



## Review

## A challenging, unpredictable world for people with Autism Spectrum Disorder

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## ABSTRACT

Autism is a pervasive neurodevelopmental disorder characterized by impairment of communication and social interaction, as well as by high levels of repetitive and ritualistic behaviours. This last dimension results in major difficulties in daily life: clinical reports of individuals with Autism Spectrum Disorder (ASD) show that they present tantrums as a response to change, or restricted interests and repetitive behaviours in order to prevent or minimize change. Such a crucial need to maintain sameness suggests substantial differences in how the ASD brain predicts the environment, and this might have a fundamental role in the deficit revealed in the highly unpredictable social world. Several lines of evidence indicating difficulties in generating or using predictions in ASD due to atypical information processing will be presented in this review. For instance, several studies have revealed that people with ASD demonstrate a unique profile of cognitive abilities, with strategies that depend to an abnormally large extent on sensory systems, at the expense of more integrative processing requiring an awareness of contextual subtleties necessary for prediction. At a more elementary level, patients with autism manifest unusual processing of unpredictable events, which might be rooted in a basic difference in how the brain orients to changing, novel sensory stimuli. This review presents results from ERPs and fMRI studies illustrating the psychophysiological mechanisms and neural bases underlying such phenomena in ASD. We propose that such dysfunction in the ability to build flexible prediction in ASD may originate from impaired top-down influence over a variety of sensory and higher level information processing, a physiopathological hypothesis which dovetails with the cortical under connectivity current theory.

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## 1. Introduction

Interacting with the environment is a particularly demanding activity. The brain has quickly and simultaneously to process very complex multi-sensory information. This seems to require attentional preparation in order to ignore irrelevant information and privilege the processing of the most relevant information for appropriate adaptation of future behaviour. Part of the adaptation thus consists of generating mental simulations or previews of future events, which are then used as a basis for forecasts or predictions about an event's likely consequences. In this respect a recent model proposes that in complex circumstances such as social interactions the brain builds predictions by combining multiple analogies (Bar, 2004). Such predictions do not need to be created afresh in new situations, but rely instead on existing scripts, which are the result of real as well as expected experiences. Our perception of the environment thus relies on existing knowledge as much as it does on incoming sensory information. This 'proactive brain' model has been mainly studied in the domain of visual perceptual

theory of why we use prediction in social interaction

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recognition using fMRI (Bar, 2004; Bar et al., 2006). The findings have revealed that low-level visual perception in occipito-temporal areas is not the result of pure bottom-up processes but is guided by information from high-level cognitive frontal areas. In this regard predictions are intimately associated to attentional processes as they enable the brain to allocate its resources of information processing to selected sensory inputs for reducing its computational load. Although the 'proactive brain' model has been developed in the domain of visual recognition, the general principles could also be applied to auditory perception where rapid coarse information processing also occurs from subcortical nuclei through extra-lemniscal projections to the prefrontal regions (Kraus et al., 1994; Martinez-Moreno et al., 1987). Prefrontal activity in turn participates in guiding auditory perception performed at the level of the auditory associative cortex in the superior temporal gyrus and superior temporal sulcus (Garrido et al., 2009). Given the omnipresence of predictions, it is likely that their influence pervades far more than just sensory object perception and also affects emotion processing (Kveraga et al., 2007). Prediction processes may thus be critical to adaptive cognitive, behavioural, and social function.

Neurodevelopmental disorders offer an opportunity for identifying cognitive and brain mechanisms underlying altered trajectories of development of adaptive behaviour. Autism Spectrum Disorder (ASD) is a pervasive neurodevelopmental disorder marked by social deficits and verbal

and non-verbal communication deficiencies together with stereotyped behaviour and limited activities and interests, also characterized by strong resistance to changes in the surrounding environment (APA, 2000). Most researchers now agree on the biological origin of this disorder and although the cause is still largely unknown, it has been suggested that genetic and environmental factors could be involved alone or in combination as possible causal or predisposing elements to developing ASD.

Several psychological and theoretical theories have been proposed to account for the behavioural and cognitive difficulties that characterize ASD. The present review is framed in relation to the 'proactive brain' cognitive neuroscience theoretical account, with the aim of explaining a variety of symptoms in ASD, ranging from resistance to change to deficit in planning and social interaction. Our intention here is not to perform an exhaustive literature review, but rather to assemble results from experiments suggesting a dysfunction in the ability to build flexible prediction in ASD, that may originate from impaired top-down influence over a variety of sensory and higher level information processing. Findings from electrophysiological and neuroimaging studies exploring the neural bases of both basic perceptual and more complex cognitive information processing will be presented.

