

Possible Links among Mirror Neurons and Genes Related to Autism

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Abstract

Autism includes many neurodevelopmental disorders and deficits in communication. Although researchers have considered various origins, the onset mechanism is still not clear. The aim of this article is to provide some clues for interaction of autism with mirror neuronal and genetic factors. First, the impact of neural brain cells considered to influence autism will be discussed with reference to mirror neurons. Then, the discussion will move to genes related to autism. Consequently, it is argued that a single factor cannot explain the mechanism of autism, yet the relations among various factors are responsible for autism.

Keywords: Autism, Mirror Neurons, *CAPS2*, *SHANK3*, *CTNND2*, *FOXP2*

0. Introduction

Autism is well known for its relation to deficits in communication and impaired social interaction. The mechanism of autism has been investigated. However, it is not fully clear. It seems obvious that many factors are involved in autism; for example, mirror neurons or genes and so on. This article shows the relation between autism and these factors. Section 1 revisits autism, its definition, and characteristics. In section 2, we explore the relation between autism and mirror neurons. Section 3 discusses the related genetic factors to autism. *CAPS2*, *SHANK3*, and *CTNND2* will mainly be introduced. Section 4 considers the implications of recent studies and makes some proposals. Finally, in section 5, we summarize the ideas in this article and suggest a future perspective.

1. Autism and its Symptoms

Autism is a well-recognized impairment for communication. However, the causes and symptoms are not fully recognized. Autism is recently called, “Autistic Spectrum Disorder (ASD).” It is a range of conditions classified as neurodevelopmental disorders in American

Psychiatric Association ed. (2000) *Diagnostic and Statistical Manual of Mental Disorders* 5th edition (DSM-5). The main symptoms are a delay in speech development, echolalia, difficulty in imitating, non-verbal communication disorder, and difficulty in joint attention.

Autism has some characteristic symptoms. The characteristic behaviors of ASD may be apparent in infancy (18 to 24 months), but they usually become clearer during early childhood (24 months to 6 years) (Autism Society of America). The American Autism Association provides main symptoms as follows:

1) Communication Impairments

- Delays in development of spoken language
- Idiosyncratic repetitive language
- Lack of pragmatic aspect of language
- Inability to initiate or maintain language

2) Social Interaction

- Lack of appropriateness in verbal and non behavior
- Lack of ability to develop peer relationships
- Lack of apparent social and emotion reciprocity

3) Behavior Patterns

- Restricted, repetitive and stereotyped patterns of behavior
- Difficulty in motor control
- Peculiar attachment to inanimate objects
- Distressed by a change in routine

(American Autism Association 2015)

Alternatively, autism has a lot of pathognomonic characteristics. Although the typical characteristics of autism are mentioned above, the Autism Society of America shows more signs to look for in children as follows:

- Lack of or delay in spoken language
- Repetitive use of language and/or motor mannerisms (e.g., hand-flapping, twirling objects)
- Little or no eye contact
- Lack of interest in peer relationships
- Lack of spontaneous or make-believe play
- Persistent fixation on parts of objects

(Autism Society of America 2015)

It follows that a child who shows these symptoms is suspected to have autism.

2. Mirror Neurons

Mirror neurons consist of nerve cells producing an action potential in the brain such as primates. They react like “mirrors,” and are therefore named “Mirror neurons.” This system is called, the “Mirror Neuron System (MNS)” which is thought to control sympathy. The mirror neuron was discovered by a group of Italian researchers led by Giacomo Rizzolatti in 1996. He recorded neuronal activity related to specific movement when a macaque monkey was going to eat food. He showed that the neuron of approximately 10% of the inferior frontal cortex and inferior parietal cortex of the monkey showed a similar reaction to both the specific hand movement and the overall movement. Conclusive evidence of the existence of the human mirror neuron is not provided because the experiment (installing an electrode in the inferior frontal cortex of the macaque monkey) is non-replicable in human subjects. However, it is clear that inferior frontal gyrus and the superior parietal lobe of the Homo Sapiens showed activity in both when they observed an action that a subject acted time and others by a brain imaging study by fMRI (functional magnetic resonance imaging). Given the data of the newborn baby of the Homo Sapiens using the eye-tracking device, the mirror neuron system develops by 12 months after birth, and it assists a newborn baby in understanding the action of others (Terje et al. 2006).

Recently, it is pointed out that autism results from the mirror neuron defect. Although scientists have conducted some research, this relation is not yet clear. We will consider other related factors in the next section.

2.1 Empathy

One of the characteristics of autism is a lack of empathy and emotional engagement with others (APA, 2000; C.L. Gillberg, 1992). Empathy is the ability to share someone else’s feelings. Human beings usually possess sympathy instinctively. However, Preston and de Waal (2002) define 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 an early sign of autism (Charman et al. 1997, Sigman, Kasari, Kwon, and Yirmiya 1992), and we have shown empathic behavior deficits as early as 20 months of age in children with autism.

