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Chapter 6

MIRROR NEURON SYSTEM AND AUTISM

Nouchine Hadjikhani
Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA
Division of Health Sciences and Technology, Harvard-MIT, Cambridge, MA
Brain and Mind Institute, EPFL, Lausanne, Switzerland

ABSTRACT

Autism Spectrum Disorders (ASD) affect as many as 1 in 166 children and are four times more prevalent in boys than girls. Impairment in communicative abilities and reciprocal social interactions are core features of autism. Autistic individuals have difficulty relating to others and recognizing other people's emotions, and they fail to show the usual empathic reactions when others demonstrate emotions of pleasure, fear or pain.

A dysfunction of the mirror neuron system (MNS), critically involved in the perception of others' intentions and empathy, may underlie many clinical features of autism. We review several anatomical and functional imaging studies showing evidence of MNS dysfunction in autism.

We argue that some of the behavioral changes observed in autism may be the outcome of dysfunctions of the distributed neural circuitry for social cognition, including the MNS and the amygdala. This might have important implications for the development and use of early behavioral interventions aimed precisely at training basic mechanisms supported by the MNS, rather than attempting to correct higher levels of complex behaviors which might be the consequence or epiphenomena of MNS deficits.

AUTISM: DEFINITION

Autism is a neurodevelopmental disorder, characterized by mild to severe qualitative impairment in communicative abilities and reciprocal interactions, as well as repetitive and stereotyped behaviors. Autism is commonly considered a spectrum disorder (Autism Spectrum Disorder, ASD), ranging from profoundly isolated mentally-retarded individuals to

intellectually brilliant individuals who only behave oddly during social interactions. However, the question of whether autism is one or many diseases remains open, and some authors suggest that autism may be a syndrome (many separate disease entities) rather than a spectrum (variation of a single disease), and that autism may be a final common phenotype expressed by many underlying diseases (Coleman, 2005; Eigsti and Shapiro, 2003; Reiss, Feinstein, and Rosenbaum, 1986).

The work presented in this chapter arises from studies done with high-functioning individuals with autism (HFA - IQ within the normal range) or Asperger syndrome, and the theoretical ideas presented here should be considered within this paradigm.

The prevalence of autism seems to have dramatically increased during the last decade, and recent studies by Fombonne et al. (Fombonne, 2003, 2005) report that as many as 1 in 166 children may be affected by ASD. This is in strong contrast with literature from the 1970's and the 1980's that only reported up to 0.2% prevalence (C. Gillberg, 1984; Wing and Gould, 1979). There are many possible reasons for this increase in prevalence, including changes in diagnostic criteria and increased awareness. However, the presence of a real increase in the incidence of the disease due to environmental risk factors as well as specific genetic-social changes remains a possibility under investigation (C. Gillberg, 2005; Herbert et al., 2006; Silberman, 2001).

One of the earliest symptoms of autism is a lack of attention to faces that can be apparent by one year of age (Osterling and Dawson, 1994), followed by deficits in joined attention (Mundy, Sigman, and Kasari, 1993). Individuals with autism are impaired at using information from faces, such as gaze, facial expression and facial speech, to regulate social interaction. They have difficulties making social judgment, relating to others and recognizing their emotions. Furthermore, they fail to show the usual empathic reaction when other people demonstrate emotions of fear, pleasure or pain (Hobson, 1993).

EMPATHY

One of the characteristics of autism is a lack of empathy and of emotional engagement with others (APA, 2000; C. L. Gillberg, 1992). Empathy relates to the ability to recognize, share and understand emotions of others. The perception-action model proposed by Preston and de Waal (Preston and de Waal, 2002) defines empathy as a phenomenon in which the perception of an object's state activates the subject's corresponding representation, which in turn activates somatic and autonomic responses.

Lack of empathy is a very early sign of autism, and deficits in empathic behavior have been shown as early as 20 months of age in children with autism (Charman et al., 1997; Sigman, Kasari, Kwon, and Yirmiya, 1992). Baron-Cohen and Wheelwright have recently objectified empathy deficits in autism. (Baron-Cohen and Wheelwright, 2004).

Below we develop the possible connections between mechanisms of imitation, the mirror neuron system and empathy.

