HAL

archives-ouvertes.fr

From neuronal to human communication disorders: A novel approach to autism

Bruno Gepner

▶ **To cite this version:**

Bruno Gepner. From neuronal to human communication disorders: A novel approach to autism. Interactions, Association for Computing Machinery, 2008, 1 (1), pp.1-25. <hal-00484203>

HAL Id: hal-00484203

https://hal.archives-ouvertes.fr/hal-00484203

Submitted on 19 May 2010

**From neuronal to human communication disorders
A novel approach to autism**

Bruno Gepner (MD, PhD)

Child Psychiatry Department, Montperrin Hospital
& 'Speech and Language Laboratory', Mixt Unity of Research CNRS 6057,
University of Provence, Aix-en-Provence, France

Address :
Dr Bruno Gepner
Child Psychiatry Department,
Montperrin Hospital
109, Avenue du Petit Barthélémy
13617 Aix-en-Provence, France
E-mail: bruno.gepner@up.univ-aix.fr

Abstract
In this paper we draw the first lines of a novel gene-to-behaviour approach to Autism Spectrum Disorders (ASD). This approach is presented from behaviours and upstream to genes. We first present again our threefold -clinical, experimental and theoretical-approach to autism, the so-called *E-Motion mis-sight and other temporospatial processing disorders*. According to our view, subjects with ASD present from the beginning of their life different degrees of disability in processing sensory events online and in producing real-time sensory-motor adjustments and motor outputs. The environmental world is changing too fast to be processed on time by the autistic brain, leading to the primary communicative, cognitive and imitative disorders of persons with ASD, and to their secondary adaptive and compensatory strategies. Confirming this view, we present several results demonstrating that slowing down visual and auditory flows around individuals with ASD enhances their performance in imitation, verbal comprehension and facial expression recognition. Then we show that these temporospatial processing disorders are based on *multisystem dissynchrony* and *disconnectivity (MDD),* i.e., disorders in neuronal synchronization (hypo- and/or hypersynchronization) and functional connectivity (over- and/or under-connectivity) between multiple neurofunctional territories and pathways. We show that *MDD* is based

itself on structural and functional abnormalities of the brain, and we finally relate these neuronal and synaptic abnormalities to their genetic counterparts.

Keywords: Autism spectrum disorders; motion; emotion; perception; speed; temporal processing; slowing down; rehabilitation; imitation; synchronization; connectivity; neuron; synapse; genes.

I-INTRODUCTION

Autism and other related autism spectrum disorders (ASD) are known as behavioural syndromes including verbal, nonverbal and social impairments, and restricted or stereotyped interests and activities, with early onset (before 30 months) (WHO, 1992; APA, 2000), and long-lasting handicapping social and cognitive consequences. It is also widely accepted that these disorders altogether have a prevalence of about 0.6 % (Fombonne, 2002), and therefore 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 CNS development, numerous questions concerning etiopathology and physiopathology of these affections are still unsolved, and their treatment remain consequently disappointing because unspecific (e.g., Volkmar & Pauls, 2003; Tardif & Gepner, 2003).

ASD remain enigmatic for numerous reasons, some of which are briefly summarized here: there is not *One Autism*, but a constellation of complex and fairly heterogeneous *autistic spectrum disorders* (Rapin, 2002), along a *continuum* of autistic disorders (Grandin, 1995). There is not *One Cause* of autistic disorders, but a multiplicity of genetic, epigenetic and environmental (ante-, per- and post-natal) risk factors affecting one or several stages of neurodevelopment (e.g., Gepner & Soulayrol, 1994; Persico & Bourgeron, 2006). There is not *One Mechanism* of ASD, but numerous physiopathological mechanisms involving different stages of CNS organization and integration (neurobiological, neurophysiologic and neuropsychological) and affecting numerous interconnected neurofunctional systems, territories and pathways (e.g., Gepner, 2001; Waterhouse et al., 1996). There is not *One isolated autistic disorder* among normal conditions, but there are various neurodevelopmental disorders associated with autism (mental retardation, epilepsy), as well as various clinical and neuropsychological overlaps between autism and other neurodevelopmental disorders, such as attention deficit with/without hyperactivity, language learning impairments – dysphasia, dyslexia - and obsessive compulsive disorders (e.g., Volkmar & Pauls, 2003 ; Tardif & Gepner, 2003). Finally, there is not *One psychological profile* typical of autism, there are various psychological reactions (depression, anxiety, distress…) which influence the personality and behaviour of individuals with ASD in one or another direction (Gepner & Tardif, 2006; Gepner, 2006).

New advances in the comprehension and treatment of these complex diseases are likely to emerge from a deeper investigation of each level of CNS organization (i.e., genetics and epigenetics, neurobiology, neurophysiology, neuropsychology), but also undoubtedly from interactions between these several levels.

In the present paper, we confront and combine data from various fields, i.e., genetics, neuropathology, neurophysiology, neuroimagery and cognitive neuroscience, in order to propose a developmental scenario linking genes to behaviour in ASD. The aim of this article is describe some maldevelopmental cascades connecting gene disorders to their clinical consequences in ASD. However, we will describe these maldevelopmental cascades from observable behaviours, and upstream to their genetic counterparts.

II-BIRTH OF A NEW CONCEPT: *E-MOTION MIS-SIGHT* IN AUTISM

Several arguments coming from (1) clinical observations, (2) developmental psychopathology, (3) self-reports from adults with high-functioning autism, (4) adult neuropsychology, and (5) experimental cognitive neuropsychology, lead us to suppose that at least some individuals with autism may suffer visual-motion processing disorders affecting attention to visual-motion, motion perception and/or visuo-motor integration of motion. This visual-motion integration disorder was named *E-Motion mis-sight* (Gepner, Lainé & Tardif, 2005; Gepner & Tardif, 2006).

 (1) Clinical observations
When we meet a person with autism for the first time, we are generally fascinated and/or disturbed by the frequent contrast between the physical presence and psychical absence of this person. When we observe this person carefully, we rapidly discover that the 'autistic world' in which this person lives and moves in is obviously different from our world.
What ever our grid of interpretation is, we promptly think that this person with autism processes and interprets the world differently than we do. People exhibiting so peculiar manners and behaviours cannot be like us.
Similarly, with some adults having an Asperger syndrome, or with some parents of individuals with autism, we feel subtle differences between them and us in the field of facial speech, 'eye speech', empathy, emotional expression or social contact.
But how do we differ? Who are the autistic persons, how do they function? Since Kanner (1943), this question is still passionately discussed. As a matter of fact, in the first description of eleven children with autistic disorders, Kanner observed in almost all of them several behavioural peculiarities that are directly or indirectly related to movement processing (perception and integration of movement, or action), consisting in processing impairments of their surrounding dynamic or static physical and human world, e.g., gaze and face avoidance ; attraction or aversion for moving, spinning and rolling objects ; attraction for details of objects, static forms, puzzles; motor clumsiness, awkwardness; sensory-motor disorders (e.g., oculomanual, oculomotor or imitative disorders) ; manual, gestural and postural stereotypes...
All of these symptoms plead for a possible dissociation between movement and static vision in children with autism, with a deficit in movement vision and an excess of static vision (Gepner, 2001, for a review), as well as for a sensory-motor decoupling (Gepner & Mestre, 2002a). It should be noted that forty years ago, Ornitz & Ritvo (1968) have already examined precisely the autistic perceptual inconstancy and suggested the existence of a deficit in sensory-motor integration, i.e., reciprocal modulation between sensory inputs and motor outputs.

(2) Developmental psychopathology
Given that physical and biological movement is ubiquitous from birth, and that it is crucial for the development of motor imagery, posture, gait and motor activity, as well as

for that of imitation, and verbal and emotional interactions (Gepner, 1997, 2001 for review), it is not difficult to imagine the various possible drastic developmental consequences of early motion processing disorders in a baby.

Since two decades, several studies using family home movies identified numerous early signs of autism in babies aged 0 to 24 months, in various aspects of development, i.e. perception (visual, auditory, proprioceptive) and sensory-motor behaviours, verbal and non verbal communication, and socialization (Sauvage, 1988). Below, we describe early signs of autism that can be related to a possible deficit in visual-motion perception and/or visuo-motor integration. These early signs are sometimes very subtle, and are not observed in babies who exhibit signs of an autistic syndrome after a period of normal or quasi-normal development (e.g., a desintegrative disorder).

In the first weeks of life, autistic babies may exhibit anomalies of gaze contact and ocular pursuit of moving objects or persons. Around 3 months of life, autistic babies may present a deficit in attention to familiar persons, and poor facial expressions. Around 6 months, visual contact disorders such as « empty gaze », squint, impression of blindness may remain. At the same time, babies may exhibit atypical interests for their hands, details of objects, static forms, and a lack of interest for moving games and objects. Between 6 and 12 months of life, autistic babies may be impaired in imitating facial expressions, and present a lack of interest for people; they generally withdraw from social interaction; simultaneously, they exhibit new self-stimulating sensory and sensory-motor behaviours, like fingers and hand flapping in front of their eyes. In the second year, autistic children may present a lack of visual attention (with a peripheric gaze) and joint attention, and peculiar interests for light sources, reflected lights, shadows, wind in trees…(Sauvage, 1988).

In the domain of motor development, autistic babies may present disturbances in some or all of the milestones of development, including lying, righting, sitting, crawling and walking (Teitelbaum et al., 1998). Besides, they frequently exhibit postural adjustments disorders, a lack or a delay in anticipating attitudes, as well as in oculo-manual coordination, a lack of exploration of their environment , and stereotyped behaviours like swinging, rocking, swaying (Sauvage, 1988 ; Leary and Hill, 1996 for a review).

To summarize, the first signs of autism concern especially (but not only) visual development, and consist in dissociation between movement vision (that is poor, deficient, aversive) and static vision (that is normal or rather overdeveloped, with a visual attraction for details), as also found later in children and adults with high-functioning autism and Asperger syndrome (see Frith, 1989 ; Happé, 1999 ; Mottron, 2004). Secondly, whereas autistic babies present a developmental delay in several domains (that we could name the 'negative signs of autism'), they also exhibit atypical self-stimulating visual and visuo-motor behaviours, i.e., a deviant developmental trajectory (that we could name the 'productive signs of autism'), some of which probably have an adaptive and/or compensatory value. Third, it is possible to consider the progression of autistic symptoms during childhood as successive *maldevelopmental cascades*, in which impairment of visual behaviours secondarily impair visuo-motor development, as well as communicative and social interactions between an autistic child and his human and physical environment (Gepner, 2001 ; 2004 ; 2005 ; see also Figure 1 below). Finally, it

is worth noting that all the autistic symptoms related to audition, which also widely contribute to language developmental disorders in autism, are lacking in this description of early signs of autism. We consider these elements below (see § IV and Figure 2).