## 2. Clinical observations

Clinical observations have demonstrated that people with ASD show unusual reactivity to sensory stimuli. Self reports commonly mention atypical sensory responses (Bogdashina, 2003; Williams, 1992), especially during childhood, and a systematic review of the literature indicates that rates of sensory processing dysfunction may be as high as 90% in individuals with ASD (Baker et al., 2008; Baranek et al., 2006; Leekam et al., 2007; Tomchek and Dunn, 2007). These specific sensory particularities affect all modalities and mainly include enhanced perceptual function such as visual hyperacuity (Ashwin et al., 2009), hyperacusis (Khalfa et al., 2004) and acute tactile sensitivity (Blakemore et al., 2006). However, hypo-reactivity to sensory stimuli has also been extensively reported in all sensory modes (Ben-Sasson et al., 2009; Reynolds and Lane, 2008). These paradoxical responses to sensory stimuli often observed in the same individual with ASD, lead to a lack of consensus on the exact nature of the underlying sensory dysfunction, but could explain many of the characteristic autistic behaviours, such as stereotyped behaviour and quest for sameness (see Gerrard and Rugg (2009) for a comprehensive review). Sensitivity to any change occurring in the environment is also a fundamental feature of ASD that appears to be a durable treatment-resistant symptom, which prevents the individual from adapting. For instance, enhanced detection of specific features in the auditory modality suggest an exaggerated perception of even slight changes in the environment and a feeling of stimulus overload, triggering distressful reactions to specific sounds (O'Riordan and Passetti, 2006). This oversensitivity to changes may lead to an inability to anticipate and adapt to new sensory inputs, in both the visual (Loth et al., 2008) and the auditory (Gomot et al., 2010) modalities.

In this respect the processes involved in pre-attentional detection of changes in stimulus features based on prediction regarding regularity of sensory input, as well as attentional processes involved in novelty and target detection, have been extensively investigated in ASD.

## 3. Violation of prediction: deviance and novelty processing

### 3.1. Mismatch negativity

In the auditory modality, representations of regularity are involved in the deviance detection process reflected by mismatch negativity (MMN), an event-related potential (ERP) that reflects a marker of error detection caused by a deviation from a learned regularity. It results from comparison between the auditory input and a memory trace of previous sounds embodied in top-down predictions, thus reflecting an on-line updating of the model for predicting auditory inputs (Naatanen

and Winkler, 1999; Winkler et al., 1996). This has been supported by Escera et al. (2003) who supplied evidence for the involvement of the prefrontal cortex in providing top-down modulation of the deviance detection system in the temporal cortices. This notion of top-down guiding of auditory change detection has been further developed by Garrido et al. (2008; 2009), in the framework of the predictive coding model (Friston, 2005), a view highly consistent with the model of a visual proactive brain presented by Bar (2004).

#### 3.1.1. MMN to tones and speech stimuli

Contrary to most auditory ERPs, the MMN matures very early and its underlying mechanisms are assumed to be similar across the lifespan (Cheour et al., 2000; Gomot et al., 2000). As MMN recording does not require the subject's participation, it is very appropriate to study the dynamics of the central auditory processes involved in change detection in clinical populations.

MMN has long been considered as useful in the study of speech sounds discrimination and has thus been investigated in clinical populations with communication disorders, including individuals with ASD. Most studies have reported either normal or reduced MMN amplitudes in response to vowel change in these patients (Kemner et al., 1995; Kuhl et al., 2005; Lepisto et al., 2008; Lepisto et al., 2006). However studies of auditory deviance detection using elementary stimuli had previously provided information on the ability of the neural system to predict and react to changing events. MMN studies involving more basic auditory stimuli such as tones have been performed in people with ASD, but the findings reported have been rather inconsistent. Some studies have indicated that MMN amplitude for pitch deviants in individuals with ASD is in the normal range (Ceponiene et al., 2003) whereas others have shown a reduced response (Dunn et al., 2008; Lepisto et al., 2006). Shorter (Gomot et al., 2002; Kujala et al., 2007), normal and longer latencies (Jansson-Verkasalo et al., 2003; Oram Cardy et al., 2005; Seri et al., 1999) have also been reported in this population. These findings support the notion that there are differences, but not necessarily impairments, in the speed and robustness of the early stage of auditory change detection in ASD.

