mGluR-LTD. In utero exposure to valproic acid (VPA) is the only environmental prenatal insult clearly associated with autism (Christensen et al., 2013). When modeled in mice, exposure to VPA also produces a hyper connectivity at the mini-columnar scale (Rinaldi et al., 2008; Silva et al., 2009), and stimulates BDNF expression (Almeida et al., 2014). The neurobiological effects of several factors predisposing to autism in humans are thus conserved in mouse models despite the questionable similarity between the phenotype of mouse models and autistic symptoms. Table 1 summarizes the main genes involved in nonsyndromic and syndromic autism, their effect on synaptic plasticity, and their "hyperplastic" consequences.

4.2. Enhanced vs. altered synaptic plasticity

One of the most complex questions raised by the involvement of upregulated synaptic plasticity in autism is how (dis) similar these processes are from their equivalent in the neurotypical population. Do these mechanisms exist in all individuals, and are they atypically *triggered* by various genetic alterations, leading to *enhanced* synaptic plasticity? Alternatively, are these mechanisms "abnormal", without an equivalent in non-autistic individuals, and thus can we describe them as *altered* synaptic plasticity? One possibility is that both exist at either end of a spectrum, with possible intermediate conditions. In this model, nonsyndromic autism is found at one end of the spectrum and syndromic autism at the other. In non-syndromic autism, the upregulated transcription of genes involved in the plasticity of network branch(es) (Kelleher et al., 2008; Gkogkas et al., 2013) may generate hyper connectivity (i.e., hyperplasticity) within certain local neuronal circuits (Tabuchi et al., 2007). Alternatively, in syndromic autism, a mutation may alter the basic synaptic mechanism involved in the construction of all synapses and neural networks (Knoth and Lippé, 2012). For instance, in "dysplastic" syndromes (e.g., Fragile X, tuberous sclerosis) that are associated with autism, neurogenetic alterations disrupt normal mechanisms of synaptic plasticity, and are associated with intellectual disability and dysmorphic features. Knockout Fmr1 mice have large dendrite spines and high spine density, enhanced long-term depression, a high rate of protein synthesis and up-regulation of the mGluR-mediated signaling pathway, indicative of hyperplasticity (Hayashi et al., 2007; Connor et al., 2011). PTEN mutations, which are associated with another neurogenetic condition characterized by macrocephaly (more severe than that commonly observed in nonsyndromic autism) and a high

Table 1
The main genes involved in nonsyndromic and syndromic autism, and their particular action on synaptic plasticity. "Syndromic" and "nonsyndromic" nature of the autistic phenotype resulting from the mutation is indicated by the name of the neurodevelopmental syndrome associated with autism.

