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To cite this version:

Bruno Gepner, François Féron. Autism: a world changing too fast for a mis-wired brain ?. Neuroscience and Biobehavioral Reviews, 2009, 33, pp.1227-1242. 10.1016/j.neubiorev.2009.06.006 . hal-00483957

HAL Id: hal-00483957

https://hal.science/hal-00483957v1

Submitted on 17 May 2010

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Référence de l'article:
Gepner, B. & Féron, F. (2009). Autism: a world changing too fast for a mis-wired brain? *Neuroscience and Biobehavioral Reviews*, 33, 1227-1242.

Autism: a world changing too fast for a mis-wired brain?

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Abstract

Disorders in verbal and emotional communication and imitation, social reciprocity and higher-order cognition observed in individuals with Autism Spectrum Disorders (ASD) are presented here as phenotypic expressions of Temporo-Spatial Processing Disorders (TSPD). TSPDs include various degrees of disability in i) processing multi-sensory stimuli online, ii) associating them into meaningful and coherent patterns and iii) producing real-time sensory-motor adjustments and motor outputs. In line with this theory, we found that slowing down the speed of facial and vocal events enhanced imitative, verbal and cognitive abilities in some ASD children, particularly those with low functioning autism. We then argue that TSPDs may result from Multi-system Brain Disconnectivity-Dissynchrony (MBD), defined as an increase or decrease in functional connectivity and neuronal synchronization within/between multiple neuro-functional territories and pathways. Recent functional magnetic resonance imaging (fMRI) and electrophysiological studies supporting MBD are outlined. Finally, we review the suspected underlying neurobiological mechanisms of MBD as evidenced in neuroimaging, genetic, environmental and epigenetic studies. Overall, our TSPD/MBD approach to ASD may open new promising avenues for a better understanding of neuro-physio-psychopathology of ASD and clinical rehabilitation of people affected by these syndromes.

Key-words: autism spectrum disorders; temporo-spatial processing; motion; emotion; speech processing; imitation; cognition; rehabilitation; slowing down; connectivity; synchrony; neurotransmission**.**

Abbreviations: ASD (Autism Spectrum Disorders); TSPD (Temporo-Spatial Processing Disorders); MBD (Multisystem Brain Disconnectivity-Dissynchrony).

I- Introduction

Autism and other related autism spectrum disorders (ASD) (Rapin, 2002) are known as behavioral syndromes including various degrees of verbal, nonverbal and social impairments as well as restricted or stereotyped interests and activities, with early onset (before 36 months) (WHO, 1992; APA, 2000), and long-lasting handicapping social and/or cognitive consequences. It is also currently accepted that these disorders altogether have a prevalence of about 0.6 % (Fombonne, 2002) and constitute a major public health problem all over the world.

Although there is an international consensus for considering these syndromes as phenotypic expressions of impairments affecting the development of the Central Nervous System (CNS), numerous questions concerning the etio-pathology and physio-pathogeny of these affections are still unsolved. Their treatments are consequently unspecific and disappointing. Clinically, ASD remain enigmatic for numerous reasons. They represent a *constellation* (Gepner & Tardif, 2006) of fairly heterogeneous disorders, that are rendered even more complex by the frequent association to mental delay, epilepsy, attention deficit with/without hyperactivity, language learning impairments – dysphasia, dyslexia - and obsessive compulsive disorders (Volkmar & Pauls, 2003). Furthermore, anxiety and mood disorders often influence personality and behavior of individuals with ASD (Tardif & Gepner, 2003; Lecavalier, 2006). Understanding the pathogenesis of ASD at molecular and cellular levels is an even more daunting task as it involves combinations of numerous genetic, epigenetic and environmental risk factors (Gepner & Soulayrol, 1994; Persico & Bourgeron, 2006) that affect different stages of neurodevelopmental and neurofunctional mechanisms.

In the present paper, we combine data from clinics, neuropsychology, neurophysiology, neuroimaging, genetics and epidemiology in a coherent approach to ASD. We first propose that Temporo-Spatial Processing Disorders (TSPD) of multi-sensory flows represent a common neuropsychological basis for the main behavioral, cognitive and motor disturbances observed in people with ASD. According to this hypothesis, ASD individuals would present various degrees of disability in processing dynamic multi-sensory stimuli online, associating them into meaningful and coherent patterns, and producing real-time sensory-motor adjustments and motor outputs. We also present results demonstrating that slowing down the speed of facial and vocal events enhance imitative, verbal and cognitive abilities of some ASD children. Then, we propose that TSPDs are based on Multi-system Brain Disconnectivity-Dissynchrony (MBD), i.e. disorders of functional connectivity and neural synchrony within/between multiple brain regions, and review the recent fMRI and electrophysiological data supporting MBD. Finally, we list the suspected neurobiological mechanisms underlying TSPDs and MBD.

II- Temporo-spatial processing disorders (TSPD) of multi-sensory flows

The TSPD hypothesis emerged from recurrent observations indicating that ASD patients exhibit various degrees of disability in i) perceiving and integrating environmental dynamic mutli-sensory stimuli online and ii) producing real-time sensory-motor coupling, postural adjustments and adequate verbal and nonverbal outputs.

Neuropsychological findings

It was first demonstrated that children with autism display a weak postural reactivity to visually perceived environmental motion (Gepner et al., 1995). Then, it was reported that i) children with low-functioning autism are posturally hypo-reactive to environmental movements, particularly when the speed of movement is high and ii) children with Asperger

syndrome exhibit normal or even over-postural reactivity to the same type of stimuli (Gepner & Mestre 2002a). This disordered (under- or over-) visuo-postural coupling in children with ASD may partly explain executive dysfunction in ASD patients (Hill, 2004 for a review) and sensory-motor and motor disturbances, such as poor motor coordination, poor or enhanced postural control, gross or fine motor clumsiness (Ornitz et al., 1974; Damasio and Maurer, 1978; Kohen-Raz et al., 1992; Leary & Hill, 1996 and Green et al., 2009 for reviews). Interestingly, visuo-postural mis-coupling is a good example of sensory-motor coupling disorders described 40 years ago (Ornitz & Ritvo, 1968; Ornitz, 1974).

In a second series of studies, it was demonstrated that ASD children have trouble perceiving the motion of small squares on a computer screen, especially at high speed and when the direction was less predictable (Gepner, 1997). Consistently, Bertone et al. (2003) showed that high-functioning autistic subjects exhibit a deficit in the perception of second order radial, translational and rotational direction of movement (see also Dakin & Frith, 2005, for a review).

Additional evidence supporting TSPD hypothesis stem from observed impairments in children and adolescents with ASD who were tested for their ability to extract online relevant information among noisy stimuli, through 3 types of tasks and measurements: a) oculo-motor reactivity to global movement of a coherent pattern of lighting points (a random dot kinematogram) through opto-kinetic nystagmus, b) speech flow perception and segmentation through categorization of simple and complex phonemes, and c) proprioception and motor anticipation in a bimanual load lifting task, through electromyographic and kinematic index (Gepner & Massion (dir. by), 2002).

First, the group of ASD subjects showed weak oculo-motor reactivity in response to global motion, i.e. higher motion coherence thresholds, when compared to control children (Mestre et al., 2002), as also observed by others (Spencer et al., 2000; Milne et al., 2002 ; Pellicano et al., 2005; Milne et al., 2005 for a review). Noticeably, this weaker oculo-motor reactivity was observed in reaction to high motion velocities (Mestre et al., 2002). This deficit, which supposes a defect in rapid temporal analysis of visual-motion stimuli embedded in noise, is a strong argument for a degraded temporo-spatial integration in the visual modality. Interestingly, this difficulty to integrate single points into a global coherent motion is also an argument for weak central coherence (Mestre et al., 2002; Pellicano et al., 2005). Impaired oculomotor reactivity to fast visual-motion, along with above-mentioned results demonstrating postural hypo-reactivity to fast environmental movements in children with autism and results suggesting impairments in rapid human movements processing (see below), led us to propose the rapid visual-motion integration deficit hypothesis of autism (Gepner & Mestre, 2002b).

Second, the same group of ASD subjects exhibited a deficit in speech phoneme categorization. Compared to control children who categorized an ambiguous phoneme such as MNA (made of an algorithmic superimposition of MA and NA) in a MA or a NA random response, autistic children over-categorized MNA in a NA response. This deviant over-categorization specifically appeared in autistic subjects when speech phonemes were displayed at normal speed, whereas their phoneme categorization was normalized when phonemes were slowed down by a factor of 2. Phoneme categorization deficit may partly be due to a difficulty in rapid speech flow processing and thus to a temporal integration deficit in the auditory modality (Tardif et al., 2002). As a consequence, the deficit may account for the receptive and expressive language and verbal communication impairments observed in individuals with ASD. Given the parallel between language disorders in ASD and developmental language disorders (Rapin & Dunn, 2003), it is not surprising that the same deficit was found in children with language learning impairments (Tallal, 1976), and was ameliorated by slowing down the speed of speech flow (Tallal et al., 1996; Gaab et al., 2007;

Tallal and Gaab, 2006 for a review). In line with these results, Oram Cardy et al. (2005), measuring evoked neural activity (M50, M100) to two 40 ms tones passively presented in rapid succession *via* magnetoencephalography, found that 80% of individuals with intact language (Asperger syndrome, typical development, normal adults) responded to the second tone, which required rapid temporal processing demands, while 65% of patients with impaired language (autism, specific language impairment) failed to do so, although they had reacted to the first tone. The authors concluded that deficient rapid temporal processing may contribute to impaired language development by interfering with the processing of brief acoustic transitions, crucial for speech perception.