In our previous work involving children with ASD, we have investigated the processes involved in the automatic detection of minor frequency changes, using a similar oddball paradigm in electrophysiological (Gomot et al., 2002) and fMRI studies (Gomot et al., 2006). The electrophysiological results showed abnormal MMN topography over the frontal regions in children with ASD compared to controls. fMRI confirmed the hypothesis of atypical frontal change processing in ASD as it demonstrated smaller activity in the anterior cingulate (a region mainly involved in the distribution of attentional resources) in children with ASD than in controls in response to deviant events. These studies using different brain investigation techniques provided evidence of normal auditory temporal activity but atypical functioning of the left prefrontal cortex, during the automatic detection of acoustic changes in children with autism.

However, the involvement of these neurophysiological particularities in the behavioural need to preserve sameness in ASD remained to be clarified. We therefore examined further the relationships between electrophysiological responses to a passive auditory oddball paradigm and clinical assessments focusing on intolerance of change in order to provide evidence of possible brain-behaviour relationships (Gomot et al., 2010). Subjects with ASD displayed significantly shorter MMN latency than controls, indicating atypical sensory expectation. Indeed basic research on MMN has shown that shorter MMN latencies were recorded for greater intensity deviation (Schroger and Winkler, 1995) and for larger frequency deviation (Naatanen et al., 1982; Tiitinen et al., 1994). Children with ASD would thus process slightly deviant events as if they were presented with large deviants, either because of an atypical formation of the standard sensory memory trace or due to dysfunction in the mismatch process itself. Bioclinical relationships indicated that these electrophysiological particularities were significantly more

marked in children who displayed greater difficulties in tolerating change, suggesting that the atypical neurophysiological mechanism of change perception identified might be associated with one of the hallmark behavioural manifestations of ASD.

### 3.1.2. MMN to prosody

The voice is a key vector of social information and it has an important adaptive role very early in human development. Auditory change detection in control populations, as reflected by MMN, is enhanced for rare stimuli spoken with emotion as compared to neutral prosody (De Baene et al., 2004; Schirmer et al., 2005). MMN might thus constitute a suitable electrophysiological index of automatic change detection embedded in an emotional context.

Disorder of emotional prosody has been frequently identified as a core feature of the syndrome in individuals with ASD who develop language (Paul et al., 2005b). Clinical observations report monotonic or machine-like intonation, deficits in the use of pitch and control of volume, and use of aberrant stress patterns. When these differences are present they are persistent and show little change over time, even when other aspects of language improve. Compared to the extensive studies reporting atypical expressive prosody, few studies have focused on receptive prosody. Nevertheless, behavioural experiments have provided evidence that receptive prosody scores in ASD correlated with expressive prosody performance (Paul et al., 2005a; Peppe et al., 2007). Only two studies have investigated MMN in response to changes in emotional prosody of a two syllable word in ASD (Korpilahti et al., 2007; Kujala et al., 2005), and both reported smaller activity in the right hemisphere compared to controls. However, as mentioned above, previous findings by our team and others using tone pitch variations to examine MMN in ASD support the possibility that deficits in the detection of changes in basic auditory features may be underlain mostly by particularities in prefrontal activity (Gomot et al., 2008; Gomot et al., 2006; Gomot et al., 2002). Such findings support the hypothesis of particular top-down processes involved in the automatic detection of auditory irregularity in ASD, which might contribute to abnormal prosody perception in this population.

### 3.1.3. Visual MMN

Recent studies have provided convincing evidence for a visual equivalent of MMN (vMMN) in response to deviancy based on various stimulus features such as colour (Czigler et al., 2002), form (Berti and Schroger, 2004); (Stagg et al., 2004), motion (Kremlacek et al., 2006; Pazo-Alvarez et al., 2004), spatial frequency (Kimura et al., 2006; Maekawa et al., 2005), and orientation (Astikainen et al., 2008; Czigler and Csibra, 1992). A number of studies in adults have identified vMMN as a negative detection peaking 100–250 ms post stimulus change onset (see Pazo-Alvarez et al., 2003 for a review). Similar to the auditory MMN, the vMMN is thought to reflect the memory-based detection of deviants as demonstrated by equiprobability paradigms that make it possible to control the effects of global presentation (Czigler et al., 2002).

