

A "global" network dysfunction in the mirror neuron system in autism is modulated by task complexity and age: A meta-analysis of neuroimaging studies

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Research

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Abstract

Background Impaired imitation has been found to be an important factor contributing to social communication deficits in individuals with autism spectrum disorder (ASD). It has been hypothesized that the neural correlates of imitation, the mirror neuron system (MNS), are dysfunctional in ASD, resulting in imitation impairment as one of the key behavioral manifestations in ASD. Previous MNS studies produced inconsistent results, leaving the debate of whether mirror neurons are “broken” in ASD unresolved.

Methods This meta-analysis aimed to explore the differences in MNS activation patterns between typically developing (TD) and ASD individuals when they observe/imitate biological motions with/without emotional components. Effect-size signed differential mapping (ES-SDM) was adopted to synthesize the available fMRI data.

Results The MNS is dysfunctional in ASD; not only the brain regions containing mirror neurons were affected, the brain regions supporting MNS functioning were also impaired. Second, MNS dysfunction in ASD is modulated by task complexity; differential activation patterns during the presentation of “cold” and “hot” stimuli might be a result of atypical functional connectivity in ASD. Third, MNS dysfunction in ASD individuals is modulated by age. MNS regions were found to show delayed maturation; abnormal lateralization development in some of the brain regions also contributed to the atypical development of the MNS in ASD. Limitations We have attempted to include a comprehensive set of original data for this analysis. However, whole brain analysis data were not obtainable from some of the published papers, these studies could not be included as a result. Moreover, the results indicating the age effect on MNS in ASD could only be generalized to individuals aged 11-37, as MNS activation remains unstudied for populations beyond this age range. Also, the ES-SDM linear regression modelling might not be ideal to illustrate the associations between age and MNS activation; the meta-regression results should be treated with caution.

Conclusion There is a “global” rather than a “local” network dysfunction, which may underlie the imitation impairments in individuals with ASD. Task complexity and age modulate the functioning of the MNS, which may explain the previous peculiar results contributing to the unresolved “broken mirror neuron” debate.

Background

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder that affects 1 in 59 people worldwide (1). Individuals with ASD are characterized by social communication deficits, e.g., difficulties in the production and comprehension of nonverbal gestures, that manifest very early in their lives. Such deficits significantly impair their social and occupational functioning (2). In the past decade, researchers have attempted to identify critical components underlying lifelong social communication difficulties in ASD, one of which is the deficit in imitation.

Imitation, defined as the ability to simultaneously observe and replicate an action displayed by another person (3, 4), has been considered an important skill for early social and intellectual development (5). Research with typically developing individuals has revealed that imitative skills progressively develop from the imitation of simple actions to the imitation of complicated gestures in the first two years of life as a child continuously interacts with the environment (6). This developmental trajectory of imitation, however, has been found to be delayed in individuals with autism (7). Moreover, imitation is a form of social learning and imitation problem was found to be a significant predictor of communication development and intellectual outcomes in children with ASD (8, 9). This research collectively suggests that impaired imitation early in life contributes to behavioral manifestations in ASD.

It has been proposed that the mirror neuron system (MNS) supports the ability to imitate in humans. The MNS is a neural circuit involving interconnected brain regions that process information related to the perception and execution of biological motions (10, 11). Some of these brain regions, i.e., the pars opercularis of the inferior frontal gyrus, ventral premotor cortex and inferior parietal lobule (12), contain mirror neurons, which are neurons that “discharge both when individuals perform a given motor act and when individuals observe another person performing a motor act with a similar goal” (13, p.757). Other regions within the MNS do not contain mirror neurons. Instead, these regions support imitation by providing sensory/perceptual/affective inputs to frontal and parietal mirror neuron regions (14). Previous research has shown that the organization of the MNS is task-specific. For example, imitation of hand actions involves the frontoparietal regions with mirror neurons (i.e., inferior frontal gyrus pars opercularis, dorsal premotor cortex, supplementary motor area, precentral gyrus and inferior parietal lobule), as well as superior temporal sulcus and visual cortex for visual processing (14, 15). Imitation of facial expressions, which requires additional affective processing compared to hand action imitation, involves a more extensive activation of brain regions beyond the mirror neuron regions and visual regions. The core MNS regions include the inferior frontal gyrus (pars orbitalis, pars triangularis) coactivated with other cortical regions for face processing (i.e., fusiform face area) and visual attention/attentional control to face stimuli (i.e., middle occipital gyrus/median cingulate cortex), as well as subcortical regions for emotional processing (e.g., amygdala; 16).

Given that the MNS is a plausible neural correlate for imitation, individuals with ASD, who have been found to have impairments in imitation, have been hypothesized to show a dysfunctional MNS. A number of functional magnetic resonance imaging (fMRI) studies have been conducted to compare the activation patterns of the MNS in ASD individuals with age- and/or IQ-matched typically developing (TD) controls during the observation of biological motions. The visual stimuli used in these fMRI studies can largely be classified into two categories: (1) “cold” stimuli—biological motions without an emotional component, such as hand grasping (e.g., 2, 17 and 18) “hot” stimuli—biological motions that convey emotions, such

as human faces expressing different emotions (19, 20). These fMRI studies, however, have presented inconsistent results. For example, in a study in which images of “cold” actions were presented to participants, greater activation in the right dorsal premotor cortex (a brain region with mirror neurons) was recorded in ASD participants than in TD participants (17). A similar action observation paradigm was adopted by Pokorny (18), although they did not find significant differences in brain activation within the MNS between the ASD and TD participants. With respect to the observation of “hot” stimuli, there have also been inconsistencies. For example, Kim, Choi (19) and Sato, Toichi (20) displayed both happy and fearful faces to participants with and without ASD. Kim, Choi (19) reported that ASD individuals exhibited a reduction in activation in some MNS regions (i.e., inferior frontal gyrus and amygdala) in the right brain only, while Sato, Toichi (20) reported reductions in bilateral activation in these regions. These contradictory results have led us to two important questions regarding MNS function in individuals with ASD: Is the MNS truly dysfunctional in individuals with ASD? If their MNS is dysfunctional, how can the previous contradictory findings be explained?

Summarizing the available data with meta-analytical methods would be helpful for us to answer these questions. To our knowledge, one relevant meta-analysis has been conducted. Rather than including all MNS studies regardless of the nature of stimuli (“cold” vs “hot” stimuli), this meta-analysis included only the data from “cold” action observation and imitation studies among adolescents and adults (mean age = 12-33) with and without ASD using the activation likelihood estimation (ALE) method (21). From the 13 included studies, the meta-analytic data revealed greater activation in the ASD than TD individuals at the right anterior inferior parietal lobule, a brain region with mirror neurons. This study appeared to provide some evidence that part of the MNS might be dysfunctional in individuals with ASD during “cold” action processing. However, whether there is a global deficit in both “cold” and “hot” action processing remains unclear. Additionally, having found that the complexity of the neural network required for different visual stimuli might account for the discrepancies in fluctuating behavioral performance in individuals with ASD (22, 23), and given that the observation/imitation of “hot” stimuli requires a more extensive MNS (10), it is reasonable to postulate that the nature (i.e., “cold” vs “hot”) of stimuli presented to trigger MNS activities may play a role in explaining the inconsistent results. Furthermore, provided that the gray matter volumes in frontal, parietal and occipital regions, where mirror neurons are situated, atypically decline in ASD compared to TD individuals starting from early adolescence (age 10-15) through adulthood (24), the age of participants across different studies may be another factor modulating the inconsistent results. An updated meta-analysis including all fMRI studies that investigated the MNS in ASD would thus be essential to draw conclusions regarding these unanswered questions.