Gene	Associated neurogenetic syndrome	Gene function	Overall mutation effects	Specific effects of mutation on synaptic plasticity
FMR1	Fragile X	Produces fragile X mental retardation protein (FMRP); Represses translation of several mRNAs.	Translational derepression of mRNAs; Up-regulation of the mGluR-mediated signaling pathway	Enhanced long-term depression (LTD); increase in the rate of cerebral protein synthesis and of excitatory activity (mGluR-dependent LTD).
TSC1/TSC2	Tuberous sclerosis	Inhibits the mTOR-raptor complex; regulator of cell growth in mitotic cells	Derepresses mTOR signaling; up-regulates the signaling pathway which promotes cell growth and proliferation	Enhanced translation in neurons; Increased excitatory activity
PTEN	Cowden syndrome	Negative regulator of PI3K-mTOR signaling	Heightened mTORC1 activity	Neuronal hypertrophy and macrocephaly; Increased excitatory activity
MCP2	Rett syndrome (mutation)	Regulates neurotrophic factors, such as brain-derived neurotrophic factor (BDNF)	Increased transcription of genes and number of excitatory hippocampal synapses	Hypoplasticity (mutation);
	MECP2 duplication Syndrome (duplication)			Hyperplasticity (duplication)
NF1	Neurofibromatose	Inhibits mTOR/PI3 K pathway	Upregulation of Ras-dependent ERK and mTOR activation	Hyperplasticity; increased availability of synaptic proteins
UBE3A	Angelman syndrome	Regulates ubiquitin-dependent protein turnover	Elevated synaptic protein levels	Increased/abnormal dendritic spine development
CACNA1C	Timothy syndrome	Regulation of inward calcium ion currents	Hyperactivation of the signal to nucleus path	Overabundance of plasticity related proteins
NLGN 3.4	None	Regulates the formation and function of excitatory and inhibitory postsynaptic transmission	Increased/ectopic GABAergic synapse formation	Gain of function when mutation does not completely inactivates the gene
NRX 1,2,3	None or Pitt–Hopkins-like syndrome	Synaptic adhesion. Interacts with NLGN to induce neurite outgrowth; initiates synapse formation	Impaired synaptic adhesion and neuron differentiation	Increase in excitatory synaptic transmission
SHANK 1,2,3	none or Phelan McDermid syndrome	Pre/postsynaptic signaling through the Neurexin–Neuroligin complex; regulates AMPA and NMDA receptor-synaptic transmission	Shank 1: reduction of dendritic spines Shank 2: increase in number of glutamate receptors and upregulation of shank 3	Shank 2: increase in the number, size, and strength of excitatory synapses; increased LTP Shank 3:alteration of glutamatergic synapses
NBEA	None	Synaptic scaffolding protein, spine formation. Regulator of membrane trafficking; formation of central synapses	Reduced number of spines	Alteration of neurotransmitter transport by large dense-core vesicles

prevalence of autism, may result in hyper connectivity in sensory areas (Xiong et al., 2012). The conditions associated with several types of syndromic autism are thus characterized by *altered* plasticity. These conditions (e.g., Fragile X or Tuberous sclerosis 1–2), are associated with dimorphism, intellectual disabilities, aberrant cell proliferation and a high prevalence of epilepsy even in the absence of autism.

5. The Trigger-Threshold-Target model of autism

A heterogeneous neurogenetic origin, a characteristic developmental course, variability in language and intelligence level, and superior perceptual or language abilities (depending on the subgroup) are key features of autism (Cowen, 2011). In parallel, there is increasing evidence for a role of genetic (Kelleher et al., 2008), micro-structural (Markram and Markram, 2010) and macrostructural cortical (Samson et al., 2011a) plasticity in autism. We propose the Trigger-Threshold-Target (TTT) model to account for this combination of features as well as for their variability. In this model, autism occurs when genetic mutation(s) ***trigger***(s) a neuroplastic reaction in individuals with a genetically-determined low ***threshold***. In this model, variability in autistic phenotype and cognitive strengths result from the unique combination of genetic triggers and thresholds, and neurofunctional ***target*** regions of this plastic reaction. Thus, the TTT model proposes that autism results from a plastic reaction targeting the most variable cortical regions; this plastic reaction may create a cascade effect yielding the particular pattern of strengths and weaknesses of each autistic individual.

5.1. Accounting for autistic strengths by cortical recycling

The "hijacking" of a region typically dedicated to a certain type of informational input by another neurological function, may result in enhanced perceptual or verbal performance in autistic individuals. For instance, there are now clear indications of cortical reallocations involving the fusiform gyrus during the processing of written material (Samson et al., 2011a), which is a strength of autistic individuals, and of enhanced temporo-occipital connectivity associated with advanced decoding ability in autism (Kikuchi et al., 2013).

This associative perceptual region appeared quite late, and its expansion was strongly selected for in human evolution (Waltereit et al., 2013). This region displays a remarkable potential for plasticity and is a striking example of a functional specialization that may be further promoted by enhanced plasticity. Similarly, autistic individuals may develop a strong perceptual "approach" to problem solving, in which case, the application of advanced perceptual processing to reasoning tasks would result in strong fluid intelligence (Dawson et al., 2007). This is confirmed by neuroimaging showing that associative visual areas are strongly activated in autistic individuals solving Raven matrices, but only for the most difficult problems (Soulières et al., 2009). The activity in BA9 and BA7 is lower in autistic individuals than in non-autistic individuals during the same task, which suggests that functional recycling of perceptual brain regions is involved in tasks normally requiring frontal and parietal regions. Reliance on perceptual regions for the completion of reasoning activities would considerably modify the approach of autistic people to these tasks such that autistic individuals complete them faster and with less verbal mediation than non-autistic individuals.