In contrast to the increasing literature on vMMN in adults, no studies have been published on its maturation. Nevertheless automatic deviancy detection has recently been investigated in the visual modality in 11-year-old children with ASD. These children showed an earlier visual mismatch response with atypical morphology: they displayed positive occipito-parietal activity spreading over the central region whereas the control group showed a negative response localized over the bilateral occipito-parieto-temporal sites. These findings suggest that unusual reactions to change are underlain by atypical general change processing independent of the sensory modality (Cléry et al., in revision).

## 3.2. P3a

p3a definition

The P3a response has been used to assess how individuals with ASD involuntarily orient to unattended changes in their environment. When elicited by attention-catching novel sounds or deviants, the P3a response was generally found to be smaller in amplitude in adolescents

and young adults with ASD (Courchesne et al., 1984; Courchesne et al., 1985; Ferri et al., 2003; Kemner et al., 1995; Townsend et al., 2001), but might be enhanced in children (Ferri et al., 2003; Gomot et al., 2002). Furthermore, the amplitude of the P3a was found to be correlated with behavioural measurements of intolerance to change in children with ASD, suggesting that greater difficulties in dealing with unexpected events might be due to greater brain activity in response to attention-catching rare stimuli (Gomot et al., 2010). Differences in findings in children and in adults with ASD raise the question of the development of compensatory mechanisms and highlight the need of carrying out studies using the same paradigm at all ages in order to distinguish between age-related and stimulus feature-related effects.

Delayed P3a latency has been repetitively found in ASD (Townsend et al., 2001). In a three stimulus oddball paradigm, Sokhadze et al. (2009) showed that ASD subjects displayed delayed P3a response to visual novel stimuli, especially in the right hemisphere, suggesting that individuals with ASD require more time to process information needed for the successful differentiation of target and novel stimuli. These findings indicating differences in amplitudes and longer latencies of the electrophysiological index of attention-dependent novelty-processing suggest unusual violation of sensory expectancy in ASD, possibly due to difficulties in building flexible predictions about the upcoming event.

### 3.3. P3b

Predictions related to contextual processing has been linked to the P300 component of the ERP (Donchin and Coles, 1988; Polich and Criado, 2006). A quite extensive literature supports the notion that hypotheses about the environment are continuously generated as a function of incoming information (Donchin and Coles, 1988), and that the target P300 component (P3b) provides a measure of the evaluation of environmental signals as a function of context (Squires et al., 1976; Fogelson et al., 2010). Such processing has been shown to rely on the prefrontal cortex activity (Barcelo and Knight, 2007).

ERP studies on target detection and attention to novelty have demonstrated clear deficits in individuals with ASD. While P3b latency remains fairly unchanged (Courchesne et al., 1989; Lincoln et al., 1993; Oades et al., 1988), several studies have reported that the P3b amplitude to targets in ASD subjects was smaller than in controls in the auditory (Dawson et al., 1988; Kemner et al., 1995; Lincoln et al., 1993; Townsend et al., 2001), visual (Kemner et al., 1999) or both modalities (Ciesielski et al., 1990; Courchesne et al., 1985; Courchesne et al., 1989; Hoeksma et al., 2004; Novick et al., 1980) despite normal performance on the task. This reduced P3b amplitude has been interpreted as reflecting dysfunctions in context updating and in the ability to sustain attention to target stimuli, again suggesting that individuals with ASD process novelty differently and display unusual cognitive expectancy.

Overall, these ERP findings suggest that the neural circuits necessary for the processing of irregularities in the sensory stream, such as automatic discrimination of stimulus features, pre-attentive novelty detection, or target detection may be aberrant in ASD (see Jeste and Nelson (2009) for an exhaustive review), and might be considered in relation to the difficulty that ASD individuals have in properly allocating attention and modifying their expectancy of contextually-relevant sequences of sensory information. Interestingly, low-frequency rTMS has been applied over the dorsolateral prefrontal cortex of ASD patients during an oddball task, to increase the inhibitory circuitry in this area known to be involved in attentional executive processes. rTMS resulted in a short-term functional reorganization of cortical activity leading to modifications of ERPs (Sokhadze et al., 2010): the amplitude of the P3a component to rare novel stimuli normalizing in ASD subjects, and the P3b showing increased reactivity to targets and decreased reactivity to frequent standards. The authors concluded that low-frequency rTMS minimized cortical responses to irrelevant stimuli and increased responses to relevant stimuli and might represent a remarkable lead for future treatment development.