From Imitation to Empathy

Imitation and resonance behavior are natural mechanisms that involve perception and action coupling. Imitation plays a central role in the development of understanding other people, as both imitation and the attribution of mental states involve translating from another person's perspective into one's own. It is an important precursor of developmental accomplishment such as symbolic thought and language (Piaget, 1952), and is an innate capacity to relate to others. Imitation and resonance behavior are already present in neonates who, at 36 hours, are able to discriminate facial expressions and imitate facial gestures (T. Field, Guy, and Umbel, 1985; T. M. Field, Woodson, Greenberg, and Cohen, 1982; A.N. Meltzoff and Moore, 1977, 1983). This ability indicates the presence in the newborn of an active intermodal matching: because they do not see their own face, the only way newborns can match expression in through proprioception (A. N. Meltzoff and Moore, 1997). Until recently, it was thought that neonatal imitation was unique to the apes and to humans, but recent data have shown that this capacity to match facial and hand gesture is also present in rhesus macaques (Ferrari et al., 2006).

Contagious yawning can be interpreted as a resonance behavior. Yawning is a very common yet poorly understood phenomenon. It is an example of behavioral continuity within mammals: dogs, cats, lions, monkeys and apes yawn and in humans it can even be observed in utero. The function of yawning is still a matter of controversy: It does not increase oxygen levels in the body, as neither breathing 100% O2 nor various CO2 mixtures influences the rate of yawning (Provine, Tate, and Geldmacher, 1987). In primates, ethologists have observed that yawning occurs in a variety of social contexts, and suggested that it might have a communicative role (Deputte, Johnson, Hempel, and Scheffler, 1994), synchronizing the state of mind of a group.

Yawning *contagion* however, defined as an urge to yawn when seeing or hearing a yawn, seemed to be exclusively human (Baenninger, 1987) until it was also shown recently in chimpanzees (J. A. Anderson, Myowa-Yamakoshi, and Matsusawa, 2004), one of the rare primates showing rudimentary form of empathy (Hare, Call, and Tomasello, 2001). Yawning contagion only emerges between the first and the second year of life (Piaget, 1951). It is easily triggered by observed yawns, and yawn-related stimuli, such as a sound of a yawn, features of a yawning face, and even reading or thinking about yawns (Provine, 1986). Platek et al. (Platek et al., 2003), tested the hypothesis that contagious yawning is part of the more general phenomenon of mental state attribution, and found that the degree of contagious yawning was positively related to performance in empathic aspects of mental state attribution in young adults.

Subjects rating higher at tests of schizotypal personality were poorly susceptible to yawning, and the authors concluded that yawning might be occurring as a result of unconscious empathic modeling. Autistic individuals seem to be less susceptible to yawning contagion (Hadjikhani et al, unpublished observations), possibly reflecting a resonance mechanism dysfunction.

THE MIRROR NEURON SYSTEM

Resonance behavior, defined as a neural activity spontaneously generated during movement, gestures or action, and that is also elicited when the individual observes another individual making similar movements, gestures or actions, has its underlying neural substrate in *mirror neuron system* (MNS). The MNS was discovered serendipitously in the monkey, by a group of Italian researchers, G. Rizzolatti, L. Fogassi and V. Gallese. These scientists were performing electrophysiological recording in area F5 of the monkey, a region specialized for the control of hand action. The recorded neurons were firing when the monkey was grasping objects (food) – but to their surprise, they noticed that the same neurons would also fire when the experimenter was performing the same grasping action. (Gallese, Fadiga, Fogassi, and Rizzolatti, 1996; Rizzolatti, Fadiga, Fogassi, and Gallese, 1999; Rizzolatti, Fadiga, Gallese, and Fogassi, 1996). These neurons 'mirror' the behavior of other animal/human, as though the observer were performing the action; they are not involved in imitation, but rather in action understanding: by allowing a direct matching between the visual description of an action and its execution, the results of the visual analysis of an observed action can be translated into an account that the individual is able to understand (Rizzolatti, Fogassi, and Gallese, 2001). In the monkey, mirror neurons have been found in the ventral premotor cortex (F5) (Gallese et al., 1996; Rizzolatti, Fadiga, Gallese et al., 1996), in the inferior parietal lobule (Fogassi, Gallese, Fadiga, and Rizzolatti, 1998; Gallese, Fogassi, Fadiga, and Rizzolatti, 2002) and in the STS (Oram and Perrett, 1996; Perrett et al., 1989),.