This meta-analysis aimed to explore the differences in MNS activation patterns between TD and ASD individuals when they observe/imitate biological motions with/without emotional components. Effect-size signed differential mapping (ES-SDM), a mixed voxel-based meta-analytic method, was adopted (25) to synthesize the available fMRI data.

It was hypothesized that the MNS activation patterns were different in TD and ASD individuals; such differences in activation patterns would be modulated by the nature of the stimuli (i.e., biological motions

with/without emotional components) and age (i.e., adolescent/adult). Meta-regressions, enabled by the ES-SDM, were also performed to explore clusters that exhibited statistically significant changes in activation across ages in ASD and TD individuals.

Methods

Literature search and study inclusion

A literature search was conducted from August to October 2019; a second search was then conducted around one month before this review was submitted for publication (i.e., 7 January 2020) to ensure that the data included in this study were as up-to-date as possible. To identify relevant studies, the electronic databases PsycINFO, Scopus, PubMed, Embase, Web of Science and Science Direct were used with the primary keywords “mirror neuron”, “mirroring”, “action observation”, and “imitation” and secondary keywords “autism”, “autistic”, “autism spectrum disorder”, “autism spectrum condition”, “ASD” and “ASC” together with tertiary keywords “functional magnetic resonance imaging” and “fMRI”. No limit was set to the publication dates. A manual search of the reference lists in previously published review papers (12-14, 21, 26) was also conducted to identify possible studies for the current review. A total of 543 studies were retrieved.

After 157 duplicate records were removed, the abstracts of the remaining studies were screened with the following exclusion criteria applied: 1) nonhuman studies, 2) treatment-related studies, 3) studies without an English version of the full text, 4) studies without empirical findings (e.g., book chapters, study protocols and review papers), 5) studies that did not contain an experimental group with participants diagnosed with ASD and a healthy control group, 6) non-fMRI studies, and 7) resting fMRI studies.

The full texts of the 53 remaining records were further assessed. Studies were excluded if 1) peak coordinates/raw statistical parametric maps could not be obtained from the published papers/contacted authors or 2) analyses were limited to specific regions of interest (ROIs). The complete process of article selection is outlined in Figure 1.

Data extraction

The demographic data, experimental details and fMRI data of the included papers were extracted and entered into a database by the first author and checked by the second author to minimize errors. Demographic data included the sample size of each experimental and control group, mean IQ, mean age, gender and group-matching criteria. Experimental details included the visual stimuli presented in the individual experiments (e.g., hand gestures, emotional facial expressions) and whether the experimental tasks contained interactive/communicative elements (i.e., the presence of other people/figure in the stimuli), whether the experimental tasks contained real human body parts (vs nonbiological stimuli that involved the use of point-light displays, cartoon, and ball-and-stick figures as stimuli).

Data analysis

All meta-analytic procedures were performed using ES-SDM software (25).

To compare the overall differences in MNS activation patterns between the ASD and TD individuals during the observation/imitation of “cold” and “hot” stimuli, all data from individual studies were pooled and meta-analyzed with the maximum-likelihood random effects model. To evaluate the effects of task complexity on the differences in MNS activation patterns between patient and control groups, the data from studies were first categorized by the visual stimuli presented (“cold” versus “hot”), followed by a random effects analysis between the two groups. To evaluate the effects of age on the between-group differences in MNS activation patterns, data were meta-analyzed after they were categorized by the age group to which the participants belonged. If the mean age of the ASD participants in a particular study was 18 years old or older, the fMRI data from the study were categorized into the “adult” group; otherwise, “adolescent” group membership would be assigned. To supplement the evaluation of age effects on MNS activation, clusters that exhibited significant changes in activation across ASD groups at both ages were explored by performing meta-regressions with the mean age of the ASD participants. This was a simple linear regression weighted by the squared root of sample size and restricted to predict only possible SDM values (i.e., from -1 to 1) in the observed range of values of the chosen variable (i.e., participants’ mean age; 27).

As in previous studies, the significance level of the main analyses was kept at $p < 0.005$, which requires a peak $Z > 1$ with a cluster size of 10 voxels, as suggested by Radua, Mataix-Cols (25) to optimize the sensitivity of results while controlling for type-I error. The significance level of the meta-regression analyses was kept at $p < 0.0005$ to avoid false-positive results (28).

Results

Characteristics of the included studies

A total of 20 records (including 24 experiments) were included in the meta-analysis, which represented 284 individuals with ASD (111 adolescents and 173 adults) compared with 290 matched, typically developing controls (114 adolescents and 176 adults). Ten studies presented biological motions without emotion (“cold”) components (29-37), and the remaining ten studies presented biological motions with emotion (“hot”) components (38-47). The demographic data of the participants and the experimental details of each study are summarized in Table 1.

[Insert Table 1 here]

Global differences in MNS activation patterns between ASD and TD individuals (*Table 2*)

When relevant visual stimuli (i.e., hand gestures, photos of different facial expressions) were presented to activate the participants' MNS, it was found that people with autism exhibited hyperactivation in the cluster of the left precentral gyrus (BA6) and right amygdala (brain clusters highlighted in red in *figure 2*). In contrast, the right inferior frontal gyrus (orbital part; BA45, BA47), left supplementary motor area (BA6) and left inferior parietal lobule (BA40) were hypoactivated (brain clusters highlighted in blue in *figure 2*).

Brain regions with peak activation						Cluster breakdown
Anatomical region	L/R	Total number of voxels	MNI coordinates	SDM-Z	P (uncorrected)	Anatomical regions (Brodmann area)
<i>ASD>TD</i>						
Precentral gyrus	L	664	-42,-6,48	2.169	<0.0001	Precentral gyrus (BA6) Postcentral gyrus (BA6)
Amygdala	R	262	28,-8,-24	1.451	<0.005	Amygdala (BA34) Hippocampus (BA20) Median cingulate
<i>ASD<TD</i>						
Inferior frontal gyrus, orbital part	R	1053	48,28,-4	-2.827	~0	Inferior frontal gyrus, orbital part (BA47) Inferior frontal gyrus, orbital part (BA45) Inferior frontal gyrus, triangular part (BA45)
Supplementary motor area	L	483	-4,8,54	-2.044	<0.0005	Supplementary motor area (BA6)
Inferior parietal lobule	L	38	-52,-40,40	-1.710	<0.005	Inferior parietal lobule (BA40)

Table 2 Difference in MNS activation during observation of “cold” and “hot” stimuli

Effects of task complexity on the differences in MNS activation patterns in ASD and TD individuals
(Table 3a, 3b)

