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Review

A strategic plan to identify key neurophysiological mechanisms and brain circuits in autism

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A B S T R A C T

Autism and Autism Spectrum Disorder (ASD) cover a large variety of clinical profiles which share two main dimensions: social and communication impairment and repetitive behaviors or restricted interests, which are present during childhood. There is now no doubt that genetic factors are a major component in the etiology of autism but precise physiopathological pathways are still being investigated. Furthermore, developmental trajectories combined with compensatory mechanisms will lead to various clinical and neurophysiological profiles which together constitute this Autism Spectrum Disorder. To better understand the pathophysiology of autism, comprehension of key neurophysiological mechanisms and brain circuits underlying the different bioclinical profiles is thus crucial. To achieve this goal we propose a strategy which investigates different levels of information processing from sensory perception to complex cognitive processing, taking into account the complexity of the stimulus and whether it is social or non-social in nature. In order to identify different developmental trajectories and to take into account compensatory mechanisms, we further propose that such protocols should be carried out in individuals from childhood to adulthood representing a wide variety of clinical forms.

1. Introduction

With approximately 67 million individuals affected worldwide, Autism Spectrum Disorder (ASD) is the fastest growing neurodevelopmental disorder (United Nations, 2011) with a prevalence estimated to be 1/100. Autism and ASD cover a wide variety of clinical profiles which share two main dimensions, which are present during childhood: social and communication impairment and repetitive behaviors or restricted interests.

These qualitative abnormalities are the basis of the diagnostic criteria used in international classifications: the American Psychiatric Association Manual of Psychiatric Diseases, 5th Edition (DSM-5) and the World Health Organization's (WHO) International Classification of Diseases, 10th edition (ICD-10). No reliable biological markers have been found and diagnosis is still based on extensive clinical characterization of behavior, language development and communication abilities, sensory-psychomotor development, and cognitive functioning.

2. An early neurodevelopmental disorder with complex genetic factors

The origin of ASD is neurodevelopmental, which means that one or several stages of brain development are disrupted, as opposed to a neurodegenerative disorder, in which mature nerve cells are progressively lost. There are nine different stages of brain development: neurogenesis, neural migration, differentiation, axonal growth, dendritic growth, synaptogenesis, synaptic selection and apoptosis (programmed cell death). All of these stages could be candidates for disturbance in autism, but recent studies (supported by results in genetics) have usually focused on development and conservation of synaptic connections, as well as on axonal growth and on the establishment of tracts connecting different brain areas (Rane et al., 2015).

Furthermore, the "critical time window" in which different factors impact on neuronal development likely plays a crucial role in determining developmental outcome. Timing of gene expression, combined with environmental factors, determines brain development (Mandy and Lai, 2016). Thus a key point of convergence of expression of some ASD candidate genes in midfoetal

layer 5/6 cortical projection neurons has been reported (Willsey et al., 2013). Parikshak et al. (2013), who used an alternative approach to identify spatial and temporal convergence in genes involved in ASD, also reported the implication of midfoetal cortical projection neurons. One hypothesis is that the complex combination of timing of gene expression and various environmental factors may lead to different clinical profiles in autism.

There is now no doubt that genetic factors are a major component in the etiology of autism. Research in favor of this hypothesis has been undertaken which is based on strong clinical and epidemiological arguments, particularly twin studies finding much higher concordance rates for the syndrome among monozygotic compared to dizygotic twins (Bailey et al., 1995). The risk of reoccurrence has also been found to be much higher in siblings of children with autism.

Since 2003, several studies in genetics have presented evidence for functional mutations in genes encoding for proteins localized at the glutamatergic synapse in patients with autism (and/or mental retardation). The first studies concerned genes in the neuroligin family (NLGN4, NLGN3), cell-adhesion molecules and their presynaptic partners, the neurexins (Laumonnier et al., 2004; Jamain et al., 2003; Bonnet-Brilhault et al., 2016). These molecules are involved in synaptic development and conservation, where they play an important role in the balance between excitatory and inhibitory transmission. Other studies have pointed to genes encoding proteins localized at the glutamatergic synapse such as the SHANK3 protein, which binds with the neuroligins, enabling membrane proteins to bind to the cytoskeleton of the synapse, and also to the KCNMA1 gene involved in a postsynaptic channel regulating neuronal excitability (Daoud et al., 2009). The hypothesis of a deficit in synaptic development and functioning is now at the frontline in pathophysiological research on autism.

However, each mutation discovered accounts for at the most 1% of cases, suggesting that many different genes are involved, each one having a limited effect (Gandal et al., 2016). Finally, the identification of abnormalities common to several conditions such as copy number variations (CNVs), or the fact that certain mutations are also present in non-affected individuals, evoke interaction between these abnormalities and other genetic, developmental or environmental factors.