Third, it was found that a subgroup of the same autistic subjects displayed a deficit in motor anticipation in a bimanual load-lifting task (Schmitz et al., 2002; see also Schmitz et al., 2003). The task requires the rapid processing of proprioceptive inputs, the correct use of an internal representation of the weight to be load-lifted and the precise adjustment of the timing of muscular events. Compared to control children using a feed-forward mode of control to stabilize their forearm while lifting an object placed on it, autistic children mostly use a feedback mode of control, which results in slowing down their movement. In other words, autistic children are reacting instead of predicting. This deficit of accurate timing of anticipatory control partly results from an impaired processing of proprioceptive inputs, at least during the learning phase of the task, and thus from a temporo-spatial integration deficit in the proprioceptive modality. This impairment, along with visual-proprioceptive processing deficit (i.e. deficit of visuo-postural and visuo-oculomotor reactivity), may contribute to executive dysfunction in ASD people (Hughes et al., 1994; Hill, 2004 for a review) and particularly to slowed sensory-motor processing speed.

As a result, many ASD individuals display deficits in temporo-spatial integration of sensory inflow which is necessary to i) detect and integrate visual motion, ii) code and parse language, and iii) anticipate and program postural adjustments. To briefly summarize, the environmental world may be changing too fast in one or several sensory modalities for at least some ASD children and adults.

Slowing down sensory stimuli as a tool for rehabilitation?

If the world is changing too fast for some ASD individuals, would it be beneficial to slow it down?

It was first found that ASD subjects, who usually perform poorly in facial recognition tasks involving the processing of facial dynamics (e.g. Hobson et al., 1988; De Gelder et al., 1991; Gepner et al., 1996), perform equally as well as typically developing children of the same developmental age in emotional and facial speech recognition tasks when the stimuli are slowly displayed on video (Gepner et al., 2001). In a complementary study, Tardif et al. (2007) strenghtened these results by demonstrating that some children with autism, particularly those having the more severe autistic syndrome, recognize significantly more emotional and non-emotional facial expressions, and exhibit more facial-vocal induced imitation when facial expressions and their corresponding vocal sounds are slowed down in an ecological or artificial way.

Next, in order to further test how slowing down facial and vocal cues would impact imitative and cognitive performance in autistic children, our group devised software that slows down simultaneously visual and auditory cues. We observed that slowing down the presentation of facial and body gestures enhanced voluntary imitation of ASD children (especially the more affected ones), whereas such improvement was not seen in healthy children or in mentally retarded ones (Lainé et al., 2008a). Similarly, it was found that slowing down the visual and auditory presentation of single or double sentences enhance verbal comprehension,

particularly in children with low-functioning autism (Lainé et al., 2008b; Lainé et al., in press).
Overall, these findings may be of potential high interest for rehabilitating verbal and emotional communication disorders in at least some individuals with ASD.

What does TSPD hypothesis predict for behavior and cognition?

According to our hypothesis, TSPD-exhibiting ASD individuals would tend to avoid rapid visual, auditory or proprioceptive flows, considered as aversive stimuli. Moreover, they would inadequately perceive and respond to rapid physical and human movements, especially facial movements such as eye movements (which are the most rapid ones in humans), lip movements and emotional facial gestures, but also body movements. As a consequence, TSPDs would induce impairments in i) attention to faces (e.g. decreased visual fixations to the eye region, see Hutt et al., 1964; Klin et al., 2002; Dalton et al., 2005; Speer et al., 2007), ii) facial imitation (Loveland et al., 1994; Vivanti et al., 2008), iii) recognition of facial stimuli involving motion or emotion (e.g. Hobson et al., 1988; De Gelder et al., 1991; Davies et al., 1994; Gepner et al., 1996; Critchley et al., 2000; Dawson et al., 2005 for a review; Hadjikhani et al., 2007; Pelphrey et al., 2007), and iv) action imitation (e.g. DeMyer et al., 1972; Rogers & Pennington, 1991; Rogers et al., 2003; Williams et al., 2004 for a review). In addition, impairments in rapid auditory processing would induce deficits in phoneme categorization, verbal imitation, verbal comprehension and finally in verbal and language abilities (Rapin & Dunn, 2003 and Tager-Flusberg & Caronna, 2007 for reviews). These numerous disabilities are likely to disrupt verbal and emotional communication and therefore to be detrimental for social interaction between ASD subjects and their human environment (Gepner & Tardif, 2006).
TSPD hypothesis postulates that the environmental world is changing too fast to be processed on time, and therefore also predicts that some ASD individuals would exhibit a slowed processing speed (see e.g. Welsh et al., 2005), in motor (see above Schmitz et al., 2002, 2003), perceptual and cognitive acts. For example, subjects with ASD exhibit slowed attentional processes such as shifting or orientating spatial attention (Wainwright-Sharp & Bryson, 1993; Townsend et al., 1996). Nishitani et al. (2004) observed that adults with Asperger syndrome display a delayed cortical activation from occipital cortex to superior temporal sulcus, inferior parietal lobe and inferior frontal lobe, when imitating still pictures of lip forms. McPartland et al. (2004) found electrophysiological evidence for slowed neural speed of face processing in autism. Wong et al. (2008) found that event related potentials (ERP), relating to face detection (visual cortex) and configural processing of faces (fusiform gyrus), as well as mental state decoding (medial prefrontal lobe), were significantly weaker and/or slower in autism, when compared to controls, during both explicit and implicit emotion-processing tasks. Finally, Schmitz et al. (2007) demonstrated that ASD individuals responded significantly more slowly than their controls during a cognitive assessment task, and that this reduced processing speed was correlated to decreased frontal lobe parenchymal volume.
Since the dynamic environmental world seems difficult to handle for ASD individuals, TSPD hypothesis additionally predicts an overfocused attention to static visual stimuli (Burack et al., 1997 and Mottron, 2004, for reviews) and auditory singularities (e.g. Mottron et al., 2000). Consequently, a weak central coherence (Frith, 1989; Happé, 1999; Happé & Frith, 2006), enhanced abilities in spatial memory and graphism, and increased pitch sensitivity (Bonnel et al., 2003; Mottron, 2004 for a review) may be observed.
Similarly, TSPD hypothesis predicts that some ASD individuals may develop compensatory mechanisms, *via* sensory-motor over–coupling (e.g. Gepner & Mestre, 2002a), sometimes

leading to high levels of performance and over-abilities in some fields. Others may also search for, habituate themselves and learn to handle and cope with, rapid dynamic stimuli and become more and more capable to process them (Gepner, 2004, 2008). Finally, a fraction of ASD individuals would search to slow down the speed of sensory inflow (see Williams' statement below).

Clinical arguments for TSPD

How do clinical observations support TSPDs? Several reports from ASD adults are in accordance with the rapid visual-motion integration deficit hypothesis of autism (Gepner & Mestre, 2002b) and support our TSPD approach.

The link between TSPDs and gaze aversion was substantiated by Temple Grandin who declared (1995) that *"some of the problems autistics have with making eye contact may be nothing more than intolerance for the movement of the other person's eyes. One autistic person reported that looking at people's eyes was difficult because the eyes did not stay still"*.

On the connection between time, space, speed and movement (i.e., TSPD), on the one hand, and weak central coherence, on the other hand, Van Dalen (1994), an adult with mild autism, stated: *« For me, time seems to flow out rapidly, or in other terms, a non-autistic person sees me as living slowly. During a certain period of time a non-autistic person can digest more percepts than me because I am constrained to digest each object piece by piece…Time phenomenon is relative to space, and strongly related to the number of distinct entities to be processed. I like to compare eyes of autistic persons to those faceted eyes of insects: there are numerous different subtile details, but they are not integrated together… »* .

Concerning the behavioral consequences of an excessively rapid environment and the potential usefulness of slowing down the sensory environment for ASD patients, Donna Williams (1992) wrote that *"the constant change of most things never seemed to give me any chance to prepare myself for them. Because of this I found pleasure and comfort in doing the same things over and over again. I always loved the saying, 'Stop the world, I want to get off'. The stress of trying to catch up and keep up often became often too much and I found myself trying to slow everything down and take some time out... One of the ways of making things seem to slow down was to blink or to turn the lights on and off really fast. If you blinked really fast, people behaved like in old frame-by-frame movies, like the effect of strobe lights without the control being taken out of your hands"* (p. 39-40).