The MNS is also present in humans as evidenced by many imaging studies, including transcranial magnetic stimulation (TMS) (Fadiga, Fogassi, Pavesi, and Rizzolatti, 1995; Gangitano, Mottaghy, and Pascual-Leone, 2001; Maeda, Kleiner-Fisman, and Pascual-Leone, 2002; Strafella and Paus, 2000), electroencephalographic (EEG) and magnetoencephalographic (MEG) studies (Cochin, Barthelemy, Roux, and Martineau, 1999; Hari et al., 1998).

Studies using fMRI have further studied the function and location of the MNS: The MNS is composed of a network of areas comprising the pars opercularis of the inferior frontal gyrus (BA 44) and its adjacent ventral area 6 (inferior frontal cortex, IFC), the inferior parietal lobule (IPL), and the superior temporal sulcus (STS), , and. These areas show activation during *mental representation* of one own's action, and mental representation and *observation* of another person's action (Buccino et al., 2001; Buccino et al., 2004; Decety and Grezes, 1999; Decety et al., 1997; Grafton, Arbib, Fadiga, and Rizzolatti, 1996; Grezes, Armony, Rowe, and Passingham, 2003; Grezes and Decety, 2001; Hari et al., 1998; Rizzolatti, Fadiga, Matelli et al., 1996). The MNS is also activated during *imitation of action* (Iacoboni et al., 2001; Iacoboni et al., 1999; Nishitani and Hari, 2000) and reciprocal imitation (Buccino, Solodkin, and Small, 2006; Decety, Chaminade, Grezes, and Meltzoff, 2002), including face imitation (Carr, Iacoboni, Dubeau, Mazziotta, and Lenzi, 2003; Leslie, Johnson-Frey, and Grafton, 2004). The MNS is most probably the substrate of *action understanding* (Buccino et al., 2001; Fadiga et al., 1995; Flanagan and Johansson, 2003; Gallese et al., 2002; Keysers and Perrett, 2004): by having he same neural substrate being activated by both action observation and action execution, the MNS provides an automatic simulated re-enactment of the same action (Gallese, 2003a).

In addition to action understanding, there are evidences that the MNS is involved into understanding others's intentions (Iacoboni et al., 2005), and in the *prediction of other people action goals.* In a recent study, Falk-Yter and colleagues (Falck-Ytter, Gredeback, and von Hofsten, 2006) tested the hypothesis that if the MNS is involved in social cognition, then it should be functional at the time of before children achieve communication by means of gesture or language, around 8 to 12 months of life. Using an elegant paradigm, they searched for the presence of proactive goal-directed eye movements at 6 months and at 12 months. They showed that when observing actions, 12-month-old infants focus on goal in a way similar to that of adults, whereas 5-month old infants do not, and concluded that the MNS underlies the ability to predict the outcome of others' actions and is mediating processes related to social cognition.

This model of *action understanding through shared representation* may also be applied in the domain of *emotion*, and the MNS has been hypothesized by several groups as being the possible basis of "mind reading", imitation learning, and empathy, and a neural substrate for human social cognition (Gallese, 2003b; Gallese and Goldman, 1998). According to this model, emotions are understood when implicitly mapped onto our motor representation through mirror mechanisms. This model was illustrated by the work of Leslie et al. (Leslie et al., 2004), who found a common substrate subserving both facial expression and hand gesture observation and imitation in healthy controls, with a right hemispheric dominance for facial expression passive observation.

Facial Expression Mimicry

Facial expressions of emotion have a biological basis (Darwin, 1965) and are generated by biologically given affect programs (Ekman, 1993; Tomkins, 1962) that are independent of conscious cognitive processes. Humans have a natural predisposition to react emotionally to facial stimuli (Dimberg, 1997), and to have facial reactions to facial expressions (Dimberg, 1982, 1997; A.N. Meltzoff and Moore, 1977, 1983)

Dimberg et al. (Dimberg and Thunberg, 1998) have shown that subjects exposed to facial expressions of anger or happiness tend to activate muscles that are normally involved in the production of these facial expressions, implying mimicry of the facial stimulus occurring as early as 300ms after stimulus onset. The same facial electromyographic reactions can even be elicited when people are unconsciously exposed to facial emotional expression, using short duration stimulus exposure (30ms) and a backward-masking (Dimberg, Thunberg, and Elmehed, 2000), showing that emotional reactions can be unconsciously evoked. Moreover, a significant interaction has been reported between facial muscle reaction, self-reported feelings and emotional empathy (Sonnby-Borgstrom, 2002).

