

# Walk like me, talk like me

## *The connection between mirror neurons and autism spectrum disorder*

Jillian M. Saffin, BS, RBT, Hassaan Tohid, MBBS.

### ABSTRACT

فهم الإدراك الاجتماعي يعد السمة المميزة في فك رموز طيف التوحد. فالنظريات العصبية تأخذ الدراسات السببية في عين الاعتبار، وينظر الباحثون إلى التشوّهات في تطور الدماغ كسبب في عجز السلوك الاجتماعي، والمعرفي، واللغوي. بعد اكتشافهم في 1990م أصبحت الخلية العصبية المرآتية نظرية سائدة للنظام العصبي المرآتي الذي يلعب دوراً حاسماً في الفيزيولوجيا المرضية لمرض التوحد. على مدى عقود، تطورت النظرية من تلف في النظام العصبي المرآتي إلى عجز دوائر الخلايا العصبية. لم يحصل النظام العصبي المرآتي على الدعم الكامل نتيجة عدم تناسق النتائج، نسلط الضوء هنا على تحليل شامل لمجموعة الأبحاث أو مساوئ استمرارية دراسة الخلايا العصبية المرآتية وعلاقتها بالتوحد.

Understanding social cognition has become a hallmark in deciphering autism spectrum disorder. Neurobiological theories are taking precedence in causation studies as researchers look to abnormalities in brain development as the cause of deficits in social behavior, cognitive processes, and language. Following their discovery in the 1990s, mirror neurons have become a dominant theory for that the mirror neuron system may play a critical role in the pathophysiology of various symptoms of autism. Over the decades, the theory has evolved from the suggestion of a broken mirror neuron system to impairments in mirror neuron circuitry. The mirror neuron system has not gained total support due to inconsistent findings; a comprehensive analysis of the growing body of research could shed light on the benefits, or the disadvantage of continuing to study mirror neurons and their connection to autism.

*Neurosciences 2016; Vol. 21 (2): 108-119  
doi: 10.17712/nsj.2016.2.20150472*

*From the Department of Psychology (Saffin), Northern Arizona University, Arizona, and the Department of Neurology (Tohid), University of California, Los Angeles, UCLA, the Center for Mind & Brain (Tohid), the Department of Neurology (Tohid),*

*University of California, Davis, Davis, and the Department of Psychiatry (Tohid), Napa State Hospital, California, United States of America.*

*Received 28th August 2015. Accepted 9th December 2015.*

*Address correspondence and reprint request to: Dr. Hassaan Tohid, Center for Mind and Brain, Fairfield, California, United States of America. E-mail: hassaantohid@hotmail.com*

Autism spectrum disorder (ASD) has exponentially regained public attention due to its increasing prevalence in the population.<sup>1</sup> Neurobiological models are beginning to replace neurocognitive schools of thought in order to observe underlying neurological abnormalities that could result in, or contribute to the impairments seen in individuals with ASD. Mirror neurons have taken the lead in neurobiological research to unify the social systems of the brain.<sup>2</sup> The extensive amount of research that has centered around mirror neurons and their connection to autism has led to a progressive understanding of social cognition -how different systems in the brain communicate in order to produce integrated messages of motor and symbolic behavior to generate social meaning. The first stages of mirror neurons research identified individual brain regions with mirror neuron activity; progressively, research has begun to view the mirror neuron system (MNS) as an integrative network that communicates information across multiple regions of the brain. The MNS has been found associated with empathy,<sup>3</sup> social reciprocation,<sup>4</sup> verbal and non-verbal communication, language, and several others.<sup>5</sup> These functions parallel symptoms observed in ASD.<sup>4</sup> The purpose of this review is to evaluate and compile current research on mirror neurons and their potential link to autism. Despite years of research, there remains some dissent in the role of mirror neurons in the brain. Evaluating current data information will direct future research potential and analyze the authenticity of the MNS as a dominant

theory in the involvement of mirror neurons in autism. The myriad of symptoms that characterize ASD, such as social deficits, impairments in verbal and non-verbal communication, repetitive or restrictive behaviors, abnormal social interaction, and restrictive specialized interests,<sup>6-8</sup> make it a complex disorder; and thus it has been difficult to unearth an exact pathophysiology. In 2010, it was estimated that 1 in 150 children were affected;<sup>7</sup> in 2015 that rate increased to approximately 1 in 50.<sup>9</sup>

As the name states, autism occurs on a spectrum, varying from mild impairments (high-functioning), to severe impairments (low-functioning). Those with high-functioning autism generally have less severe language and communication impairments; however, they still struggle with understanding figurative language, inferences, and language and intention comprehension.<sup>7</sup> The expanding pervasiveness of ASD in the population has led to a rapidly growing body of research into causes and cures. No majority settlement has been made on environmental versus genetic origins; however, the recent focus on neurobiological abnormalities in the brain allow scientists to observe the biological processes that are connected to the social, language, and cognitive deficits of neurodevelopmental disorders, such as autism. Since their discovery in the 1990s, mirror neurons have held a spotlight in neurobiological theories of autism.<sup>10</sup> The parallel of their functions in the brain to symptoms of autism has generated wide support and the hopes of more concisely understanding the effects of impairments in the social brain. Researchers originally discovered mirror neurons in Macaque monkeys while studying action execution and observation.<sup>11,12</sup> They were identified primarily in the premotor system, functioning in language processing and understanding the intentions of actions.<sup>13</sup> Mirror neurons fired when the monkeys performed an action and observed another monkey performing the same action.<sup>11</sup> Following this discovery, researchers extended their subject interest to humans, investigating the correlation between mirror neuron dysfunction and deficits in social behavior, language, and communication. After more than 2 decades, researchers have identified mirror neurons as being more complexly involved in social cognition than originally thought.<sup>13-15</sup> Their activities function to integrate visual, auditory, and motor stimuli to generate social cognitive processes.<sup>11,16-19</sup> The complexity of MNS, and the expansive and integrative influence it contains throughout the brain has made it difficult for researchers to fully understand its procedure of activity and the

phenotypes expressed by its dysfunction. Because humans have such a multifaceted system of social cognition and communication, appraising the value of mirror neurons in these processes has encountered inconsistencies in research and disagreement among the scientific community. Some researchers claim that the mirror neuron theory is too simple to account for all of human complexity,<sup>20,21</sup> or that it is too premature to warrant such substantial attention.<sup>22,23</sup> However, some recent research studies support this association, for example, a social cognition study by Rizzolatti and Sinigaglia<sup>24</sup> concluded that the parieto-frontal mechanism allows a person to understand the action of others, and provides a person a first-person grasp of the motor goals and others intentions.

Others view MNS as a unifying system with which to more wholly understand how social cognition is wired in the brain, and how impairments in different parts of the brain, or in the connections between them, affect social functioning.<sup>18,25-27</sup> Mirror neurons are specialized neurons that serve as a system of learning in social animals.<sup>28,29</sup> In primates, the MNS functions primarily in observing goal-directed behavior, recognizing motor actions,<sup>17,30</sup> and facilitating social cohesion.<sup>31</sup> The function of the MNS in humans parallels that of primates, but has evolved to cater to a more diverse social system<sup>28</sup> that involves motor action observation and execution<sup>11,32</sup> verbal and non-verbal communication,<sup>28,32</sup> behavioral, motor, and social communication and interpretation,<sup>14</sup> transitive and intransitive gestures<sup>33,34</sup> intention understanding,<sup>35,36</sup> intersubjectivity, and emotional understanding.<sup>15</sup> The integration of these multiple networks can lead to an array of variation in extent and type of impairments, a factor that has made understanding the MNS in humans quite complex. It is already known that there is a possible link of mirror neurons with ASD. However, the extent and exact mechanism behind this possible association is still not clear. It is also a mystery that “are mirror neurons damaged or affected in all autistic patients, or it is confined to some patients only”, and if some mirror neurons are affected in only some patients then what is the reason. We believe a complete pathophysiological knowledge will help us understand the answers to these kinds of question. Hence, this review is our attempt to accumulate various studies about the pathophysiological mechanism of autism and mirror neurons in order to unearth this association.