Another statement by Temple Grandin (1995) accounts for the various visual behavior impairments along the 'autistic continuum' (i.e. autism spectrum): *"Minor sensory processing deficits heightened my attraction to certain stimulation (e.g. airport's doors), whereas a greater sensory processing defect might cause another child to fear and avoid the same stimulus"*.

About the auditory modality, Daniel Tammet (2006), an autistic savant, mentioned that *"she spoke very fast and I found it difficult to follow her…the rapid succession of questions was intrusive…and it took me some time to answer her"*.

Long before these self reports by ASD adults, Kanner (1943) in the first description of autistic children in the literature, observed several peculiarities of visual behavior such as i) gaze or face avoidance, ii) visual avoidance or visual attraction for moving, spinning and rolling objects, iii) visual attraction for details of objects, static patterns and puzzles, iv) sensory-motor disorders, such as motor clumsiness, awkwardness, as well as hand, arm or body stereotypes. One should notice that all these symptoms directly or indirectly question the way ASD children attend to, perceive, integrate and interact with, their dynamic *versus* static environment (Gepner, 2001).

Confirming the importance of such a question, studies using family home movies in the last two decades identified early specific visual, auditory and sensory-motor mis-behaviors in the first (Zwaigenbaum et al., 2005) or second year (Werner & Dawson, 2005) of life in ASD children.

In the domain of visual behavior, in the first six months of life, autistic babies may exhibit early atypicalities of gaze contact and ocular pursuit of moving objects or individuals (Adrien et al., 1993; Sauvage, 1988) and prolonged latency to disengage visual attention (Zwaigenbaum et al., 2005). Between 6 and 12 months, while exhibiting atypical interests for their hands and focusing on particular static objects in the environment (Adrien et al., 1993; Zwaigenbaum et al., 2005), they may also display a lack of interest for moving games and objects and self-stimulating sensory and sensory-motor behaviors, like finger- and hand-flapping in front of their eyes (Adrien et al., 1993; Osterling & Dawson, 1994). Overall, vision in ASD infants appears to be dissociated between a poor or avoided *dynamic vision*, frequently followed by self-stimulation of dynamic vision, and an enhanced *static vision*, with visual attraction and overfocused attention to details and singularities, at the expense of global or contextual information (Gepner, 2001, 2008). While autistic babies generally display a developmental delay (the 'negative signs of autism'), they also show atypical self-stimulating visual, auditory and sensory-motor behaviors (the 'productive signs of autism'), some of which probably have an adaptive and/or compensatory value. These compensatory strategies may mask the primary dysfunctions (Belmonte et al., 2004b). For example, visual attraction for rapidly moving stimuli possibly veils a primary dysfunction in processing such stimuli.

In regard to the domain of auditory behavior, babies who will later be diagnosed as autistic often fail to orient to their name and present a delayed development of expressive and receptive language (Zwaigenbaum et al., 2005; Werner & Dawson, 2005), possibly as a consequence of a failure to catch the rapid dynamic aspect of verbal flow. Concerning motor development, babies who will later exhibit typical autism (Teitelbaum et al., 1998) or Asperger syndrome (Teitelbaum et al., 2004) show disturbances in some or all of the milestones of development, including lying, righting, sitting, crawling and walking. In addition, Adrien et al. (1993) and Sauvage (1988) observed that they frequently exhibit deficits of postural adjustment, a lack or a delay in anticipating attitudes as well as in oculo-manual coordination, all of these symptoms being possibly due to a distorted proprioceptive and visuo-postural integration, and stereotyped behaviors like swinging, rocking and swaying, possibly aimed at compensating it.

The time course of autistic symptoms during infanthood may then appear as succession and intrication of *maldevelopmental cascades*, in which early temporo-spatial processing disorders of visual, auditory and proprioceptive stimuli impact secondarily on i) sensory-motor development, ii) verbal and emotional communication and social interactions between a baby and his physical and human environment (Gepner, 2004; Belmonte et al., 2004b; Gepner & Tardif, 2006; Gepner, 2008). One of these maldevelopmental consequences has been named *E-Motion Mis-sight*, i.e. various degrees of disability in perceiving and integrating motional and emotional stimuli on time (Gepner, 2001; Gepner et al., 2005; Gepner, 2008). *E-Motion Mis-sight* has been proposed to be an early precursor of mindblindness (Baron-Cohen, 1995; Frith, 2001) and empathizing deficit (Baron-Cohen, 2002).

In summary, TSPDs of multi-sensory stimuli may account for numerous clinical and neuropsychological findings in ASD that are synthesized and articulated below, and schematized on Figure 1:

i) Impairments in perceiving and integrating physical movements, that may account, alone or in conjunction with proprioceptive flow processing deficits, for executive dysfunction, as well as for slowed perceptual and sensory-motor processing speed.
ii) Impairments in perceiving and integrating biological motion such as:

a. eye movements, that may result in eye direction detection deficit, eye contact disorders, joint attention deficit and mindblindness,
b. lip movements, that may result, alone and in conjunction with speech flow processing deficit, in visuo-auditory association disorders, and in language impairments,
c. emotional facial and body movements, that may result in *E-Motion Mis-sight*, empathizing deficit and mindblindness, as well as in facial and body processing deficits and peculiarities.

These impairments may also consequently account for slowed perceptual and cognitive processing speed and imitative impairments.
iii) Dynamic auditory processing deficits that may result in phoneme categorization impairment, and, in conjunction with lip movements processing deficits, may account for visuo-auditory association deficits, verbal imitation deficits and language impairments.
iv) Over-focused attention on static visual stimuli that may explain enhanced local perception and weak central coherence, enhanced spatial memory and sometimes enhanced graphic abilities; overfocused attention on auditory singularities that may trigger enhanced pitch sensitivity.
v) Enhanced facial expression recognition, increased facial and body imitation and improved verbal comprehension when visual and/or auditory stimuli are slowed down.

Suspected neurobiological correlates of TSPD

When in search for the neurobiological bases of TSPDs, we hypothesized they may be based on deficits in temporal encoding of multi-sensory inputs, temporal coupling of sensory-motor events, and temporal production of motor outputs (Gepner & Massion (dir by), 2002). The cerebellum (i.e. the *clock of the brain* as stated by Massion, 1993) is known to play a crucial role in all these stages. First, visual inputs, especially dynamic ones, travel through mossy fibres *via* the pontine nuclei before reaching the cerebellum (Glickstein & Stein, 1991). Second, the cerebellum plays a major role in speed and temporal coding and therefore in integrating multi-sensory dynamic inputs (e.g. Johnson & Ebner, 2000). Third, the cerebellum exerts a real-time fine tuning of movement (e.g. Ito, 1984). Fourth, the cerebellum contributes with the basal ganglia to motor control as well as to learning (Doya, 2000), *via* projections on motor and premotor cortices as well as on prefrontal, temporal and parietal cortices (Middleton & Strick, 2000). Yet, some of the most consistent neuroanatomic anomalies affecting people with ASD are likely to affect the cerebellum (e.g. Courchesne et al., 1988, 1994; see also below). Visuo-cerebellar pathways, among other sensory-cerebellar pathways, are therefore highly suspected to be involved in the neurophysio-pathology of ASD (Takarae et al., 2004) and could explain the unusual visuo-motor reactivity and, possibly, the bizarre cognitive style and higher-order cognitive peculiarities observed in this population (Gepner & Mestre, 2002b).
Convergent with our proposal, Welsh et al. (2005) proposed to link neuroanatomic abnormalities of the cerebellum with cognitive impairments in ASD. The authors surmised that disturbances in the inferior olive structure found in autism (see e.g. Kemper & Bauman, 1993; Bailey et al., 1998), and consequently in olivo-cerebellar pathways, would disrupt the ability of inferior olive neurons to become electrically synchronized and generate coherent rhythmic output. These anomalies of synchronization would i) impair the ability of individuals with ASD to process rapid information (e.g. their ability to use rapid sequences of

cues for the development of normal language skills), and ii) result in slowing their perceptual and cognitive processing speed. Following Welsh et al. (2005), rapid sensory information (rapid sensory flows) would arrive too quickly to be processed on time by the autistic brain. Appropriately, a neuromimetic model (i.e. a mathematic model simulating brain functioning) of brain connectivity found that the speed of synchronization depends on the dynamical and network parameters, and is most probably limited by the network connectivity (Timme et al., 2004).

III- Multisystem Brain Disconnectivity-Dissynchrony (MBD)

In an attempt to further understand the neurophysiological basis of TSPDs in ASD, we propose the concept of Multisystem Brain Disconnectivity-Dissynchrony (MBD), defined as an increase or decrease of functional connectivity and neural synchrony within/between multiple cortical and subcortical regions of the brain (Figure 2).