The recycling of perceptual brain regions for the performance of reasoning tasks also probably accounts for autistic strengths through the mechanism of *veridical mapping* (Mottron et al., 2013), which involves the use of typical pattern recognition to detect structural similarity among large input structures or abstract representations. *Veridical mapping* enables an individual to memorize the coupling between perceptually or structurally similar elements, either within or between perceptual modalities. This phenomenon exists in non-autistic individuals, and involves the processing of non-visual information by visual structures (Pascual-Leone and Hamilton, 2001). The retrieval of missing elements (e.g., phonological code, day-of-the-date) when provided with a fragment of the association (e.g., written code, date) is associated with many savant abilities including hyperlexia and calendar calculation, as well as absolute pitch and synesthesia. This key mechanism is similar to pattern completion, but is applied to large-scale patterns, for instance a musical phrase or a word. In some cases, such as synesthesia, these mappings are largely idiosyncratic, but in others such as hyperlexia, they are an adaptive method of processing large structures, and ultimately lead to the mastering of a socially relevant competence such as reading (Bouvet et al., 2014).

However, there may be drawback to cortical reallocations that stimulate perception. The perceptual origin of veridical mapping implies that it has domain-specificity: "restricted interests" in autistic individuals do not generalize easily to other domains of categorically similar information. Another drawback is a high dependence on access to materials, with a high level of expertise reached when autistic people have access to an input that fits their perceptual processing requirements. However, an environment lacking in material that can be processed by perceptual regions may produce deprivation (or "captivity") behaviors, and ultimately impair intellectual abilities (Lewis et al., 2007).

Last, these cortical reallocations may be involved in atypical face processing tasks. Several studies have found that the Face Fusiform Area for non-familiar faces is atypically activated in some individuals with autism (Scherf et al., 2010; Pierce et al., 2001). During facial processing, both autistic individuals and non-autistic individuals show activity in the expected Fusiform Face Area (medial fusiform gyrus); however, only autistic people display activity in the anterior portion of the fusiform gyrus, a region associated with object processing and perceptual expertise. This pattern of activity may reflect enhanced perceptual resource allocation in autism and the use of distinct perceptual strategies for the processing of social and non-social information in this population (Di Martino et al., 2009; Kana et al., 2006) (Fig. 1F). It also suggests hyper-plastic processes in perceptual associative regions, and a large contribution of experience to the development of these processes.

5.2. Accounting for AS subtypes by contrasted target/neglect components

In the TTT model, we used the term "Target" to describe the fact that a general mechanism (increase of synaptic plasticity) stimulates mainly a limited subset of functions in the autistic brain. The autistic plastic reaction has the potential to target either of the two domain-general regions, the associative perceptual cortex or language regions, because of their evolutionary, neural and developmental similarity; these regions expanded recently, are topographically variable and have a protracted period of development. The different pattern of cognitive strengths and cortical reallocations between AS-SOD and AS-NoSOD thus results from topographic and functional differences in the target of this plastic reaction.