To study in depth regarding the association of mirror neurons with autism, a comprehensive review of published literature was conducted in PubMed. Articles

included were those relevant to the theme of mirror neurons, ASD, and autism. We searched the database PubMed using the keywords fMRI mirror which came out with 919 articles, autistic mirror that gave 143 total articles, autism brain imaging that provided 2186 papers, cognition mirror neurons showed 310 papers, mu rhythms gave 234 papers and mu rhythms autism provided only 5 papers. Autism mirror neurons gave 110 papers, ASD mirror provided 83, autism mirror gave 229, imitation autism provided 333, theory of mind autism provided 686, MNS autism gave 42, autism spectrum mirror gave 121, MNS ASD gave 29, MNS autism provided 117, ASD MNS gave 41, mirror neurons and autistic patients provided 8, MNS autism spectrum gave 73, mirror autistic 143, ventricles mirror neurons 3, empathy ASD 96, empathy mirror ASD 10, while empathy autism provided 357 papers. As of October 2015, this search revealed 6278 published, peer reviewed scientific articles. Out of these there were some repetition of the articles. Yet, the total was over 5500 articles.

The inclusion/exclusion criteria for our analyses were as follows: 1. Studies that explicitly mentioned the mirror system in the title, keywords or abstract were included, whereas those that did not were excluded; 2. Because most articles on the subject of mirror neurons are published after the year 1991, we maintained a strict selection criteria to include all the articles published after the year 1985 including autism, ASD and mirror neurons; 3. Articles published in low impact factor journals were excluded to maintain the high standard of the review. Moreover, articles with confusing and vague findings and no clear pathophysiological association of mirror neurons with autism or with no clear outcome were also excluded; 4. Most articles in the English language were selected. Articles in languages other than English were selected only if the English translation was available; 5. The criteria of data selection strictly included articles focusing on autism, ASD, and the MNS; 6. Articles only with animal or/and human data were included, and the selection was mainly focused on the studies with neuroimaging findings. Review articles or meta-analysis with the same focus were also selected; 7. Neuroimaging studies with fMRI and EEG with other non-invasive techniques, such as positron emission tomography (PET), single-photon emission tomography (SPECT), magnetoencephalography (MEG) and TMS were included. While any study with invasive techniques was excluded; and 8. Studies in which the authors did not attribute their fMRI results directly to the mirror system were excluded. One

hundred and thirty two of the 6278 scientific papers met this criterion.

**Review.** In humans, the MNS is linked to behavior, social, and communication skills,<sup>14</sup> language and speech,<sup>32</sup> and emotional interpretation.<sup>15</sup> The neurons play a role “action execution” and “action observation”.<sup>17,37,38</sup> It is also studied that representational granularity of the motor system is not different from the mechanism of mirroring during action execution.<sup>39,40</sup> In primates, mirror neuron activity was identified in the ventral premotor cortex and inferior parietal lobule,<sup>11,13,28</sup> and hippocampus.<sup>41</sup> While in non-human primates cortical regions outside the parietofrontal circuit, like mesial frontal cortex contain mirror neurons.<sup>42</sup> According to many mirror neuron research experts, these neurons in humans extend through the dorsal premotor cortex, somatosensory system, posterior temporal cortex, ventral premotor cortex, inferior frontal gyrus, inferior parietal lobe,<sup>7,16-18</sup> bilateral cerebellum, left medial frontal gyrus, right temporal lobe, and thalamus,<sup>19</sup> Mu suppression has been extensively studied in relation to MNS in the past few years. This suppression has been found to be associated with action observation.<sup>43</sup> Evidence exists that mirror neurons fire in response to observing and executing motor action behaviors.<sup>32</sup> Mirror neurons are thought to exist in a global population.<sup>25</sup> Furthermore, predictive neurons that fire preemptively in expectation of an action have also been studied.<sup>44-46</sup> Maranesi et al<sup>46</sup> studied mirror neurons in relation to action observation and described 2 kinds of mirror neurons. They called them action mirror neurons and inaction mirror neurons. Action mirror neurons fire during action observation, while inaction mirror neurons demonstrated predictive discharge. The same study concluded that MNS fire, on average, 340 milliseconds before the behavior occurs.<sup>46</sup> It is also studied that any damage to the parietal cortex affects the imitation or understanding an observed action. This does not only include one’s own actions but also of the others.<sup>44</sup>

Various studies support the concept that mirror neurons communicate through a series of network pathways involving connections between the amygdala-hippocampal circuit, caudate nuclei, the cerebellum, and frontal-temporal regions, and surprisingly these networks are found to be damaged in autism and ASD, which point to a possible connection in the pathophysiology of mirror neurons with autism.<sup>47</sup> We believe that these kinds of studies would revolutionize the concept of the association of mirror neurons with ASD and autism. Studies demonstrated that frontal-posterior circuits, posterior superior temporal sulcus, superior temporal gyrus, right inferior frontal gyrus,<sup>48</sup>

and anterior and posterior regions of the insular cortex have also been found to be associated with autism.<sup>49</sup> Thus, further investigation is warranted in these above mentioned regions of the brain to find any presence of the MNS. More or less the same idea of studying MNS in neural networks has also been described in some recent studies published after they year 2010.<sup>50-53</sup> The above evidence molds the discussion toward a possibility that pathophysiology of autism in relation to neural networks will help us further explore deep insight into a collective pathophysiology of autism and mirror neurons. Because it is observed that dysfunctions in these neural connections can cause impairments in social reciprocity, language communication, empathy, information processing, and cognitive demands,<sup>48,49,54</sup>

The EEG and fMRI neuroimaging studies of individuals with autism have observed lack of activity in the MNS<sup>55</sup> and instances of disrupted connectivity, that is under-connectivity, and/or over-connectivity in cortical networks when compared with neurotypical persons,<sup>49,56-61</sup> resulting in the brain functioning as a less cohesive unit.<sup>48</sup> Other studies involving EEG monitoring and fMRI imaging have failed to find significant differences in brain activity between those with autism and neurotypical individuals.<sup>62-64</sup> This disparity leads some researchers to suggest further studies are needed in order to account for complexity of social cognition in the human brain.<sup>10,22,62</sup> The current body of evidence of mirror neuron dysfunction is sufficient for others to warrant investment in neurofeedback treatment procedures.<sup>7,65</sup> Studies have found that autistic patients have benefited from neurofeedback training<sup>14,66</sup> and that environmental exposure can stimulate neural connection development, reducing disparity in symptomatic behavior observed between neurotypical individuals and those with autism,<sup>67-69</sup> as well as patients with damage to related brain structures.<sup>32</sup> (Table 1)

**Discussion.** The MNS continues to be a dominant neurobiological theory for autism. However, there remains too much disparity in the scientific community to begin discounting other current theories, or retreat from discovering new ones. Research conducted on mirror neuron function in neurotypical persons as opposed to those with ASD has produced inconsistent data.<sup>20,62,63,70</sup> This could be due to the nature of experiments that historically, have observed activity of the MNS in concentrated regions rather than as a neural circuitry system. Insight into the MNS has revealed that mirror neurons process communication across various brain regions rather than in focused concentration in specific areas.<sup>18,26,56,60</sup> Mirror neurons function to assimilate multiple strands of information

from various brain regions into a cohesive message.<sup>48</sup> Turning the focus of research to investigating anatomical abnormalities in neural circuitry could prove more conducive to understanding mirror neuron activity.<sup>60</sup> and how to implement treatment programs for ASD.