Imitation and observation of emotional facial expressions activate a similar network of areas, including the IFC, the STS, the insula and the amygdala, suggesting that we understand other's feeling by a mechanism of action representation (Carr et al., 2003; Nakamura et al., 1999), and facial mimicry can be understood as a feedback system in which the facial muscle activity provides proprioceptive information and influences the internal emotional experience.

There is a large degree of overlap between neural substrates of emotion perception and emotional experience, and deficits in the production of an emotion and deficits in the face-based recognition of that emotion reliably co-occur: patients with insula damage, an area

implicated in the experience of disgust, are also impaired at facial recognition of disgust (Calder, Keane, Manes, Antoun, and Young, 2000; Sprengelmeyer et al., 1996; Wicker et al., 2003); similarly, patients with bilateral amygdala damage, a region involved with experience and recognition of fear, have trouble recognizing facial expression of fear (Adolphs, Tranel, Damasio, and Damasio, 1994; Adolphs, Tranel, Damasio, and Damasio, 1995; Bechara et al., 1995). Lesion of the somatosensory cortex in the face area impairs face emotion recognition (Adolphs, Damasio, Tranel, and Damasio, 1996). Conversely, voluntary facial action generates emotion-specific autonomic nervous system activity (Adelman and Zajonc, 1989; Levenson, Ekman, and Friesen, 1990).

All these above observations are in line with Damasio's somatic marker hypothesis (Damasio, 1994, 1999) describing the mechanism by which we acquire, represent and retrieve the values of our actions. According to this model, the feeling of emotions relies on the activation of internal activation of sensory maps, that create a representation of the changes experienced by the body in response to an emotion. A similar mechanism for empathy can be postulated, by which the same sensory maps are activated when observing emotions in others via a mirror system mechanism.

In conclusion, the MNS may be neuronal substrate of imitative behavior and empathy, and a system allowing us to understand others' goals and actions. Imitation, empathy and the understanding of other's goal all seem to be abilities that are challenged in autism. What evidences do we have that these might be the consequences from a deficient MNS?

AUTISM AND MNS

Imitative Deficits in Autism

Several studies have found imitative deficits in autism (for review, see (Williams, Whiten, and Singh, 2004)). Autistic children have deficits in imitating simple body movements and actions with symbolic meaning (Rogers and Pennington, 1991). In infants, Charman et al. (Charman et al., 1997) have found that compared with developmentally delayed and normally developing children, 20-month-old infants with autism were specifically impaired on some aspects of empathy, joint attention, and imitation, pointing to a basic-level imitation impairment in autism. Individuals with autism tend to have limitations in imitating the "style" of another person's action (Hobson and Lee, 1999), and they tend to lack the natural preference for imitation in a mirror-image fashion (Avikainen, Wohlschlager, Liuhanen, Hanninen, and Hari, 2003). Moreover, children with autism have an impairment in imitation of facial expression of emotion (Hertzig, Snow, and Sherman, 1989; Loveland et al., 1994).

Anatomical and Functional Studies of MNS in Autism

The hypothesis of a deficient MNS in autism was first formulated in 1999 by Riitta Haris's group (Avikainen, Kulomaki, and Hari, 1999) and two years later Williams et al. published the first review on imitation, mirror neurons and autism (Williams, Whiten, Suddendorf, and Perrett, 2001). In this paper, Williams and colleagues underline the role of a deficit in early imitation as part of the autistic development, and point to the important

resemblances that exist between imitation and the attribution of mental states, as both involve the translation from one perspective to the other. They offer a series of testable predictions that flow from their hypothesis of a deficient MNS in autism – and anatomical and functional studies have been done for the past four years that support their proposition.

Anatomical Studies

The anatomical substrate of autism is still unknown. Our group conducted a MRI study in a group of autistic adults carefully matched for gender, age, intelligence quotient and handedness (Hadjikhani, Joseph, Snyder, and Tager-Flusberg, 2006b). The technique we used (Fischl and Dale, 2000) allows a precise measure of the thickness of the cortical mantle, validated by histological measures (Rosas et al., 2002). We found that adults with HFA display significantly reduced cortical thickness in areas of the MNS, including the pars opercularis of the inferior frontal gyrus, the IPL and the STS. In addition, the degree of cortical thickness decrease was correlated with the severity of communicative and social symptoms of the subjects.