Brain regions with peak activation						Cluster breakdown
Anatomical region	L/R	Total number of voxels	MNI coordinates	SDM-Z	P (uncorrected)	Anatomical regions (Broadmann area)
<i>ASD>TD</i>						
Postcentral gyrus	L	156	-42,-14,48	1.665	<0.001	Precentral gyrus (BA6) Postcentral gyrus (BA6)
Middle occipital gyrus	R	87	32,-84,2	1.651	<0.001	Middle occipital gyrus (BA18) Inferior network, inferior longitudinal fasciculus
Postcentral gyrus	R	27	26,-46,60	1.384	<0.005	Postcentral gyrus (BA2)
Amygdala	R	25	28,-8,-22	1.331	<0.005	Amygdala
<i>ASD<TD</i>						
Inferior parietal lobule	L	608	-44,-50,48	-2.015	<0.001	Inferior parietal lobule (BA40) Inferior parietal lobule (BA2) Supramarginal gyrus (BA40)
Supplementary motor area	L	159	-4,8,54	-1.873	~0.001	Supplementary motor area (BA6)

During the observation of “cold” stimuli (i.e., hand gestures), the bilateral postcentral gyrus and right middle occipital gyrus were hyperactivated in the ASD compared to TD individuals. Notably, the right amygdala and nearby hippocampal region also showed statistically significant hyperactivation during observation of gestures without emotional content among those with ASD. Meanwhile, the individuals with ASD also showed hypoactivation in the left IPL (significant cluster that extended to the

supramarginal gyrus) and left supplementary motor area (BA6; *figure 3a*). These regions remained significantly hypoactivated with mean age or mean IQ as a covariate.

Table 3a Difference in MNS activation between ASD and TD during observation of hand gestures

During the observation of “hot” stimuli (i.e., biological motions containing emotional components, such as facial expressions), hyperactivation of the MNS in the ASD individuals was found in the left precentral gyrus, right lingual gyrus and right middle temporal gyrus (BA20, BA21) extending to the superior temporal gyrus (BA20, BA22). In contrast, there were highly statistically significant hypoactivations in the right IFG pars orbitalis (BA47) and pars triangularis (BA45), left amygdala (BA34) and left middle occipital gyrus (BA18) among the ASD individuals compared to the TD individuals (*figure 3b*). The hypoactivation in the right IFG left amygdala remained highly significant with age and IQ as covariates.

Brain regions with peak activation						Cluster breakdown
Anatomical region	L/R	Total number of voxels	MNI coordinates	SDM-Z	P (uncorrected)	Anatomical regions (Broadmann area)
<i>ASD>TD</i>						
Precentral gyrus	L	21	-44,-8,46	1.540	<0.005	Precentral gyrus (BA6) Postcentral gyrus (BA6)
Lingual gyrus	R	17	14,-76,-4	1.694	<0.005	Inferior network, inferior longitudinal fasciculus Lingual gyrus (BA18)
Middle temporal gyrus	R	11	52,-12,-14	1.549	<0.005	Middle temporal gyrus (BA20, BA21) Superior temporal gyrus (BA20, BA22)
<i>ASD<TD</i>						
Inferior frontal gyrus, orbital part	R	1310	48,28,-4	-3.385	~0	Inferior frontal gyrus, orbital part (BA47) Inferior frontal gyrus, triangular part (BA45)
Amygdala	L	384	-20,-4,-14	-2.011	<0.0005	Amygdala (BA34)
Middle occipital gyrus	L	20	-22,-92,8	-1.588	<0.005	Middle occipital gyrus (BA18) Corpus callosum

Table 3b Difference in MNS activation between ASD and TD during observation of facial/bodily emotional expressions

Effects of age on the differences in MNS activation patterns between ASD and TD individuals (*Table 4a, 4b*)

In the adolescent subgroup (ASD mean age = 11.3-17.6; TD mean age = 11.5-17.1; *figure 4a*), the ASD individuals showed hyperactivation in the left fusiform gyrus (BA18, BA19), left cerebellum (hemispheric lobule VI) and right median cingulate around the hippocampal region (BA20). Hyperactivation in the left fusiform gyrus remained statistically significant with IQ and age as covariates. Hypoactivation in the ASD compared to TD individuals was found in the bilateral inferior frontal gyrus pars orbitalis and pars triangularis, right postcentral gyrus extending to the precentral gyrus, and the left supramarginal gyrus extending to the inferior parietal gyrus (BA40, BA2). The hypoactivation in the bilateral inferior frontal gyrus remained highly statistically significant with IQ and age as covariates.

Brain regions with peak activation						Cluster breakdown
Anatomical region	L/R	Total number of voxels	MNI coordinates	SDM-Z	P (uncorrected)	Anatomical regions (Broadmann area)
<i>ASD>TD</i>						
Fusiform gyrus	L	300	-24,-82,-18	1.780	<0.001	Fusiform gyrus (BA18, BA19) Lingual gyrus (BA18)
Median cingulate	R	121	32,-12,-26	1.409	~0.001	Hippocampus (BA20) Median cingulate
Cerebellum, hemispheric lobule VI	L	56	-38,-62,-26	1.350	<0.005	Cerebellum, hemispheric lobule VI (BA37) Cerebellum, crus I (BA37)
<i>ASD<TD</i>						
Inferior frontal gyrus (orbital part)	R	931	48,30,-8	-2.441	<0.0001	Inferior frontal gyrus, orbital part (BA47) Inferior frontal gyrus, triangular part (BA45)
Inferior frontal gyrus (orbital part)	L	485	-44,24,-8	-1.882	<0.001	Inferior frontal gyrus, orbital part (BA47) Inferior frontal gyrus, triangular part (BA47)
Postcentral gyrus	R	414	62,-14,34	-1.659	~0.001	Postcentral gyrus (BA3, BA43) Precentral gyrus (BA4,BA6)

Supramarginal gyrus	L	20	-56,-40,36	-1.531	<0.005	Supramarginal gyrus (BA40, BA2) Inferior parietal gyrus (BA40)
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Table 4a Difference in MNS activation between ASD and TD in adolescent subgroup

In the adult subgroup (ASD mean age = 23-37; TD mean age = 21-37; *figure 4b*), the left precentral gyrus extending to the postcentral gyrus (BA6, BA4), and the right cerebellum (hemispheric lobule VI extending to crus I) was hyperactivated, whereas the right inferior frontal gyrus (orbital part extending to the triangular part) and the left supplementary motor area (BA6, BA24) were hypoactivated in the ASD compared to TD individuals.