Before reviewing the recent functional brain imaging and electrophysiological studies supporting our MBD approach to ASD, it should be emphasized that numerous data emerging from i) animal and human physiology (Varela et al., 2001, for a review), ii) human psychophysiopathology (Babiloni et al., 2004 for epilepsy; Symond et al., 2005 for schizophrenia; Just et al., 2004 for autism) and iii) neuromimetic models (e.g. Borgers & Kopell, 2003; Breakspear, 2004), evidenced functional interdependence and equivalence between neural synchronization (at the level of neuron assemblies), brain rythmicity and functional connectivity. Neural synchrony can therefore be considered as a mechanism of temporal connectivity.

Functional Magnetic Resonance Imaging (fMRI) studies

Functional connectivity is the mechanism allowing the achievement of a cognitive task or perceptual process by coordinating and spatio-temporally correlating activities between different neural assemblies (Fingelkurts et al., 2005). Based on several arguments, some authors have suspected that the functional connectivity between brain areas could be abnormal in subjects with ASD (Horwitz et al., 1988; Brock et al., 2002; Castelli et al., 2002; Belmonte et al., 2004a). Studies using functional magnetic resonance imaging (fMRI) during the past 5 years have confirmed that functional brain connectivity could either be decreased (see Wickelgren, 2005, Geshwind & Levitt, 2007 and Minshew & Williams, 2007 for reviews), or sometimes increased (Rippon et al., 2007 for a review) in subjects with ASD, during either resting state and simple or complex cognitive tasks.

Under resting state, Cherkassky et al. (2006) observed that, although the anterior and posterior midline regions were similar in volume and in organization in ASD subjects and control individuals, a functional under-connectivity between these regions was observed in ASD individuals.

During sentence comprehension tasks, Just et al. (2004) found a diminished functional connectivity between Wernicke's area and Broca's area in autistic subjects. In another sentence comprehension task with imagery content, Kana et al. (2006) showed that the language and spatial centres in autistic patients were not as well connected as in controls.

In an inhibition task, Kana et al. (2007) observed that subjects with autism exhibited a decreased connectivity between anterior and middle cingulate gyri, and insula, on the one hand, and the right middle, inferior frontal and right inferior parietal regions, on the other hand. In an executive function task, Just et al. (2007) demonstrated an under-connectivity between frontal and parietal regions in autistic subjects.

In a visuo-motor task, Villalobos et al. (2005) described a decreased functional connectivity between V1 and bilateral inferior frontal cortex. However, during another visuo-motor coordination task, Turner et al. (2006) showed that, although there was a decreased connectivity between associative, orbitofrontal oculomotor and motor circuits in subjects with autism, the same individuals exhibited a diffuse increased connectivity, mostly in pericentral regions and visual cortex. Similarly, in another visuo-motor coordination task, Mizuno et al. (2006) demonstrated a more extensive connectivity between thalamus and cortex (especially left insula, right postcentral and middle frontal regions) in autistic subjects. For these authors, this hyper-functional subcortico-cortical connectivity could potentially compensate a reduced cortico-cortical connectivity.

During facial identity processing, Kleinhans et al. (2008) found that greater social impairments were correlated to reduced connectivity between fusiform face area (FFA) and amygdala, and increased connectivity between FFA and right inferior frontal cortex in subjects with ASD.

Furthermore, Wicker et al. (2008) demonstrated that, whereas subjects with ASD perform equally as well as healthy controls when viewing emotional expressions, they present abnormal patterns of effective connectivity (which is defined as the influence one system exerts over another in respect to a given experimental context, Büchel and Friston, 2000). What was found in autistic subjects compared to controls was mainly under-connectivity (e.g. between V1/V2 and fusiform gyrus, between amygdala and dorso-medial prefrontal cortex, and between ventro-lateral prefrontal cortex and STS), but over-connectivity was also found between right dorso-lateral prefrontal cortex (dLPFC) and fusiform gyrus. As suggested by the authors, an abnormally strong influence of right dLPFC on fusiform gyrus could represent the neural instantiation of a compensatory cognitive mechanism that would explain the similar levels of performance in the explicit emotional task in both groups.

Finally, Kennedy and Courchesne (2008) recently showed that there was an altered functional organization of the network involved in social and emotional processing in autistic subjects but no group difference in the functional organization of the network involved in sustained attention and goal-directed cognition. This finding is in accordance with the Systemizing-Empathizing and Extreme male brain theories of autism (Baron-Cohen, 2002; Baron-Cohen et al., 2005).

In order to take into account not only under- but also over-connectivity between multiple brain areas in ASD, we proposed to name these processes *multisystem functional disconnectivity* (Gepner et al., 2005; Gepner & Tardif, 2006; Tardif et al., 2007; Gepner, 2008).

EEG and MEG studies

Functional MRI studies are useful to investigate the interaction between brain areas in ASD. However, these investigations provide only indirect evidence for dysfunctional neural synchrony in ASD, as interactions between and within brain areas occur with a precision in the millisecond range, a time resolution that fMRI cannot provide (Singer, 2007). As also stated by Singer (2007), most of the brain's cognitive functions (such as perceptual organization, memory and attention) and executive functions are based on the coordinated interactions of large numbers of neurons that are distributed within and across different specialized brain areas. Transient synchronization of neuronal discharges in the beta (13-30 Hz) and gamma (30-80 Hz) frequency ranges has been proposed as possible mechanism to dynamically bind widely distributed sets of neurons into functionally coherent ensembles that represent the neural correlates of a cognitive content or an executive program (Singer, 1999).

A new generation of experiments on neural synchrony using EEG coherence during both resting conditions and simple or complex cognitive tasks has emerged. Findings obtained through these experiments parallel and complete results obtained in fMRI sudies.
Assessing functional connectivity with electroencephalographic coherence among adults with ASD and control adults in an eyes-closed resting state, Murias et al. (2007) found patterns of over- and under-connectivity that were apparent at distinct spatial and temporal scales.
In another eyes-closed resting condition study, Coben et al. (2008) also found dysfunctional integration of frontal and posterior brain regions in autistic subjects along with a pattern of neural under-connectivity.
In the domain of complex visual processing, Brown et al. (2005) showed an overall increased gamma-activity in individuals with autism in comparison to healthy individuals whilst identifying the presence or absence of an illusory Kanizsa shape. This abnormal gamma activity was interpreted as a decreased "signal to noise" processing due to decreased inhibitory processing in ASD.
In regard to auditory processing, Wilson et al. (2007) used magnetoencephalography to examine the integrity of local circuitry by focusing on gamma band activity in auditory cortices of children and adolescents with autism and control subjects, while listening to 500 ms duration monaural click trains with a 25 ms inter-click interval. The authors demonstrated that the production and/or maintenance of left hemispheric gamma oscillations appeared abnormal in participants with autism. These findings evidence that aberrations in local circuitry could underlie putative deficiencies in long-range neural communication. Specifically, the authors suggest that deficits in neural synchrony may not exclusively involve long-range synchronization between cortical regions, but also local synchronization within cortical areas. According to Singer (2007), these findings add crucial evidence that precise timing of neural activity is disturbed in ASD, suggesting the possibility that this impairment may underlie the deficits in cognition and behavior associated with the disorder.
Studying sustained visual attention, Orekhova et al. (2007) investigated whether beta and gamma range EEG abnormalities are characteristic for young boys with autism. EEG was recorded during sustained visual attention in two independent samples of autistic boys aged 3 to 8 years, and in age matched typically developing boys. In both samples, boys with autism demonstrated a pathological increase of gamma (24.4–44.0 Hz) activity. According to the authors, given the important role of high frequency EEG rhythms for perceptual and cognitive processes, early abnormalities in the neuronal mechanisms generating high frequency EEG rhythms may contribute to the development of the disorder.
Altogether, findings from fMRI and EEG coherence studies evidenced modifications in functional connectivity and neural synchronization in the brain of ASD patients, during resting state and cognitive tasks. What seems to emerge from the latter studies is that when they have to process dynamic visual (such as facial movements) and auditory stimuli (such as click trains and verbal speech), subjects with ASD generally exhibit functional under-connectivity or neuronal hypo-synchronization. Conversely, when sustaining attention or processing static visual stimuli, subjects with ASD generally exhibit over-connectivity or hyper-synchronization. Also supporting these findings, Pelphrey et al. (2007) found a lack of modulation of social brain regions including the amygdala, posterior superior temporal sulcus and fusiform gyrus by dynamic *versus* static emotional expressions.
The co-occurrence of a disconnected and dissynchronized brain led us to propose the unifying concept of Multisystem Brain Disconnectivity-Dissynchrony (MBD), which may be a key signature of the developmental and functional brain anomalies observed in ASD patients.
It should finally be added that numerous areas and pathways involved in motion, emotion, facial and auditory processing in daily life, are functioning or highly suspected to function inadequately in ASD subjects. Among the most studied, we can cite the visual magnocellular

system (Gepner & Mestre, 2002b; Milne et al., 2002; Deruelle et al., 2004), the dorsal stream (e.g. Pellicano et al., 2005; Spencer et al., 2000; Villalobos et al., 2005), the cerebellum (e.g. Courchesne et al., 1988, 1994; Allen and Courchesne, 2003), and especially the "social brain", i.e. the amygdala (e.g. Baron-Cohen et al., 2000; Amaral et al., 2003; Schumann & Amaral, 2006), the fusiform gyrus (e.g. Schultz et al., 2003; van Kooten et al., 2008), the mirror neuron system (e.g. Oberman et al., 2005; Dapretto et al., 2006; Hadjikhani et al., 2006), and the superior temporal sulcus (e.g. Gervais et al., 2004; Hadjikhani et al., 2007). It can therefore be surmised that MBD within and/or between these key territories and pathways may be a nodal neurophysiological mechanism of ASD, responsible for various temporo-spatial processing disorders of visual and auditory stimuli. Further fMRI studies focusing on these various regions of interest could test this hypothesis in the future.