Our data represent a snapshot in time, and prospective studies are needed to understand the direction of the causality between MNS function and symptomatology. However, from these data we can postulate that an early dysfunction of the MNS may be the 'primum movens' of the deficits in imitation, empathy and experiential sharing present in autism.

Magnetoencephalographic Studies

Magnetoencephalography (MEG) is a method which allows us to measure the minute magnetic field changes associated with brain electrical activity non-invasively with a millisecond resolution. The spatial resolution is enhanced compared to EEG due to the skull not smearing MEG signals (Hamalainen, Hari, Ilmoniemi, Knuutila, and Lounasmaa, 1993). MEG directly relates to neural activity and yields dynamic images that inform us about the speed of the neural processes as well as their sequence in the different brain areas involved. This allows separate examination of the integrity of the different components of a network and their individual role in brain activation.

The first study testing the hypothesis of a deficient MNS in autism was performed using MEG by Hari's group in Finland. The results of this first study, however, were negative, and no differences could be found between autism subjects and the controls. However, in 2003 the same group (Avikainen, Wohlschlager, Liuhanen, Hanninen, and Hari, 2003) pursued this hypothesis and showed in a behavioral experiment that Asperger subjects, unlike normal controls, did not profit from mirror-image movement of others during an imitation task. A year later they published another MEG study (Nishitani, Avikainen, and Hari, 2004) showing delayed and weaker activation of the inferior frontal lobe and of the primary motor cortex in Aperger subjects during imitation of still pictures of lip forms, providing evidence of MNS dysfunction.

Transcranial Magnetic Stimulation Studies

Transcranial magnetic stimulation (TMS) uses rapidly changing magnetic fields to induce electric fields in the brain. With TMS, cortical excitability in chosen areas of the brain can be temporally modulated to test hypotheses relative to their involvement in task performance. Theoret et al. applied TMS over the primary motor cortex (M1) during observation of

intransitive meaningless finger movements (Theoret et al., 2005). They revealed an impairment in the system matching action observation and execution in autism, with a failure of the observation of movement to modulate the excitability of the motor cortex, and concluded that a dysfunction of the MNS could underlie the social deficits characteristics of autism.

Eletroencephalographic Studies

Two eletroencephalographic (EEG) studies have been conducted so far examining the MNS in autism, and they both concluded to the existence of MNS dysfunction in autism (Lepage and Theoret, 2006; Oberman et al., 2005). The study by Oberman et al. (Oberman et al., 2005) examined the responsiveness of EEG oscillations at the mu frequency (8-13 Hz) to actual and observed movement. In normal controls, it is known that mu power is reduced both when the individuals perform as well as when they observe an action, reflecting an observation/execution system. In adults and teenagers with autism, they observed that while mu power was reduced during action performance, it was unchanged during action observation, supporting the hypothesis of a dysfunctional MNS in autism. The same data were observed by Lepage et al. (Lepage and Theoret, 2006) in children with autism.

Functional MRI Studies

Two fMRI studies have recently been published examining the function of the MNS in autism (Dapretto et al., 2006; Hadjikhani, Joseph, Snyder, and Tager-Flusberg, 2006a).

In the study by Dapretto et al. (Dapretto et al., 2006), children with autism were examined during observation and imitation of facial emotional expressions and compared with typically developing children. Both groups were able to perform the imitation task – however, only the typically developing children showed enhanced activation in the pars opercularis of inferior frontal gyrus, while the autism children had no mirror neuron activity in that area. The same pattern was observed during passive observation of facial expressions. In addition, and similarly to the findings of the anatomical study described above (Hadjikhani et al., 2006b), an inverse correlation was found between the level of brain activity in the pars opercularis of inferior frontal gyrus and the severity of symptoms in the social domain, further suggesting a relationship between MNS dysfunction and social deficits in autism.

Our study (Hadjikhani et al., 2006a) was the follow up of our first examination of face perception in autism (Hadjikhani et al., 2004). In our first study, we had challenged the findings of other groups reporting no 'face area' (FFA) activation in autism subjects when viewing faces. By introducing a fixation cross in the eye-region of the face and asking the subject to fixate it, we ensured that the subjects were actually looking at the faces – it is indeed well known that autistic subjects tend to avoid looking at faces, especially at the eye-region (Dalton et al., 2005; Klin, Jones, Schultz, Volkmar, and Cohen, 2002; Pelphrey et al., 2002). By using this strategy, we were able to show robust activation in the FFA of autistic subjects, that did not differ from that of normal controls. However, it is known that autistic subject have behavioral deficits with faces, and that they have difficulty recognizing facial expressions. To identify the substrate of this deficit we examined another group of adults with autism, using the same stimuli as in our first study. However, we this time we acquired data covering the entire brain as opposed to only examining the visual regions as we had done previously (Hadjikhani et al., 2006a).