Difference in MNS activation between ASD and TD in adolescent group						Cluster breakdown
Brain regions with peak activation						
Anatomical region	L/R	Total number of voxels	MNI coordinates	SDM-Z	P (uncorrected)	Anatomical regions (Brodmann area)
<i>ASD>TD</i>						
Precentral gyrus	L	697	-42,6,48	2.565	~0.00001	Precentral gyrus (BA6) Postcentral gyrus (BA4, BA6)
Cerebellum, hemispheric lobule VI	R	706	18,-72,-28	1.987	<0.001	Cerebellum, hemispheric lobule VI (BA18) Cerebellum, crus I (BA19)
<i>ASD<TD</i>						
Supplementary motor area	L	266	-4,2,50	-2.017	<0.0005	Supplementary motor area (BA6, BA24)
Inferior frontal gyrus (orbital part)	R	81	54,26,-4	-1.826	~0.001	Inferior frontal gyrus, orbital part (BA45) Inferior frontal gyrus, triangular part (BA45)

Table 4b Difference in MNS activation between ASD and TD in adult subgroup

Meta-regression

Meta-regression results indicated that there was a statistically significant positive relationship ($p < 0.0005$) between age and activation in the right cerebellum crus I, as well as a significant negative relationship between age and activation in the left inferior temporal gyrus (*figure 5*). However, these results should be interpreted with caution as they were driven by only two studies.

Between-study heterogeneity and publication bias

The heterogeneity map revealed no significant between-study heterogeneity. Visual inspection of the funnel plots of the peaks did not show obvious publication bias (*figure 6*). Egger's tests for all peaks remained statistically nonsignificant (lowest $p=0.08$).

Discussion

This meta-analysis sought to identify the activation pattern of classic MN regions and other related brain areas during observation of hand gestures and mixed facial expressions among individuals with ASD compared to age-matched typically developing controls. After a comprehensive literature search and the application of inclusion/exclusion criteria, 20 journal articles (with 24 sets of fMRI data) were selected to be included in the meta-analysis. In summary, this coordinate-based fMRI meta-analysis indicated three main points. First, the MNS is dysfunctional in ASD; not only the brain regions containing mirror neurons were affected (i.e., the inferior frontal gyrus, inferior parietal lobule, and supplementary area) but also the brain regions supporting observation/imitation of biological motions (i.e., the precentral gyrus and amygdala) were also impaired. Second, MNS dysfunction in ASD individuals is modulated by task complexity, for example, when visual stimuli without emotional components (i.e., “cold” stimuli) were presented, the amygdala and middle occipital gyrus were hyperactivated in ASD compared to TD individuals, but when visual stimuli with emotional components (i.e., “hot” stimuli) were presented, these two brain regions became hypoactivated. Third, MNS dysfunction in ASD individuals was modulated by age; for example, in the adolescent subgroup, the bilateral inferior frontal gyrus was found to be hypoactivated in ASD individuals; in the adult subgroup, however, only the right inferior frontal gyrus was hypoactivated. The following discussion is divided into three parts, with each of the parts discussing the possible implications of the points listed above.

MNS dysfunction is a “global” but not a “local” problem in ASD

There has been a hot debate in the past decade on whether mirror neurons are “broken” in ASD, leading to the impairment in imitation in this group of individuals. The “broken mirror neuron theory” for autism asserts that the frontal and parietal brain regions with mirror neurons were found to be abnormally activated in individuals with ASD and given the property of mirror neurons (i.e., discharges during both activation observation and execution) that appears to support imitation, impaired imitation might be associated with the “broken” frontoparietal mirror neurons (26, 42). This meta-analysis indeed shows abnormal activations in the frontoparietal mirror neuron regions in individuals with ASD. However, at the same time, abnormal activations were also shown in MNS brain regions without mirror neurons. Given that these regions without mirror neurons support the functions of frontoparietal mirror neuron regions, it might be more sensible to understand MNS dysfunction in ASD as a “global” system deficit rather than

problems in “local” brain regions that contribute to a cascade of social communication impairments. In fact, the disrupted connectivity theory in autism supports the claim that “global” neural network abnormalities might underlie the manifestation of behavioral phenotypes in ASD (48). Numerous empirical studies, including those using electrophysiological (49, 50) and neuroimaging (51) techniques, have pointed to disrupted neural connectivity in individuals with ASD. In particular, abnormal connectivity was found within the MNS. Regarding the neural connectivity between brain regions with mirror neurons, Rudie, Shehzad (52) recorded hypoconnectivity between the left inferior frontal gyrus pars opercularis and left parietal cortex in individuals with ASD relative to healthy controls. Regarding the connectivity between mirror neuron regions and the supporting MNS regions, it was revealed that the amygdala was hypoconnected with the frontal regions where the MNS is situated (53). This evidence collectively implies that atypical connectivity within the MNS contributes to dysfunction, which might be associated with the abnormal MNS activation patterns found in this meta-analysis.

Task complexity modulates the activation of MNS

Two findings in the comparison between ASD and TD individuals regarding the differences in activation patterns induced by “cold” and “hot” stimuli confirm our hypothesis that task complexity might be one of the modulators of neural activation of the MNS. First, regarding the activation of the amygdala and middle occipital gyrus (BA18), they were hyperactivated during the observation of “cold” stimuli but hypoactivated during the observation of “hot” stimuli in individuals with ASD. The hyper and hypoactivation of the amygdala and middle occipital gyrus appears to be paradoxical at first glance but can be clearly understood from the perspective of atypical neural connectivity in ASD. Previous evidence has revealed enhanced processing when individuals with autism were given tasks that demanded more from local networks but reduced processing when tasks required the integration of information between specialized networks located in different brain regions (22). Given that the observation/imitation of biological motions with emotional components requires subcortical input for emotional processing (e.g., amygdala) unlike the observation/imitation of motions without an emotional component, the neurointegrative demand can be said to be higher for “hot” stimuli processing than “cold” stimuli processing. As a result, it is reasonable to find hyperactivation during tasks with lower neurointegrative demand but hypoactivation during tasks with higher neurocognitive demand. Second, regarding the precentral gyrus activation difference between the ASD and TD individuals, it was found that the bilateral precentral gyrus (BA6) were hyperactivated during “cold” action observation, while the left precentral gyrus (BA6) remained hyperactivated during the observation of emotional expressions. A previous study documented atypical connectivity within the precentral gyrus (54), leading to inefficient motor organization in ASD (55). Meanwhile, an increase in neural activation (usually bilateral) measured by fMRI has been found to indicate an increase in mental effort during tasks to maintain behavioral performance (56). This evidence together may imply that, during the observation/imitation of “cold” stimuli, ASD requires extra mental effort for task completion, resulting in hyperactivation in the bilateral precentral gyrus. During the observation of “hot” stimuli, where the task becomes more complex for the

healthy controls as well, only the hyperactivation in the left precentral gyrus remained statistically significant. Taken together, these results indicated a disorganized precentral gyrus leading to abnormal activation.