MBD and other neurobiological theories of ASD

Our MBD hypothesis is in accordance with several other neurobiological theories of ASD, such as the temporal binding deficit hypothesis (Brock et al., 2002; see also Rippon et al., 2007), the theory of imbalance between neuronal excitation and inhibition (Rubenstein and Merzenich, 2003) and the neural information processing disorders hypothesis (Belmonte et al., 2004b; see also Belmonte & Bourgeron, 2006). However, we moved a step further since our postulate i) is based on relevant data accounting for either under- or over-connectivity (and hypo- or hyper-synchronization) within/between local and distant networks, according to the nature of the tasks to be processed, ii) lies on functional disconnectivity involving not only cortical but also subcortical regions, and iii) accounts, *via* TSPD of multi-sensory stimuli, for a large spectrum of behavioral, cognitive and motor anomalies observed in ASD people .

MBD in other developmental and neuro-psychiatric disorders

Brain disconnectivity and dissynchrony is not specific to ASD and has been found to occur in other neurodevelopmental disorders such as epilepsy (e.g. Schevon et al., 2007), dyslexia (Cao et al., 2008), attention deficit/hyperactivity (Wolf et al., 2008), schizophrenia (Spencer, 2004; Symond et al., 2005; Uhlhaas et al., 2006), but also depression (Vasic et al., 2008) and neurodegenerative disorders, i.e. Parkinson's disease and Alzheimer's disease (Uhlhaas & Singer, 2006 for a review). Brain dissynchrony and disconnectivity is therefore likely to constitute a universal signature of mental diseases. Further studies assessing and comparing brain connectivity and/or synchronization within and between various neurodevelopmental and mental disorders will uncover similarities and differences between their underlying neural and neuro-functional mechanisms.

III- Neurobiological correlates

In this section, we review some of the structural brain abnormalities that lie beneath MBD (Figure 2).

Anatomic neuroimaging studies during the last 20 years have shown that multiple cortical and subcortical areas are altered in adults with ASD, primarily the cerebellum (e.g. Courchesne et al., 1988, 1994), frontal (e.g. Carper and Courchesne, 2000) and temporal (e.g. Zilbovicius et al., 2000) cortices, hippocampus (Nicolson et al., 2006), amygdala (Aylward et al., 1999), and corpus callosum (Piven et al., 1997), and sometimes the brainstem, basal ganglia, striatum and thalamus (e.g. Cody et al., 2002; Santangelo & Tsatsanis, 2005 for

reviews). As highlighted by Müller (2007), ASD are distributed disorders, especially at the neuroanatomical and neurofunctional levels.

Post mortem studies, reviewed by Bauman & Kemper (2005), revealed consistent findings in the limbic system, cerebellum and related inferior olive. Within the cerebellum, a significantly reduced number of Purkinje cells was reported. However, discrepancies were observed: in cerebellar nuclei and inferior olive, numerous and abnormally enlarged neurons were observed in the brains of young autistic subjects whereas small, pale and under-numbered neurons were described in adult autistic brains, strengthening the idea that the neuropathology of autism may represent an on-going process.

Likewise, Amaral et al. (2008)'s review on *post mortem* and structural magnetic resonance imaging studies highlighted the frontal lobes, amygdala and cerebellum as the most frequent pathological areas in autism. However, the authors conclude that there is no clear and consistent neuro-pathological signature that has emerged for autism, due to heterogeneity of both the core and co-morbid features of ASD. Moreover, the time course of brain development, rather than the final product, is most disturbed in autism.

Courchesne et al. (2005, 2007) underline that recent magnetic resonance imaging studies have revealed brain growth abnormalities involving gray and white matter in the first few years of life, sometimes followed by an arrest or a retardation of growth (e.g. Courchesne et al., 2001). Head circumference studies indicated that this early brain overgrowth might begin as early as the first year of life, thus, preceding and overlapping with the onset of the symptoms.

Finally, using a computerized imaging program to measure details of cell column morphologic features in the prefrontal and temporal cortices, Casanova et al. (2002) found that cell mini-columns in brains of autistic patients were more numerous, smaller, and less compact in their cellular configuration, with reduced neuropil space in the periphery. The authors inferred that increased number of mini-columns might result in a more extensive innervation and heightened activation, whereas the reduced neuropil spaces could induce a diminished lateral inhibition, possibly leading to an imbalance between neuronal excitation and neuronal inhibition, as postulated by Rubenstein & Merzenich (2003). This mini-columnopathy may therefore account for association and high-order cognitive processes abnormalities seen in ASD (Casanova, 2007), as well as for the high incidence of epilepsy and epileptiform activity that are associated with ASD (Tuchman & Rapin, 2002).

These various aspects of CNS formation found as disrupted in ASD may be at least partly correlated to genetic abnormalities inducing i) decreased apoptosis and/or increased cell proliferation, ii) altered cell migration with disrupted cortical and subcortical cytoarchitectonics and iii) abnormal cell differentiation with reduced neuronal size, and altered synaptogenesis. Alternatively, they may partly be due to environmental factors: in particular, brain enlargement can be related to neuroglial (i.e. astroglial and microglial) activation and neuroinflammation in the brain of patients with ASD (Vargas et al., 2005).

IV- Genetic and environmental factors

Many molecular abnormalities observed in ASD patients impact on the communication between neurons and therefore support MBD hypothesis of ASD (see e.g. Garber, 2007, and Figure 3).

Genetic factors

Data from numerous epidemiological, twin and family studies provided substantial evidence that ASD are amongst the most heritable complex brain disorders (e.g. Smalley et al., 1988;

Folstein & Rosen-Sheidley, 2001; Bacchelli and Maestrini, 2006). During the last decade, over 100 positional and/or functional candidate genes for autism were analyzed. Whole-genome screens in multiplex families indicate that 29 genes (Sutcliffe, 2008), and probably more, interact to predispose to ASD. Cytogenetic abnormalities in individuals with autism have been found in virtually every chromosome and new deleterious gene expressions are on the way to be identified (Abrahams and Geschwind, 2008). Determining specific genetic changes that increase the susceptibility to developing ASD is however extraordinarily complex due to the polygenic nature of these disorders and the interactions between genes and environmental influences through epigenetic processes. According to Happé et al. (2006), twin data and cognitive studies even suggest that non-overlapping genes act on each of the autistic traits, such as social impairment, communication difficulties and rigid and repetitive behaviors. However, it is currently accepted that ASD candidate genes encode products known to play a role in brain development and/or neurotransmission (Muhle et al., 2004). Copy number variations and mutations affecting genes implicated in cortical organization, synapse formation, synaptic transmission and neuromodulation have been found to be associated with ASD.

Genes implicated in cortical organization

Alterations in the protein Reelin (involved in neuronal migration and cortical layering during development) can affect cortical and cerebellar development. Mutations in the RELN gene and impaired Reelin signaling in ASD (Fatemi et al., 2005) are consistent with the cell migration defects found in autism and cerebellar neuronal abnormalities which are among the more consistent findings in ASD (Bauman & Kemper, 2005).

The neurotrophin family, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 and neurotrophin-4, is known to play a role in the regulation of cell proliferation and neuronal migration as well as in the modulation of axonal and dendritic growth and synapse formation. Elevated levels of BDNF have been found in the blood of children with ASD in several studies (e.g., Nelson et al., 2001) and auto-antibodies against BDNF were also found in serum of children with ASD or other associated syndromes (Connoly et al., 2006).

The tumor suppressor genes TSC1 and TSC2 are involved in cell growth regulation, dendrite morphology and glutamatergic neurotransmission (Tavazoie et al., 2005). Mutations have been identified in TSC1 and TSC2, which are responsible for tuberous sclerosis, a disorder often associated to mental retardation, epilepsy and autism (Baker et al., 1998). Abnormalities in genes involved in neuronal migration and corticogenesis, by their consequences on the construction of neural networks, may impact on neuronal communication (see e.g. Welsh et al., 2005).