(3) Self-reports from adults with autism
Some adults with high-functioning autism (HFA) gave us important testimonies about their sensory world, some of which are directly related to their difficulties with movement processing and speed of changes, and compensatory strategies of their sensory limitations.

For example, Donna Williams, a well-known adult with HFA wrote: *"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'. Perhaps I'd been caught up in the spots and the stars at a time when other children kept developing and so I had been left behind. The stress of trying to catch up and keep up often became 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"* (Williams, 1992, p. 39-40).

The main point for our purpose is the difficulty Donna felt in handling the constant change of most things and her behavioural strategies to slow down these things in order to prepare herself for them and catch them.

Temple Grandin, another famous adult with Asperger syndrome wrote: *"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. 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 (…) Distorted visual images may possibly explain why some children with autism favor peripheral vision. They may receive more reliable information when they look out of the corners of their eyes. One autistic person reported that he saw better from the side and that he didn't see things if he looked straight at them"* (Grandin, 1995, p. 73-75). As a spokeswoman for people with autism, Temple Grandin emphasizes peculiar visual behaviours of individuals with autism as a continuum between aversion and attraction for movement, according to the degree of sensory processing defect.

(4) Adult neuropsychology
Zihl, von Cramon and Mai (1983) reported the case of a woman aged 43 who suffered bilateral cerebral lesions affecting the lateral temporo-occipital cortex and the underlying white matter, which selectively affected her movement vision. The authors report that *« The visual disorder complained of by the patient was a loss of movement vision in all three dimensions. She had difficulty, for example, in pouring tea or coffee into a cup because the fluid appeared to be frozen, like a glacier. In addition, she could not stop*

pouring at the right time since she was unable to perceive the movement in the cup when the fluid rose. Furthermore the patient complained of difficulties in following a dialogue because she could not see the movements of the face, and especially the mouth of the speaker. In a room where more than two other people were walking she felt very insecure and unwell, and usually left the room immediately, because 'people were suddenly here or there but I have not seen them moving'. The patient experienced the same problem but to an even more marked extent in crowded streets or places, which she therefore avoided as much as possible. She could not cross the street because of her inability to judge the speed of a car. 'When I'm looking at the car first, it seems far away. But then, when I want to cross the road, suddenly the car is very near'. She gradually learned to 'estimate' the distance of moving vehicles by the means of the sound becoming louder ».

This case study lets us measure the extremely important impact of a selective disturbance of movement vision affecting a young – previously normal - woman on her perceptual, sensory-motor, communicative and social behaviours. Because of her sensory impairments, she started to avoid physical and social events, to live isolated. It is already possible, on the basis of this study case, to imagine the various developmental consequences of a visual-motion processing disorder affecting a baby from the very beginning of its life.

(5) Experimental cognitive neuropsychology

Since human face is the primary and most powerful source of information mediating emotional and verbal communication as well as social interaction, it is not surprising that face processing has often and regularly been studied in the autistic population for the past twenty-five years (Dawson et al., 2005, for a review). Indeed, a growing body of data demonstrated that individuals with ASD generally process various aspects of faces in a different way than typically developing and/or mentally retarded control subjects. Peculiarities have been shown in the processing of facial identity (Langdell, 1978; Davies et al., 1994; Deruelle et al.; 2004) and emotional facial expression (Hobson et al., 1988), in lip-reading (de Gelder et al., 1991) and eye direction detection or interpretation (Gepner et al., 1996; Baron-Cohen et al., 1995). Studies using fMRI confirmed facial processing peculiarities in subjects with ASD (Critchley et al., 2000; Schultz et al., 2000; Hadjikhani et al., 2004; Pierce et al., 2004).

Following this line of neuropsychological exploration, an important question was to know whether each aspect of face processing is impaired separately, or based on more general and basic impairments affecting the processing of environmental physical and/or social world. In order to answer to this question, a study assessing various aspects of face processing (identity, emotional expressions, eye direction detection and lip-reading) was conducted by our group in young children and adolescents with autism. This study revealed that autistic subjects were particularly impaired in whole face processing, visuo-auditory association (as already shown with simple visuo-auditory stimuli by Martineau et al., 1992) and in processing the facial dynamics, i.e., lips' movements, eyes' movements and emotional facial expressions (Gepner et al., 1996). These results suggested that difficulties of children with autism in processing faces were neither related to impairments in recognizing facial identity *per se*, nor to impairments in recognizing

emotional aspects of faces *per se*, but rather to anomalies in processing facial movements.

To conclude, all the arguments reviewed in this paragraph pushed us to investigate directly how subjects with ASD process visual movements, physical movements as well as biological (and particularly emotional) ones.

III. PREVIOUS AND RECENT WORKS ON PHYSICAL AND BIOLOGICAL MOTION PROCESSING

In this paragraph, we review available data related to physical and biological movements processing disorders in subjects with ASD, and we propose a first synthetic neuropsychological view of autism called *E-Motion mis-sight*.

(1) Physical movements processing

As Milne et al. (2005) said, our group was the first to assess directly visual-motion processing in children with ASD. In this first study, Gepner, Mestre, Masson & de Schonen (1995) explored postural reactivity to visually perceived environmental movements in children with autism and normal control children.

Vision is known to be an important source of information used in postural control. One of the most relevant hypotheses in this context is the 'ex-proprioceptive' role of optic flow (Lee & Aronson, 1974). Since the body's displacements generate a global motion of the visual scene (i.e., an optic flow) across the retina, and this optical flow specifies the kinematic properties of the ongoing movements, Gibson (1979) established that these optical flow fields due to ego-motion serve to regulate and control a subject's self-orientation. It has been clearly demonstrated thirty years ago that humans make postural readjustments in response to an optical flow (Lee & Aronson, 1974). A number of studies have shown that young infants react posturally to movements in their visual environment as soon as they are able to stand unaided (Butterworth & Hicks, 1977), and even earlier (Jouen, 1988), confirming that visual proprioception plays a major role in the control of stance.

Since children with autism have sometimes very poor verbal and/or motor performance, it was necessary to explore their visual-motion processing with a reflex-like paradigm, requiring neither voluntary verbal nor motor answers: it is why we used postural reactivity to motion vision. Results of our first study revealed that, contrary to normal control children, children with autism have a very poor postural reactivity to this kind of environmental movements (Gepner et al., 1995). This weak visuo-postural coupling in autistic children may account for their motor disturbances (poor motor control, poor motor imitation, motor clumsiness…), and is a good example of perception-action coupling disorder in this population.

In a replication and extension study, we showed that postural reactivity of children with autism was particularly poor when *speed of movement* was high (slow movements inducing a small postural reactivity), whereas children with Asperger syndrome (the mildest autistic spectrum disorder) were reacting normally, and even maybe overreacting, to the same kind of stimuli. In other terms, visuo-postural coupling is deficient in children

with autism, and conversely, children with Asperger rather exhibit a visuo-postural over-coupling. Thus, visuo-postural coupling (and more generally, sensory-motor coupling) may be a good neuropsychological marker of autism, and possibly a good predictor of the severity of ASD (Gepner & Mestre, 2002a). Besides, the question of *speed of movement* was raised with this latter study.

Indeed, speed of movement seems to be critical for children with ASD. Gepner (1997) showed that children with autism are impaired in the perception of moving small squares in central vision, and that their performance is all the less so as speed of moving points is high and direction is complex (i.e., less foreseeable).

As far as direction of movement is concerned, Bertone et al. (2003) also showed that high-functioning subjects with autism exhibit a deficit in the perception of second order radial, translational and rotational direction of movement.

Other works by Spencer et al. (2000) and Milne et al. (2002) showed that, when presented with a random dot kinematogram animated by lateral displacements, children with autism need higher motion coherence to detect movement than normal control children, i.e., they overall show less optokinetic nystagmus (OKN) then their controls. Mestre et al. (2002), using the same motion coherence paradigm but with a video-oculographic measure of OKN, showed that children with autism present particularly higher motion coherence thresholds than normal control children when speed of motion is high, thus confirming a rapid visual-motion integration deficit in autism. A reasonable interpretation of these results is a lack of spatio-temporal integration of singular points in a global coherent motion (a form of central coherence deficiency). These results are interpreted by all these authors as an argument of a dorsal stream deficiency, an interpretation being also confirmed by Pellicano et al. (2005).

Interesting finding on pursuit eye movements deficits in HFA children (Takarae et al., 2004) is also to be reported, which suggests a disturbance in the extrastriate areas that extract motion information, or in the transfer of visual motion information to the sensory-motor areas that transform visual information into appropriate oculomotor commands.

(2) Biological motion processing

Our group was also the first to introduce a new paradigm, i.e., *facial motion*, in order to further investigate and reinterpret the vast literature on facial processing in autism. Indeed, we showed that children with autism, comparatively to normally developing children, have relatively good performance in emotional and non emotional facial recognition tasks when facial expressions are displayed slowly on video (Gepner, Deruelle and Grynfeltt, 2001). We thus argued that children with ASD are impaired in rapid facial movements processing, and that this impairment could secondarily explain gaze avoidance and poor performance in emotional and non-emotional facial processing in these children (Gepner, 2004).

In a replication and extension study, Tardif et al. (2007) demonstrated that children with autism recognize significantly more emotional and non-emotional facial expressions and exhibit more facial-vocal imitation when facial expressions and their corresponding vocal sounds are slowed down naturally or artificially than when they are displayed at normal speed or statically. Based on these results, our group created an original software aimed

at slowing down *simultaneously* visual and auditory signals of the environment in order to facilitate cognitive and imitative abilities in autistic children. Our first study using this software shows that *slowing down* the presentation of facial and body gestures enhances voluntary imitation in children with ASD (Lainé et al., in press). Similarly, the same children with ASD understand better simple and complex sentences when the visual and auditory presentations of these sentences are *slowed down* (Lainé et al., 2008). Therefore, slowing down the speed of facial and vocal events enhances imitative, verbal and cognitive abilities of some children with autism, generally those having the lower verbal level and the more severe autistic syndrome. Given that deviant and/or delayed imitation has been very well documented in individuals with autism for more than thirty years (see Smith & Bryson, 1994 and Williams et al., 2004, for reviews), even from the very beginning of their life (Zwaigenbaum et al., 2005), and particularly in the domain of facial expressions' imitation (e.g., Hertzig et al., 1989; Loveland et al., 1994; Rogers et al., 2003), these studies suggest the existence of a key-link between visual-motion processing disorders and deficits of imitation in autism, and are of particular interest in the perspective of rehabilitating imitation deficits in this population (Gepner, 2001, 2005; Gepner et al., 2005).