Age-related changes in the MNS in ASD

The age effect on MNS activation may also explain the previously reported inconsistent results regarding MNS functioning in ASD. There are two findings from this meta-analysis demonstrating how age influenced the differences in MNS activation between the ASD and TD individuals. First, in the adolescent subgroup, extensive portions of the inferior frontal gyrus in both the left and the right brain and other regions with human mirror neurons (i.e., the left supramarginal gyrus and right post/precentral gyrus) were hypoactivated in the individuals with ASD; the extent of this hypoactivation was reduced and remained only in the frontal MNS regions (i.e., left supplementary motor area and right inferior frontal gyrus pars orbitalis) in the adult subgroup. Consistent with a previous study, such a reduction in the extent of MNS abnormalities may be explained by the delayed maturation of the prefrontal cortex in individuals with ASD (57). Previous studies have shown that the inferior frontal gyrus is an important hub for social information processing (58). Specifically, the inferior frontal gyrus *pars orbitalis* and *pars triangularis* are specialized for social cognition, whereas the inferior frontal gyrus *pars opercularis* is specialized for flexible motor activation and inhibition (59). Thus, the delayed and immature development in the *pars orbitalis* and *pars triangularis* may be an important neural deficit underlying impaired social information processing in individuals with ASD. Second, using the linear meta-regression method, we identified a significant linear decrease in the activation of the left fusiform gyrus as age increased in the ASD group. The meta-analytic results also reflected that hyperactivation in the left fusiform gyrus was only shown in the adolescent subgroup but not in the adult subgroup. This echoed the results in a previous study, in which the fusiform gyrus gray matter volume changed from leftward asymmetry (i.e. thicker gray matter on the left side) toward symmetry in individuals with autism from childhood through adulthood (60). Conversely, the right cerebellum exhibited a linear age-related increase in activation. In the adolescent subgroup, the right cerebellum exhibited hyperactivation, and the degree of hyperactivation was further increased in the adult subgroup. However, the hyperactivated right cerebellum can be explained by abnormal cerebellar lateralization (i.e., left-lateralized in TD versus right-lateralized in ASD (61); the increase in the intensity of hyperactivation may be a consequence of increased lateralization with age (62).

Limitations

We have attempted to obtain a comprehensive set of relevant fMRI data for meta-analysis by extending our scope of search. Using multiple search engines and manual searches from the reference lists of multiple previous review papers, we found 20 suitable studies that provided us whole brain analytic data

for meta-analysis. In addition to these 20 studies, we found an addition of 12 studies that could have been included if whole brain analysis data were available. However, these papers only included region of interest analyses in their papers, or the whole brain analysis data were not obtainable from the corresponding authors. If the whole-brain results were available, the power of this meta-analysis would have been increased, and a more comprehensive picture regarding MNS functioning in ASD could have been presented. In addition, the age of the participants in the included studies ranged from 11.3–37 for ASD individuals and 11.5–37 for TD individuals. Thus, the age effect on MNS can be examined within this age range only; the difference between the ASD and TD individuals in MNS activation remains unknown for populations beyond this age range. Future fMRI studies related to the MNS that target these age ranges are recommended so that the age effect on the MNS can be examined more holistically. Moreover, the meta-regression we performed using the ES-SDM software was a linear regression, which assumed the variable of interest (i.e., mean age) has a linear relationship with brain activation. However, a previous study has shown that the developmental trajectory of the ASD brain appeared to be u-shaped (24), implying that our meta-regression may not be ideal for articulating the association between age and MNS activation; together with the fact that the statistical significances found in the reported brain regions were driven by only two studies, results have to be treated with caution.

Conclusions

This meta-analysis aimed to explore the differences in MNS activation patterns between TD and ASD individuals when they observe/imitate biological motions with/without emotional components. ES-SDM meta-analytic method was adopted to synthesize the available fMRI data. After a comprehensive literature search, whole-brain analysis data from 20 journal articles with 24 experiments were included in the meta-analysis. In summary, this meta-analysis indicated three main points. First, “global” dysfunction of MNS was found in ASD, which might be attributable to the disrupted neural connectivity in this group of individuals. Previous inconsistent results regarding MNS dysfunction in ASD might be modulated by the difference in visual stimuli given to stimulate the MNS, resulting in variable task complexity that led to the generation of conflicting results. Third, MNS dysfunction in ASD is modulated by age; not only were the core MNS regions found to exhibit a delayed maturation pattern, but brain regions that support core MNS regions also exhibited an abnormal developmental trajectory in individuals with ASD.

Abbreviations

ALE: Activation Likelihood Estimation; ASC: Autism Spectrum Condition; ASD: Autism Spectrum Disorder; BA: Brodmann Area; ES-SDM: Effect-size signed differential mapping; fMRI: functional magnetic resonance imaging; IPL: inferior parietal lobule; MNS: mirror neuron system; ROIs: regions of interest; TD: typically developing

Declarations

Ethics approval and consent to participate

Not applicable.

Consent of publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MYMC participated in the design of the study, performed the article screening and statistical analysis, interpreted the data and drafted the manuscript. MYYH assisted with the article screening and data extraction, interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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Figures