Genes implicated in synapse formation and synaptic plasticity

Neuroligins are cell adhesion molecules, localized post-synaptically at glutamatergic (NLGN1, NLGN3 and NLGN4X/Y) or GABAergic synapses (NLGN2) (Varoqueaux et al., 2006). Mutations in the coding sequences of X-linked NLGN3 and NLGN4 have been identified in individuals with ASD and mental retardation (Jamain et al., 2003). Although these mutations have not been confirmed in other studies and probably explain less than 1% of ASD (Persico & Bourgeron, 2006), they shed light on the potentially crucial role of synapse abnormalities in ASD. Another study showed that mutations in neuroligin 1 abolished neuroligin binding to neurexin 1 beta, and blocked synapse formation (Chubykin et al., 2005). Indeed, neuroligins, expressed post-synaptically, induce the formation of fully functional presynaptic terminals in contacting axons. Moreover, the association of NLGNs with scaffolding proteins is likely to regulate the glutamate-GABA equilibrium, which is

impaired in the neuronal networks of 30-50% ASD patients with clinical or infra-clinical epilepsy (Hughes & Melyn, 2005; Tuchman & Rapin, 2002). Another gene, SHANK3 (located in the 22q13 region), a neuroligin-binding partner regulating the structural organization of dendritic spines, has been found to be deleted in two brothers with ASD and delayed expressive speech (Durand et al., 2007).

Genes encoding neurexins (and particularly NRXN1) which are localized pre-synaptically and play an important role in glutamatergic and GABAergic synaptogenesis, *via* a neuroligin-neurexin link (Graf et al., 2004). These genes have clearly been implicated in ASD by the Autism Genome Project Consortium (2007) in the largest linkage scan of 1168 families with at least two individuals affected by ASD.

The Fragile-X syndrome, which is often accompanied by an autistic syndrome, is caused by mutations in the FMR1 gene (Chelly & Mandel, 2001). The FMR1 gene, localized on chromosome X, encodes FMRP (fragile-X mental retardation protein), which is involved in mRNA transport and translation at the synapse (Bagni & Greenough, 2005).

Genes implicated in neurotransmission and neuromodulation

Several studies reveal that variants of genes encoding neurotransmitter receptors and transporters might be susceptibility factors or modulators of the behavioral phenotype of ASD. The most studied gene involved in neurotransmission is SLC6A4, which encodes the serotonin transporter (5-HTT). Whereas Cook et al. (1997) found preferential inheritance of a short promoter variant of SLC6A4 in affected individuals, other teams reported that a long promoter variant of the 5-HTT transporter was inherited more frequently by affected family members (Yirmiya et al., 2001).

Several studies strongly suggest the involvement of glutamate receptors in the physiopathogeny of ASD (Muhle et al., 2004 for a review). For example, excessive glutamatergic activity is associated with epileptiform activity, which is frequently linked to autism (Tuchman & Rapin, 2002; Hughes & Melyn, 2005) and increased levels of glutamate have been found in adults with autism (Shinohe et al., 2006). An autistic population possessed a single amino acid substitution in GluR6 with a higher frequency than a control population (Jamain et al., 2002). Finally, the metabotropic glutamate receptor GRM8 in the chromosome 7q31-q33 autism susceptibility locus exhibits Linkage Disequilibrium with autism (Serajee et al., 2003).

In parallel, defects in the GABAergic inhibitory system have been found in ASD. Given its role in inhibiting excitatory neural pathways and its expression in early development (see below), it is not surprising that the $GABA_A$ receptor gene cluster (which contains genes for 3 of the receptor's subunits: *GABRB3*, *GABRA5* and *GABRG3* in chromosome 15q11-13) could be implicated in ASD (Menold et al., 2001). In addition to the GABA receptor genes themselves, genes involved in the differentiation and migration of GABAergic neurons have also been linked to ASD. Mutations in ARX (which encodes a transcription factor thought to regulate the development of GABAergic neurons in the basal ganglia and cortex) have been discovered in patients with epilepsy, movement disorders, cortical malformations, mental retardation and autism (Turner et al., 2002; see also Sherr, 2003, for a review). However, no association between ARX mutation and autism has been found in a study involving 226 patients with ASD and mental retardation (Chaste et al., 2007).

Deficiencies in i) GABA receptor expression or function and ii) differentiation and migration of GABAergic neurons into the cortex are likely involved in ASD. These findings are consistent with the idea that ASD can be caused by a reduced activity of GABAergic pathways, leading to hyperexcitability in neural networks and disorders in filtering out excessive stimuli from environmental and intrinsic sources (Rubenstein & Merzenich, 2003).

Finally, mutations of the 7-dehydrocholesterol reductase gene (DHCR7) cause the Smith-Lemli-Opitz syndrome (SLOS), an autosomal recessive malformation syndrome caused by a deficiency of the last step of cholesterol biosynthesis (Tint et al., 1994). Principal abnormalities of SLOS include facial dysmorphy and microcephaly, hypotonia, hypogenitalism, 2–3 toe syndactyly and a characteristic behavioral profile including autism, usually accompanied by mental retardation. Altered cholesterol metabolism may impact numerous stages of CNS development and functions including myelination, transport of serotonin, GABA and glutamate, steroid production and functioning of oxytocin receptor (Bukelis et al., 2007).

Genes implicated in voltage-gated ion channels

Recent studies reviewed by Krey & Dolmetsch (2007) showed that functional mutations in genes encoding voltage-gated Ca^{2+} channels can lead to ASD. One of these studies reports the Timothy syndrome, a new multisystem disorder, often associated to autism, which is due to a recurrent *de novo CACNA1C* calcium channel mutation (Splawski et al., 2004). This mutation prevents voltage-dependent channel inactivation and leads to prolonged inward Ca^{2+} currents. Yet, these prolonged inward Ca^{2+} currents are known for their neurotoxicity, e.g. they are responsible for atrophy of dendritic spines and decreased synaptic connections, leading to apoptosis in socially isolated rats (Silva-Gomez et al., 2003).

Furthermore, mutations have been found in genes encoding other ion channels. These include several point mutations in *SCN1A* and *SCN2A*, which encode the voltage-activated Na^{+} channels $Na_v1.1$ and $Na_v1.2$ respectively, both associated with childhood epilepsy and autism (Weiss et al., 2003). One of the mutations in SCN1A lies in the calmodulin binding site of the channel and reduces its affinity for Ca^{2+}/calmodulin.

Another study reports a decrease in Ca^{2+}-activated K^{+} channel (BK_{Ca}) activity due to a disruption of the BK_{Ca} gene (*KCNMA1*) in one subject with ASD (Laumonnier et al., 2006). The reported decrease in BK_{Ca} channel activity, together with the reduced inactivation of voltage-gated Ca^{2+} channels in autistic patients, suggests that some forms of ASD are related to abnormally sustained increases of intracellular Ca^{2+} levels (Krey & Dolmetsch, 2007).

Environmental and epigenetic factors

Genetic factors are undoubtedly important in the pathogenesis of ASD, as reviewed above and as indicated by much higher concordance rates among monozygotic twins when compared to dizygotic ones (Folstein & Rosen-Sheidley, 2001). However, it cannot be ignored that prevalence of autism has spectacularly soared from 4 in 10,000 children in the 1960s to the current rate of 30-60 in 10,000 (Rutter, 2005). Although this increased prevalence in the last 40 years may be partly explained by changes in autism diagnostic criteria and growing awareness of the disorder (e.g. Waterhouse, 2008), there is also strong evidence to suggest that several environmental factors contribute, either *per se* or *via* epigenetic mechanisms, to the pathogenesis of ASD.

Pre- and perinatal infections by viral agents like rubella (Chess et al., 1978) and cytomegalovirus (Yamashita et al., 2003) have been found to increase the risk for ASD. These environmental factors are suspected to disrupt the normal encephalogenesis by perturbing neurodevelopmental pathways and/or interacting with the neuroimmune system. In addition, prenatal exposures to thalidomide (Strömland et al., 1994; Strömland et al., 2002) or valproic acid (Christianson, 1994; Rasalam et al., 2005) have also been found to be linked to ASD.

It has also been suggested that thimerosal, an ethylmercury derivative added in vaccines, could be partly responsible for the rising rates of ASD (Bernard et al., 2002; Desoto & Hitlan, 2007). Although highly controversial (see e.g. the absence of correlation between autism and

exposure to thimerosal in Heron & Golding, 2004; see also Parker et al., 2004 for a review), this proposal raises the question of the detrimental role of threatening chemicals, found in increasing number in water and food, on brain development.

Recently, advanced maternal age has been identified as a risk factor for ASD, probably because of an increased risk for obstetric complications, such as low birth weight and shorter duration of gestation, and intrapartum hypoxia (Kolevzon et al., 2007, for a review). It is also recognized that advanced paternal age is associated to ASD (Reichenberg et al., 2006), a finding that might be related to *de novo* copy number variation in this population (Sebat et al., 2007).