differences of P3a across lifespan

explanation of how rTMS can reduce deficit in ASD



#### 4. Context processing and change blindness

Contextual processing is essential for the performance of cognitive functions (Braver and Barch, 2002; Braver et al., 2005) and enables extraction of relevant environmental information to guide our behaviour in facilitating the selection of an appropriate task-specific response (Fogelson et al., 2010). Proper use of contextual information requires the ability to move from a local to a global level of processing. As such, it entails the capacity to combine information in order to construct higher-level meanings in context that contributes to predicting incoming events. Evidence from neuropsychological, event-related potential and neuroimaging studies supports a key role of the prefrontal cortex in contextual processing (Barcelo and Knight, 2007; Huettel et al., 2005; MacDonald et al., 2000).

People with ASD demonstrate a unique profile of perceptual and cognitive abilities, characterised by overly focusing on the local level at the expense of the global view. This pattern has been evidenced during visual processing (Jolliffe and Baron-Cohen, 1997), as well as in the context of a conceptual deficit as originally demonstrated in homograph reading tasks (Snowling et al., 1986). Similarly, people with ASD are not fooled by visual illusions such as Tichener Circles which depend on whether the context is taken into account or not (Happé, 1999). Moreover, it has been shown that subjects with ASD are not affected by interfering visual (Jolliffe and Baron-Cohen, 1997) or auditory (Foxton et al., 2003) 'gestalts'. This lack of interference as well as the weaker tendency to integrate separate events has been interpreted as reflecting a deficit in the 'coherent whole' representation (Happé and Frith, 2006). Rather than a dysfunction of global processing, it was then proposed, mostly on the basis of study of auditory attention processes that revealed enhanced pitch processing (Bonnell et al., 2003; Heaton et al., 2008), that low-level information processing systems for sensory stimuli might be over-developed in ASD (Mottion et al., 2000; Plaisted et al., 2003). This hypothesis has been further conceptualised within the Enhanced Perceptual Functioning Model (EPF) (Mottion et al., 2006). EPF notably proposes that the automatic progression from local to global visual processing that normally occurs in vision is compromised and that, as a consequence, individuals with ASD retain access to local structures. Following this line, Bertone et al. (2003) proposed that people with ASD encounter specific difficulties with the processing of complex information involving not only primary but also associative brain areas.

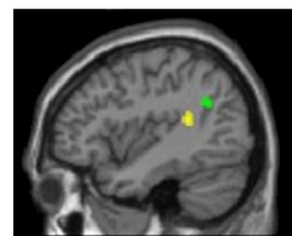
Few brain imaging studies have investigated the neural correlates of context processing in ASD. In a study employing fMRI while subjects performed Embedded Figures Tasks, Ring et al. (1999) tested local/global processing during visual search for a simple shape in a complex figure. Whereas prefrontal areas were preferentially activated in typical subjects, individuals with ASD demonstrated greater activation of ventral occipito-temporal regions, associated with superior task performance. The authors concluded that the ASD group strategy depends to an abnormal extent on visual systems for analysis of object features, at the expense of more integrative processing. Such hypo-activation of prefrontal areas during visuo-spatial context processing has subsequently been confirmed by other groups (Lee et al., 2007; Manjaly et al., 2007). Another study addressed brain activity associated with global information processing, in which context was provided by gaze direction (Pelphrey et al., 2002). The findings suggested that gaze processing deficits in ASD subjects is not due to weak gaze discrimination *per se*, but rather linked to an inability to use information from gaze direction to anticipate and to solve social situations that demand awareness of contextual subtleties.