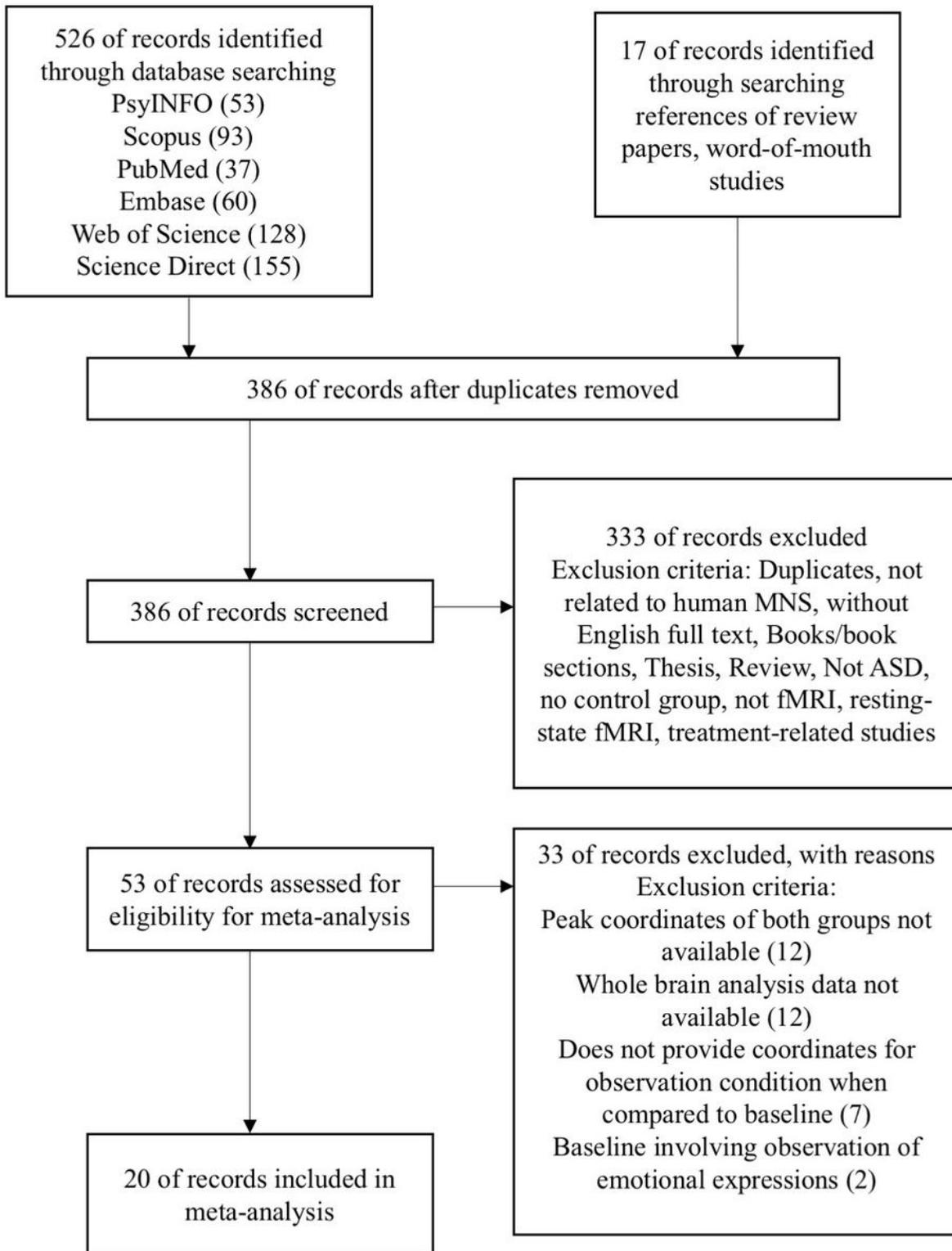


Figure 1

Flowchart of the article screening process

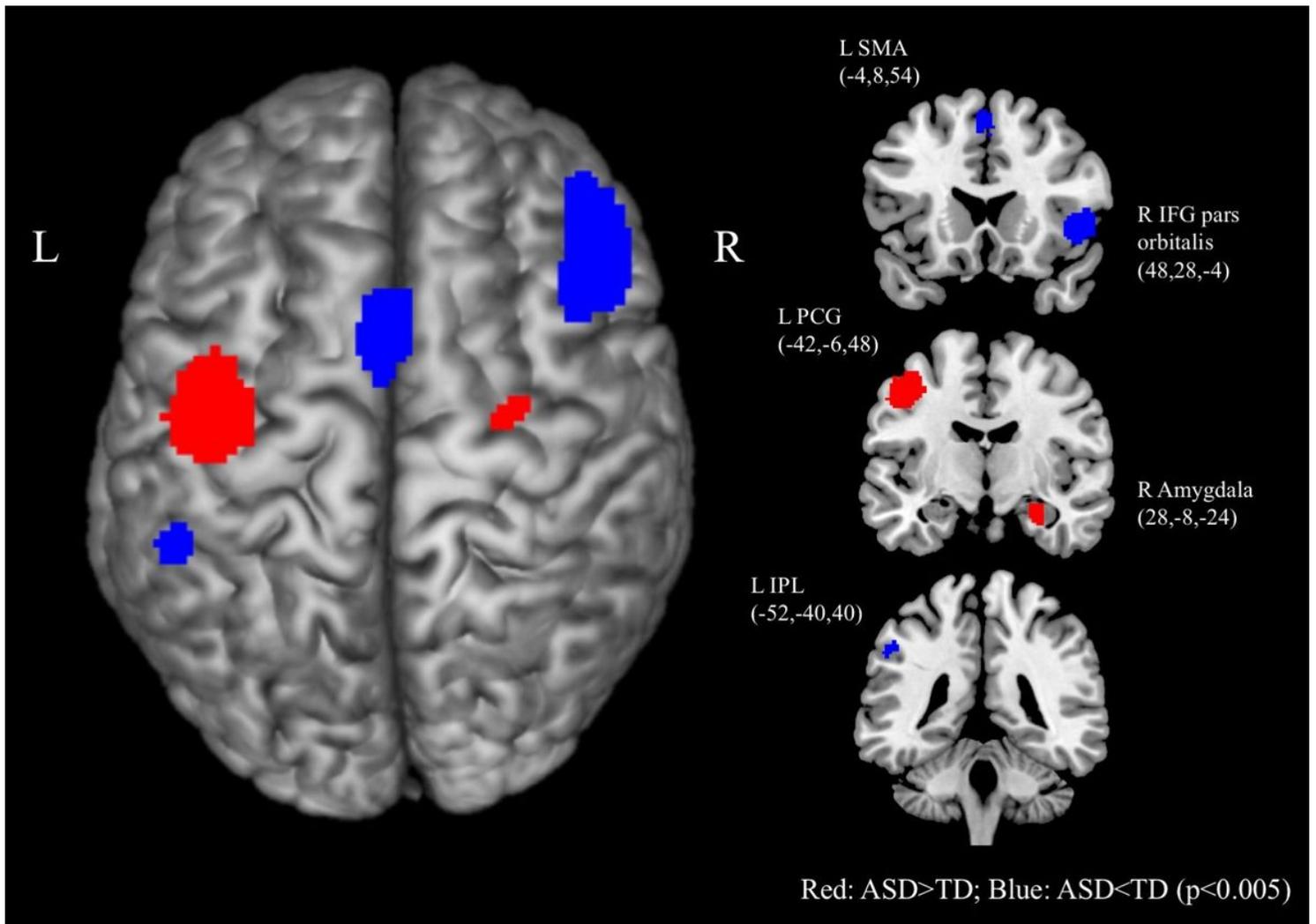


Figure 2

Difference in MNS activation between ASD and TD (Note: L=left; R=right; SMA=supplementary motor area; IFG=inferior frontal gyrus; PCG=precentral gyrus; IPL=inferior parietal lobule)

