Title: About Eighty Percent of Brain Grey Matter Shows Autism Signs in FMRI

Running Title: Autism biomarkers in fMRI

Authors: Seyed Amir Hossein Batouli¹,², Foroogh Razavi², Minoo Sisakhti²,³, Zeynab Oghabian², Haady Ahmadzade¹,²,⁴ Mehdi Tehrani Doost¹,⁵*

¹ Department of Neuroscience and Addiction Studies, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran.
² Neuroimaging and Analysis Group, Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran.
³ Institute for Cognitive Sciences Studies, Tehran, Iran.
⁴ Tehran University of Medical Sciences, International Campus (TUMS-IC), Tehran, Iran.
⁵ Research Center for Cognitive and Behavioral Sciences, Roozbeh Psychiatry Hospital, Tehran University of Medical Sciences, Tehran, Iran.

* Corresponding Author: Mehdi Tehrani Doost; Professor; Research Center for Cognitive and Behavioral Sciences, Roozbeh Psychiatry Hospital, Tehran University of Medical Sciences, Tehran, Iran. Email: tehranid@tums.ac.ir

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with its symptoms appearing from early childhood. Behavioral modifications, special education, and medicines are used to treat the ASD; however, the effectiveness of the treatments depends on early diagnosis of the disorder. The main approach in diagnosing ASD is currently based on clinical interview and valid scales; however, methods based on brain imaging could also be possible diagnostic biomarkers for the ASD in the future. To identify the amount of information the functional Magnetic Resonance Imaging (fMRI) reveals on ASD, we reviewed 292 task-based fMRI studies on ASD individuals. We observed that face perception, language, attention, and social processing tasks were mostly studied in ASD. In addition, 73 brain regions, estimated as about 83% of brain grey matter, showed an altered activation between the ASD and normal individuals during these four tasks, either a lower or a higher activation. Using imaging methods such as fMRI for the diagnosis or prediction of ASD is a big aim; however, works like this could be the initial steps to make it happen. This study is part of a systematic review with the registration number of CRD42017070975.

Keywords: Autism, Task-based fMRI, Diagnosis
1. Introduction

Autism is a cognitive impairment which is consisted in a spectrum of heterogeneous neurodevelopmental disabilities. It is characterized by possible difficulties, including impaired social interactions, remarkably isolated living conditions, language difficulties, degraded face recognition, abject empathy, as well as constrained and repetitive behaviors, thoughts and actions (Spencer et al., 2011). There are usual therapeutic methods used for ASD, such as multiple pharmacological treatments and target maladaptive co-occurring conditions, as well as behavioral interventions and advance adaptive skills (Zwaigenbaum et al., 2015); however, a treatment is more successful if it begin in the earlier stages of the disease. Early diagnosis means an early intervention and treatment, which shows the effects earlier, and the affected children would benefit from this early treatment before they reach their maximum brain plasticity and neural development (Calderoni et al., 2016; Dawson et al., 2010).

There is no generally accepted diagnostic biomarker for autism (Howsmon, Kruger, Melnyk, James, & Hahn, 2017). A biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. The new biomarkers are expected to optimize or betterment the current behavioral ASD diagnosis and early recognition of the pathological conditions, but none of those ASD biomarkers has yet represented enough accuracy and specificity to be construed as the clinical utility (Walsh, Elsabbagh, Bolton, & Singh, 2011). As a result, researchers have tried the neuroimaging biomarkers to achieve an earlier diagnosis and enable earlier intervention (Zheng et al., 2017).

Functional magnetic resonance imaging (fMRI) is a non-invasive method capable of identifying the pattern and extent of activity of brain areas during a cognitive function (Batouli & Sisakhti, 2020). The popularity of fMRI is mostly due to its widespread availability, being non-invasive, low cost, and appropriate spatial resolution (Glover, 2011). It has shown many research applications, such as in studies relevant to imaging genetics (Sachdev et al., 2013), addiction (Zare Sadeghi et al., 2017), language (Alemi, Batouli, Behzad, Ebrahimpoor, & Oghabian, 2018), memory (Batouli & Sisakhti, 2019), emotion regulation (Batouli & Saba, 2020), motor (Batouli, Hasani, Gheisari, Behzad, & Oghabian, 2016), sensory (Parker et al., 2018), and vision (Schindler...
& Bartels, 2018). Besides, numerous reports are available on the clinical applications of fMRI, and examples include depression (Neufeld et al., 2018), bipolar disorder (G. Li, Liu, Andari, Zhang, & Zhang, 2018), Alzheimer’s disease (Oghabian & Batouli, 2010), ageing (Batouli et al., 2009), autism (He et al., 2018), epilepsy (Klugah-Brown et al., 2018), and coma (Tomaiuolo et al., 2016). It is also used as a biomarker for diseases (Batouli et al., 2021; Batouli, Alemi, Khoshkhouy Delshad, & Oghabian, 2020; Greicius, Srivastava, Reiss, & Menon, 2004), to monitor a therapy (Richards & Berninger, 2008), or for studying pharmacological efficacy (Wise & Preston, 2010).