Mirror neurons fire when an individual observes and executes actions;<sup>11,18</sup> but in humans, compared to primates, the MNS is theorized to serve a more social function.<sup>17,18,28</sup> The MNS activity is present in infants as young as six months<sup>71,72</sup> and imitative behaviors have been observed in neonates in their first days of life<sup>73</sup> indicating that they immediately begin responding to their social environment. Discovering when the MNS begins to develop is a vital step in fully understanding how and when disruptions in neural circuitry occur, and thereby its influence on neurodevelopmental disorders. Early development of the MNS suggests it functions to facilitate social learning, social reciprocity, and to allow infants to communicate with and respond to their environment.<sup>72-74</sup> Being able to predict others' behavior would instigate the development of social cognition in which the infant learns the social nuances in its environment, how to use behaviors to get what it needs, and the subtle social cues that precede impending actions. Predicting the behaviors that follow preceding cues would require an initial understanding of the social environment. Infants as young as 6 months usually mirror activities performed by others before they have fully developed the motor skills to execute and imitate action behaviors and gestures.<sup>45,71,72</sup> This shows us that social imitation is a learned process; individuals do not respond to unfamiliar behavior the same way they mirror actions that have previously been observed, this phenomenon is also referred to as "brain mapping".<sup>45</sup> On the other hand, sensory-to-motor mapping is a process, in which the one observing an action creates a simulation in their mind.<sup>75</sup> These mapping procedures are pairing stimuli with an appropriate response, creating automatic response capability. When an action has not been previously mapped, automatic response and motor resonance are suppressed.<sup>76</sup> The maps created by infants in response to their early environment stimulate functional connectivity in the brain and influences skill development later in life.<sup>73</sup> Construing the meaning and intent of actions is an integral part of reciprocal social behavior. This mapping system allows individuals to build a repertoire of social meaning to communicate through motor, verbal, behavioral, and symbolic actions. Brain mapping not only functions to allow an individual to communicate with others, but serves to interpret their own internal stimuli<sup>77</sup> and integrate these stimulus-response behaviors with social meaning.

**Table 1 -** Relevant studies showing the association of the mirror neurons with autism.

| Authors/Publication Year                     | Country         | Study design    | Population  | Sample size | Diagnostic criteria   | Main findings  |
|--|-----------------|-----------------|---|-------------|---|--|
| Marshall and Meltzoff, <sup>74</sup> 2014    | USA             | Review          | N/A   | N/A         | N/A   | Early development of the MNS suggests it functions to facilitate social learning, social reciprocity, and to allow infants to communicate with and respond to their environment  |
| Cross and Iacoboni, <sup>76</sup> 2014       | USA             | Cross-sectional | 20 females and 17 males, after exclusion a total of 32 participants were included         | 37          | N/A   | When an action has not been previously mapped, automatic response and motor resonance are suppressed   |
| Gallese et al, <sup>78</sup> 1996            | Italy           | Cross-sectional | Monkey  | 2           | N/A   | 532 (17%) neurons in F5 of the macaque monkey fulfilled the criterion to be referred to as mirror neuron   |
| Murata et al, <sup>80</sup> 1997             | Japan           | Cross-sectional | Monkey  | 1           | N/A   | Canonical neurons exist, these are the neurons that respond just by observing a graspable object without performing any action   |
| Masconi et al, <sup>81</sup> 2015            | USA             | Review          | N/A   | N/A         | N/A   | Size and cerebellar circuitry is also affected in autism spectrum disorder   |
| Bailey et al, <sup>82</sup> 1998             | United Kingdom  | Cross-sectional | 6 ASD brains  | 6           | ADI   | Fewer cerebellar Purkinje cells are seen in ASD patients compared to controls  |
| Whitney et al, <sup>86</sup> 2009            | USA             | Cross-sectional | 6 autistic and 4 controls   | 10          | N/A   | Fewer cerebellar Purkinje cells are seen in ASD patients compared to controls  |
| Wegiel et al, <sup>87</sup> 2014             | USA             | Cross-sectional | 21 subject brains 18 controls (total 28 were selected after inclusion exclusion criteria) | 39          | Postmortem application of the ADI-R   | Fewer cerebellar Purkinje cells are seen in ASD patients compared to controls  |
| Von Hofsten and Rosander, <sup>91</sup> 2012 | Sweden          | Review          | N/A   | N/A         | N/A   | Mirror neurons possibly exist in cerebellum  |
| Pohl et al, <sup>100</sup> 2013              | Germany         | Cross-sectional | 32 (27 finally selected)  | 32          | N/A   | During imitation, higher activity in right hemisphere in the happy compared to the non-emotional condition in the right anterior insula and the right amygdala, plus pre-supplementary motor area, middle temporal gyrus and the inferior frontal gyrus was observed |
| Van der Gaag et al, <sup>102</sup> 2007      | The Netherlands | Cross-sectional | 17 healthy young adults(9 F, 8 M)   | 17          | N/A but Edinburgh handedness Questionnaire as selection criteria  | Amygdala was activated during observation of emotional and non-emotional facial expressions  |
| Sussman et al, <sup>108</sup> 2015           | Canada          | Cross-sectional | 194 autistic participants and 280 Developing control participants                         | 378         | DSM-IV  | Increase in size of the brain lobes of autistic individuals.   |
| Solso et al, <sup>110</sup> 2015             | USA             | Cross-sectional | 61 ASD patients 33 TD (typically developing)  | 94          | Autism Diagnostic Observation Schedule.<br><br>Vineland-II Adaptive Behavior Scales, Second Edition.<br><br>Mullen Scales of Early Learning | Increase size of the frontal lobe in ASD patients  |

**Table 1 -** Relevant studies showing the association of the mirror neurons with autism. (continued)

| Authors/Publication Year                | Country     | Study design    | Population  | Sample size                  | Diagnostic criteria   | main findings  |
|---|-------------|-----------------|---|------------------------------|---|--|
| Sato et al, <sup>119</sup> 2014         | Japan       | Cross-Sectional | 29 ASD<br>12 Asperger<br>17 Pervasive developmental disorder not otherwise specified (PDD-NOS)  | 58                           | DSM-IV-TR   | Age-dependent gray matter differences in prefrontal cortex, primary sensorimotor cortex, and temporoparietal junction  |
| Doyle-Thomas et al, <sup>120</sup> 2014 | Canada& USA | Cross-Sectional | 20 ASD patients   | 36                           | DSM-IV  | Autistic patients have elevated glutamate/ creatine in the putamen   |
| Damiano et al, <sup>121</sup> 2015      | USA         | Cross-Sectional | 16 Controls<br>26 ASD children  | 48                           | ADOS  | Right caudate nucleus activation during non-social negative reinforcement was linked with individual differences in social motivation  |
| Wolff et al, <sup>122</sup> 2013        | USA         | Cross-sectional | 22 Controls<br>30 Fragile X Boys<br>16 Idiopathic Autism  | 46                           | DNA testing using Southern blotting for Fragile X.<br>ADOS-G for autism | The caudate nucleus plays a role in the early pathogenesis of self-injurious behavior associated with both idiopathic autism and the caudate may be differentially linked with compulsive behavior |
| Marshall et al, <sup>123</sup> 2011     | USA         | Review          | N/A   | N/A                          | N/A   | mu rhythms that desynchronise in order to activate the mirror neuron system  |
| Cannon et al, <sup>126</sup> 2014       | USA         | Cross-Sectional | Total=33<br>8 Males<br>25 Females<br>-11 Females performers.<br>-10 (4 M , 6 F) were observers.<br>-12 (4 M, 8 F) Novices – were unfamiliar with the procedure and research | 33<br>8 Males<br>25 Females. | N/A   | Participants performing an action show the greatest mu rhythm desynchronization in the 8-13 Hz band, in the right hemisphere as compared to observers and novices                                  |
| Simpson et al, <sup>73</sup> 2014       | Italy       | Review          | N/A   | N/A                          |   |  |