In AS-SOD individuals, low level and mid-level perceptual strengths, combined with the strong contribution of perception to intelligence, encompass their enhanced abilities (Mottron et al., 2012a). Furthermore, performances in perceptual tasks co-vary between individuals in this subgroup, indicating that they depend on a single domain-general factor (Meilleur et al., 2014). In contrast, speech is delayed or impaired in this subgroup. However, the frequent late catch-up of delayed speech, and the preservation of some language functions in prototypical autism, suggest that the early impairment of speech does not result from a primary dysfunction of the brain mechanisms devoted to spoken language. Instead, impairment may result from the early neglect of these functions. The TTT model proposes that superior perceptual processing is an obstacle for the development of speech (Heaton et al., 2008a), because neural resources are oriented toward perceptual dimensions of language. Accordingly, the fractionation of language into perceptual and linguistic components explains why some language components are defective whereas others are over-functioning. A perceptual processing of speech would account for echolalia, the superior discrimination of pitch in speech (Heaton et al., 2008b), early decoding strengths, and the occurrence of speech delay with perceptual strengths. Conversely, perceptual processing of speech may be detrimental if speech conflicts with perception, or if speech cannot be perceptually mapped with nonlinguistic perceptual input, as is the case for joint attention including a verbal component, or in the expression of subjective states. Thus, language may be processed primarily within perceptual brain networks in individuals with AS-SOD, resulting in various impairments and strengths of verbal abilities. Alternatively, in AS-NoSOD individuals, incoming information is primarily processed by an overextension of typical language-related processes, resulting in language strengths, but not perceptual ones (Samson et al., 2009). Thus, AS-NoSOD involves *overdevelopment* of language functions, both in terms of performance and brain activity. The domain targeted by the plastic reaction would consume neuronal resources, resulting in competition between speech and motor abilities in AS-NoSOD. This explains why the early overdevelopment of speech coexists with motor clumsiness in this subgroup (Barbeau et al., 2013b).

5.3. Neglect of socially oriented behaviors in the two main ASD subgroups

We will now briefly address how the TTT model accounts for autistic social behaviors (Forgeot D'Arc and Mottron, 2012). Autistic toddlers are less overtly oriented toward social materials (Dawson et al., 1998) than non-social ones, they disengage faster from faces than typical toddlers (Chawarska et al., 2010), and they

preferentially look at audiovisual synchrony rather than biological motion (Klin et al., 2009), or at geometric figures rather than social scenes (Pierce et al., 2011). Preference for non-social over social material is therefore a diagnostic feature of autism in toddlers. However, social prioritization is not perturbed in autistic individuals (New et al., 2010) and the amygdala is activated during the processing of non-social information (Forgeot D'Arc and Mottron, 2012; Grelotti et al., 2005). Furthermore, a review of behavioral studies on face perception in adults (Weigelt et al., 2012) revealed that facial identity is processed in a similar way between autistic and non-autistic people. These observations suggest that the defective "social brain" may not be the primary cause of the cascade of alterations characterizing autism.

From a TTT perspective, the cascade of events caused by competition coming from hyperplastic functions affects social cognition to a similar extent as competition impacts different cognitive domains in non-autistic individuals. Although some "neglected" domains (motor ability and speech) differ between AS-SOD and AS-NoSOD, neglect for socially-oriented signals is shared by the two AS subgroups. In AS-SOD, perceptual cognition outcompetes social cognition for brain resources. This results in weak exposure to social information (Chawarska et al., 2010) during the development of regions dedicated to perceptual expertise in the autistic brain, which contributes further to the reallocation of brain resources. Category-specific cortical allocation appears to be built at a later age (Scherf et al., 2007) for faces than for objects, which makes it particularly sensitive to variations in early input. Similarly, the superior temporal sulcus, which is a multimodal area (Redcay, 2008) implicated in socially oriented behaviors as well as social and speech perception (Redcay, 2008; Glasel et al., 2011), is one of the cortical regions which is colonized after sensory loss (Bavelier et al., 2001; Sadato et al., 2004). It is also a region which is frequently under-activated by speech and other socially-oriented operations in autism (Redcay, 2008; Zilbovicius et al., 2006), which may result from its colonization by other functions (Paakki et al., 2010).