To date, a limited number of studies have investigated the role of epigenetic misregulation in ASD. We can however cite a few: i) Rett syndrome, a pervasive developmental disorder characterized by autism, loss of language, hand wringing and seizures is due to mutation of MeCP2 (Amir et al., 1999); ii) children exposed *in utero* to sodium valproate (a medicine used for decades in the treatment of epilepsy and migraine) present an increased risk for ASD. It is now well established that valproic acid acts as a potent inhibitor of histone deacetylase activities (Göttlicher, 2004); iii) Prader-Willi and Angelman syndromes which are often associated to ASD may be due to abnormal methylation of the imprinted region of the UBE3A gene on chromosome 15q (Jiang et al., 2004); iv) finally, Hogart et al. (2007) showed that, in addition to alterations in absolute levels of gene expression, the relative expression of parental $GABA_A$ alleles is altered in ASD, demonstrating a potential role for imprinting.

Research on epigenetic modifications in ASD is in its infancy and represents a promising avenue for a deeper insight on the nature and consequences of gene-environment interactions in ASD and other related disorders.

To summarize, environmental factors, *per se* or *via* epigenetic mechanisms, possibly in association with genetic abnormalities, are suspected to disrupt the normal encephalogenesis. They perturb neurodevelopmental pathways and/or interact with the neuroimmune system. As a consequence, brain development is impaired, resulting in structural and functional anomalies.

Overall, the genetic, environmental and epigenetic factors reviewed above, either alone or by complex interactions, are thought to induce a large amount of abnormalities in CNS development and functioning such as those seen in ASD and other related neurodevelopmental disorders, and referred to as MBD. It should however been precised that studies linking directly the former with the latter are quasi-absent, due to the lack of longitudinal and multidisciplinary studies including and integrating clinical and multi-level experimental considerations.

V- Synthesis and conclusion

The TSPD hypothesis aims at understanding and unifying numerous clinical and neuropsychological findings in ASD individuals. As shown, TSPDs of multi-sensory stimuli are defined as abnormalities in perceiving and integrating rapid and transient sensory events such as rapid physical movements, rapid facial movements, rapid speech flow and rapid proprioceptive inputs. TSPDs would consequently account for multiple cascades of disabilities in i) sensory-motor coupling, motor anticipation, inhibitory control and executive function, ii) higher order cognitive processes such as language abilities, iii) temporo-spatially grouping and associating multi-sensory and emotional stimuli in context and into coherent and meaningful patterns. TSPDs would also impact on the speed of perceptual, motor and cognitive processing, resulting in slowed and delayed motor and cognitive acts. Failing to process rapid sensory events online could consequently explain the difficulties and peculiarities of individuals with ASD in perceiving, imitating, understanding and producing emotional and verbal events on time, and therefore in interacting here and now with human

and social environment. TSPDs may also be responsible for over-focused attention on static and local information, and thus for weak central coherence, and for deficits in empathizing, at the advantage of systemizing. Logically, slowing down visual and auditory events in the environment of children and adolescents with ASD (especially the most affected ones and those having the lowest developmental levels) has been demonstrated to enhance their performance in recognition and imitation of facial expressions and body gestures, and in verbal comprehension.

We hope that our TSPD and MBD approaches to the behavioral, motor and cognitive abnormalities seen in ASD people (see Figure 4 for a synthesis) may open new avenues for the comprehension of neurobio-, neurophysio- and neuropsycho-pathology of ASD as well as for the treatment of autistic people.

Acknowledgements

This work was financially supported by Fondation de France, Fondation Orange, CNRS and INSERM. We are grateful to the two reviewers who helped us to improve the manuscript. We are also grateful to Carole Tardif and Nouchine Hadjikhani for their helpful comments on the manuscript, and to Simon Baron-Cohen for his encouragements. We also warmly thank Sacha Gepner for his artistic contribution on the figures.

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Figure 1. Behavioral, motor and cognitive consequences of Temporo-Spatial Processing Disorders (TSPD) of multi-sensory flows.
Findings by our group revealed the existence of TSPDs of multi-sensory flows in subjects with ASD, including various degrees of disability in perceiving and integrating visual, auditory and proprioceptive stimuli online and in producing real-time sensory-motor coupling, postural adjustments and adequate verbal and nonverbal outputs. TSPDs are considered as central early neuropsychological disorders, resulting in numerous maldevelopmental cascades, i.e. the various behavioral, motor and cognitive manifestations seen in ASD subjects. In the first or second year of life, ASD children display basic sensory and sensory-motor anomalies and, later in life, their disturbances become more complex and intricate, affecting higher order cognitive functions. Each maldevelopmental cascade is represented with a specific colour (red for visual-motion processing deficit, yellow for speech flow processing deficit, blue for proprioceptive flow processing deficit). Disorders generated by two distinct sensory cascades are represented in a composite colour (e.g. violet for disorders generated by visual and proprioceptive processing deficits). Disorders generated by three distinct sensory pathways are represented in white.

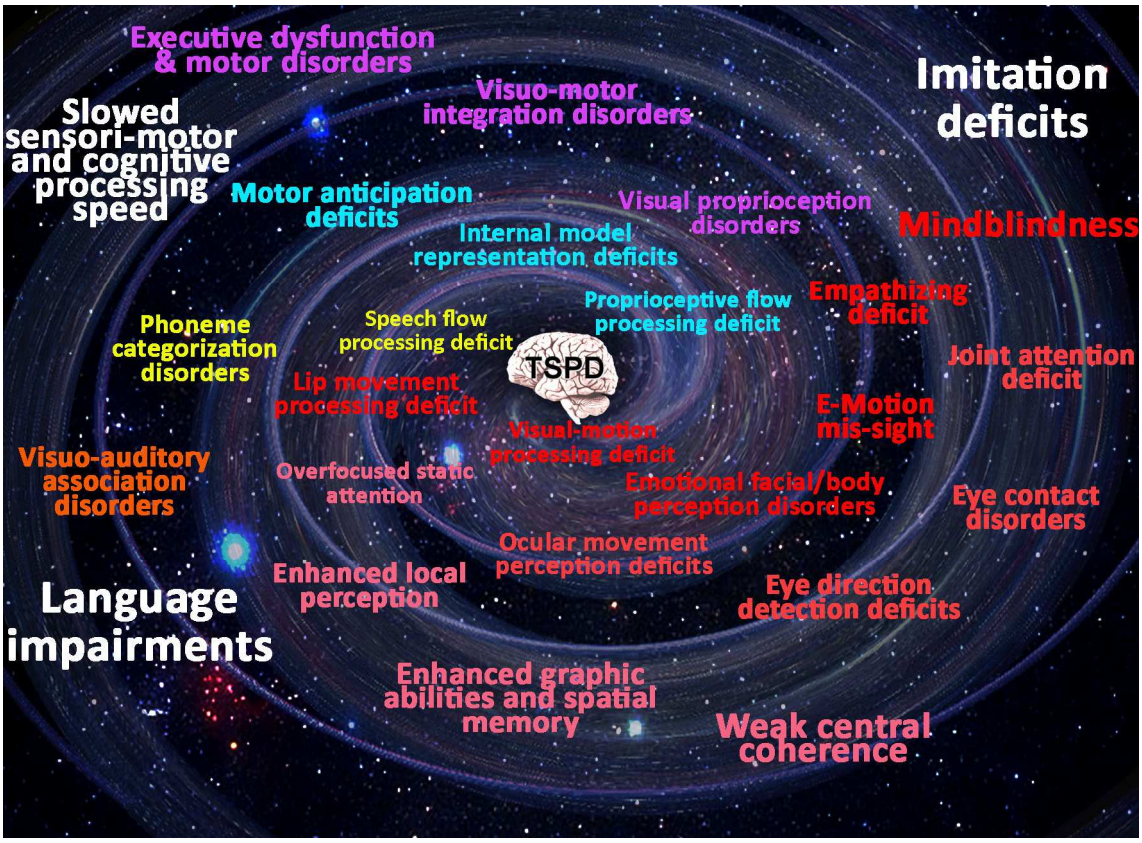

Figure 2. The main functional and structural brain abnormalities in ASD.
The Multisystem Brain Disconnectivity-Dissynchrony (MBD) hypothesis includes numerous functional brain anomalies (i.e. functional under- or over-connectivity, neuronal hypo- or hyper-synchrony, within/between multiple brain areas and pathways). Structural brain abnormalities underlie MBD.