N/A - not applicable, ADI- Autism Diagnostic Interview, DSM-IV - Diagnostic & Statistical Manual IV, ASD - Autism spectrum disorder, TD - Toddlers, MNS - mirror neuron system, ADI-R - Autism Diagnostic Interview-Revised, ADL - Autism Diagnostic Interview, ADOS-G - Autism Diagnostic Observations Schedule-Generic, ADOS - Autism Diagnostic Observation Schedule, DSM-IV-TR - Diagnostic & Statistical Manual IV Text Revision

If development of these maps is disrupted, impairments in neurotypical function could be observed in the stages when children are developmentally expected to begin performing the motor, social, and language skills they had previously observed. In the years to follow, we will get a clear picture of the relationship of brain mapping and sensory-to-motor mapping with autism. In addition, we believe it is imperative to correctly distinguish mirror neurons from another set of neurons called “canonical neurons” to correctly study the pathophysiology of ASD with mirror neurons.

Single-cell studies have shown that in order to be fit into the definition of “mirror neuron”, a neuron must be activated when observing an action as well as while executing an action. It is noteworthy that Gallese et al<sup>78</sup> demonstrated that 92 (17%) out of 532 neurons in F5 of the macaque monkey fulfilled the criterion to be referred to as mirror neuron. While it is also true that most fMRI studies include either observation or execution condition. Very few studies include both conditions. Conversely canonical neurons are the neurons that respond just by observing a graspable object

without performing any action. These neurons were initially studied by Rizzolatti et al<sup>79</sup> and later studied by Murata et al.<sup>80</sup> Thus, we believe that in order to properly understand the pathophysiology of autism with mirror neurons. Experiments involving both conditions “action observation” and “action execution” must be conducted. Brain areas common to autism, ASD and MNS. Several neuroimaging studies have shown the affected areas in autistic patients. As already discussed above, these areas include cerebellum, hippocampus and amygdala, cerebrum, ventricles and caudate nucleus. While mirror neurons are observed in the inferior frontal gyrus, ventral premotor cortex, and the inferior parietal lobule, visual cortex and the cerebellum. We will highlight each area which is involved in autism and also contains mirror neurons to get a better understanding about a possible pathophysiological connection.

**Cerebellum.** Many studies have revealed that cerebellum is affected in autism and ASD. A reduction in the size of cerebellum or certain parts of cerebellum are observed on imagining studies in autistic and ASD patients. In addition to the size, cerebellar circuitry is also affected in ASD which explains the sensorimotor impairments in these individuals.<sup>81</sup> Evidence shows that 35-95% fewer cerebellar Purkinje cells are seen in ASD patients compared with controls<sup>82-87</sup> and remaining cells show decrease in size.<sup>88</sup>

Surprisingly some studies hint toward the notion about a possibility of existence of mirror neurons in cerebellum.<sup>89-91</sup> Molenberghs et al<sup>92</sup> conducted a meta-analysis with 125 fMRI studies to study what areas contain mirror neurons. The analysis showed that 14 separate clusters are present in brain regions with mirror properties, surrounding 9 different Brodmann areas. These clusters were present in regions of brain, such as the inferior parietal lobule, inferior frontal gyrus and the ventral premotor cortex. Some unexpected area such as the primary visual cortex, cerebellum and areas of the limbic system also found to have these clusters.<sup>92,93</sup> However, still lack of number of studies makes this association dubious. Therefore, future investigations must be done to look for the possibility of the existence of mirror neurons in cerebellum. If consistent research studies found the same findings as above then we would be able to claim with confidence that mirror neurons are damaged in autism because cerebellum contains MNS.

**Limbic system (Hippocampus, amygdala and insula).** Hippocampus and amygdala of autistic individuals have small volume. Moreover, neurons in these areas are smaller and more tightly packed showing higher cell density. Involvement of the limbic system in autism has been extensively studied and enough evidence exists to

support this involvement.<sup>94-96</sup> In a rat study of autism spectrum and valproic acid, quantitative analysis of the thickness of the prefrontal cortex showed a decreased size in the cingulate 1 area of the prefrontal cortex and CA1 of the dorsal hippocampus in prenatally exposed animals compared with controls. At the level of the basolateral amygdala, a reduction in the size was observed at PD35 and PD70 in the valproic acid group. In addition, a reduced thickness was observed in the prelimbic parts of the prefrontal cortex in valproic acid animals at PD35.<sup>97</sup> The mirror neurons system is surprisingly also seen in motor cortex M1, M2, cingular cortex, hippocampus in mice groups in other studies of the same nature.<sup>98,99</sup>

The amygdala and insula were studied by Pohl et al during observation and execution of facial expressions. Individuals imitated, executed and observed happy and non-emotional facial expressions, the study also included seeing neutral faces. During imitation, higher activity in right hemisphere in the happy compared to the non-emotional condition in the right anterior insula and the right amygdala, plus pre-supplementary motor area, middle temporal gyrus and the inferior frontal gyrus was observed. Region-of-interest analyses revealed that the right insula was associated with imitation and execution than by observation of facial expressions and the insula was more activated by happy as compared to a non-emotional facial expressions during observation and imitation. It was also observed that the activation differences in the right amygdala between happy and non-emotional facial expressions were augmented during execution and imitation. Pohl et al<sup>100</sup> suggested that the insula and the amygdala contribute mainly to the happy emotion of the facial expressions. In the same study by Pohl et al,<sup>100</sup> the amygdala, a central part of the emotion-circuitry, was activated during observation of emotional and non-emotional facial expressions. Same results have been demonstrated in another study.<sup>101</sup> Stronger effect sizes of amygdala activation during observation of faces compared with pictures have been found.<sup>102</sup> Evidence shows that the amygdala also behaves as a ‘relevance detector’ during observation.<sup>103</sup> Affect-specific increase of the right amygdala during imitation and execution were also found by Pohl et al<sup>100</sup> Moreover, autonomic arousal and emotional experience is augmented by the execution of emotional facial expressions.<sup>104</sup> Furthermore, involvement of the insula in emotional tasks has been shown in several studies<sup>105-107</sup>

**Cerebral lobes.** Involvement of cerebral hemisphere and the lobes of the brain in autistic patient’s brain is well known. Size of the lobes is known to be increased in autism. Recent studies verify this information regarding

the changes in brain lobes in ASD and autism.<sup>108-110</sup> It is also discussed above and is also well known that the mirror neurons are located in the parietal and frontal cortex. In fact, action observation is found to be linked with premotor cortex and parietal lobe. It is also observed that dorsal areas like dorsal premotor cortex and superior parietal lobules observation respond more to observation of foot action as compared to hand and arm movements.<sup>111</sup> Some interesting findings by Keyser et al<sup>112</sup> showed that the secondary somatosensory cortex was activated both when individuals observed another person being touched, and when they were touched by someone or they touched themselves. These studies provided a rock foundation in the concept of mirror neurons.<sup>112</sup> Furthermore, another study claims that the primary somatosensory cortex is activated when we observe another person being touched. However, this is true when the action is intentional rather than accidental.<sup>113</sup> Motor activation is not involved in observing touch, however with auditory stimuli, the observation of being touched is enough to activate somatosensory cortex<sup>114,115</sup>

**Brain ventricles.** Ventricles increase in size in ASD and autistic patient.<sup>116,117</sup> Ventricles are also known to be increased in many other psychiatric disorders like schizophrenia. However, the presence of mirror neurons in the brain ventricles has not been proven yet. We will have to wait for decades long of research to get some concrete knowledge regarding the presence or the absence of mirror neurons in this part of the brain.