The example of facial processing is highly informative. The fusiform gyrus is responsible for processing faces in non-autistic individuals. It was first thought to be dysfunctional in autism (Schultz et al., 2000), because it was responsive to objects rather than faces. However, brain activity during facial processing appears to normalize with age in autism and brain regions normally involved in facial recognition are activated when familiar faces or an attention cue is used during experiments (Pierce et al., 2004; Hadjikhani et al., 2004). This indicates that faces can be processed by adult autistic people, particularly under optimal conditions. Thus, it appears that face perception in autism is initially constrained by cortical functional reallocation, and by input competition. This leads us to question the dominant view of autistic social cognition, that a weak emotional response toward socially relevant figures (as indicated by perturbed activation of the amygdala (Swartz et al., 2013; Kleinhans et al., 2014) during exposure to faces) impairs facial recognition. However, the reverse may also be true (Klin et al., 2009). Perceptually defined patterns (for AS-SOD) or verbal information (for AS-NoSOD) maybe emotionally appealing or disturbing for autistic persons because they are more salient, as is the case for blind people with auditory information (Klinge et al., 2010b).

5.4. Accounting for neurogenetic variability

Two-hit genetic models (Girirajan and Eichler, 2010; Vorstman et al., 2011; Leblond et al., 2012) and polygenic models (Murdoch and State, 2013), propose that a combination of rare genetic events and either common predisposition genes or specific environmental conditions account for the occurrence and variability of some neurodevelopmental disorders. Here, we describe a two-hit genetic model required for the occurrence of autism. A ***Trigger*** mechanism accounts for variability in causal genes, and a plasticity ***threshold*** component accounts for the fact that autistic and non-autistic outcomes are associated with similar mutations. Finally, plasticity could be further described as enhanced (associated with non-syndromic autism) or altered (associated with syndromic autism).

5.4.1. A Trigger mechanism accounts for the genetic variability of autism

It is now well established that a large series of mutations (Betancur, 2011), either de novo or transmitted, are associated with a common autistic phenotype in a subset of cases. A first generation of synthetic reviews established that these various mutations commonly affect synapses (Gillis and Rouleau, 2011; Kelleher et al., 2008; Shinoda et al., 2013; Zoghbi and Bear, 2012; Waltereit et al., 2013). A second generation of synthetic reviews established details of the underlying mechanism and revealed that enhanced plasticity is a common result of both genetic and environmental factors (e.g., VPA) associated with autism (Baudouin et al., 2012; O'Roak et al., 2012; Chung et al., 2012; Shinoda et al., 2013; Chiocchetti et al., 2014; Bateup et al., 2013; Ebert and Greenberg, 2013; Markram and Markram, 2010). In summary, we propose that de novo or inherited mutations in genes involved in synaptic plasticity *trigger* a plasticity reaction (Markram and Markram, 2010). This reaction involves a cascade of plastic mechanisms, beginning at the synapse, and ending with cortical organization, and is the final common result of an indefinite number of genetic alterations or rare, prenatal insults. Perturbation of the experience-dependent development of cortical organization and behavioral phenotypic consequences are the final results of this reaction. The events that can trigger this plastic reaction are inherently variable. Variability in the effect of the causative mutation accounts for a part of the phenotypic heterogeneity, and characteristics of each syndrome (Fig. 2).

According to the Trigger-Threshold model the link between the trigger and the subsequent plastic reaction, at least in non-syndromic autism, may be quite tenuous. Therefore, the potential inventory of genetic triggers is indefinite. Genetic events may initiate a chain of plastic modifications, they may be part of this chain, or both. Accordingly, as observed in cross modal plasticity following sensory loss, most synaptic mechanisms associated with the enhanced performance and function of neuroplastic regions are already present and ready to function in a typically developing individual. For instance, Ben-David and Shifman (2012), computed a gene co-expression network for common and rare variants described in the genetics of autism literature, and identified functionally interconnected modules involved in synaptic and neuronal plasticity that are expressed in brain areas associated with learning, memory and perception.