Blake et al. (2003) also showed that children with autism are impaired in the recognition of human movements (e.g., walking, running or jumping) displayed through animated lighting points, and that their performance was correlated to the severity of their autistic syndrome. Finally, at the intersection of physical and biological motion processing, Castelli et al. (2002) showed in a TEP study that adults with high-functioning autism or Asperger syndrome have a hypoactivation of median prefrontal cortex and superior temporal sulcus (STS) when they have to attribute mental states to animated shapes, and a diminution of connectivity between extrastriatal cortex and STS.

(3)   First synthesis

All these studies confirm that subjects with ASD have visual-motion perception and integration disorders, that we have named previously *motion mis-sight* in autism (Gepner, 2001).

In particular, Gepner & Mestre (2002b) reached the conclusion that children with autism have a rapid visual-motion integration deficit. According to this hypothesis, some autistic individuals having major movement processing disorders early in their life avoid rapid physical and biological movements (considered as aversive stimuli), thus disrupting secondarily social interaction. Some of these individuals, or some autistic persons having minor motion processing disorders, will search for, habituate themselves to, and learn to handle and cope with such kind of stimuli. To summarize, rapid visual-motion processing deficit constitutes a core neuropsychological marker of autism and secondarily accounts for the deficit in social interaction (Gepner & Mestre, 2002b; Gepner, 2004).

In order to integrate the various developmental consequences (*maldevelopmental cascades*) of this disorder, we proposed to name it *E-Motion mis-sight* (see Figure 1).

Figure 1. Cascades of neurodevelopmental consequences of a visual-motion integration deficit in autism (*from Gepner, Lainé & Tardif, 2005*)
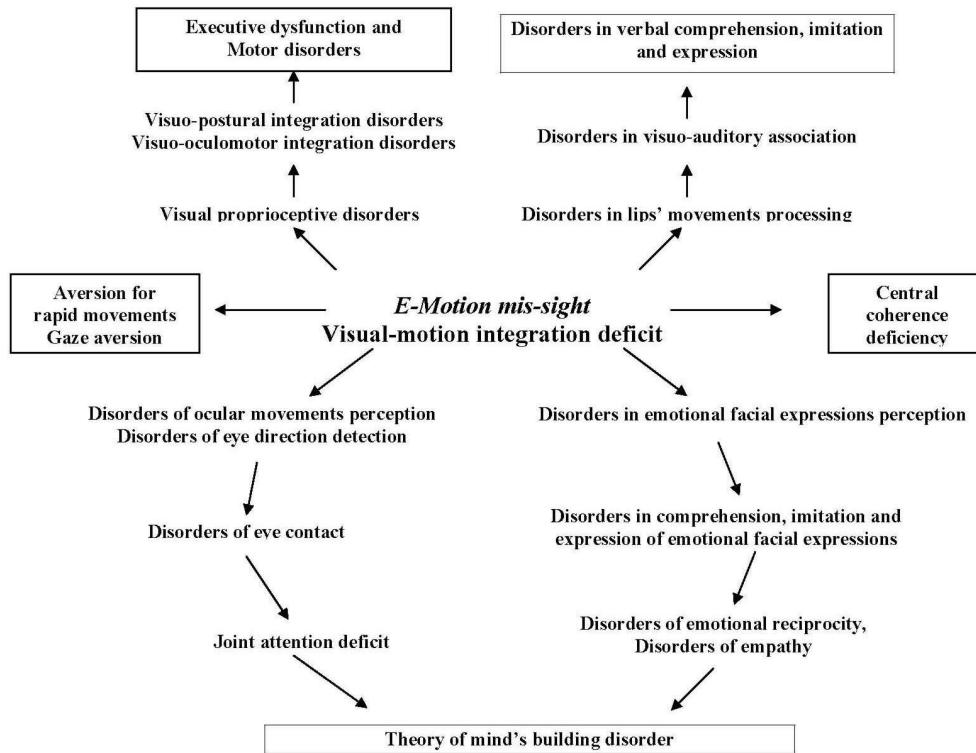
At the neurobiological level, the physiopathology of ASD most probably involves the following pathways: i) the visual magnocellular system which conveys information on movement (optic flow), global form and low spatial frequency from retina to lateral geniculate nucleus and prestriate cortex (Livingstone & Hubel, 1988); ii) the dorsal stream, which receives information from magnocellular system and distributes them from prestriate cortex to temporal, parietal, prefrontal and frontal cortices, as well as to cerebellum and to thalamic mesencephalic and pontic structures (Boisacq-Schepens & Crommelinck, 1994). Among these connections, prestriate-cerebellar pathways are crucial since cerebellum plays a major role in speed and temporal coding of multisensory inputs (Johnson & Ebner, 2000) and has been found hypo- and/or hyperplastic in autism (Courchesne et al., 1994a), which supposes hypo- and/or hyperconnectivity according to a neuromimetic model (Cohen, 1994). In the same line, it was found that a specific damage of the cerebellar vermian lobules VI and VII is responsible for a deficit in the accuracy of ocular saccades (Lewis and Zee, 1993), and thus may negatively impact visual-motion integration. Also important are the connections between prestriate cortex and superior temporal sulcus (STS), since STS is known for its role in biological motion processing (Allison et al., 2000); iii) finally, the cerebello-premotor-motor cortices loops,

which are responsible with basal ganglia for real-time fine-tuning of motor outputs (Ito, 1984; Doya, 2000), and the projections from cerebellum to prefrontal, parietal and temporal cortices which are responsible for motor and cognitive learning (Middleton & Strick, 2000).

This neurophysiological view of ASD takes into account the complexity of CNS connectivity as well as a vast majority of neurological and anatomic disorders found in ASD; this view may also bring interpretation guidelines for future research.

IV. OTHER TEMPOROSPATIAL PROCESSING DISORDERS IN AUTISM

Even though *E-Motion mis-sight* may account for some of the major sensory-motor, behavioural and communicative disorders presented by children with ASD, it is however unable to explain autistic symptoms occurring in other sensory modalities (e.g. auditory or proprioceptive ones). A crucial question coming next was thus to know whether this visual-motion integration deficit reflects, or results from, a more primary and pervasive neuropsychological deficit. A plausible candidate-deficit concerns *temporospatial processing* in various sensory modalities.

(1)   Other arguments for temporospatial processing disorders in autism

In order to explore the effectiveness of a temporospatial processing deficit in autism in other sensory modalities, we tested, within a same group of 22 children and adolescents with ASD, the ability to extract a relevant information among a noisy stimulus *on line*, through three types of tasks : a) oculomotor reactivity to visual-motion of a coherent pattern of lighting points, via the measurement of optokinetic 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. Results of this study were as follows (Gepner & Massion (directed by), 2002).

As already mentioned above (see Mestre et al., 2002), the group of subjects with ASD showed very weak oculomotor reactivity (i.e., a reduced occurrence of slow phase tracking eye movements) to visual-motion of a coherent pattern (especially for high motion velocities), and higher motion coherence thresholds (i.e., the necessity of higher percentage of points going in a direction out of the whole points, for inducing OKN) as compared to normal children of the same mean age, as already shown previously (Spencer et al., 2000 ; Milne 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.

Secondly, the same group of autistic subjects showed a deficit in speech phoneme categorization. Indeed, compared to normal children who categorize an ambiguous phoneme such as MNA (made of an algorithmic superimposition of MA and NA) in a MA or a NA response randomly, autistic children over-categorize MNA in a NA response. This deviant over-categorization specifically appears in autistic subjects when speech phonemes are displayed at normal speed, whereas their phoneme category perception is normalized when phonemes are slowed down 2 times. This phoneme

categorization deficit may partly be due to a difficulty in processing rapid speech flow, and thus to a temporal integration deficit in the auditory modality (Tardif et al., 2002). A similar temporal processing deficit has been found in children with language-learning impairments (Tallal, 1976); it has been related to a deficit in visual magnocellular system (Talcott et al., 2000) and/or auditory magnocellular system (Stein, 2001), and has also been found to be ameliorated by slowing down the speech flow (Tallal et al., 1996; Habib et al., 1999). As already said, autism and language learning impairments very probably share common physiopathologic mechanisms and neurofunctional pathways (Gepner & Mestre, 2002b). From a neurophysiological point of view, since superior temporal sulcus is involved not only in facial movement processing (Allison et al., 2000), but also in voice processing (Belin et al., 2000), and that it was found hypoactivated in adults with HFA in response to vocal sounds (Gervais et al., 2004), this region is of strong interest in the pathophysiology of ASD.

Finally, it also appeared that a subgroup of the same autistic subjects present a deficit in motor anticipation in a bimanual load-lifting task (Schmitz et al., 2002), a result confirmed by another study (Schmitz et al., 2003). This task requires the rapid processing of proprioceptive inputs, the correct use of an internal representation, and the precise timing adjustment of the muscular events. Compared to control children who use 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 could partly result from an impaired processing of proprioceptive inputs at least during the learning phase of the task, and thus from a temporospatial integration deficit in the proprioceptive modality. In this context also, impairments in the structure and/or function of cerebellum, which is crucial for temporal processing of sensory inputs and motor outputs (Massion, 1993), plays a major role

According to these three series of results, subjects with ASD have deficiencies in the temporal processing of visual, auditory and proprioceptive stimuli *on line* (Gepner and Massion (directed by), 2002). Altogether, these results suggest that subjects with ASD have a deficit in the temporospatial processing of sensory inflow which is necessary to detect and integrate visual motion, code and parse language and program postural adjustments. To summarize, *the world is changing too fast* for at least some autistic persons, particularly those having the more severe autistic syndrome. This view could account for the sensory and social avoidance of autistic subjects (when sensory inflow induces aversion), for the desynchronization and discontinuity in their perception-action coupling and sensory-motor tuning, as well as for their mis-understanding of, and disorders in their action and interaction with, the physical and human world.

In conclusion, our temporospatial processing disorder hypothesis of autism has the strong advantage to account for the vast majority of developmental disorders seen in ASD, and to be compatible with the major contemporary theories of autism, such as the weak central coherence theory, the deficit of theory of mind, and the theories of imitation deficit and executive dysfunction.

(2)   Second synthesis: *E-Motion mis-sight* and other temporospatial processing disorders in autism

We showed that the various deficits affecting visual-motion, vocal sounds and proprioceptive processing in a same group of subjects with autism (Gepner & Massion (directed by), 2002), may be related to a more basic impairment, i.e., a deficit in the temporospatial processing of multi-sensory events. In order to take into account all the neuropsychological previous findings, we called our synthetic approach *E-Motion mis-sight and other temporo-spatial processing disorders* in autism. According to this approach, subjects with autism present different degrees of disability in processing sensory events online and in producing real-time sensory-motor adjustments, motor outputs and adequate verbal and nonverbal outputs (Gepner et al., 2005) (see Figure 2).