**Basal ganglia, putamen & caudate nucleus.** Decreased volume of basal ganglia, putamen, and caudate nucleus is observed when brain imaging studies of autism are conducted. The autism spectrum disorder patients also show gray matter augmentation mostly in the frontal and temporal lobes plus medial frontal gyrus, Broca's area and posterior temporal cortex, as well as certain parietal and occipital subcortical regions. Reduction in gray matter are observed only near the temporoparietal area. Subcortical gray matter increases in the putamen and caudate nucleus are observed. However, reduction in subcortical gray matter are seen in cerebellum. Moreover, age-dependent gray matter differences in prefrontal cortex, primary sensorimotor cortex, and temporoparietal junction are also seen.<sup>118,119</sup>

Besides anatomical changes, metabolic changes are also seen in autistic patients. According to a study by Doyle-Thomas et al<sup>120</sup> autistic patients have elevated glutamate/creatine in the putamen. They found ASD patients show hypoactivation of the right caudate nucleus during anticipating non-social negative reinforcement and hypoactivation of a network of frontostriatal regions with the nucleus accumbens,

caudate nucleus, and putamen during anticipating social negative reinforcement. Furthermore, right caudate nucleus activation during non-social negative reinforcement was linked with individual differences in social motivation.<sup>121</sup> These findings suggest a specific role for the caudate nucleus in the early pathogenesis of self-injurious behavior associated with both idiopathic autism. The study also suggested that the caudate may be differentially linked with compulsive behavior, this highlights the utilization of brain-behavior associations within and between ASD subtypes.<sup>122</sup>

Researchers are beginning to lean away from investigations into regional abnormalities in favor of studying the effects of impairments in communicatory connections between regions. While it is clear that more research is needed to investigate the connection between mirror neurons and autism, there is a sufficient body of evidence to suggest that impairments in the MNS could be involved in social, behavior, and communicative deficits in autistic patients. The variability of these deficits among individuals with neurodevelopmental disorders, such as ASD, could be due to disparity in exposure as well as variation in under-connectivity and over-connectivity. The underlying cause of dysfunction in the MNS is still conjecture; research has uncovered connected processes, such as mu rhythms that desynchronise in order to "activate" the MNS.<sup>123-130</sup> Neurofeedback procedures targeting mu rhythms specifically have met with success in improving communication skills.<sup>14</sup> The discovery of mu rhythms requires researchers to examine causation and correlation between mu desynchronisation and the MNS, as well as how mu rhythms correlate with newer theories targeted at disruptions in MNS connectivity. Additionally, abnormalities in white and grey matter volumes have been observed in conjunction with mirror neuron functionality.<sup>47,57</sup> Problems with the volume of white and grey matter could lead to impairments in functional connectivity.<sup>46</sup> The connection of mu rhythms and white and grey matter to mirror neuron activity should direct researchers to keep in mind the intricate processes in the brain. The obscure complexities of brain systems that researchers are increasingly becoming aware of sheds light on the notion of interconnectedness and not singular regional abnormalities. It is becoming apparent that the brain operates as a continuous, rather than discrete, system, with each operation influencing another; the MNS should be considered in much the same way.<sup>29</sup>

In conclusion, understanding social cognition and its origins of development will not stop at the genesis of the MNS in fetal development. Research will need



to consider the growth of other global processes such as mu rhythms and white and grey matter volume integrity in the womb and through infancy and early childhood development. Taking on this neurobiological approach should not discourage neurocognitive or environmental factor investigations but rather supplement them. Concentrating neurobiological research on infant development and the sensory-to-motor mapping response to early environmental stimuli exposure could unveil environmental influence on potential genetic susceptibility, and its subsequent effects on motor resonance. Additionally, following how neural connections and communication networks change over time, (paying attention to over and underconnectivity and connectivity compensation) could reveal the extent of the MNS's capacity to adapt, and thus the veracity of using neurofeedback training for individuals with autism. While the current body of research pertaining to the MNS is insufficient and multifarious, maintaining current treatment practices, as well as investing in the development of new neurofeedback training technologies will continue to be beneficial. Treatment practices also offer researchers and opportunity to study mirror neuron activity and the influence of other systems in the brain.

The understanding of the MNS has come a long way in the past 2 decades since their first discovery. The enthusiasm over studying its effect on social cognition has not faltered, despite the fact that research has resulted in a more perplexing understanding of the brain. There is enough evidence regarding its influence on social processes to warrant continued exploration; however, researchers should also continue to examine connected systems and invest in studying these systems in the early stages of life. Current bodies of research into the causes of autism should signify that a single cause is unlikely; it is more likely that the cause of autism is just as convoluted as the brain itself. The study concludes that besides other factors which are considered as the possible cause of autism and ASD. Mirror neurons damage or alteration could be associated with autism, and this theory of mirror neuron involvement could describe the pathophysiology of many symptoms of autism in great detail in the near future after more research is brought to surface.