We replicated our initial results of robust FFA activation during face perception in autism (see also (Aylward, Bernier, Field, Grimme, and Dawson, 2004; Dalton et al., 2005; Pierce, Haist, Sedaghat, and Courchesne, 2004)). But we found that areas of the MNS were hypoactivated in the HFA compared to controls. We also found hypoactivation in right motor and somatosensory cortex corresponding to the face representation. Furthermore, and similarly to the findings of Dapretto et al. (Dapretto et al., 2006), we found an inverse correlation between the activation in the IFC and the severity of the social symptoms.

In addition to these findings, we found that the hypoactivated areas in the HFA group that were overlapping with areas of cortical thinning observed in another group of HFA patients in the anatomical study described above (Hadjikhani et al., 2006b).

We concluded that areas belonging to the MNS are involved in the face-processing disturbances in autism.

Electromyographic Studies

Individuals with autism are delayed in comprehending the meaning of facial expression and communicative gestures (Braverman, Fein, Lucci, and Waterhouse, 1989), and the ability of autistic children to imitate facial expression of emotion is limited (Hertzig et al., 1989; Loveland et al., 1994). A recent electromyographic (EMG) study casts light on both fMRI results described above (McIntosh, Reichmann-Decker, Winkielman, and Wilbarger, 2006). McIntosh et al. examined automatic and voluntary mimicry of facial expressions of emotions in adolescents and adults with autism, using the same protocols as those used by Dimberg et al (see above, and (Dimberg, 1982)). They found that while both autistic subjects and controls were able to produce voluntary mimicry, autistic subjects did not show any automatic mimicry of facial expression.

The production of voluntary and automatic emotional facial movements depends on two dissociated neural circuits, that can selectively be affected. Selective loss of voluntary facial expression, Foix-Chavany-Marie syndrome, is a classical clinical finding in stroke; but the selective loss of emotional facial movement while voluntary facial movement are preserved has also been described (Sim, Guberman, and Hogan, 2005).

Emotional facial mimicry is an automatic process that relies on the MNS, and the emotion deficits present in autism could be explained by a basic deficit in the MNS system.

In summary, a number of anatomical and functional studies all seem to point to dysfunctions of the MNS in autism.

Implication for Treatment

As mentioned in the introduction, most of the studies presented here, showing evidence of MNS dysfunction, were conducted in a subgroup of ASD, namely HFA or Asperger syndrome, and they may not pertain to mentally retarded autistic subjects. However, a dysfunction of the MNS in HFA may open interesting therapeutical approaches.

The brain is a plastic organ, and training can modify its structure and its function. This has been shown in the animal model: motor skill learning increases cortical thickness in rats (B. J. Anderson, Eckburg, and Relucio, 2002; B. J. Anderson et al., 1994), implying that the repetitive environmental demand leads to structural changes in the brain. Similar results have recently been shown in humans: increases in gray matter have been shown in volunteers

learning to juggle (Draganski et al., 2004), in musicians (Gaser and Schlaug, 2003), and in bilingual individuals (Mechelli et al., 2004). In all these cases, brain gray matter increase corresponds to skill-training, and was probably due to an increase in the number of connections in the neuronal population.

An approach consisting in a training of imitative skill may be a valid way to develop not only imitation per se, but also socio-cognitive aspects in autism. Recent data from Wallen and Bulkeley showing that three sessions of adult imitation increased some appropriate social behaviors of young children with autism, supports this hypothesis (Wallen and Bulkeley, 2006).

FUTURE RESEARCH DIRECTION

Several questions need to be answered regarding the functioning of the MNS in autism. First, is the MNS primarily deficient, and are the behavioral abnormalities a consequence of this, or is there another primary problem that results in an 'involution' of the MNS in autism? Second, does behavioral therapy have any effect on the MNS structure and function? And ultimately, we will need to understand what are the genetical/environmental mechanisms leading to a MNS dysfunction in autism.

Longitudinal and prospective studies will be needed to answer these questions.

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