At a more elementary perceptual level, it is admitted that the context in which sensory stimuli occur does pervade their subsequent processing. During an active auditory oddball task, Gomot et al. (2008) showed enhanced activation of the inferior parietal and prefrontal regions in ASD subjects in response to novel targets. Interestingly, using the same auditory oddball sequence but presented in passive conditions, they found that the inferior parietal lobule (IPL) was hypo-activated in children with ASD in response to novel stimuli, whereas this same region was

found to be hyper-activated during the active run (Gomot et al., 2006) (Fig. 1). The IPL is assumed to be involved in the pre-attentive gating mechanism that determines the extent to which unattended novel stimuli enter awareness (Jaaskelainen et al., 2004), such pre-attentive mechanisms being influenced by frontal top-down processes (Cycowicz and Friedman, 1998). Therefore, depending on the context (instruction), individuals with ASD may have an abnormally narrow or an abnormally broad focus of attention toward changing events. Similar attention impairments were demonstrated in the spatial domain in a task that required stimulus discrimination following a spatial cue that preceded the target presentation with either a long (voluntary spatial attention) or a short (automatic attention) inter-stimulus interval (Haist et al., 2005). The pattern of fMRI findings suggest that ASD is associated with a deficit in automatic spatial attention and with atypical voluntary spatial attention skills.

In the same trend, several reports suggested that individuals with ASD focus their attention on less contextually relevant aspects of the visual scene, show superior perceptual discrimination, and notice details which are often ignored by typical observers. The ability to detect changes in a visual scene has therefore been investigated in ASD using the change blindness paradigm that makes it possible to assess the influence of context on automatic attention. However, analysis of the few studies in this domain reveals inconsistent findings. Of the five studies performed, one showed superior levels of task performance in ASD (Smith and Milne, 2009) and another reported a similar error detection rate (Fletcher-Watson et al., 2008). The other three reported decreased levels of performance, one showing a lack of attentional bias toward faces (Kikuchi et al., 2009) and the other two a default in context facilitation effect (Fletcher-Watson et al., 2006; Loth et al., 2008). For instance, the ASD participants did not show the usual top-down facilitator effect of scene-schema expectations on scene-unrelated substitutions and were thus significantly slower and less accurate than the control group in detecting scene-unrelated objects (Loth et al., 2008). These findings suggest a weaker influence of schematic expectations on spontaneous attention in individuals with ASD.

To summarise, the reduction in the normal tendency to process information within its context may be a consequence of a processing bias for featural and local information, and a relative failure to extract the general picture. This lack of building and/or using context can be interpreted in the framework of the proactive brain, with the hypothesis that the core difficulty in processing socially-relevant information in ASD might be based on a more general deficit of prediction. The social environment is permanently and rapidly moving and changing, and social situations are those where predictions are the most important and the most solicited. In this context, building predictions would act as an attentional filter, allowing minimizing processing of incoming stimuli and allocating mental resources to more relevant contextual information. Interestingly, this propensity to invest in the predictable is thought to be primarily a top-down, internally driven process, supported by long-range connectivity between prefrontal and posterior associative brain areas (Bar, 2007).



RFX analysis,  $p < 0.001$ , uncorrected;  $X = -38$

Fig. 1. Atypical left Inferior Parietal Lobule (IPL) activity associated with novelty detection in children with ASD depends on the instruction. Novel vs. Standard: Unattended condition, Ctrl>ASD (yellow); Attended condition, ASD>Ctrl (green).

summary

explanation of  
contextual  
processing  
related to  
prediction

## 5. Planning and flexibility

Executive functions refer to a range of abilities, including behavioural control, planning, working memory, and set shifting (Baddeley, 1986; Robbins, 1996; Shallice, 1982), allowing to adapt flexibly to changing environmental contingencies. Among these adaptive skills, planning necessitates building prediction about our own actions and their consequences, and set-shifting requires flexible adaptation to changes in ongoing rule or stream of events that fail to match with our expectation. In this regard these executive processes closely rely on predictive abilities. Executive dysfunction in ASD has been a particularly active topic of investigation since the pioneer studies (Ozonoff et al., 1991; Rumsey, 1985; Russell et al., 1999) to such an extent that an **Executive Dysfunction model** has been proposed (Hill, 2004; Hill and Bird, 2006) and is still being developed (Corbett et al., 2009; Happe et al., 2006; Ozonoff et al., 2004). Some authors argue that executive dysfunction can explain the main symptoms of ASD (Hill, 2004). For instance, problems with social interaction might be due to a lack of flexibility leading to difficulties in taking another individual's perspective, whereas repetitive behaviours may stem from a lack of generative ability or difficulty in set shifting to a new behaviour (Turner, 1999). Research into executive functioning suggests that individuals with ASD generally experience difficulties, especially in planning (Ozonoff and Jensen, 1999) and cognitive flexibility (Kaland et al., 2008; Ozonoff and Jensen, 1999). Only a few functional magnetic resonance imaging studies have investigated the neural substrates of these executive cognitive functions in ASD. Just et al. (2007) used the Tower of London task to explore brain activations associated with planning. Behavioural results showed that ASD individuals displayed similar error rates but longer reaction times than controls when the number of moves required to perform the task increased. During this planning task the same brain areas were activated to similar degrees in both groups. However, the degree of functional connectivity between frontal and parietal areas was lower in ASD than in controls. The authors concluded that the neural basis of impaired planning in ASD entails a lower degree of integration of information across certain cortical areas resulting from reduced intracortical connectivity (Just et al., 2007). Functional connectivity analysis performed during a cognitive control task (while subjects were preparing to overcome a prepotent response) also revealed lower levels of functional connectivity and less network integration between frontal, parietal, and occipital regions in the ASD group, associated with higher error rate in response to the most difficult trials that need greater involvement of cognitive control process (Solomon et al., 2009). Altogether these findings showed roughly similar performance in control and ASD groups but differences in the temporal connectivity of the different brain areas engaged by the cognitive task. This supports the hypothesis of the development of alternative strategies in ASD possibly rooted in atypical fronto-parietal functional connectivity, rather than a cognitive deficit per se.