## References

- Lai MC, Lombardo MV, Auyeung B, Chakrabarti B, Baron-Cohen S. Sex/gender differences and autism: setting the scene for future research. *J Am Acad Child Adolesc Psychiatry* 2015; 54: 11-24.
- Root NB, Case LK, Burrus CJ, Ramachandran VS. External self-representations improve self-awareness in a child with autism. *Neurocase* 2015; 21: 206-210.
- Lamm C, Majdandžić J. The role of shared neural activations, mirror neurons, and morality in empathy--a critical comment. *Neurosci Res* 2015; 90: 15-24.
- Schunke O, Schöttle D, Vettorazzi E, Brandt V, Kahl U, Bäumer T, et al. Mirror me: Imitative responses in adults with autism. *Autism* 2016; 20: 134-144.
- Cerri G, Cabini M, Blasi V, Borroni P, Iadanza A, Fava E, et al. The mirror neuron system and the strange case of Broca's area. *Hum Brain Mapp* 2015; 36: 1010-1027.
- Myers SM, Johnson CP. American Academy of Pediatrics Council on Children With Disabilities. Management of children with autism spectrum disorders. *Pediatrics* 2007;120: 1162-1182.
- Llaneza DC, DeLuke SV, Batista M, Crawley JN, Christodulu KV, Frye CA. Communication, interventions, and scientific advances in autism: a commentary. *Physiol Behav* 2010; 100: 268-276.
- Lauvin MA, Martineau J, Destrieux C, Andersson F, Bonnet-Brilhault F, Gomot M, et al. Functional morphological imaging of autism spectrum disorders: current position and theories proposed. *Diagn Interv Imaging* 2012; 93: 139-147.
- Ngounou Wetie AG, Wormwood KL, Russell S, Ryan JP, Darie CC, Woods AG. A Pilot Proteomic Analysis of Salivary Biomarkers in Autism Spectrum Disorder. *Autism Res* 2015; 8: 338-350.
- Ramachandran VS, Oberman LM. Broken mirrors: a theory of autism. *Sci Am* 2006; 295: 62-69.
- Gallese V, Goldman A. Mirror neurons and the simulation theory of mind-reading. *Trends Cogn Sci* 1998; 2: 493-501.
- Di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G. Understanding motor events: a neurophysiological study. *Exp Brain Res* 1992; 91: 176-180.
- Gallese V. Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition. *Philos Trans R Soc Lond B Biol Sci* 2007; 362: 659-669.
- Pineda JA, Carrasco K, Datko M, Pillen S, Schalles M. Neurofeedback training produces normalization in behavioural and electrophysiological measures of high-functioning autism. *Philos Trans R Soc Lond B Biol Sci* 2014; 28: 369.
- Mathon B. Mirror neurons: from anatomy to pathophysiological and therapeutic implications. *Rev Neurol* 2013; 169: 285-290.
- Mori K, Mori T, Goji A, Ito H, Toda Y, Fujii E, et al. [Hemodynamic activities in children with autism while imitating emotional facial expressions: a near-infrared spectroscopy study]. *No To Hattatsu* 2014; 46: 281-286. Japanese
- Murata A, Maeda K. [What mirror neurons have revealed: revisited]. *Brain Nerve* 2014; 66: 635-646. Japanese.
- Kilner JM, Lemon RN. What we know currently about mirror neurons. *Curr Biol* 2013; 23: R1057-R1062.
- Braadbaart L, Williams JH, Waiter GD. Do mirror neuron areas mediate mu rhythm suppression during imitation and action observation? *Int J Psychophysiol* 2013; 89 :99-105.
- Casartelli L, Molteni M. Where there is a goal, there is a way: what, why and how the parieto-frontal mirror network can mediate imitative behaviours. *Neurosci Biobehav Rev* 2014; 47: 177-193.
- Kosonogov V. Why the Mirror Neurons Cannot Support Action Understanding. *Neurophysiology* 2012; 6: 499-502.

22. Southgate V, Hamilton AF. Unbroken mirrors: challenging a theory of Autism. *Trends Cogn Sci* 2008;12: 225-229.
23. Hamilton AF. Goals, intentions and mental states: challenges for theories of autism. *J Child Psychol Psychiatry* 2009; 50: 881-892.
24. Rizzolatti G, Sinigaglia C. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat Rev Neurosci* 2010; 11: 264-274.
25. Spengler S, Bird G, Brass M. Hyperimitation of actions is related to reduced understanding of others' minds in autism spectrum conditions. *Biol Psychiatry* 2010; 68: 1148-1155.
26. Williams JH. Self-other relations in social development and autism: multiple roles for mirror neurons and other brain bases. *Autism Res* 2008; 1: 73-90.
27. Oberman LM, Ramachandran VS. The simulating social mind: the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychol Bull* 2007; 133: 310-227.
28. Oztop E, Kawato M, Arbib MA. Mirror neurons: functions, mechanisms and models. *Neurosci Lett* 2013; 540: 43-55.
29. Heyes C. Where do mirror neurons come from? *Neurosci Biobehav Rev* 2010; 34: 575-583.
30. Agnew ZK, Wise RJ, Leech R. Dissociating object directed and non-object directed action in the human mirror system; implications for theories of motor simulation. *PLoS One* 2012; 7: e32517.
31. Paukner A, Suomi SJ, Visalberghi E, Ferrari PF. Capuchin monkeys display affiliation toward humans who imitate them. *Science* 2009; 325: 880-883.
32. Sale P, Franceschini M. Action observation and mirror neuron network: a tool for motor stroke rehabilitation. *Eur J Phys Rehabil Med* 2012; 48: 313-318.
33. Lui F, Buccino G, Duzzi D, Benuzzi F, Crisi G, Baraldi P, et al. Neural substrates for observing and imagining non-object-directed actions. *Soc Neurosci* 2008; 3: 261-275.
34. Oosterhof NN, Wiggett AJ, Diedrichsen J, Tipper SP, Downing PE. Surface-based information mapping reveals crossmodal vision-action representations in human parietal and occipitotemporal cortex. *J Neurophysiol* 2010; 104: 1077-1089.
35. Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science* 2005; 308: 662-667.
36. Haroush K, Williams ZM. Neuronal prediction of opponent's behavior during cooperative social interchange in primates. *Cell* 2015; 160: 1233-1245.
37. Woodruff CC, Maaske S. Action execution engages human mirror neuron system more than action observation. *Neuroreport* 2010; 21: 432-435.
38. Agnew ZK, Brownset S, Woodhead Z, de Boissezon X. A step forward for mirror neurons? Investigating the functional link between action execution and action observation in limb apraxia. *J Neurosci* 2008; 28: 7726-7727.
39. D'Ausilio A, Bartoli E, Maffongelli L. Grasping synergies: a motor-control approach to the mirror neuron mechanism. *Phys Life Rev* 2015; 12: 91-103.
40. Cattaneo L. Granularity within the mirror system is not informative on action perception: comment on "Grasping synergies: a motor-control approach to the mirror neuron mechanism" by D'Ausilio et al. *Phys Life Rev* 2015; 12: 123-125.
41. Mukamel R, Ekstrom AD, Kaplan J, Iacoboni M, Fried I. Single-neuron responses in humans during execution and observation of actions. *Curr Biol* 2010; 20: 750-756.
42. Yoshida K, Saito N, Iriki A, Isoda M. Representation of others' action by neurons in monkey medial frontal cortex. *Curr Biol* 2011; 21: 249-253.
43. Hogeveen J, Chartrand TL, Obhi SS. Social Mimicry Enhances Mu-Suppression During Action Observation. *Cereb Cortex* 2015; 25: 2076-2082.
44. Fontana AP, Kilner JM, Rodrigues EC, Joffily M, Nighoghossian N, Vargas CD, et al. Role of the parietal cortex in predicting incoming actions. *Neuroimage* 2012; 59: 556-564.
45. Shmuelof L, Zohary E. Mirror-image representation of action in the anterior parietal cortex. *Nat Neurosci* 2008; 11: 1267-1269.
46. Maranesi M, Livi A, Fogassi L, Rizzolatti G, Bonini L. Mirror neuron activation prior to action observation in a predictable context. *J Neurosci* 2014; 34: 14827-14832.
47. Lauvin MA, Martineau J, Destrieux C, Andersson F, Bonnet-Brilhault F, Gomot M, et al. Functional morphological imaging of autism spectrum disorders: current position and theories proposed. *Diagn Interv Imaging* 2012; 93: 139-147.
48. Kana RK, Libero LE, Moore MS. Disrupted cortical connectivity theory as an explanatory model for autism spectrum disorders. *Phys Life Rev* 2011; 8: 410-437.
49. Ebisch SJ, Gallese V, Willems RM, Mantini D, Groen WB, Romani GL, et al. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum Brain Mapp* 2011; 32: 1013-1028.
50. Ishida H, Suzuki K, Grandi LC. Predictive coding accounts of shared representations in parieto-insular networks. *Neuropsychologia* 2015; 70: 442-454.
51. Inui T. [Human mirror neuron system]. *Brain Nerve* 2014; 66: 647-653. Japanese
52. Ferrari PF. The neuroscience of social relations. A comparative-based approach to empathy and to the capacity of evaluating others' action value. *Behaviour* 2014; 151: 297-313.
53. Kim YT, Seo JH, Song HJ, Yoo DS, Lee HJ, Lee J, et al. Neural correlates related to action observation in expert archers. *Behav Brain Res* 2011; 223: 342-347.
54. Kana RK, Murdaugh DL, Libero LE, Pennick MR, Wadsworth HM, Deshpande R, et al. Probing the brain in autism using fMRI and diffusion tensor imaging. *J Vis Exp* 2011; 12: 55.
55. Dapretto M, Davies MS, Pfeifer JH, Scott AA, Sigman M, Bookheimer SY, et al. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci* 2006; 9: 28-30.
56. Villarreal M, Fridman EA, Amengual A, Falasco G, Gerschovich ER, Ulloa ER, et al. The neural substrate of gesture recognition. *Neuropsychologia* 2008; 46: 2371-2382.
57. Fishman I, Keown CL, Lincoln AJ, Pineda JA, Müller RA. Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder. *JAMA Psychiatry* 2014; 71: 751-760.
58. O'Connor K, Kirk I. Brief report: atypical social cognition and social behaviours in autism spectrum disorder: a different way of processing rather than an impairment. *J Autism Dev Disord* 2008; 38: 1989-1997.
59. Williams JH, Waite GD, Gilchrist A, Perrett DI, Murray AD, Whiten A. Neural mechanisms of imitation and 'mirror neuron' functioning in autistic spectrum disorder. *Neuropsychologia* 2006; 44: 610-621.
60. Duffy FH, Als H. A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls - a large case control study. *BMC Med* 2012; 10: 64.