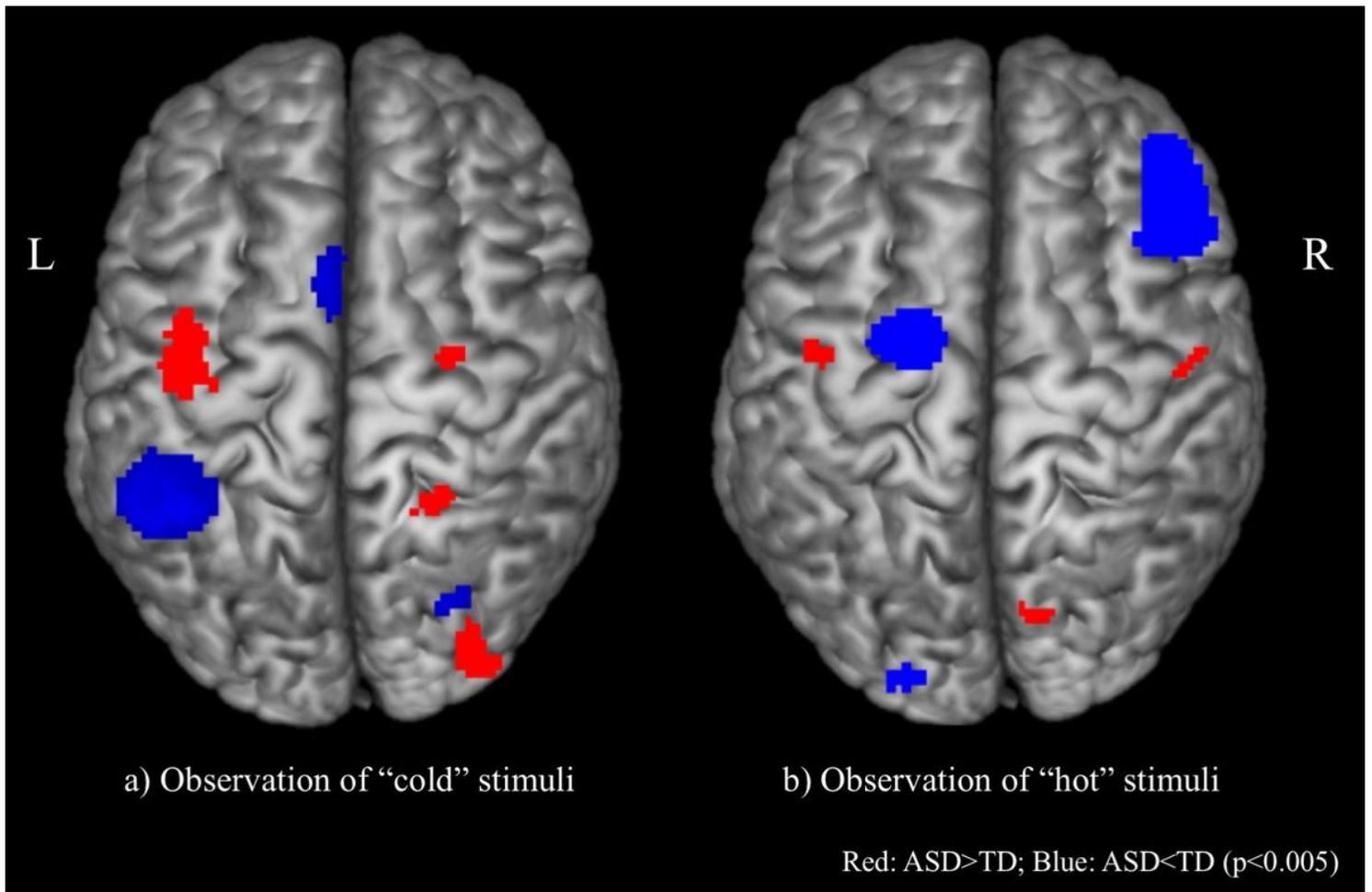


Figure 3

Effects of task complexity in MNS activation between ASD and TD (Note: L=left; R=right)

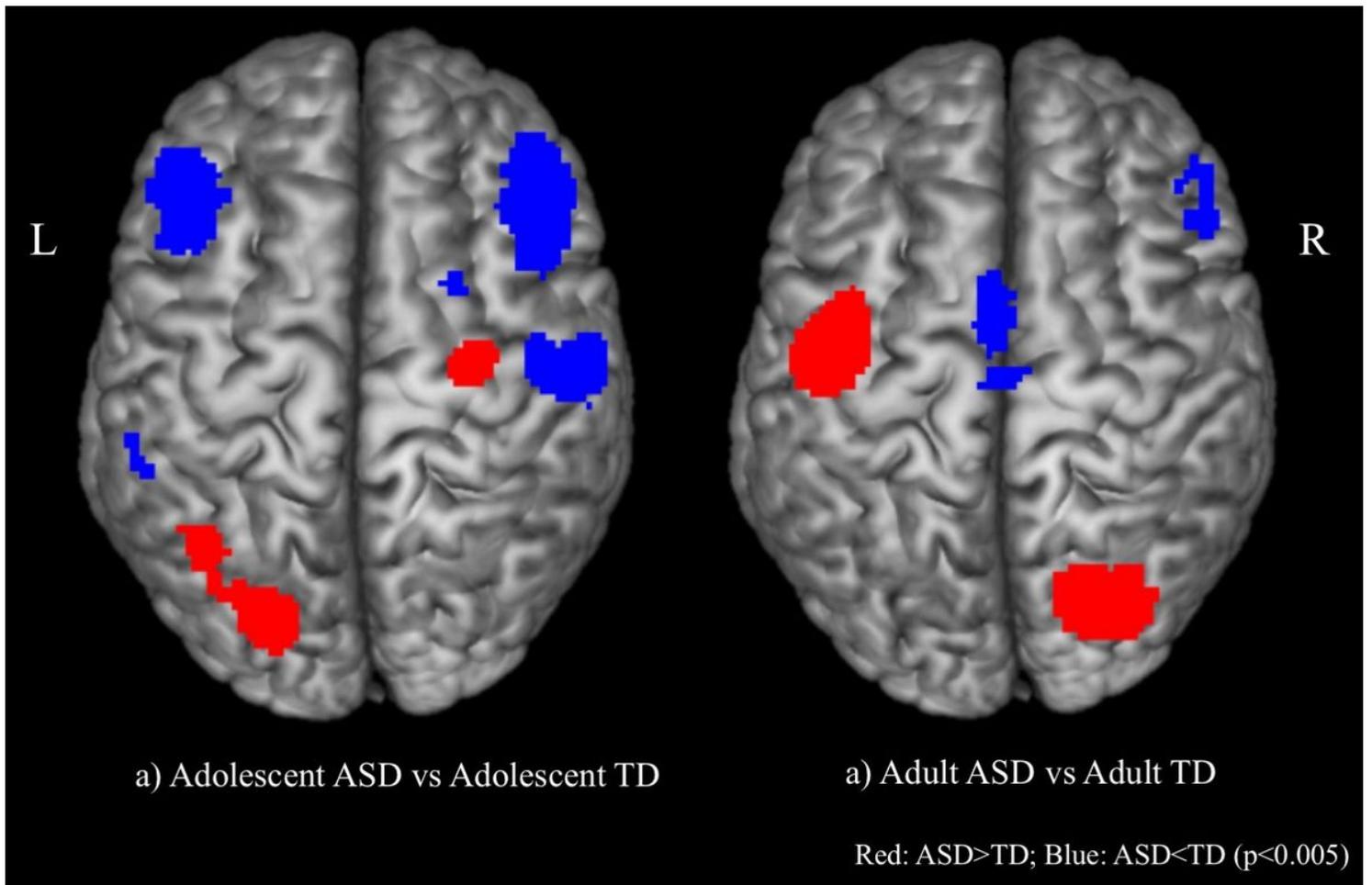


Figure 4

Effects of age in MNS activation between ASD and TD (Note: L=left; R=right)