3. Developmental cascade: research on a moving target

Over the last thirty years, the neurodevelopmental hypothesis has been expanded through clinical observations and studies in anatomy and anatomical pathology. In developmental psychopathology, several hypotheses have been put forward. They are not mutually exclusive; some even share conceptual components. Abnormalities in the functioning of neural networks play an essential role in this disorder of the perception of others, of their intentions, emotions and reactions. The neural theories of autism can be linked to models proposed by cognitive psychologists who have described particular intellectual and social functioning in the syndrome. Another hypothesis is that anomalies in circuits underpinning sensory-anomalies occurred during early development and then developmental trajectories combined with compensatory mechanisms will lead to various clinical and neurophysiological profiles which together constitute the Autism Spectrum Disorder (ASD). Unusual responses to sensory input (hyperor hyposensitivity, distortions, cutoffs, shutdowns), observed in all sensory modalities, and also particular social functioning, could be linked to impaired processing of auditory and visual stimuli, and especially when these stimuli have social content, as is the case for voices or faces. Data from functional brain imaging and neurophysiological measures have also shown particular functioning of sensory systems. Nevertheless, and especially in the auditory domain, unusual activation patterns are also found with neutral stimuli without social content (i.e. tones). This early atypical sensory perception could have consequences on the social synchronization process and may lead to atypical cognitive profiles observed later in autism. This dynamic aspect of physiopathology has to be taken into account when

results of scientific protocols are interpreted. This “developmental cascade,” based also on brain plasticity (Bonnet-Brilhault, 2017), may explain the large heterogeneity observed in autism research results.

4. A strategic plan to identify neurophysiological mechanisms: exploration of processing levels

To better understand the pathophysiology of autism, the comprehension of key neurophysiological mechanisms and brain circuits underlying the different bioclinical profiles is thus crucial. Such research is rooted in the neurodevelopmental hypothesis of autism and may help in the identification of neurophysiological markers which can provide the foundation for the application of precision medicine in autism. Thus this research may help to target specific interventions to subgroups of patients and to complete clinical outcome measures with neurophysiological indices of brain processing and maturation.

To reach this goal, our research team has developed a strategy using protocols which explore the different levels of information processing, from sensory perception to complex cognitive processing, taking into account the complexity of the stimulus and whether it is social or nonsocial in nature. In order to identify different developmental trajectories and to take into account compensatory mechanisms, we further propose that such protocols should be carried out in individuals from childhood to adulthood representing a wide variety of clinical forms. Using this strategy, our team has revealed several markers which highlight sensory perception abnormalities in autism and which have strong bioclinical correlations to both dimensions of ASD.

4.1. Identifying and understanding social interaction impairment in autism

It is now widely accepted that in autism atypical face and movement processing are core features of impaired social interaction. Using behavioral and neurophysiological investigations (Event-related potentials (ERP), eye-tracking), we have studied brain correlates of social information processing, from extraction to perception, in normal children and in children with autism.

4.1.1. Face processing

In typical subjects, visual ERPs were shown to be modulated by emotional face content and to be correlated to subjects’ emotional sensitivity and expressivity, and also to subjects’ ability to control their emotions, which suggests that these measures could be used as individual markers to assess emotional skills (Meaux et al., 2014c). Combining ERPs and eye-tracking during face processing, we found that the proportion of early fixations on the eye region was correlated with visual ERP characteristics in young children, highlighting a link between the development of ERPs and oculomotor behavior. These developmental dynamics may be sustained by a gradual, experience-dependent specialization in face processing which produces a more automatic and efficient network associated with effortless identification of faces, and allows for the emergence of human-specific social and communication skills (Meaux et al., 2014b).

Children with ASD showed an atypical pattern of face exploration which was characterized by reduced time exploring socially relevant information (Martineau et al., 2011) and which was correlated with intensity of autistic symptoms (Guimard-Brunault et al., 2013). This atypical exploratory behavior echoes the finding that ERP responses to faces are affected in children with ASD (Batty et al., 2011), suggesting that emotional and facial processing difficulties in autism could arise from atypicalities in visual exploration and perceptual processes.

Two behavioral studies using emotional faces confirmed a propensity for processing local

information and a deficit in global processing (Meaux et al., 2011, 2014a); however, these peculiarities were also observed for non-social stimuli (Bangel et al., 2014; Meaux et al., 2014d). We therefore suggest that while atypicalities in sensory and perceptual processing are not specific to the social domain (Clery et al., 2013c; Kovarski et al., 2017), they could strongly affect the development of social and emotional abilities in children with ASD.

Atypicalities in face and biological movement processing have also been noted in the domain of gaze perception (Senju et al., 2003, 2004, 2005, 2008), particularly in infants where it seems to be potentially predictive of autism emergence (Elsabbagh et al., 2012).

4.1.2. Movement processing

Beside facial expressions, social interactions are also supported by visuo-posturo-motor adjustments. For example, autistic children have been reported to be impaired in the execution of pantomime actions, and in imitation of meaningless gestures (Gizzonio et al., 2015). The dynamics of movement is another component essential for assignment of a meaning to an action and is thus crucial in social interactions. Individuals with autism also display severe deficits in recognizing the dynamics of movement (Rochat et al., 2013). Particularities of the mirror neurons that are activated when a significant movement is perceived could also be linked to impaired processing of social stimuli.