2.2 Imitation

Lack of ability to imitate is also a characteristic of autism. Imitation plays a central role in the development of understanding other people, as both imitation and the attribution of mental states involve translation from another person’s perspective into one’s own (Hadjikhani 2007). This ability indicates the presence in the newborn of an active intermodal matching. Because they do not see their face, only the way newborns can match expressions is thought proprioception (A.N. Meltzoff and Moore, 1997). Until recently, it was thought that neonatal imitation was unique to apes and humans, but recent data has shown the capacity to match facial and hand gesture is also present in rhesus macaques (Ferrari et al. 2006).

2.3 Facial Expression

Facial expression is present in mammals mainly. The facial expression of emotion has a biological basis (Darwin 1965). Poverty of facial expression is also one of the characteristics of autism. Furthermore, most autistic children do not meet eyes with another person. This is possibly connected to joint attention. Joint attention is the shared focus of two individuals on an object. Joint attention is hard to develop in children with autism. It has understanding and expression. First, a baby understands the thing that others see, and the stage appears that the joint ownership of eyes is watching together. Next, they understand the thing that others prick with a finger. Then, they ask for joint attention themselves; for example, a baby shows others an object to attract their attention. This connects with the theory of mind that we argue in the next section.

2.4 Theory of Mind

Theory of Mind (ToM) is the ability to attribute mental states including beliefs, intents, desires, pretending, and knowledge. ToM refers to the notion that many autistic individuals do not understand that other people have their own plans, thoughts, and points of view (Autism Research Institute). Furthermore, it appears that they have difficulty understanding other people's beliefs, attitudes, and emotions. The origin of this is a philosophical debate. ToM was originally based on Premack and Woodruff (1978). Primates such as chimpanzees pay attention to what other animals of similar species feel or think and act accordingly. They discovered this function worked and called it "Theory of Mind."

The ToM development begins early in life. At five months of age, typical children can recognize different facial expressions, but understanding the meaning occurs a few months later (Indiana Resource Center for Autism). Once young children can reliably interpret the facial expressions of others, and begin to use this nonverbal information to guide their behavior. Most investigation of ToM development has focused on 3 to 4-year-old children. It is evident that there is a rapid development in this area between the ages of 3 to 4. Three-year-olds typically fail to recognize their own and other's false-beliefs (holding beliefs that conflict with reality). Wimmer and Perner (1983) developed a means of measuring false-belief understanding, and although many subsequent studies have modified the task, the classic false-belief task is as follows:

A story character, Maxi puts chocolate into a cupboard x. In his absence his mother displaces the chocolate from x into cupboard y. Subjects have to indicate the box where Maxi will look for the chocolate when he returns. Only when they are able to represent Maxi's wrong belief ('Chocolate is in x') apart from what they themselves know to be the case ('Chocolate is in y') will they be able to point correctly to box x. (Wimmer and Perner: 1983: 106)

Correct responses to false-belief tasks increase with age: children at 30 months answer false-belief questions correctly only about 20% of the time. Children at 44 months are correct about 50% of the time, and at four years of age children perform better than chance, answering most correctly (Wellman et al., 2001). Various studies have shown that the majority (around 80%) of children with autism, even those with average intelligence, fail measures of false-belief (Baron-Cohen, 1993). In other words, children with autism across the age span will often answer that Maxi will immediately search for the candy in the drawer. As typical children mature, they increasingly would understand Maxi's perspective and would suggest that Maxi would search for candy in the cabinet.

All autistic children do not necessarily fail in the false-belief task. Therefore, the Theory of Mind hypothesis is still disputed.

3. Autism and Other Factors

In the previous sections, I have argued for the relation between autism and mirror neuron. In recent years, new possibilities have been pointed out. The recent autistic study develops into genetics. The rate of autistic boys is double the rate of girls (Rutter et al. 1990). Moreover, monozygotic twins have a higher ratio of autism than dizygotic twins (Folstein & Rutter 1997). Some genes that may affect autism are as follows:

3.1 *CAPS2*

We expect that the study of *CAPS2* will lead to an elucidation of the onset mechanism of autism.

Sadakata et al. hypothesized that *CAPS2* is a candidate autism susceptibility gene (Sadakata et al. 2007 and Sadakata et al. 2009). Therefore, they conducted tests on mice and obtained a relevant result (see Sadakata et al. 2013). They suggest that adequate levels of *CAPS2* protein should be critical for normal brain development and behavior and that allelic changes due to copy number variation (CNV) may contribute to autistic symptoms in combination with deficits in other autism-associated genes.

3.2 *SHANK3*

It is likely that the mutation of *Shank3* is related to autism. Lana et al. conducted tests and obtained a relevant result (Duffney et al. 2015). The *Shank3* gene, located on chromosome 22q13.3 in humans, was first implicated in ASD from genetic analysis of the 22q13.3 microdeletion syndrome (Duffney et al. 2015). They discovered that *Shank3*-deficient mice exhibit autism-like social deficits and repetitive behaviors, as well as the significantly diminished NMDA receptor (NMDAR) synaptic function and synaptic distribution in the prefrontal cortex. Interestingly, they found that juvenile male *Shank3*-deficient mice exhibited ASD-like behavioral deficits, including social interaction deficiency and repetitive grooming

(Duffney et al. 2015). This study may lead to an explanation for why that there are more autistic boys than girls.