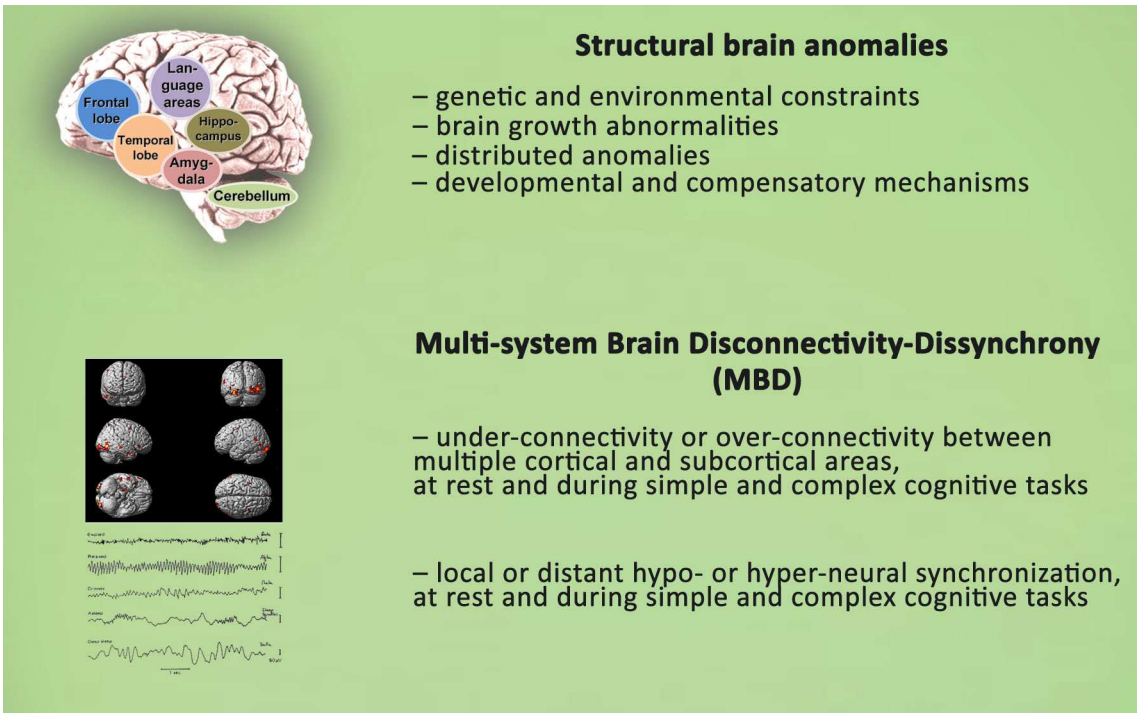

Figure 3. Selection of misexpressed genes in ASD brains.
A subset of genetic abnormalities (reelin, neurotrophin family…) impacts on neuronal migration and corticogenesis. Another subset of genetic anomalies affects synaptogenesis (neuroligins, neurexins, Shank3) and neurotransmission (serotonin transporter, GABA and glutamate receptors, voltage-gated ion channels). As a consequence, neural networks and inter-neuron communication are disrupted.

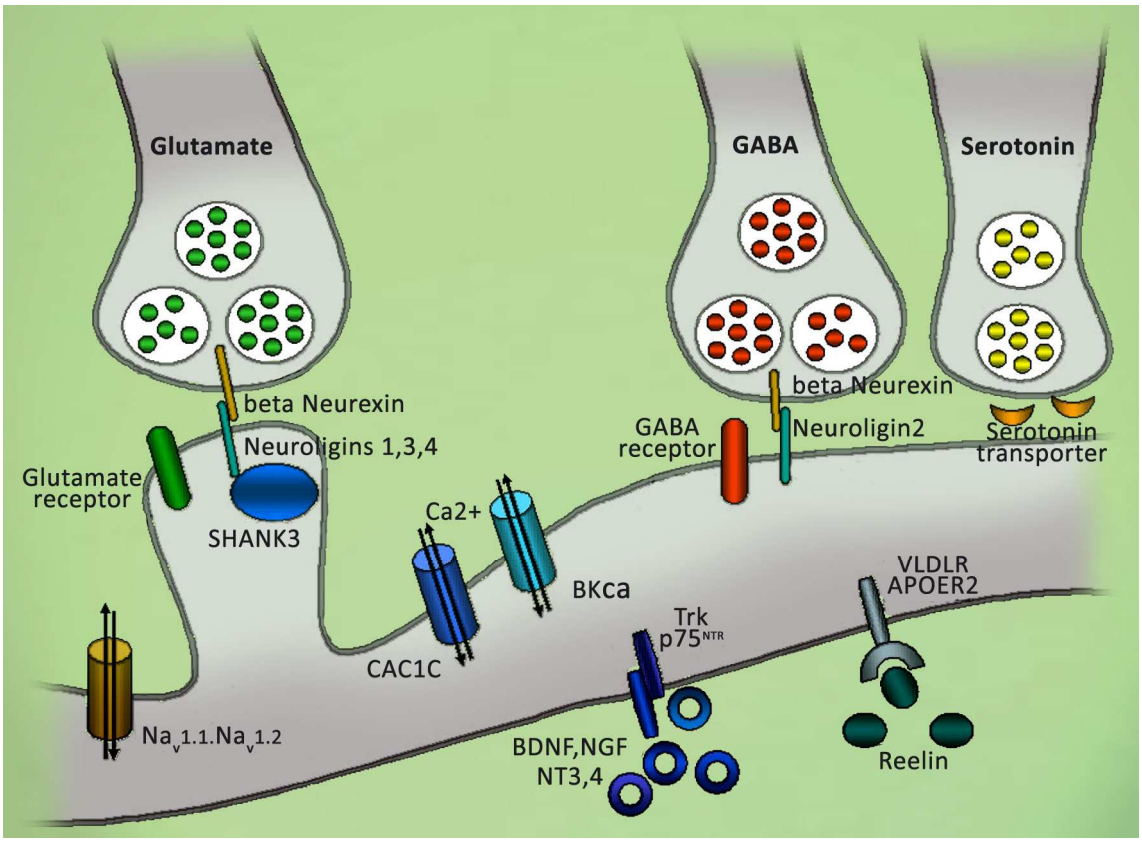
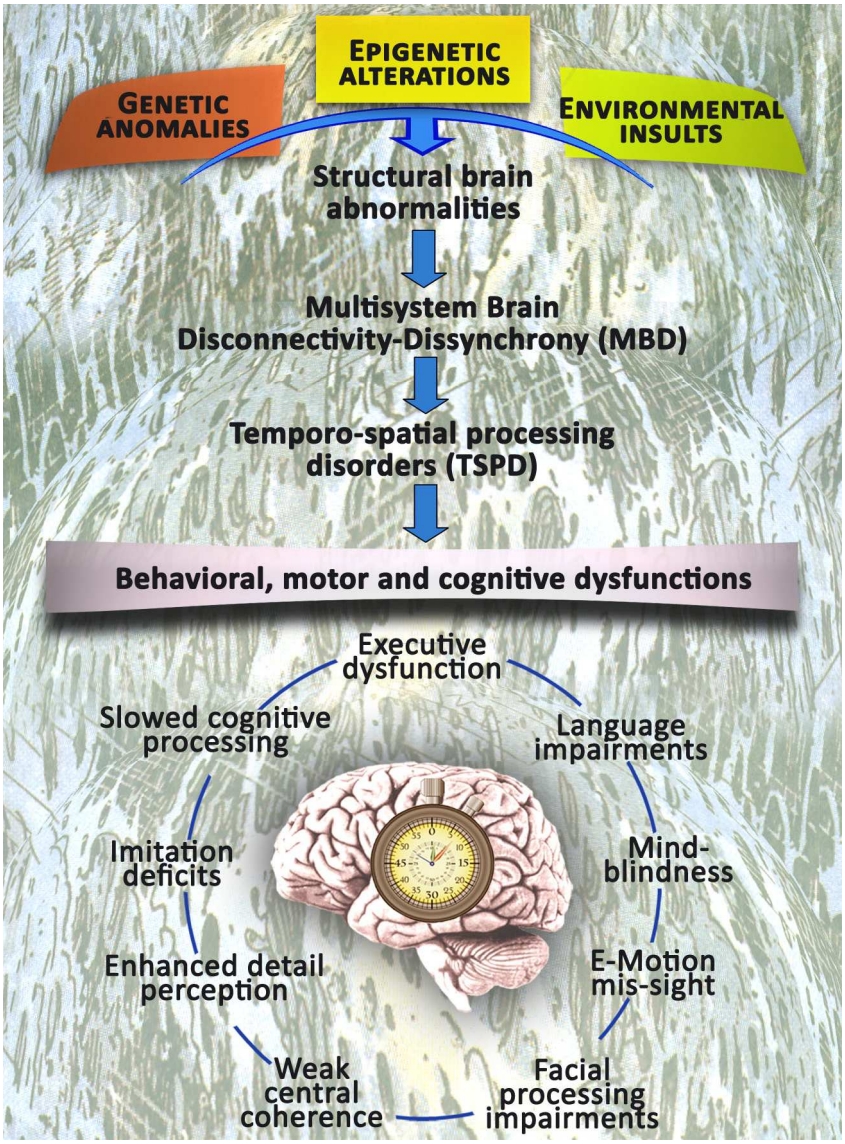
Figure 4. Schematic overview of our TSPD and MBD approaches to ASD.
Genetic, environmental and epigenetic anomalies induce structural brain abnormalities that are responsible for Multisystem Brain Disconnectivity-Dissynchrony (MBD). As a result, the autistic brain is affected by various temporo-spatial processing disorders (TSPD) of multi-sensory stimuli that in turn generate numerous behavioral, motor and cognitive dysfunctions.