## 6. A brain connectivity bias

Research in ASD over the last ten years has been marked by specific focus on socio-emotional processing. Brain function in ASD has mainly been investigated with tasks related to social cognition such as face perception, emotion recognition, or theory of mind. Particularities have been revealed within the socio-emotional brain areas including the medial prefrontal cortex, fusiform gyrus, posterior superior temporal sulcus and amygdala (Frith, 2001; Gervais et al., 2004; Pierce et al., 2004; Schultz et al., 2003). The **under-connectivity theory of autism** has further been proposed on the basis of neuroimaging evidence of anatomical and functional connectivity disruption in ASD (Belmonte et al., 2004; Just et al., 2004; Thai et al., 2009; Wicker et al., 2008). This suggests that the behavioural markers of ASD are directly or indirectly caused by limitations in the communication between frontal and posterior brain regions, and predicts that these limitations will impact on those tasks that require

extensive coordinated functioning of remote processing centres. The ASD brain might thus not develop from a local to a distributed organizations as currently observed during normal maturation (Fair et al., 2009).

Taken together, results from functional connectivity analysis during executive functioning tasks provide converging evidence in line with the (long-range) under-connectivity hypothesis proposed by Just et al. (2004), which might constitute the neural basis of a fault in automatic anticipation of ongoing information. A recent study directly investigated the influence of global processing on lower-level visual perception in ASD using a paradigm in which local and global processes were requested at the same time (Liu et al., 2011). In such a task, the automatic global processing of the background information usually interferes with the concurrent local processing, causing additional cognitive resources to be recruited to deal with the interference. Thus, greater activation in the frontal brain regions and increased functional connectivity between these executive regions and the visuospatial regions was found in controls. Conversely the participants with ASD did not show increased activation in the superior frontal and medial frontal brain regions, nor increased functional connectivity between the medial frontal and posterior regions. This again suggests impairment in top-down regulation on perceptive regions necessary to catch the whole picture.

Anatomically, recent studies of axonal connectivity of area 32 of anterior cingulate cortex (ACC) and prefrontal areas revealed an exuberance of thin axons that course over short or medium distances in the ASD brain, which may lead to occupation of sites normally available to the considerably sparser long-distance pathways (Zikopoulos and Barbas, 2010). The latter are at a competitive disadvantage, not only because they develop later, but also because they need additional time to extend long axons to form synapses in the prefrontal cortex. Reduction in the strength of long-distance pathways in ASD may thus be secondary to the excessive short-range connections of ACC. Again, this connectivity bias may help explain why individuals with ASD do not adequately shift attention when necessary, and engage in repetitive and inflexible behaviour.

## 7. Link with other theories of ASD suggesting impairment in predictions

Finally, particular features in predicting forthcoming events have previously been mentioned, although not necessarily further developed, in neuropsychological models of ASD.