Figure 2. Cascades of neurodevelopmental consequences of a temporal processing deficit in autism (*from Gepner, Lainé & Tardif, 2005)*
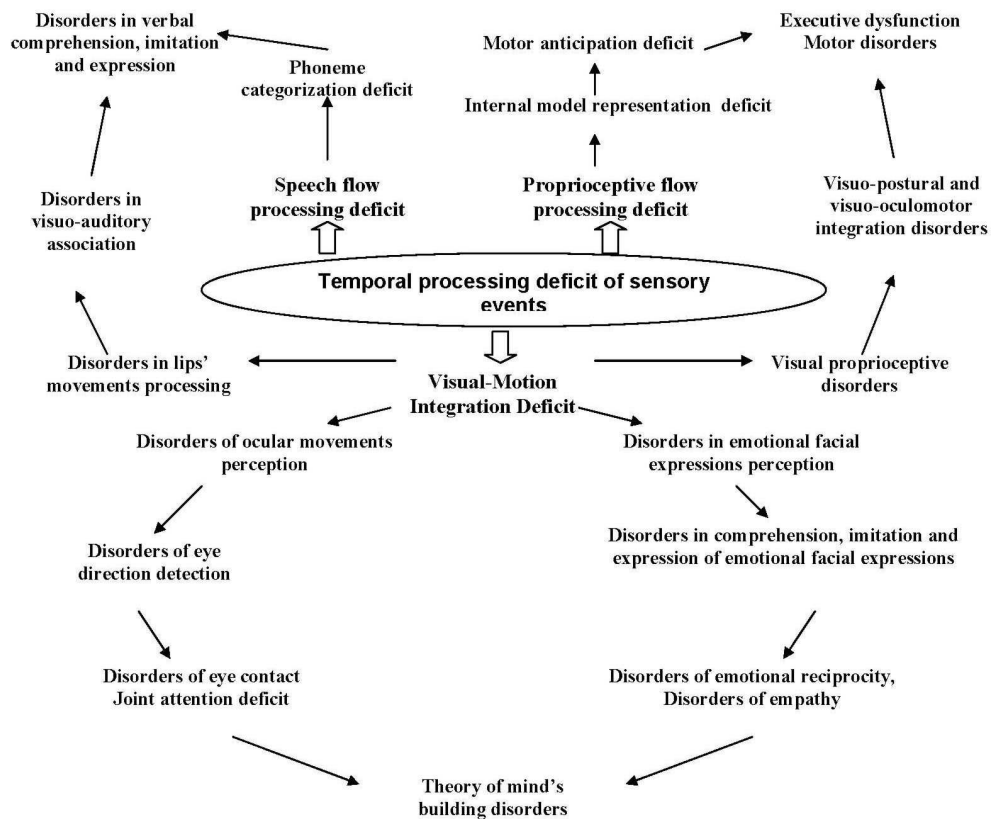
V- FROM TEMPOROSPATIAL PROCESSING IMPAIRMENTS TO FUNCTIONAL AND STRUCTURAL ABNORMALITIES OF THE BRAIN

(1) Functional abnormalities

We already proposed (Gepner & Massion (dir. by), 2002; Tardif et al., 2007) that these temporospatial processing disorders may be related, at the neurofunctional level, to a deficit in temporal encoding of multi-sensory inputs, temporal coupling of sensory-motor events, and temporal production of motor outputs, in which cerebellum is known to play a crucial role (e.g., Johnson & Ebner, 2000). Trying to go further, Welsh et al. (2005) argued that disturbances in inferior olive structure found in autism (e.g., Bailey et al., 1998; Kemper & Bauman, 1993) and consequently in olivo-cerebellar pathways, would disrupt the ability of inferior olive neurons to become electrically synchronized and to generate coherent rhythmic output, thus impairing the ability of individuals with autism to process rapid information, and therefore slowing their overall cognitive processing speed. Fitting very well with this assumption, it was shown that subjects with ASD exhibit slowed perceptual and cognitive processes such as shifting or orientating spatial attention (Courchesne et al., 1994b; Townsend et al., 1999). Similarly it was demonstrated that adults with Asperger syndrome present 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 (Nishitani et al., 2004).

Following Welsh et al. (2005), we propose that rapid sensory information (rapid sensory flows) would arrive too quickly to be processed *online* by the autistic brain, thus disrupting simultaneous firing (synchronization) of neurons of a same assembly, which would consequently disorganize, desynchronize and delay information processing. Abnormal temporal synchronization of local neural networks within each sensory modality would in turn produce anomalies of temporal binding between multiple sensory modalities.

This view is also referred to the *temporal binding deficit hypothesis* of autism proposed by Brock et al. (2002) according which autistic individuals would suffer a deficit in synchronization of high frequency (30-100 Hz) gamma activity between distant neural networks. In a recent study, however, and contrary to their own theoretical prediction, individuals with autism showed an overall *increased* gamma-activity whilst identifying the presence or absence of an illusory Kanizsa shape (Brown et al., 2005).

We therefore propose that, according to the type of stimuli they are exposed to, individuals with autism would suffer neural *dissynchrony*, i.e., either neural hypo- or de-synchronization (e.g., for rapidly moving or changing sensory stimuli) or neural hyper- or over-synchronization (e.g., for local or static sensory stimuli), that would be both responsible for impaired attentional, perceptive and/or cognitive acts in these patients. For example, in some individuals with autism, a local neural desynchronization within visual and auditory pathways respectively would occur during *everyday-life* facial motion and vocal sounds processing, resulting in difficulties to extract a relevant information from these relatively rapid sensory flows, and would generate a distant neural desynchronization between these sensory pathways, resulting in difficulties to associate these rapid visual and auditory cues into a coherent, unified and meaningful pattern. A

variety of cognitive functions, such as perceptual grouping, attention–dependent stimulus selection and sensory-motor integration, which normally involve oscillatory neuronal responses in the β and γ-band (high frequency oscillations), have been shown to be impaired in ASD (see Uhlhaas & Singer, 2006, for a review). However, the same authors claim for further studies to confirm and strengthen this new approach of autism and other brain disorders and mental diseases.

Given that multiple areas and pathways have been found or supposed to function inadequately in subjects with ASD, and especially the visual magnocellular system (Gepner & Mestre, 2002a; Deruelle et al., 2004), the dorsal stream (Spencer et al., 2000; Pellicano et al., 2005; Villalobos et al., 2005), the cerebellum (Courchesne, 1997), the mirror neuron system (Oberman et al., 2005; Dapretto et al., 2006), and the superior temporal sulcus (Castelli et al., 2002; Gervais et al., 2004), we suppose that in the general context of visual and auditory processing a *multi-system temporal dissynchrony* (hypo- and/or hyper-synchronization) within and/or between the key neural networks and pathways mentioned above may be a crucial neuropsychological mechanism of ASD, responsible for various attentional, perceptive, sensory-motor, communicative and cognitive impairments in this pathology.

Besides, given the equivalence between functional connectivity and neural synchronization (which can be considered as temporal connectivity), the spatial counterpart of this *multisystem temporal dissynchrony* is therefore a *multisystem functional disconnectivity* (under- and/or over-connectivity) within/between multiple neurofunctional networks.

Functional under- or over-connectivity in the brain of individuals with autism have already been hypothesized (Brock et al., 2002; Courchesne & Pierce, 2005; Belmonte et al., 2004). Studies using functional magnetic resonance imaging (fMRI) confirmed in the last 8 years that functional connectivity (i.e., reciprocal modulation and co-activation) between cortical areas or between cortical and subcortical areas is frequently impaired in these disorders (Wickelgren, 2005; Minshew & Williams, 2007; Geshwind & Levitt, 2007). For example, functional connectivity between structures has been shown to be increased or reduced in individuals with ASD during rest (increased in Kennedy et al., 2006; reduced in Cherkassky et al., 2006) and during several cognitive tasks such as facial processing (reduced in Hadjikhani et al., 2004 and Pierce et al., 2004; reduced or increased in Wicker et al., 2008), visuo-motor coordination (increased in Mizuno et al., 2006 and Turner et al., 2006), theory of mind functioning (reduced in Castelli et al., 2002), executive function (reduced in Just et al, 2007), working memory (Koshino et al., 2005), sentence comprehension (reduced in Just et al., 2004) and 'thinking in pictures' (reduced in Kana et al., 2006).

(2)   Structural abnormalities

Turning now to the structural abnormalities of the brain, the relatively rare post-mortem studies of autistic brains have uncovered various alterations, such as i) reduced neuronal size and increased cell packing density in the hippocampus, amygdala, and anterior cingulate gyrus (Bauman and Kemper, 1985), but also in the neocortex (Bailey et al., 1998), ii) reduced number of Purkinje cells in the cerebellum (Ritvo et al., 1986), iii)

reduced complexity and extent of dendritic arbors in pyramidal neurons of hippocampus (Raymond et al., 1996). However, many observations reveal that the autistic brain in childhood differ from that of the adult (Bauman and Kemper, 2005). More recently, studies of the amygdala showed an abnormal pattern of growth with an overall decrease number of neurons (Schumann & Amaral, 2006). Finally, minicolumns in brain from patients with autism have been found to be more numerous, smaller and less compact in their cellular configuration in the frontal and temporal regions as compared with those of controls (Casanova et al., 2002).

Anatomic neuroimagery in the last 20 years confirmed that several cortical and subcortical areas can be impaired in persons with ASD, particularly the frontal and temporal cortices, cerebellum (Courchesne et al., 1994a), hippocampus and amygdala (Schumann et al., 2004), but also sometimes striatum and thalamus (Haznedar et al., 2006) and corpus callosum (Paul et al., 2007) (see Santangelo & Tsatsanis, 2005 for a review).

In adults, grey matter is reduced in various areas including associative cortices, hippocampus and amygdala (e.g., Herbert et al., 2003; Petropoulos et al., 2006), but it can also sometimes be increased in frontal and temporal cortices (Hazlett et al., 2006). A study using proton magnetic resonance spectroscopic imaging revealed widespread reductions in grey matter neuronal integrity and a dysfunction of cortical and cerebellar glutamatergic neurons of subjects with ASD (DeVito et al., 2007). Other studies reported an overall enlargement of brain volume associated with increased subcortical white matter in all lobes but particularly the frontal lobe (Herbert et al., 2003, 2004). And abnormalities of the structural integrity of white matter with a decreased cellularity or density were found in children (Friedman et al., 2006) as well as in adults with ASD (Keller et al., 2007). Moreover, MRI studies in young children with ASD found a transient brain overgrowth (between 2 and 4 years and half), including grey and white matter, followed or not by a retarded growth or an arrest of growth (Courchesne et al., 2001; Hazlett et al, 2005; Courchesne et al., 2007 for a review).

All these abnormalities suggest that the pathophysiology of ASD involve many aspects of CNS formation, such as reduced programmed cell death (apoptosis) and/or increased cell proliferation, impaired cell migration with disrupted cortical and subcortical cytoarchitectonics, abnormal cell differentiation with reduced neuronal size, impaired synaptogenesis (Bauman and Kemper, 2005), but also astroglial and microglial activation and neuroinflammation in both white and grey matter (Vargas et al., 2005).