61. Schipul SE, Keller TA, Just MA. Inter-regional brain communication and its disturbance in autism. *Front Syst Neurosci* 2011; 5: 10.
62. Hamilton AF. Reflecting on the mirror neuron system in autism: a systematic review of current theories. *Dev Cogn Neurosci* 2013; 3: 91-105.
63. Ruyschaert L, Warreyn P, Wiersema JR, Oostra A, Roeyers H. Exploring the role of neural mirroring in children with autism spectrum disorder. *Autism Res* 2014; 7: 197-206.
64. Raymaekers R, Wiersema JR, Roeyers H. EEG study of the mirror neuron system in children with high functioning autism. *Brain Res* 2009; 1304: 113-121.
65. Vivanti G, Rogers SJ. Autism and the mirror neuron system: insights from learning and teaching. *Philos Trans R Soc Lond B Biol Sci* 2014; 369: 20130184.
66. Pineda JA, Juavinett A, Datko M. Self-regulation of brain oscillations as a treatment for aberrant brain connections in children with autism. *Med Hypotheses* 2012; 79: 790-798.
67. Perkins T, Stokes M, McGillivray J, Bittar R. Mirror neuron dysfunction in autism spectrum disorders. *J Clin Neurosci* 2010; 17: 1239-1243.
68. Bastiaansen JA, Thioux M, Nanetti L, van der Gaag C, Ketelaars C, Minderaa R, et al. Age-related increase in inferior frontal gyrus activity and social functioning in autism spectrum disorder. *Biol Psychiatry* 2011; 69: 832-838.
69. Saby JN, Meltzoff AN, Marshall PJ. Infants' somatotopic neural responses to seeing human actions: I've got you under my skin. *PLoS One* 2013; 8: e77905.
70. Perkins TJ, Bittar RG, McGillivray JA, Cox II, Stokes MA. Increased premotor cortex activation in high functioning autism during action observation. *J Clin Neurosci* 2015; 22: 664-669.
71. Nyström P. The infant mirror neuron system studied with high density EEG. *Soc Neurosci* 2008; 3: 334-347.
72. Nyström P, Ljunghammar T, Rosander K, von Hofsten C. Using mu rhythm desynchronization to measure mirror neuron activity in infants. *Dev Sci* 2011; 14: 327-335.
73. Simpson EA, Murray L, Paukner A, Ferrari PF. The mirror neuron system as revealed through neonatal imitation: presence from birth, predictive power and evidence of plasticity. *Philos Trans R Soc Lond B Biol Sci* 2014; 28: 369.
74. Marshall PJ, Meltzoff AN. Neural mirroring mechanisms and imitation in human infants. *Philos Trans R Soc Lond B Biol Sci* 2014; 28: 369.
75. Shmuelof L, Zohary E. Watching others' actions: mirror representations in the parietal cortex. *Neuroscientist* 2007; 13: 667-672.
76. Cross KA, Iacoboni M. Neural systems for preparatory control of imitation. *Philos Trans R Soc Lond B Biol Sci* 2014; 369: 20130176.
77. Buccino G, Amore M. Mirror neurons and the understanding of behavioural symptoms in psychiatric disorders. *Curr Opin Psychiatry* 2008; 21: 281-285.
78. Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Action recognition in the premotor cortex. *Brain* 1996; 119: 593-609.
79. Rizzolatti G, Camarda R, Fogassi L, Gentilucci M, Luppino G, Matelli M. Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movement. *Exp Brain Res* 1988; 71: 491-507.
80. Murata A, Fadiga L, Fogassi L, Gallese V, Raos V, Rizzolatti G. Object representation in the ventral premotor cortex (area F5) of the monkey. *J Neurophysiol* 1997; 78: 2226-2230.
81. Mosconi MW, Wang Z, Schmitt LM, Tsai P, Sweeney JA. The role of cerebellar circuitry alterations in the pathophysiology of autism spectrum disorders. *Front Neurosci* 2015; 9: 296.
82. Bailey A, Luthert P, Dean A, Harding B, Janota I, Montgomery M, et al. A clinicopathological study of autism. *Brain* 1998; 121: 889-905.
83. Bauman M, Kemper TL. Histoanatomic observations of the brain in early infantile autism. *Neurology* 1985; 35: 866-874.
84. Arin DM, Bauman ML, Kemper TL. The distribution of Purkinje cell loss in the cerebellum in autism. *Neurology* 1991; 41: 307.
85. Whitney ER, Kemper TL, Bauman ML, Rosene DL, Blatt GJ. Cerebellar Purkinje cells are reduced in a subpopulation of autistic brains: a stereological experiment using calbindin-D28k. *Cerebellum* 2008; 7: 406-416.
86. Whitney ER, Kemper TL, Rosene DL, Bauman ML, Blatt GJ. Density of cerebellar basket and stellate cells in autism: evidence for a late developmental loss of Purkinje cells. *J Neurosci Res* 2009; 87: 2245-2254.
87. Wegiel J, Flory M, Kuchna I, Nowicki K, Ma S Y, Imaki H, et al. Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. *Acta Neuropathol Commun* 2014 18; 2: 141.
88. Fatemi SH, Halt AR, Realmuto G, Earle J, Kist DA, Thuras P, et al. Purkinje cell size is reduced in cerebellum of patients with autism. *Cell Mol Neurobiol* 2002; 22: 171-175.
89. Braadbaart L, Williams JH, Waiter GD. Do mirror neuron areas mediate mu rhythm suppression during imitation and action observation? *Int J Psychophysiol* 2013; 89: 99-105.
90. Brunner IC, Skouen JS, Erslund L, Grüner R. Plasticity and response to action observation: a longitudinal fMRI study of potential mirror neurons in patients with subacute stroke. *Neurorehabil Neural Repair* 2014; 28: 874-884.
91. Von Hofsten C, Rosander K. Perception-action in children with ASD. *Front Integr Neurosci* 2012; 6: 115.
92. Molenberghs P, Cunnington R, Mattingley JB. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. *Neurosci Biobehav Rev* 2012; 36: 341-349.
93. Kana RK, Wadsworth HM, Travers BG. A systems level analysis of the mirror neuron hypothesis and imitation impairments in autism spectrum disorders. *Neurosci Biobehav Rev* 2011; 35: 894-902.
94. Codagnone MG, Podestá MF, Uccelli NA, Reinés A. Differential Local Connectivity and Neuroinflammation Profiles in the Medial Prefrontal Cortex and Hippocampus in the Valproic Acid Rat Model of Autism. *Dev Neurosci* 2015; 37: 215-231.
95. Ameis SH, Catani M. Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder. *Cortex* 2015; 62: 158-181.
96. Zalla T. Amygdala, oxytocin, and social cognition in autism spectrum disorders. *Biol Psychiatry* 2014; 76: 356-357.
97. Sosa-Díaz N, Bringas ME, Atzori M, Flores G. Prefrontal cortex, hippocampus, and basolateral amygdala plasticity in a rat model of autism spectrum. *Synapse* 2014; 68: 468-473.
98. Ushakov VL, Kartashov SI, Zavyalova VV, Bezverhiy DD, Posichanyuk VI, Terentev VN, et al. Network activity of mirror neurons depends on experience. *J Integr Neurosci* 2013; 12: 35-46.
99. Mihov Y, Kendrick KM, Becker B, Zschernack J, Reich H, Maier W, et al. Mirroring fear in the absence of a functional amygdala. *Biol Psychiatry* 2013; 73: 9-11.