There is another result of research on *Shank3*. Researchers at MIT and Duke succeeded in recreating autism, in mice (MIT News 2011). The researchers focused on *Shank3*, which mutated in mice used for this study. They show that mice with *Shank3* deletions exhibit self-injurious repetitive grooming and deficits in social interaction (Peca et al. 2011). Their findings demonstrate a critical role for *Shank3* in the normal development of neuronal connectivity and establish causality between a disruption in the *Shank3* gene and the genesis of autistic-like behaviors in mice.

3.3 *CTNND2*

Recently, a new factor was discovered. As I have mentioned earlier, autism emerges in more men than women. However, this gene was discovered in a female autistic. Turner et al. (2015) investigated the genes of 13 women who suffered from severe autism. As a result of the investigation, in the genes of 13 people, much mutation was observed in heredity sequence named *CTNND2* in comparison with persons who do not have autism. It is a major discovery to find a gene peculiar to a women.

4. Discussion

A relation between autism and certain factors has been argued. Due to the development of the brain imaging study, neuroscience has been paid much attention. Moreover, the recent autism study is mainly based on genetics. The relations between autism and mirror neurons have been pointed out, but recently the genetic factor is also investigated. Thus, it is clear that autism is not attributed to only one factor. If there are such interactions, they may explain the impairment severity in sex differences with regard to symptoms. The sex differences are relevant to *Shank3* (Duffney et al. 2015). It was a result that there were many ratios of the autism of male mice. Autism is four times more prevalent in male than female (Kogan 2007). On the other hand, a gene peculiar to women is discovered (Turner 2015). We discovered many mutations in heredity sequence called *CTNND2*. In the explanation on mice, the gene showed an influence on the hippocampal neurons that were important to the long-term memory of the brain. This genetic study needs further research. Note also that monozygotic twins have a higher ratio of autism than dizygotic twins (Folstein & Rutter 1997). Thus, it is obvious that a hereditary factor is related to autism.

Also, *FOXP2* may well be related to autism. This gene was first found to be involved in a speech and language disorder. The disorder was first discovered in a British family known as KE family. Various disruptions in the *FOXP2* gene have been reported, and the symptoms caused by disruptions mentioned above tend to include a broad spectrum of deficits, including speech and language problems, verbal dyspraxia, low-performance IQ, developmental delay,

and brain abnormalities (Nudel et al. 2013). Moreover, as a thorough study on genes repressed by *FOXP2*, *CNTNAP2* has been implicated in disorders such as specific language impairment and autism, among others, it shed some light on the mechanism through which *FOXP2* may influence speech and language (Nudel et al. 2013). Practically, autistics have a speech impediment. *FOXP2* may control other genes, and mutations may happen in genes such as *CAPS2* by an accident of *FOXP2*. Because it is clear that *FOXP2* is related to speech, further study of *FOXP2* and autistic genes is expected in future research.

Considering the circumstances mentioned above, it is clear that there is a relation between autism and genetic factor is obvious. Autism has several symptoms (see section 1.1.), and there is an individual difference. The optional factors such as genes or mirror neurons may cause these factors. It is the mutation of *FOXP2* that may trigger some mutations of several genes causing autism. However, further research is necessary to conform this speculation.

On the other hand, there is quite a unique case --- Christopher. He is a language savant. Savants are people who are mentally and often physically impaired but who have one dazzling talent; mathematical, artistic or musical ability (Smith and Tsimpli 1995). Normally savants have language impairment and low-performance IQ. However, Christopher can read, write, translate and communicate in fifteen or twenty different languages. In this case, there may be no mutation of *FOXP2*. It may be the case that only mutation of other genes is involved. Further study of this case is necessary for the future.

5. Conclusion

What we have so far observed is that the relations among various factors are responsible for autism. The recent cutting-edge imaging research allows us to study autism in many aspects. As it stands, the mechanism of autism is still mysterious and difficult to elucidate. However, new factors such as *CAPS2*, *SHANK3*, and *CTNND2* among other genes would lead to elucidation of the mechanism of autism. There will be more discoveries about the mechanism of autism in the future. Especially, an interdisciplinary study of autism is indispensable for the elucidation of the mechanism. Consequently, we may also discover new genes that may be peculiar to language (the faculty of language).

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Internet Resources

Autism Society

<http://www.autism-society.org/what-is/symptoms/>

American Psychiatric Association

https://www.appi.org/Course/Book/Subscription/JournalSubscription/id-3457/DSM-5®_Classification?utm_source=Internal-Link&utm_medium=Banner-Row&utm_campaign=DSM-5-Classification

American Autism Association

<https://www.myautism.org>

Autism Research Institute

<http://www.autism.com>

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