VI- FROM CEREBRAL TO GENETIC ABNORMALITIES

Data from numerous epidemiological twin and family studies provide substantial evidence that ASD are amongst the most heritable complex brain disorders (Bacchelli and Maestrini, 2006). In the last decade, over 100 positional and/or functional candidate genes for autism have been analyzed. Data from whole-genome screens in multiplex families strongly indicate that at least 10 genes, and probably much more, interact to cause autism (Risch et al., 1999). Cytogenetic abnormalities in individuals with autism have been found in virtually every chromosome (Gillberg, 1998). But the identity and

number of genes involved are not yet known: the clear involvement of a specific single gene has indeed not been conclusively identified (Bacchelli and Maestrini, 2006). What is currently accepted is that ASD candidate genes encode products known to play a role in brain development and/or neurotransmission (Muhle et al., 2004), i.e., mutations affecting genes implicated in neuronal and cortical organization, in synapse formation, in synaptic transmission and neuromodulation have been found to be associated with ASD.

(1) Genes implicated in neuronal and cortical organization
The protein Reelin, which is coded by a gene which localizes to a site of chromosomal translocation at 7q22, is potentially involved in neuronal migration (Fatemi, 2005) and cortical layering during development (Forster et al., 2006), and alterations in this protein can affect cortical and cerebellar development (Hong et al., 2000). 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 (Bailey et al. 1998) 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 (Hallbook, 1999) contains interesting candidates in the pathobiology of ASD. In fact their main functions during neurodevelopment involve not only regulation of cell proliferation and neuronal migration, but also modulation of axonal and dendritic growth and synapse formation (Huang & Reichardt, 2001), i.e., stages of neurodevelopment that are strongly suspected to be impaired in ASD (see below). Besides, elevated levels of BDNF have been found in the blood of children with ASD (but also with mental retardation) in several studies (Nelson et al., 2001; Miyazaki et al., 2004), and auto-antibodies against BDNF were also found in serum of children with ASD but also with other related or associated syndromes (Connoly et al., 2006).

(2) Genes implicated in synapse formation
Neuroligins are cell adhesion molecules, localized post-synaptically at glutamatergic synapses (NLGN1, NLGN3 and NLGN4X/Y) or GABAergic synapses (NLGN2). 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; Laumonnier et al., 2004). Although these mutations have not been found in several other studies (Vincent et al., 2004; Gauthier et al., 2005) and probably explain less than 1% of ASD (Persico & Bourgeron, 2006), they shed light on the possible crucial role of synapse abnormalities in ASD: indeed, the post-synaptic expression of neuroligins induces 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 (Chih et al., 2005), which is impaired in the neuronal networks of 30-50% of patients with ASD having clinical or infra-clinical epilepsy (Tuchman & Rapin, 2002; Hughes & Melyn, 2005).
Another gene, *SHANK3*, located in the 22q13 region, has been found to be deleted in two brothers with ASD and delayed expressive speech (Durand et al., 2007). This gene

regulates the structural organization of dendritic spines (Boeckers et al., 2002) and is a binding partner of neuroligins (Meyer et al., 2004).

Finally, performing the largest linkage scan in 1168 families with at least two individuals affected by ASD, the Autism Genome Project Consortium (2007) found that chromosome 11p12-p13 and genes encoding neurexins (and particularly NRXN1) were implicated. Neurexins have been shown to induce postsynaptic differentiation in contacting dendrites, while neuroligins induce presynaptic differentiation in glutamatergic synapses; the neurexin-neuroligin complex is fundamentally important for glutamatergic as well as GABAergic synaptogenesis (Graf et al., 2004; Varoqueaux et al., 2006).

(3) Genes implicated in neurotransmission and neuromodulation

First, several studies reveal that variants of genes encoding neurotransmitter receptors and transporters might be susceptibility factors or modulators of the behavioural phenotype of ASD, but probably not sufficient or direct causes of ASD.

The most studied gene involved in neurotransmission is therefore 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, others reported that a long promoter variant of the 5-HTT transporter was inherited more frequently by affected family members (Klauck et al., 1997; Yirmiya et al., 2001). But these data are contradicted by reports of little or no association between ASD and the serotonin transporter promoter variants (e.g., Maestrini et al., 1999; Persico et al., 2000). According to Persico & Bourgeron (2006), these contradictory results are likely to be compatible with a small effect of SLC6A4 gene variants on 5-HT blood levels and on ASD status, with perhaps greater effects on the cortical gray matter overgrowth characterizing autistic children aged 2 to 4 years old (Wassink et al., 2007). Besides an interaction between SLC6A4 and ITGB3 (another candidate gene in the serotonin metabolic and neurotransmission pathway) has been found to play a role in autism aetiology and in determining serotonin levels, providing evidence for a common mechanism underlying the association of platelet hyperserotoninemia with ASD (Coutinho et al., 2007).

In this category of genes, several lines of evidence also strongly suggest the involvement of glutamate receptors in the physiopathogeny of ASD (Muhle et al., 2004). For example, excessive glutamatergic activity is associated with epileptiform activity, which is frequently associated with autism (Hussman, 2001). Recently, increased levels of glutamate have also been found in adults with autism (Shinohe et al., 2006).

A study using proton magnetic resonance spectroscopic imaging revealed widespread reductions in gray matter neuronal integrity and a dysfunction of cortical and cerebellar glutamatergic neurons in subjects with ASD (DeVito et al., 2007). Upregulated expression of the glutamate transporter gene was reported in postmortem studies of autistic brain tissue (Purcell et al., 2001). Moreover, the ionotropic glutamate receptor 6 (GluR6) gene on chromosome 6q21 is significantly associated with autism by Linkage Disequilibrium and multipoint linkage analysis, and a surveyed 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). The effects of these polymorphisms are not well known but they raise the possibility that alterations in glutamate signaling are associated with some forms of ASD.

Other lines of evidence support defects in the GABAergic inhibitory system 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) is implicated in ASD (e.g., Menold et al., 2001; Dykens et al. 2004).

In addition to the GABA receptor genes themselves, genes involved in the differentiation and migration of GABAergic neurons have also been associated with ASD. Mutations in ARX (which encodes a transcription factor thought to regulate the development of GABAergic neurons in the basal ganglia and cortex, Friocourt et al., 2006) can lead to epilepsy, movement disorders, cortical malformations, mental retardation and autism (Turner et al., 2002).

To summarize, deficiencies in GABA receptor expression or function, but also deficiencies in the differentiation and the migration of GABAergic neurons into the cortex appear to be 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; Hussman, 2001).

(4) Genes implicated in voltage-gated ion channel

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 including cardiac abnormalities and autism, which is due to a recurrent, de novo *CACNA1C* calcium channel mutation (Splawski et al., 2004), i.e., a mutation preventing voltage-dependent channel inactivation and leading to prolonged inward Ca^{2+} currents.

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, which are 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.

Finally, 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).

VII- FROM GENETIC TO BEHAVIOURAL ABNORMALITIES: A SYNTHESIS

In this paragraph, we wish to synthesize and summarize the large body of data presented above in a plausible step-by-step scenario linking gene abnormalities to behavioural impairments in ASD.

Most of the gene abnormalities reviewed above impact synaptogenesis (neuroligins, neurexins, Shank3) and neurotransmission (serotonin transporter, receptors of GABA and glutamate, voltage-gated ion channels), i.e., the contact and functional interaction between neurons. Even abnormalities of genes involved in neuronal migration or differentiation, by their consequences on the construction of neural networks, impact communication and temporospatial binding between neurons (e.g., Belmonte & Bourgeron, 2006; Welsh et al., 2005). In particular, according to Rubenstein & Merzenich (2003), cortical networks in ASD may be characterized by an imbalance between excitation and inhibition due to abnormalities in GABAergic and glutamatergic transmitter systems, which lead to hyperexcitability and unstable cortical networks.

These abnormalities affecting neurotransmission directly account for the disorders occurring in functional connectivity (under- and/or over-connectivity) and neural synchronization (hypo- and/or hyper-synchronization) between cortical, cerebellar and subcortical territories seen in ASD (see above), that was called *the multisystem disconnectivity and dissynchrony (MDD) hypothesis* of ASD (Gepner & Tardif, 2006; Tardif et al., 2007).

Given that when a group of neurons cannot fire simultaneously (i.e., become electrically synchronized), it cannot generate a coherent rhythmic output, thus impairing its ability to process information *online* (see e.g., the case of neurons in inferior olive and the olivocerebellar pathway, Welsh et al., 2005) and particularly rapid information, it is not surprising that this *MDD* results in abnormalities in perceiving and integrating rapid and transient sensory events (Gepner & Mestre, 2002b), such as rapid physical movements (Gepner & Mestre, 2002a), rapid facial movements (Tardif et al., 2007) and rapid speech flow (Tardif et al., 2002) in some people with ASD. Failing to process rapid sensory events would consequently explain their difficulties and peculiarities to process, imitate, understand and produce emotional and verbal events *on time*, and interact adequately with the physical and human world (Gepner et al., 2005; Gepner & Tardif, 2006; Gepner, 2006; Lainé et al., in press). All in all, this *MDD* would be responsible for impaired and peculiar attentional, perceptive and/or cognitive acts in subjects with ASD, and particularly for their slowed down perceptual and cognitive processes (Courchesne et al., 1994b; Townsend et al., 1999). Slowing down visual and auditory events of the environment of persons with ASD could enhance their performance in recognition, comprehension and imitation of emotional facial expressions, language and gestures (Tardif et al., 2007 ; Lainé et al., 2008 ; Lainé et al., in press), and might therefore open new perspectives for rehabilitating these persons.

VII- PERSPECTIVES

Our global approach of ASD, aimed at understanding the links between behaviours and their underlying neurobiological bases, reveals that impairments at the level of human communication and interaction, which constitute the core of autism, are correlated with disorders at the level of neuronal communication and interaction. We propose to name it a "neuronal to human communication disorders" approach of ASD.

Much work is necessary to further investigate these neuronal communication and interaction disorders, at cellular and molecular levels. As far as we are concerned, we collaborate with a neurobiologist, François Féron, into a research program (granted by Fondation de France) aimed at studying the genomic and proteomic (and if possible functional) properties of stem cells-derived neurons, extracted from olfactory mucosa of adults with ASD and normal control adults. An electrophysiological analysis of these stem cell-derived neurons (if possible), combined with genomic and proteomic analyses of the same neurons, should provide new insights into the physiopathology of ASD and may uncover novel therapeutic strategies.

References

Allison, T., Puce, A., McCarthy, G. (2000). Social perception from visual cues: role of the STS region. Trends in Cognitive Sciences, 4, 267-278.

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), APA: Washington DC.