100. Pohl A, Anders S, Schulte-Rüther M, Mathiak K, Kircher T. Positive facial affect - an fMRI study on the involvement of insula and amygdala. *PLoS One* 2013; 8: e69886.
101. Van der Gaag C, Minderaa RB, Keyers C. The BOLD signal in the amygdala does not differentiate between dynamic facial expressions. *Soc Cogn Affect Neurosci* 2007; 2: 93-103.
102. Sergerie K, Chochol C, Armony JL. The role of the amygdala in emotional processing: a quantitative meta-analysis of functional neuroimaging studies. *Neuroscience & Biobehavioral Reviews* 2008; 32: 811-830.
103. Sander D, Grafman J, Zalla T. The human amygdala: an evolved system for relevance detection. *Rev Neurosci* 2003; 14: 303-316.
104. Adelman PK, Zajonc RB. Facial efference and the experience of emotion. *Annual Review of Psychology* 1989; 40: 249-280.
105. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 2002; 16: 331-348.
106. Craig AD. How do you feel - now? The anterior insula and human awareness. *Nat Rev Neurosci* 2009; 10: 59-70.
107. Anders S, Lotze M, Erb M, Grodd W, Birbaumer N. Brain activity underlying emotional valence and arousal: A response-related fMRI study. *Human Brain Mapping* 2004; 23: 200-209.
108. Sussman D, Leung RC, Vogan VM, Lee W, Trelle S, Lin S, et al. The autism puzzle: Diffuse but not pervasive neuroanatomical abnormalities in children with ASD. *Neuroimage Clin* 2015; 8: 170-179.
109. McKavanagh R, Buckley E, Chance SA. Wider minicolumns in autism: a neural basis for altered processing? *Brain* 2015; 138: 2034-2045.
110. Solso S, Xu R, Proudfoot J, Hagler DJ Jr, Campbell K, Venkatraman V, et al. Diffusion Tensor Imaging Provides Evidence of Possible Axonal Overconnectivity in Frontal Lobes in Autism Spectrum Disorder Toddlers. *Biol Psychiatry* 2015; 4: S0006-3223.
111. Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, et al. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 2001; 13: 400-404.
112. Keyers C, Wicker B, Gazzola V, Anton JL, Fogassi L, Gallese V. A touching sight: SII/PV activation during the observation and experience of touch. *Neuron* 2004; 42: 335-346.
113. Ebisch SJ, Perruci MG, Ferretti A, Del Gratta C, Romani GL, Gallese V. The sense of touch: embodied simulation in a visuotactile mirroring mechanism for observed animate or inanimate touch. *J Cogn Neurosci* 2008; 20: 1-13.
114. Keyers C, Gazzola V. Expanding the mirror: vicarious activity for actions, emotions, and sensations. *Curr Opin Neurobiol* 2009; 19: 666-671.
115. Keyers C, Kaas JH, Gazzola V. Somatosensation in social perception. *Nat Rev Neurosci* 2010; 11: 417-428.
116. Lange N, Travers BG, Bigler ED, Prigge MB, Froehlich AL, Nielsen JA, et al. Longitudinal volumetric brain changes in autism spectrum disorder ages 6-35 years. *Autism Res* 2015; 8: 82-93.
117. Movsas TZ, Pinto-Martin JA, Whitaker AH, Feldman JF, Lorenz JM, Korzeniewski SJ, et al. Autism spectrum disorder is associated with ventricular enlargement in a low birth weight population. *J Pediatr* 2013; 163: 73-78.
118. Foster NE, Doyle-Thomas KA, Tryfon A, Ouimet T, Anagnostou E, Evans AC, et al. Structural Gray Matter Differences During Childhood Development in Autism Spectrum Disorder: A Multimetric Approach. *Pediatr Neurol* 2015; 53: 350-359.
119. Sato W, Kubota Y, Kochiyama T, Uono S, Yoshimura S, Sawada R, et al. Increased putamen volume in adults with autism spectrum disorder. *Front Hum Neurosci* 2014; 8: 957.
120. Doyle-Thomas KA, Card D, Soorya LV, Wang AT, Fan J, Anagnostou E. Metabolic mapping of deep brain structures and associations with symptomatology in autism spectrum disorders. *Res Autism Spectr Disord* 2014; 8: 44-51.
121. Damiano CR, Cockrell DC, Dunlap K, Hanna EK, Miller S, Bizzell J, et al. Neural mechanisms of negative reinforcement in children and adolescents with autism spectrum disorders. *J Neurodev Disord* 2015; 7: 12.
122. Wolff JJ, Hazlett HC, Lightbody AA, Reiss AL, Piven J. Repetitive and self-injurious behaviors: associations with caudate volume in autism and fragile X syndrome. *J Neurodev Disord* 2013; 5: 12.
123. Marshall PJ, Meltzoff AN. Neural mirroring systems: exploring the EEG  $\mu$  rhythm in human infancy. *Dev Cogn Neurosci* 2011; 1: 110-123.
124. Fan YT, Decety J, Yang CY, Liu JL, Cheng Y. Unbroken mirror neurons in autism spectrum disorders. *J Child Psychol Psychiatry* 2010; 51: 981-988.
125. Frenkel-Toledo S, Bentin S, Perry A, Liebermann DG, Soroker N. Mirror-neuron system recruitment by action observation: effects of focal brain damage on mu suppression. *Neuroimage* 2014; 87: 127-137.
126. Cannon EN, Yoo KH, Vanderwert RE, Ferrari PF, Woodward AL, Fox NA. Action experience, more than observation, influences mu rhythm desynchronization. *PLoS One* 2014; 9: e92002.
127. Vanderwert RE, Fox NA, Ferrari PF. The mirror mechanism and mu rhythm in social development. *Neurosci Lett* 2013; 540: 15-20.
128. Palau-Baduell M, Valls-Santasusana A, Salvadó-Salvadó B. [Autism spectrum disorders and mu rhythm. A new neurophysiological view]. *Rev Neurol* 2011; 521: S141-S146. Spanish
129. Palau-Baduell M, Valls-Santasusana A, Salvadó-Salvadó B, Clofent-Torrentó M. [Interest of electroencephalogram in autism]. *Rev Neurol* 2013; 56: S35-S43. Spanish
130. Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Brain Res Cogn Brain Res* 2005; 24: 190-198.