5.4.2. The Threshold component accounts for the moderate prevalence of autism in accompanying neurogenetic conditions

ASD mutations (or prenatal insults) predisposing to autism show tremendous phenotypic variability, with identical variants associated with a wide range of neurodevelopmental outcomes besides ASD, including schizophrenia, intellectual disability, language impairment, and epilepsy. This suggests that each of these mutations, on its own, is not sufficient to result in an autistic phenotype. The inclusion of a threshold component in the genetic mechanism of enhanced plasticity is based on the puzzling observations that: (a) neurogenetic disorders that are frequently associated with autism can occur without autism (Peters et al., 2013); (b) males are disproportionally represented in non-syndromic autism, and this cannot be explained by an excess of autism genes on the X chromosome; and (c) several common genetic variants with small effects, frequently not reproducible between studies (Girirajan and

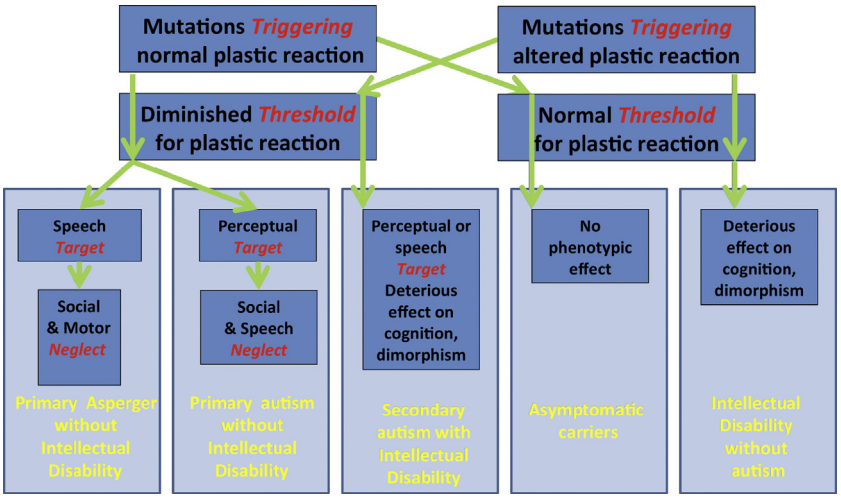

Fig. 2. The Trigger-Threshold-Target model. The causal event is a genetic alteration that affects synaptic plasticity. This mutation **triggers** a plastic reaction in individuals with a low **threshold** for plasticity, due to predisposing genes, the individual's sex and/or environmental factors. A plastic reaction **targets** a domain-general function, the identity of which determines the autism subgroup. In autism, perception is targeted and this results in enhanced visual and auditory perceptual functioning, but also in the neglect of speech. In Asperger syndrome, speech is targeted and this manifests as precocious mastering of language, concurrent with motor clumsiness. Social behaviors are **neglected** in both subgroups, as a result of the enhanced domain-specific neural investment. In nonsyndromic autism, mutations trigger a largely normal plastic reaction in individuals with a low threshold for this reaction, resulting in hyper-functioning and no intellectual disability. Individuals with a normal threshold are asymptomatic carriers of these mutations. In syndromic autism, causal mutations alter the plasticity reaction, resulting in aberrant cell proliferation, and frequent intellectual disability. In individuals with a low plastic threshold, these mutations additionally result in syndromic autism.

Eichler, 2010), slightly increase the risk for autism. It is therefore plausible that an indefinite number of factors, in addition to the causative genetic mutation, come together to lower or elevate the threshold at which the plastic reaction occurs in an individual. Among these factors, common functional polymorphisms of genes involved in plasticity may increase an individual's risk of reacting in an excessively plastic way when a triggering genetic event occurs. Males appear to be particularly sensitive to the effects of such polymorphisms. A low "threshold" would therefore account for the heterogeneity of predisposing factors, and would explain why a "trigger" mutation may or may not result in autism. It may also explain the difficulty in finding common genetic variants with significant effects, because these variants, in the absence of a trigger mechanism, cannot result in autism on their own. However, these variants may amplify the effects of de novo rare events on brain plasticity. The concept of a "threshold" may be tested by comparing plasticity mechanisms in populations possessing single gene mutations with or without autism. This strategy has proven fruitful in experiments involving neuroimaging, which demonstrated that people with Tuberous sclerosis and autism have higher local connectivity than people with Tuberous sclerosis alone (Tye and Bolton, 2013).