Bacchelli, E. & Maestrini, E. (2006). Autism spectrum disorders: molecular genetic advances. American Journal of Medical Genetics, 142C: 13-23.

Bailey, A., Luthert, P., Dean A., et al. (1998). A clinicopathological study of autism. Brain, 121, 889-905.

Baron-Cohen, S., Campbell, R., Karmiloff-Smith, A., & Grant, J. (1995). Are children with autism blind to the mentalistic significance of the eyes? British Journal of Devevelopmental Psychology, 13, 379-398.

Bauman, M.L., & Kemper, T.L. (1985). Histoanatomic observations of the brain in early infantile autism. Neurology, 35, 866-874.

Bauman, M.L., & Kemper, T.L. (2005). Neuroanatomic observations of the brain in autism: a review and future directions. International Journal of Developmental Neuroscience, 23, 183-187.

Belin, P., Zatorre, R.J., Lafaille, P., Ahad, P., Pike, B. (2000). Voice-selective areas in human auditory cortex. Nature, 403, 309-312.

Belmonte, M.K., & Bourgeron, T. (2006). Fragile X syndrome and autism at the intersection of genetic and neural networks. Nature Neuroscience, 9, 1221-25.

Belmonte, M.K., Allen, G., Beckel-Mitchener, A., Boulanger, L.M., Carper, R.A., & Webb, S.J. (2004). Autism and abnormal development of brain connectivity. Journal of Neuroscience, 24, 9228-9231.

Bertone A., Mottron L., Jelenic P, Faubert J. (2003). Motion perception in autism: a 'complex' issue. Journal of Cognitive Neuroscience, 15, 218-225.

Blake R., Turner L.M., Smoski M.J., Pozdol S.L. & Stone W.L. (2003). Visual recognition of biological motion is impaired in children with autism. Psychological Science, 14, 151-157.

Boeckers, T.M., Bockmann, J., Kreutz, M.R. & Gundelfinger, E.D. (2002). ProSAP/Shank proteins-a family of higher order organizing molecules of the postsynaptic density with an emerging role in human neurological disease. Journal of Neurochemistry, 81, 903-910.

Boisacq-Schepens, N. & Crommelinck, M. (1994). Neuro-psycho-physiologie, vol. 1, Fonctions sensori-motrices, Paris : Masson.

Brock, J., Brown, C.C., Boucher, J. & Rippon, G. (2002). The temporal binding deficit hypothesis of autism. Developmental Psychopathology, 14, 209-224.

Brown, C., Gruber, T., Boucher, J., Rippon, G., & Brock, J. (2005). Gamma abnormalities during perception of illusory figures in autism. Cortex, 41, 364-376.

Butterworth, G & Hicks, L. (1977). Visual proprioception and postural stability in infancy. A developmental study. Perception, 6, 255-262.

Casanova, M.F., Buxhoeveden, D.P., Switala, A.E. & Roy, E. (2002). Minicolumnar pathology in autism. Neurology, 58, 428-432.

Castelli F., Frith C., Happé F., Frith U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain, 125, 1839-1849.

Cherkassky, V.L., Kana, R.K., Keller, T.A. & Just, M.A. (2006). Functional connectivity in a baseline resting-state in autism. Neuroreport, 17, 1687-90.

Chih, B., Engelman, H. & Scheiffele, P. (2005). Control of excitatory and inhibitory synapse formation by neuroligins. Science, 307, 1324-1328.

Cohen, I.L. (1994). An artificial neural network analogue of learning in autism. Biological Psychiatry, 36, 5-20.

Connoly, A.M., Chez, M., Streif, E.M. et al. (2006). Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. Biological Psychiatry, 59, 354-363.

Cook, E.H., Courchesne, R., Lord, C. et al. (1997). Evidence of linkage between the serotonin transporter and autistic disorder. Molecular Psychiatry, 2, 247-250.

Courchesne E (1997). Brainstem, cerebellar and limbic neuroanatomical abnormalities in autism. Current Opinion in Neurobiology, 7, 269-278.

Courchesne, E. & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Current Opinion in Neurobiology, 15, 225-230.

Courchesne, E., Karns, C, Davis, H.R. et al. (2001). Unusual brain growth patterns in early life in patients with autistic disorder : an MRI study. Neurology, 57, 245-254.

Courchesne, E., Pierce, K., Schumann, C.M., Redcay, E., Buckwalter, J.A., Kennedy, D.P., & Morgan, J. (2007). Mapping early brain development in autism. Neuron, 56, 399-413.

Courchesne, E., Saitoh, O., Yeung-Courchesne, R. et al. (1994a). Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging. American Journal of Roentgenology, 162, 123-130.

Courchesne, E., Townsend, J., Akshoomoff, N.A. et al. (1994b). Impairment in shifting attention in autistic and cerebellar patients. Behavioral Neuroscience, 108, 848-865.

Coutinho, A.M., Sousa, I., Martins, M. et al. (2007). Evidence for epistasis between SLC6A4 and ITGB3 in autism etiology and in the determination of platelet serotonin level. Human Genetics, 121, 243-256.

Critchley, H.D., Daly, E.M., Bullmore, E.T. et al. (2000). The functional neuroanatomy of social behaviour: changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain, 123, 2203-2212.

Dapretto, M., Davies, M.S., Pfeifer, J.H., Scott, A.S., Sigman, M., Bookheimer, S.Y., Iacobini, M. (2006). Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. Nature Neuroscience, 9, 28-30.

Davies, S., Bishop, D., Manstead, A.S.R., & Tantam, D. (1994). Face perception in children with autism and Asperger's syndrome. Journal of Child Psychology and Psychiatry, 35, 1033-1057.

Dawson, G., Webb, S.J., & Mc Partland, J. (2005). Understanding the nature of face processing impairment in autism: insights from behavioral and electrophysiological studies. Developmental Neuropsychology, 27, 403-424.

De Gelder, B., Vroomen, J., & Van der Heide, L. (1991). Face recognition and lip-reading in autism. European Journal of Cognitive Psychology, 3, 69-86.

Deruelle, C., Rondan, C., Gepner, B., Tardif, C. (2004). Spatial frequency and face processing in children with autism and Asperger syndrome. Journal of Autism and Developmental Disorders, 34, 199-210.

De Vito, T.J., Drost, D.J., Neufeld, R.W. et al. (2007). Evidence for cortical dysfunction in autism : a proton magnetic resonance spectroscopic imaging study. Biological Psychiatry, 61, 465-473.

Doya, K. (2000). Complementary roles of basal ganglia and cerebellum on learning and motor control. Current Opinion in Neurobiology, 10, 732-739.

Durand, C.M., Betancur, C., Boeckers, T.M. et al. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nature Genetics, 39, 25-27.

Dykens, E.M., Sutcliffe, J.S., Levitt, P. (2004). Autism and 15q11-q13 disorders: behavioral, genetic and pathophysiological issues. Mental Retardation and Developmental Disabilities Research Review, 10, 284-291.

Fatemi, S.H. (2005). Reelin glycoprotein: structure, biology and roles in health and disease. Molecular Psychiatry, 10, 251-257.

Fatemi, S.H., Snow, A.V., Stary, J.M. et al. (2005). Reelin signaling is impaired in autism. Biological Psychiatry, 57, 777-787.

Fombonne, E. (2002). Epidemiological trends in rates of autism. Molecular Psychiatry, 7, S4-S6.

Forster, E., Jossin, Y., Zhao, S., Chai, X., Frotscher, M., Goffinet, A.M. (2006). Recent progress in understanding the role of Reelin in radial neuronal migration, with specific emphasis on the dentate gyrus. European Journal of Neuroscience, 23, 901-909.

Friedman, S.D., Shaw, D.W., Artru, A.A., Dawson, G., Petropoulos, H., Dager, S.R. (2006). Gray and white matter brain chemistry in young children with autism. Archives of General Psychiatry, 63, 786-794.

Friocourt, G., Poirier, K., Rakic, S., Parnavelas, J.G. & Chelly, J. (2006). The role of ARX in cortical development. European Journal of Neuroscience, 23, 869-876.

Frith U. (1989). Autism : explaining the enigma. Basic Blackwell.

Gauthier, J., Bonnel, A., St Onge, J. et al. (2005). NLGN3/NLGN4 gene mutations are not responsible for autism in the Quebec population. American Journal of Medical Genetics, 132, 74-75.

Gepner B. & Massion J. (dirigé par) (2002). L'autisme : une pathologie du codage temporel ? Revue TIPA (Revue des Travaux Interdisciplinaire du laboratoire PArole et langage), 21, 177-218.

Gepner B. & Mestre D. (2002a). Postural reactivity to fast visual motion differentiates autistic from children with Asperger syndrome. Journal of Autism and Developmental Disorders, 32, 231-238.

Gepner B. & Mestre D. (2002b). Rapid visual-motion integration deficit in autism. Trends in Cognitive Sciences, 6,11, 455.

Gepner B. & Tardif C. (2006). Autism, movement, time and thought. E-motion mis-sight and other temporo-spatial processing disorders in autism. In: M. Vanchevsky (ed). Frontiers in Cognitive Psychology. New York : Nova Science Publishers (pp. 1-30).

Gepner B. (1997). Face recognition and visual-motion perception in autistic children. Unpublished Doctoral dissertation. Université Aix-Marseille II.

Gepner B. (2001). « Malvoyance » du mouvement dans l'autisme infantile ? Une nouvelle approche neuropsychopathologique développementale. La Psychiatrie de l'Enfant, 1, 77-126.

Gepner B., Deruelle C., Grynfeltt S. (2001). Motion and emotion: a novel approach to the study of face processing by autistic children. Journal of Autism and Developmental Disorders, 31, 37-45.

Gepner, B. & Soulayrol, R. (1994). Utilité des concepts d'épigenèse et d'auto-organisation pour la compréhension des syndromes autistiques de l'enfant. La Psychiatrie de l'Enfant, XXXVII, 1, 115-152.

Gepner, B. (2004). Autism, movement and facial processing. The American Journal of Psychiatry, 161, 1719.

Gepner, B. (2005). Malvoyance du mouvement dans l'autisme: de la clinique à la recherche et à la rééducation. L'Autisme : de la recherche à la pratique, C. Andrès, C. Barthélémy, A. Berthoz, J. Massion, B. Rogé (Eds.), p. 205-226, Paris , Odile Jacob.

Gepner, B., de Gelder, B. & de Schonen, S. (1996). Face processing in autistics : Evidence for a generalized deficit ? Child Neuropsychology, 2, 123-139.

Gepner, B., Lainé, F. & Tardif, C. (2005). E-Motion mis-sight and other temporal processing disorders in autism. Current Psychology of Cognition/Cahiers de Psychologie Cognitive, 23, 104-121.

Gepner, B., Mestre, D., Masson, G., de Schonen, S. (1995). Postural effects of motion vision in young autistic children. NeuroReport, 6, 1211-1214.