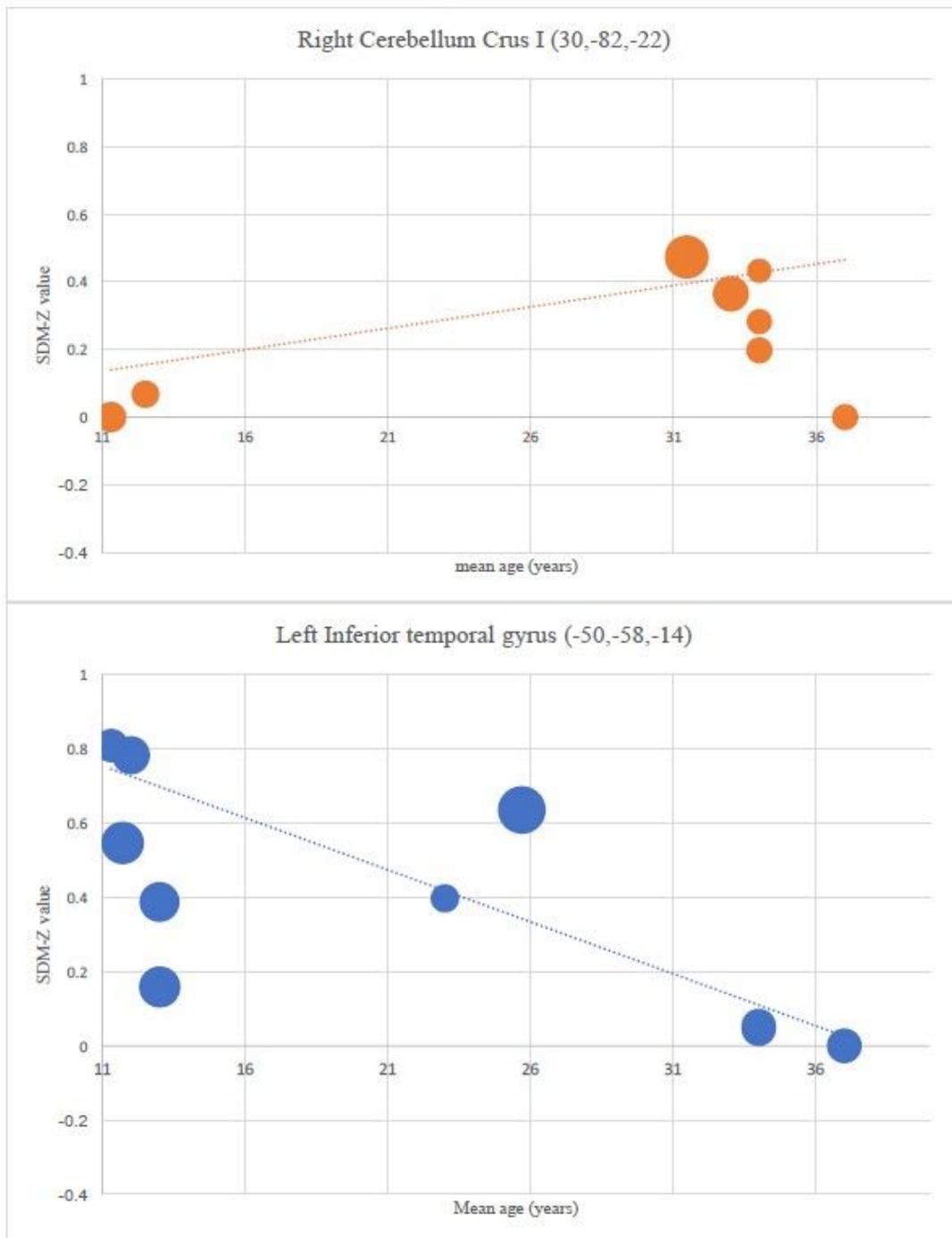


Figure 5

Meta-regression shows that the activation of two brain regions in ASD individuals were significantly associated with chronological age; the left inferior temporal gyrus is less activated and the right cerebellar crus I is more activated as age increases (Note: studies that reported a peak in these two regions were included in the calculation, each of these studies is represented as a dot; larger dots represent larger sample sizes)

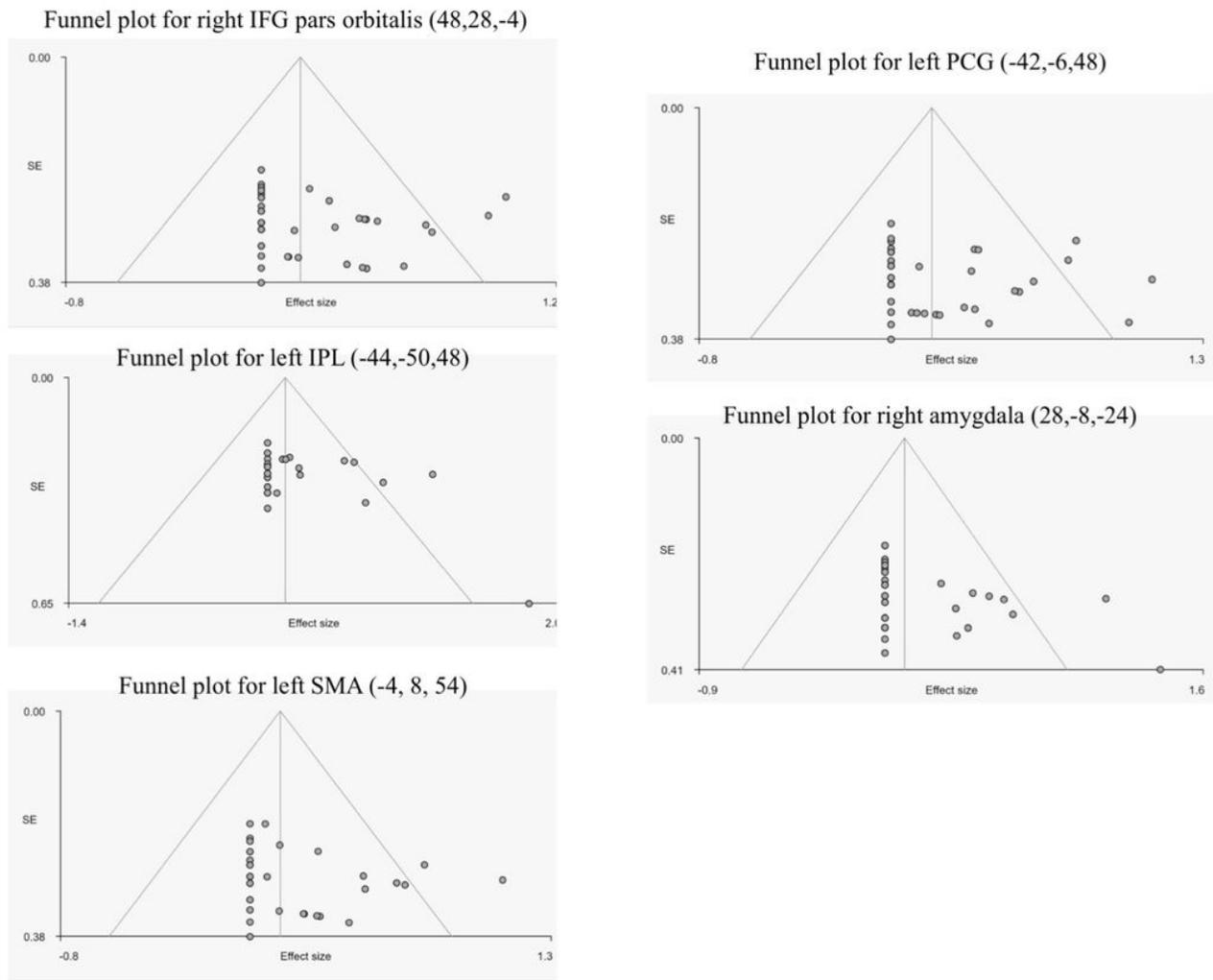


Figure 6

Funnel plots of the activation effect sizes in various MNS regions. No obvious publication bias was shown in these plots (Note: IFG=inferior frontal gyrus; IPL=inferior parietal lobule; SMA=supplementary motor area; PCG=precentral gyrus)