4.2. Identifying and understanding communication impairment in autism

4.2.1. Language development

Targeting computationally complex structures of language (Ferré et al., 2012; Prévost et al., 2011; Prévost et al., 2014; Scheidnes and Tuller, 2013; Tuller et al., 2011; Tuller and Delage, 2014) we identified specific formal properties of language affected in a subgroup of verbal French-speaking children from across the autism spectrum (including children with intellectual disability), and showed that these difficulties were the same as those found for French-speaking children with Specific Language Impairment, in both morphosyntax (syntactic displacement and sentential embedding) and phonology (syllable structure), and that furthermore difficulties were independent of nonverbal cognition (Zebib et al., 2013; Tuller et al., 2017).

To explore processes involved in language reception in children with ASD, we developed an eye-tracking task to evaluate comprehension of object pronouns (specifically, accusative clitics, dependent pronouns which do not appear in the canonical position for objects of the verb in French) and showed that involuntary eye-movement can be used to test knowledge of this clinical marker of language impairment in French, in young typically-developing children (Léger et al., 2015) and in children with ASD (and especially in those with low expressive language level).

4.2.2. Human voice perception

Voice-sensitive response was observed in healthy adults, and found to consist of two specific slow components (one frontal and one posterior) starting as early as 70 ms post-stimulus (Bruneau et al., 2013), consistent with previous findings in 4 to 5-year-old children. In contrast to typically developed individuals, children with autism did not show a preferential response to vocal sounds; an effect driven by an atypical response to non-vocal sounds (Bidet-Caulet et al., 2017).

4.3. Identifying and understanding sameness in autism

Hypersensitivity to any change occurring in the surroundings appears to be a durable treatment-resistant symptom, which prevents the subject with autism from adapting to physical and social environments. We investigated cerebral correlates of the mechanisms involved in context

processing and resistance to change using complementary brain imaging methods (fMRI, EEG-ERPs).

4.3.1. Perception

Under the hypothesis that resistance to change could reflect abnormal integration of sensory information, especially dysfunction in the processing of unusual stimuli, we investigated the brain processes involved in the detection of change, in both visual and auditory modalities.

Electrophysiological investigations associated with clinical assessment allowed for the identification of relationships between atypical brain activity to auditory deviancy (i.e. shortened Mismatch Negativity latency) and behavioral difficulties related to resistance to change (Gomot et al., 2011). Indeed the most atypical MMN pattern was observed in a subgroup of patients with severe intolerance to change. Moreover gene mutations in glutamatergic pathways were identified in two patients with ASD and members of their families, but atypical electrophysiological response patterns to auditory change were only found in the patients (Bonnet-Brilhault et al., 2016). These specific electrophysiological profiles thus appear to be closely associated with the behavioral phenotype of autism, and with the combination of identified genes.

Using complementary EEG and fMRI techniques, we also focused on visual change detection in order to identify the amodal properties of functional brain abnormalities previously observed in the auditory modality. Analysis of electrophysiological markers throughout typical development revealed that the organization of the automatic brain response to visual change is not mature at the age of 11 years (Clery et al., 2012). Major abnormalities were shown in children (EEG) and adults (EEG fMRI) with ASD, characterized by brain hyper-reactivity to visual change (Clery et al., 2013a,b,c). These results corroborate findings from the auditory modality and support the hypothesis of general atypical processing of change being behind resistance to change in ASD.

4.3.2. Prediction – context processing

Behavioral disorders observed in autism may also be related to lack of anticipation or prediction of an ongoing stimulus. Following this hypothesis, the team investigated the brain mechanisms involved in these processes in typically developing adolescents and in individuals with ASD. A sequence of predictive contextual cues was used to identify and dissociate several brain responses and to examine their functional significance in contextual cue encoding, in predictive information extraction, and in anticipatory attention and motor preparation (Bidet- Caulet et al., 2012; Thillay et al., 2015). Together, these studies reinforce the hypothesis of a deficit in top-down modulation in autism, which is likely to underlie dysfunction in the detection and anticipation of changes in the environment (Gomot and Wicker, 2012; Thillay et al., 2016).

5. Conclusion

A translational approach which includes both thorough clinical description and a wide variety of neurophysiological and behavioral investigations (EEG, ERP, fMRI, eye-tracking) carried out throughout the course of development constitutes a complex but powerful strategy for the identification of key neurophysiological markers in autism. Using this strategy and taking into account both complexity of processing and stimulus we have identified markers revealing atypical elementary information processing which are related to behavioral difficulties observed in the two basic clinical dimensions of autism. The next step will consist of exploration in different contexts, including realworld contexts, which will offer new opportunities to better understand the functional impairment of targeted neuronal networks. Finally, although current international classifications of patient subgroups (ICD10, DSM-5) do not yet take into account neurofunctional or biological differences, we believe that the strategic plan outlined here will help to develop new markers to describe more homogeneous groups of patients and to then make it possible to

personalize treatment strategies.

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