Gepner, B. (2006). Constellation autistique, mouvement, temps et pensée. *Malvoyance de l'É-Motion*, autres désordres du traitement temporospatial des flux sensoriels et *dyssynchronie* dans l'autisme. Devenir, 18, 4, 333-379.

Gervais, H., Belin, P., Boddaert, N. et al. (2004). Abnormal cortical voice processing in autism. Nature Neuroscience, 7, 801-2.

Geschwind, D.H. & Levitt, P. (2007). Autism spectrum disorders: developmental disconnection syndromes. Current Opinion in Neurobiology, 17, 103-111.

Gibson J.J. (1979). The ecological approach to visual perception. Boston, Houghton Mifflin.

Gillberg, C. (1998). Chromosomal disorders and autism. Journal of Autism and Developmental Disorders, 28, 415-425.

Graf, E.R., Zhang, X., Jin, S.X., Linhoff, M.W. & Craig, A.M. (2004). Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. Cell, 119, 1013-1026.

Grandin T. (1995). Thinking in pictures and other reports from my life with autism, Doubleday.

Habib M., Espesser R., Rey V., Giraud K., Bruas P., Gres C. (1999). Training dyslexics with acoustically modified speech : evidence of improved phonological performance. Brain and Cognition, 40, 143-46.

Hadjikhani, N., Joseph, R.M., Snyder, J. et al. (2004). Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. Neuroimage, 22, 1141-1150.

Hallbook, F. (1999). Evolution of the vertebrate neurotrophin and Trk receptor gene families. Current Opinion in Neurobiology, 9, 616-621.

Happé F. (1999). Autism: Cognitive deficit or cognitive style? Trends in Cognitive Sciences, 3, 216-222.

Hazlett, H.C., Poe, M., Gerig, G. et al. (2005). Magnetic resonance imaging and head circumference study of brain size in autism: birth through age 2 years. Archives of General Psychiatry, 62, 1366-76.

Hazlett, H.C., Poe, M.D., Gerig, G., Smith, R.G. & Piven, J. (2006). Cortical gray and white brain tissue volume in adolescents and adults with autism. Biological Psychiatry, 59, 1-6.

Haznedar, M.M., Buchsbaum, M.S., Hazlett, E.A., LiCalzi, E.M., Cartwright, C. & Hollander, E. (2006). Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. American Journal of Psychiatry, 163, 1252-63.

Herbert, M.R., Ziegler, D.A., Deutsch, C.K. et al. (2003). Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain, 126, 1192-1192.

Herbert, M.R., Ziegler, D.A., Makris, N. et al. (2004). Localization of white matter volume increase in autism and developmental language disorder. Annals of Neurology, 55, 530-540.

Hertzig, M.E., Snow, M.E,. & Sherman, M. (1989). Affect and cognition in autism. Journal of the Amercican Academy of Child and Adolescent Psychiatry, 28, 195-199.

Hobson, R.P., Ouston, J., & Lee, A. (1988). What's in a face? The case of autism. British Journal of Psychology, 79, 441-453.

Hong, S.E., Shugart, Y.Y., Huang, D.T. et al. (2000). Autosomal lissencephaly with cerebellar hypoplasia is associated with RELN mutations. Nature Genetics, 26, 93-96.

Huang, E.J., Reichardt, L.F. (2001). Neurotrophins: roles in neuronal development and function. Annual Reviews in Neuroscience, 24, 677-736.

Hughes, J.R., & Melyn, M. (2005). EEG and seizures in autistic children and adolescents: further findings with therapeutic implications. Clinical EEG and Neuroscience, 36, 15-20.

Hussman, J.P. (2001). Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. Journal of Autism and Developmental Disorders, 31, 247-248.

Ito M, (1984). The cerebellum and neural control. Raven Press :New York.

Jamain, S., Betancur, C., Quach, H. et al. (2002). Linkage and association of the glutamate receptor gene with autism. Molecular Psychiatry, 7, 302-310.

Jamain, S., Quach, H., Betancur, C. et al. (2003). Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. Nature Genetics, 34, 27-29.

Johnson, M.T., and Ebner, T.J. (2000.) Processing of multiple kinematic signals in the cerebellum and motor cortices. Brain Research Review, 33, 155-168.

Jouen F. (1988). Visual proprioceptive control of posture in newborn. In: Amblard B, Berthoz A and Clarac F, eds. Posture and gait: development adaptation and modulation. Amsterdam: Elsevier, 13-22.

Just, M.A., Cherkassky, V.L., Keller, T.A., & Minshew, N.J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. Brain, 127, 1811-1821.

Just, M.A., Cherkassky, V.L., Keller, T.A., Kana, R.K. & Minshew, N.J. (2007). Functional and anatomical cortical underconnectivity in autism: evidence from an fMRI study of an executive function task and corpus callosum morphometry. Cerebral Cortex, 17, 951-961.

Kana, R.K., Keller, T.A., Cherkassky, V.L., Minshew, N. & Just, M.A. (2006). Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. Brain, 129, 2484-93.

Kanner L (1943). Autistic disturbances of affective contact. Nervous Child, 2, 217-250.

Keller, T.A., Kana, R.K. & Just, M.A. (2007). A developmental study of the structural integrity of white matter in autism. Neuroreport, 18, 23-27.

Kemper, T.L., & Bauman, M.L. (1993). The contribution of neuropathologic studies to understanding of autism. Neurological Clinics, 11,175-187.

Kennedy, D.P., Redcay, E. & Courchesne, E. (2006). Failing to deactivate: resting functional abnormalities in autism. Proceedings of the National Academy of Sciences USA, 103, 8275-80.

Klauck, S.M., Poustka, F., Benner, A., Lesch, K.P. & Poustka, A. (1997). Serotonin transporter (5-HTT) gene variants associated with autism ? Human Molecular Genetics, 6, 2233-38.

Koshino, H., Carpenter, P.A., Minshew, N.J., Cherkassky, V.L., Keller, T.A., Just, M.A. (2005). Functional connectivity in an fMRI working memory task in high-functioning autism. Neuroimage, 24, 810-821.

Krey, J.F. & Dolmetsch, R.E. (2007). Molecular mechanisms of autism: a possible role for Ca2+ signaling. Current Opinion in Neurobiology, 17, 112-119.

Lainé, F., Tardif, C., Gepner, B. (2008). Slowing down biological motion and speech sounds enhances imitation and verbal comprehension in children and adolescents with autism. Poster at the Autism Neuroscience Conference, London, October.

Lainé, F., Tardif, C.., Rauzy, S., Gepner, B. (in press). Perception et imitation du mouvement dans l'autisme : une question de temps. *Enfance*.

Langdell, T. (1978). Recognition of faces: an approach to the study of autism. Journal of Child Psychology and Psychiatry, 19, 255-268.

Laumonnier, F., Bonnet-Brilhault, F., Gomot, M. et al. (2004). X-linked mental retardation and autism are associated with a mutation in the NLGN4 gene, a member of the neuroligin family. American Journal of Human Genetics, 74, 552-557.

Laumonnier, F., Roger, S., Guérin, P. et al. (2006). Association of a functional deficit of the BKCa channel, a synaptic regulator of neuronal excitability, with autism and mental retardation. *American Journal of Psychiatry*, 163, 1622-1629.

Leary M.R. & Hill D.A. (1996). Moving on: autism and movement disturbance. Mental Retardation, 1, 39-53.

Lee, D.N. & Aronson, E. (1974). Visual proprioceptive control of standing in human infants. Perception and Psychophysics, 15, 529-532.

Lewis, R.F. and Zee, D.S. (1993). Ocular motor disorders associated with cerebellar lesions : pathophysiology and topical localization. Revue Neurologique (Paris), 149, 665-677.

Livingstone M. & Hubel D. (1988). Segregation of form, color, movement and depth: anatomy, physiology and perception. Science, 240, 740-749.

Loveland, K.A., Tunali-Kotoski, B., Pearson, D.A., Brelsford, K.A., Ortegon, J., & Chen, R. (1994). Imitation and expression of facial affect in autism. Development and Psychopathology, 6, 433-444.

Maestrini, E., Lai, C., Marlow, A. et al. (1999). Serotonin transporter (5-HTT) and gamma-aminobutyric acid receptor subunit beta3 (GABRB3) gene polymorphisms are not associated with autism in the IMGSAC families. The International Molecular Genetic Study of Autism Consortium. American Journal of Medical Genetics, 88, 492-496.

Martineau, J., Roux, S., Adrien, J.L., Garreau, B., Barthélémy, C., & Lelord, G. (1992). Electrophysiological evidence of different abilities to form cross-modal associations in children with autistic behaviors. Electroencephalography and Clinical Neurophysiology, 82, 60-66.

Massion, J. (1993) Grandes relations anatomo-fonctionnelles dans le cervelet. Revue Neurologique, 11, 600-606.

Menold, M.M., Shao, Y., Wolpert, C.M. et al. (2001). Association analysis of chromosome 15 GABAA receptor subunit genes in autistic disorder. Journal of Neurogenetics, 15, 245-259.

Mestre D., Rondan C., Masson G., Castet E., Deruelle C., Gepner B. (2002). Evaluation de la vision du mouvement chez des enfants autistes au moyen du nystagmus opto-cinétique. Revue TIPA, 21, 192-198.

Meyer, G., Varoqueaux, F., Neeb, A., Oschlies, M. & Brose, N. (2004). The complexity of PDZ domain-mediated interactions at glutamatergic synapses: a case study on neuroligin. Neuropharmacology, 47, 724-733.

Middleton F.A. & Strick P.L. (2000). Basal ganglia and cerebellum loops: motor and cognitive circuits. Brain Research Review, 31, 236-250.

Milne E, Swettenham J, Hansen P, Campbell R, Jeffries H, Plaisted K (2002). High motion coherence thresholds in children with autism. Journal of Child Psychology and Psychiatry, 43, 255-263.

Milne, E., Swettenham, J., Campbell, R. (2005). Motion perception and autistic spectrum disorder: a review. Current Psychology of Cognition/Cahiers de Psychologie Cognitive. 23, 3-33.

Minshew, N.J., & Williams, D.L. (2007). The new neurobiology of autism: cortex, connectivity and neuronal organization. Archives of Neurology, 64, 945-950.

Miyazaki, K. Narita, N. Sakuta, R. et al. (2004). Serum neurotrophin concentrations in autism and mental retardation. Brain and Development. 26, 292-295.

Mizuno, A., Villalobos, M.E., Davies, M.M., Dahl, B.C. & Muller, R.A. (2006). Partially enhanced thalamocortical functional connectivity in autism. Brain Research, 1104, 160-174.

Mottron, L. (2004). L'autisme: une autre intelligence. Sprimont: Mardaga.