Among these models, the psychological **'extreme male brain theory'** stipulates that individuals with ASD preferentially develop a systemising style (typical male functioning) at the expense of empathising skills (Baron-Cohen, 2002). According to this assumption, people prone to the systemizing style are generally good at understanding systems that are highly predictable as they are governed by very clear rules. Systemizing is the ability to observe a physical system and make predictions about how it works (Baron-Cohen, 2006). Such cognitive style works well for phenomena that are lawful and deterministic but it is of almost no use when it comes to predicting moment-by-moment changes in a person's behaviour. To predict human behaviour, empathising is required. Empathizing allows to identify another person's emotions and thoughts, and to respond to these with an appropriate emotion. Baron-Cohen and others have shown that individuals with ASD can perform at normal or often superior levels in tasks requiring the systemization of information. People with ASD scored higher on the Systemizing Quotient (SQ) questionnaire (Baron-Cohen et al., 2003), performed better on tests of intuitive physics (Lawson et al., 2004) and can reach extremely high levels of achievement in systemizing domains, such as mathematics, physics, and computer science (Wheelwright and Baron-Cohen, 2001). Conversely patients with ASD are poor at empathizing, as dealing with information that is rather unpredictable and less controllable is particularly challenging for those people whose flexible prediction abilities are impaired. Baron-Cohen proposed that although systemising and empathising are in one way similar as both allow us to make sense of events and

task where local and global processes overlapped  
under-connectivity theory of autism

make reliable predictions, they are in other respects almost the opposite of each other. 'Whereas empathising implies a guess in the absence of much data [...] and is the most powerful way of understanding and adapting to the social world, systemising is the most powerful way of understanding and predicting the law-governed inanimate universe' (Baron-Cohen, 2002).

Markram and Markram (2010) recently proposed the 'Intense World Theory' to explain the neurobiology of ASD in an attempt to unify the various hypotheses developed in this domain. This *intense world syndrome* hypothesis was grounded in original experiments using the valproic acid rat model of autism to explore alterations across the synaptic, molecular, microcircuit and behavioural levels (Markram et al., 2007). From these findings the authors postulated that the core pathology of the autistic brain is hyper-reactivity and hyper-plasticity of local neuronal circuits that might lead to hyper sensitivity, hyper perception, hyper attention and hyper emotionality, processes that lie at the heart of most autistic symptoms. Such cognitive dysfunction would contribute to an intense, fragmented and aversive image of the world and entails for integration deficits, routines and repetition, withdrawal and social interaction problems, together with exceptional talents. The *intense world theory* also suggests that hyper functional neural microcircuits become autonomous processing modules that would escape top-down control from areas such as the prefrontal cortex. This supports our suggestion for a dysfunction in predictive processes in ASD, as such an atypical regulation by the prefrontal region would prevent building perceptual predictions guided by information from high-level cognitive frontal areas.

Automatic prediction deficit appears to be central to ASD and would result in the routines, restricted and intense interests, and lack of generalisation which are particularly incapacitating for several daily life activities. Parents and clinicians indeed report that this is the most troubling and consistent characteristic of the ASD and that it is resistant to intervention. As this aspect of the cognition in ASD prevents any flexible adaptation to unexpected or changing events, it might have a fundamental role in the social interaction deficit revealed in the highly unpredictable social world.

## 8. Conclusion

The power of predictions is that we can anticipate some context-specific aspects, to which we do not have to allocate as much attention, and therefore remain with the resources to explore our environment for novelties from which we can learn, and for surprises we should avoid (Bar, 2009). Based on evidence from ERPs, fMRI and brain connectivity studies, we propose here that the neurophysiology of Autism Spectrum Disorders might be characterised by impairment in the ability to build flexible predictions. This inability to expect new sensory inputs and events may lead to difficulties in perception and executive functions such as flexibility and planning. Deficits in prediction might also explain known differences in patterns of local and global information processing, and lead to weak central coherence. Pathological restricted and repetitive behaviours and interests, rituals and routines might then have adaptive significance, such as compensating for a failure to predict events and regulate uncertainty by preserving sameness. In ASD, the dysfunction of prediction based on context may impair the ability to adapt quickly to an ever changing socio-emotional world. Being unable to approximate the relevant future would lead to stressful reactions and a sense of overstimulation, for which the only remedy would be to avoid complex social situations and focus on highly predictable events and routines. This view may open up new lines of research for future treatments. It might contribute to building specific clinical and educational intervention programmes in order to provide ASD patients with specific cognitive strategies to overcome target weaknesses in prediction. Studies of brain processes involved in prediction still remain to be developed in ASD and the precise understanding of likely dysfunction in this domain may indeed orient cognitive behavioural therapies.

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