5.4.3. Enhanced and altered plasticity accounts for the distinction between syndromic and non-syndromic autism

In non-syndromic autism, a normal or quasi normal plastic reaction is believed to occur. In this situation, the triggering mutations would have no biological effect on the neural network and would instead initiate a cascade of plastic reactions, meaning that the stimulus needed to change synaptic connectivity in targeted regions would be decreased. In this case, most alterations would be functional reallocations resulting in the hyper functioning of targeted functions and subsequent neglect of non-targeted functions. Variations in the target of the plastic reaction and in raising conditions would account for inter-individual differences in symptoms (e.g., with or without SOD) and in the nature of the cognitive enhancements. Conversely, in syndromic autism, the triggering mutations would introduce an aberrant plasticity process where synaptic connectivity would occur in an abnormal way with no equivalent in non-autistic individuals. Thus, the causal genetic event has *altered* the plastic reaction, and the same alteration would characterize the associated condition, regardless of whether it is accompanied by autism. As is the case for non-syndromic autism, a mutation which produces a neurodevelopmental disorder would result in autism only when it occurs in individuals possessing a low threshold for a plastic reaction (Fig. 2). In individuals with a normal plasticity threshold, the mutation would only perturb the construction of neural networks, resulting in dimorphism, intellectual disability and/or epilepsy.

6. Concluding remarks

6.1. Summary of the TTT model

We suggest that a plastic reaction triggered by a series of mutations in genes encoding proteins involved in the construction of synapses accounts for enhanced perceptual or speech processing associated with autism. This alteration of synaptic plasticity affects the balance between the social vs. the perceptual or linguistic properties of materials that are preferentially processed. The structural and functional alterations targeting perceptual associative regions account for the superior performance of autistic individuals, and for the influence of perception in autistic phenotype. Competition with other cortical allocations results in the neglect of non-targeted functions, leading to autistic "negative" social behaviors. Sensory driven activity present at early stages of development influences existing organization dictated by genes, and can fundamentally alter the organization of the cortex, its connectivity and its function, resulting in enhanced perceptual functioning in autism, and poor mastering of social interactions, speech, or motor coordination. The large number of mutations with the potential to trigger a plastic reaction may explain the variety of neurological conditions associated with autism. Conversely, the specific nature of the plastic reaction found in autism and the resulting behavioral phenotype may result from the genetic source of its trigger.

6.2. Plasticity, interventions and pharmacological treatment

A plasticity model is also compatible with quantitative and qualitative variations in the post-natal environment, which is a prominent additional source of phenotypic variability (Dawson et al., 2008; Schneider et al., 2006). If autism results from a plasticity reaction, with potentially adaptive and non-adaptive consequences, at least a part of these mechanisms should be modulated by exposure to (or availability of) material associated with a high performance in autistic individuals. Plasticity processes can be modified by external interventions, and use of alternative brain regions to support impaired processes forms the basis of numerous intervention strategies (Belleville et al., 2011).

With this in mind, most early intervention programs adopt a "restorative" approach by stimulating the neglected function; for instance, social interest and competence are targetted by modeling socio-communicative markers of social reciprocity, joint attention or speech, and by limiting functions that are spontaneously enhanced in autism (like non-social perception) (Dawson et al., 2010). However, focus on only impaired functions may monopolize resources in favor of non-immediately processable material, and is unlikely to reverse the reallocation process (Dawson et al., 2008; Lyness et al., 2013). We therefore suggest that early intervention in autism should be based on lessons learned from sensory loss or memory impaired patients. For example, the congenitally deaf children with late access to sign language develop lower cross-modal plasticity (Pénicaud et al., 2012), and have generally poorer language development than children with early access to sign language (Lyness et al., 2013). A recent retrospective study compared deaf children with early cochlear implantation coming from deaf family (and thus native signers) with early-implanted deaf children coming from hearing family (and thus with limited, if any, access to sign language) at various times following implantation. Implanted deaf native signers outperformed implanted deaf non-signers on measures of speech perception, speech production and language development (Lyness et al., 2013; Hassanzadeh, 2012). These initial results then suggest that early exposure to a sign language paired with early cochlear implantation may be beneficial for an optimal spoken language development, rather than interfering with it. Interventions in blind persons promote tactile stimulation and the learning of Braille reading for the development of literacy. In another field, episodic memory training in memory-impaired patients most often relies on the teaching of non-conventional alternative encoding strategies (for instance, using visual imagery to encode verbal material) that relies on intact brain regions (Belleville et al., 2011, 2006; Belleville, 2008; Belleville and Bherer, 2012). In sum, rethinking early intervention within a TTT framework leads us to reconsider (a) the reversibility of the neglected functions; (b) the efficiency of harnessing targeted vs. neglected functions for the restoration of social functions; and (c) the possible adverse effects on the construction of cognitive architecture as a result of competition between various types of input and material.