Muhle, R., Trentacoste, S.V. & Rapin, I. (2004). The genetics of Autism. Pediatrics, 113, e472-e486.

Nelson, K.B., Grether, J.K., Croen, L.A. et al. (2001). Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation. Annals of Neurology, 49, 597-606.

Nishitani, N., Avikainen, S., & Hari, R. (2004). Abnormal imitation-related cortical activation sequences in Asperger's syndrome. Annals of Neurology, 55, 558-562.

Oberman, L.M., Hubbard, E.M., McCleery, J.P., Altschuler, E.L., Ramachandran, V.S., & Pineda, J.A. (2005). EEG evidence for mirror neuron dysfunction in autism spectrum disorders. Brain Research Cognitive Brain Research, 24, 190-198.

Ornitz, E.M. & Ritvo, E.R. (1968). Perceptual inconstancy in early infantile autism. Archives of General Psychiatry, 18, 76-98.

Paul, L.K., Brown, W.S., Adolphs, R. et al. (2007). Agenesis of the corpus callosum : genetic, developmental and functional aspects of connectivity. Nature Reviews Neuroscience, 8, 287-299.

Pellicano, E., Gibson, L., Maybery, M., Durkin, K., Badcock, D.R. (2005). Abnormal global processing along the dorsal visual pathway in autism: a possible mechanism for weak visuospatial coherence ? Neuropsychologia, 43, 1044-53.

Persico, A.M., & Bourgeron, T. (2006). Searching for ways out of the autism maze: genetic, epigenetic and environmental cues. Trends in Neurosciences, 29, 349-358.

Persico, A.M., Militerni, R., Bravaccio, C. et al. (2000). Lack of association between serotonin transporter gene promoter variants and autistic disorder in two ethnically distinct samples. American Journal of Medical Genetics, 96, 123-127.

Petropoulos, H., Friedman, S.D., Shaw, D.W., Artru, A.A., Dawson, G. & Dager, S.R. (2006). Gray matter abnormalities in autism spectrum disorder revealed by T2 relaxation. Neurology, 67, 632-636.

Pierce, K., Haist, F., Sedaghat, F., & Courchesne, E. (2004). The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain, 127, 2703-2716.

Purcell, A.E., Jeon, O.H., Zimmerman, A.W., Blue, M.E., Pevsner, J. (2001). Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurology, 57, 1618-1628.

Rapin I. (2002). The autistic spectrum disorders. The New England Journal of Medicine, 347, 302-303.

Raymond, G., Bauman, M., & Kemper, T.L. (1996). The hippocampus in autism: a Golgi analysis. Acta of Neuropathology, 91, 117-119.

Risch, N., Spiker, D., Lotspeich, L. et al. (1999). A genomic screen of autism: evidence for a multilocus etiology. American Journal of Human Genetics, 65, 493-507.

Ritvo, E.R., Freeman, B.J., Scheibel, A.B., Duong, T., Robinson, H., Guthrie, D., & Ritvo, A. (1986). Lower Purkinje cell counts in the cerebella of four autistic patients: initial findings of the UCLA-NSAC autopsy research report. American Journal of Psychiatry, 146, 862-866.

Rogers, S.J., Hepburn, S.L., Stackhouse, T., & Wehner, E. (2003). Imitation performance in toddlers with autism and those with other developmental disorders. Journal of Child Psychology and Psychiatry, 44, 763-781.

Rubenstein, J.L., & Merzenich, M.M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. Genes Brain and Behaviour, 2, 255-267.

Santangelo, S.L. & Tsatsanis, K. (2005). What is known about autism: genes, brain and behavior. American Journal of Pharmacogenomics, 5, 71-92.

Sauvage D. (1988). Autisme du nourrisson et du jeune enfant. Paris: Masson.

Schmitz C., Assaiante C., Gepner B. (2002). Modulation de la réponse anticipée en fonction du poids à délester : étude chez l'enfant sain et l'enfant autiste. Revue TIPA, 21, 207-211.

Schmitz C., Martineau J., Barthélémy C. & Assaiante C. (2003). Motor control and children with autism : deficit of anticipatory function ? Neuroscience Letters, 348, 17-20.

Schultz, R.T., Gauthier, I., Klin, A. et al. (2000). Abnormal ventral temporal cortical activity during face discrimination among individuals with autism and Asperger syndrome. Archives of General Psychiatry, 57, 331-340.

Schumann, C.M. & Amaral, D.G. (2006). Stereological analysis of amygdala neuron number in autism. Journal of Neuroscience, 26, 7674-7679.

Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L. et al. (2004). The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. Journal of Neuroscience, 24, 6392-6401.

Serajee, F.J., Zhong, H, Nabi, R., Huq, A.H. (2003). The metabotropic glutamate receptor 8 gene at 7q31: partial duplication and possible association with autism. Journal of Medical Genetics, 40, e42.

Shinohe, A., Hashimoto, K., Nakamura, K. et al. (2006). Increased serum levels of glutamate in adult patients with autism. Progress in Neuropsychopharmacology and Biological Psychiatry, 30, 1472-1477.

Smith, I.M., & Bryson, S.E. (1994). Imitation and action in autism: a critical review. Psychological Bulletin, 116, 259-273.

Spencer, J, O'Brien J, Riggs K, Braddick O, Atkinson J, Wattam-Bell J (2000). Motion processing in autism: evidence for a dorsal stream deficiency. NeuroReport, 11, 2765-2767.

Splawski, I., Timothy, K.W., Sharpe, L.M. et al. (2004). Cav1.2 calcium channel dysfunction causes a multisystem disorder including arrhytmia and autism. Cell, 119, 19-31.

Stein, J. (2001). The magnocellular theory of developmental dyslexia. Dyslexia 7, 12-36

Takarae, Y., Minshew, N.J., Luna, B., Krisky, C.M., Sweeney, J.A. (2004). Pursuit eye movement deficits in autism. Brain, 127, 2584-94.

Talcott J.B., Hansen P.C., Assoku E.L., Stein J.F. (2000). Visual motion sensitivity in dyslexia: evidence for temporal and energy integration deficit. Neuropsychologia, 38, 935-943.

Tallal P. (1976). Rapid auditory processing in normal and disordered language development. Journal of Speech & Hearing Research, 19, 561-594.

Tallal, P., Miller, S.L., Bedi, G. et al. (1996). Language comprehension in language-learning impaired children improved with acoustically modified speech. Science, 271, 81-83.

Tardif, C. & Gepner , B. (2003). L'Autisme. Collection 128, Nathan. 2nd Edition, 2007, Armand Colin.

Tardif, C., Lainé, F., Rodriguez, M., Gepner, B. (2007). Slowing down facial movements and vocal sounds enhances facial expression recognition and facial-vocal imitation in children with autism. Journal of Autism and Developmental Disorders, 37, 1469-1484.

Tardif, C., Thomas, K., Gepner, B., Rey, V. (2002). Contribution à l'évaluation du système phonologique explicite chez des enfants autistes. Parole, 21, 35-72.

Teitelbaum, P., Teitelbaum, O., Nye, J., Fryman, J. & Maurer, R. (1998). Movement analysis in infancy may be useful for early diagnosis of autism. Proceedings of the National Academy of Sciences, 95, 13982-87.

The autism genome consortium (2007). Mapping autism risk loci using genetic linkage and chromosomal rearrangements. Nature Genetics, 39, 319-328.

Townsend, J., Courchesne, E., Covington, J. et al. (1999). Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. Journal of Neuroscience, 19, 5632-43.

Tuchman, R. & Rapin, I. (2002). Epilepsy in autism. Lancet Neurology, 1, 352-358.

Turner, G., Partington, M., Kerr, B., Mangelsdorf, M. & Gecz, J. (2002). Variable expression of mental retardation, autism, seizures and dystonic hand movements in two families with an identical ARX gene mutation. American Journal of Medical Genetics, 112, 405-411.

Turner, K.C., Frost, L., Linsenbardt, D., Mellroy, J.R. & Muller, R.A. (2006). Atypically diffuse functional connectivity between caudate nuclei and cerebral cortex in autism. Behavioral Brain Function, 16, 2-34.

Uhlhaas, P. & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron, 52, 155-168.

Vargas, D.L., Nascimbene, C., Krishnan, C., Zimmerman, A.W., Pardo, C.A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. Annals of Neurology, 57, 67-81.

Varoqueaux, F., Aramuni, G., Rawson, R.L. et al. (2006). Neuroligins determine synapse maturation and function. Neuron, 51, 741-754.

Villalobos, M.E., Mizuno, A., Dahl, B.C., Kemmotsu, N., & Muller, R.A. (2005). Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. Neuroimage, 15, 916-925.

Vincent, J.B., Kolozsvari, D., Roberts, W.S., Bolton, P.F., Gurling, H.M., Scherer, S.W. (2004). Mutation screening of X-chromosomal neuroligin genes: no mutation in 196 autism probands. American Journal of Medical Genetics, 129, 82-84.

Volkmar, F. R., Pauls, D. (2003). Autism. Lancet, 362, 1133-41.

Wassink, T.H., Hazlett, H.C., Epping, E.A. et al. (2007). Cerebral cortical gray matter overgrowth and functional variation of the serotonin transporter gene in autism. Archives of General Psychiatry, 64, 709-717.

Waterhouse, L., Fein, D., & Modahl, C. (1996). Neurofunctional mechanisms in autism. Psychological Review, 103, 457-489.

Weiss, L.A., Escayg, A., Kearney, J.A. et al. (2003). Sodium channels SCN1A, SCN2A and SCN3A in familial autism. Molecular Psychiatry, 186-194.

Welsh, J.P., Ahn, E.S., & Placantonakis, D.G. (2005). Is autism due to brain desynchronization ? International Journal of Developmental Neuroscience, 23, 253-263.

Wickelgren, I. (2005). Autistic brains out of synch? Science, 308, 1856-1858.

Wicker, B., Fonlupt, P., Hubert, B., Tardif, C., Gepner, B., & Deruelle, C. (2008). Abnormal cerebral effective connectivity during explicit emotional processing in adults with autism spectrum disorder. Social Cognitive and Affective Neuroscience, doi 10.1093/scan/nsn007.

Williams, D. (1992). Nobody nowhere, Doubleday.

Williams, J.H., Whiten, A., & Singh, T. (2004). A systematic review of action imitation in autistic spectrum disorder. Journal of Autism and Developmental Disorders, 34, 285-299.

World Health Organization. (1992). The ICD-10 Classification of Mental and Behavioural Disorders (ICD-10), Geneva: WHO.

Yirmiya, N., Pilowsky, T., Nemanov, L. et al. (2001). Evidence for an association with the serotonin transporter promoter region polymorphism and autism. American Journal of Medical Genetics, 105, 381-386.

Zihl, J., Von Cramon, D., Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. Brain, 106, 313-340.

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. International Journal of Developmental Neuroscience, 23, 143-152.