Aberrant mechanisms of synaptic plasticity may also be treated by new pharmacological approaches (Pignatelli et al., 2013; Delorme et al., 2013; Walsh et al., 2008) in autism. One frequent suggestion is to *reduce* plasticity to diminish autistic symptoms. However, this should be done with caution, because it is difficult to distinguish the effects of the detrimental trigger from the adaptive effects of the plastic reaction. In cases where plasticity is altered, leading to an associated neurogenetic syndrome and intellectual disability, "repairing" the alteration is conceivable. However, if plasticity is a partially adaptive reaction to a genetic event, blocking these mechanisms may deprive the autistic person of unique strengths, and may bring back the initial, more detrimental deficit (Auerbach et al., 2011).

6.3. Limitation of the model and future research priorities

Several limitations of the TTT model need to be considered. The threshold component describes individual differences in plasticity. Alternative theories of factors favoring autism suggest that a continuous distribution of autistic traits exists in the population, which may be considered as favoring conditions, as minimal expression of the variants that cause autism, or as unrelated phenotypic overlap (Barbeau et al., 2009). Differences amongst individuals or between the sexes in the processing of social information may favor the development of an autistic or autistic-like phenotype, which may occur independently from the genetic mechanism involved in prototypical autism.

With the exception of one preliminary study that reported high LTP/LTD (Oberman et al., 2010) activity in AS individuals, most genetic and micro-structural data reported here come from experiments in animals, looking at genes involved in "altered" synaptic plasticity of syndromic autism. The next step needed is to validate our model in studies involving autistic individuals and cell cultures derived from them. In particular, it will be important to validate our principal hypothesis that mutations involved in non-syndromic autism can be understood within the context of normal plasticity. We also assume that autism associated with a neurogenetic syndrome, and non-syndromic autism, are more similar than dissimilar. Alternatively, neurogenetic syndromes may be considered as producing "phenocopies" of autism, with a low degree of similarity with non-syndromic autism. However, the convergence between synaptic processes involved in different types of syndromic autism argues against this idea, and supports instead the "Trigger" component of our model.

Enhanced micro-structural plasticity in perceptual associative brain regions has not yet been directly linked to over-performance in autism (see Hoy et al., 2013; Desgent and Ptito, 2012 for a review and for an animal example). This gap in our understanding is partially filled by sensory loss, which suggests that normal brain microstructure has the potential, under an environmental trigger, to over-develop perceptual function with measurable regional effects. However, a more direct link between synaptic and regional plasticity has to be empirically validated by combining genetic investigation, cell cultures and fMRI studies in the same group of individuals. In addition, the TTT model does not account for the mechanism of choice among the two domain-general targets, and why the two domains of enhancement are not frequently found together. Moreover, enhanced cortical allocation in the AS-NoSOD subgroup is based only on preliminary data, despite the fact that speech can be considered as a target of plastic reaction. Finally, the threshold component is the most difficult part of the genetic model to define and validate. Investigation of the sex-component of regional plasticity, in both the normal and sensory-impaired population may constitute a way to answer this question.

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