In a literature search, we identified 18 studies which had reviewed the MRI studies on ASD. The studies were mostly focused on reviewing the findings on autism, with the aim of improving the diagnosis accuracy. Among these studies, three were focused only on the findings of structural MRI in autism (Baribeau & Anagnostou, 2013; Pagnozzi, Conti, Calderoni, Fripp, & Rose, 2018; Palmen & van Engeland, 2004), two only reviewed resting state fMRI works (Jack, 2018; D. Li, Karnath, & Xu, 2017), and among the 12 studies which reviewed the task-based fMRI studies on autism, 11 studies were old (more than 6 years ago) (Anagnostou & Taylor, 2011; Brambilla et al., 2004; Cody, Pelphrey, & Piven, 2002; Dichter, 2012; Mueller, Keeser, Reiser, Teipel, & Meindl, 2012; Philip et al., 2012; Pina-Camacho et al., 2012; Stigler, McDonald, Anand, Saykin, & McDougle, 2011; Verhoeven, De Cock, Lagae, & Sunaert, 2010; Voineagu & Yoo, 2013; D. L. Williams & Minshew, 2007), and only 5 of them aimed at providing biomarkers for autism diagnosis. Finally, except one study (Philip et al., 2012), none provided a map in which the fMRI findings on ASD were summarized. The study by Philip, et al. (Philip et al., 2012) is a good attempt to provide neuroimaging biomarkers for ASD. In this meta-analysis on 95 fMRI papers on ASD, six categories of cognitive functions were of interest: motor, visual, executive, auditory, social, and complex cognition functions. Using the activation likelihood estimation algorithm, they provided maps in which the brain areas with both higher and lower probabilities of activation in the ASD group were compared to that of typically developing individuals. The maps and the main brain areas of difference were provided for all the six groups of cognitive functions.

In using any diagnostic method for ASD, having access to the most reliable and frequent biomarkers is necessary. As a result, this study reviewed the available task-based fMRI studies
on ASD, with the following aims: to identify the cognitive functions which are mostly studied on the ASD patients, to evaluate the potentials of fMRI for ASD diagnosis, and to identify the differences of fMRI maps between ASD and normal individuals, as diagnostic biomarkers. A biomarker in this study is defined as a brain area which shows a different pattern of activation in fMRI in the ASD group compared to normal.

2. Methods
This study was part of a systematic review which was registered at the PROSPERO (International prospective register of systematic reviews; https://www.crd.york.ac.uk/prospero/), with the registration number of “PROSPERO_2017_CRD42017070975”.

2.1. Data sources
The Pubmed and ScienceDirect databases were searched to identify the relevant studies (no date limitation). Different combinations (and/or) of the following keywords were used for the search: functional MRI; brain functionality; task-based fMRI; brain networks; autism spectrum; ASD; PDD; pervasive developmental disorder; autistic; and Asperger. This search resulted in the identification of 651 papers. Due to the large number of studies being identified in our initial search, a manual search of the references of the selected studies in search of any missing document was not performed. Our detailed search strategy is provided while registering the study.

2.2. Study selection
The title, abstract, and (if needed) the full text of the identified manuscripts were studied for selection of the appropriate reports. The studies with the following conditions were initially excluded: non-human studies; studying diseases other than the ASD, or only studying patients without normal population; any imaging modality other than the fMRI; and resting-state fMRI or functional/effective connectivity analyses. The inclusion criteria were: published in a peer-reviewed journal and in English language; comparing autistic and typically developed individuals using task-based fMRI; to have fully and clearly explained the methodology of their study; and reporting the brain areas with a different activation between the normal and ASD individuals in the considered fMRI stimulus.
These criteria resulted in 292 papers; the papers were categorized in terms of their evaluated cognitive function, and the number of papers in each category was as follows: language (26); facial expression (21); attention (17); reward (17); TOM (Theory of Mind) (16); social cognition (15); face processing (13); eye gaze (13); emotion (13); social interaction (11); working memory (11); decision making (9); sensory processing (9); executive function (8); inhibition (8); visuospatial processing (8); face detection (7); location detection (7); response monitoring (7); body motion (7); imitation (6); social perception (5); pain (5); mirror neurons (4); learning (4); voice processing (4); temporal discounting (2); self-face processing (2); counting (1); restricted interests (1); object recognition (1); judgment (1); mentalizing (1); physical condition (1); cognitive flexibility (1); geometric reasoning (1); analogical reasoning (1); self-evaluative processing (1); change detection (1); deviance detection (1); novelty detection (1); empathy processing (1); spatial working memory (1); gesture expression (1); and mental rotation (1).

Due to the high number of papers, we selected four categories of the stimulus types with the highest number of studies. As a result, facial expression, face processing, and face detection papers were regarded as category one (41 papers); social cognition, social interaction, social perception, and theory of mind studies were regarded as category two (47 papers); language was category three (26 papers), and attention was selected as category four (17 papers).

2.3. Quality Check
The quality of the included studies was checked. In this process, each study was scored between 0 and 12, with a higher score showing a better quality. This assessment included questions on: a) case definition being adequate (score: 0,1,2); b) how much the patients group represented the community of ASD (score: 0,1); c) how the control group participants were selected (score: 0,1,2); d) adequate definition of the control group (score: 0,1); e) how comparable were the patient and control groups regarding the statistical analysis (score: 0,1,2); f) how reliable were the imaging and neurocognitive instruments and task (score: 0,1,2); g) the patients and controls being assessed in a similar methodology (score: 0,1); and h) how the non-participation rate of the study was (score: 0,1). Based on this assessment and the scoring instructions, all the included papers received a score above 9.
2.4. Data extraction
The following information was extracted from each study: I) Study: authors, journal, originality, study design, number of sessions, and any intervention; II) Participants: inclusion and exclusion criteria, number of cases and controls, age, gender, and handedness; III) Data acquisition: type of MR machine and head coil, details of the imaging protocol, and the fMRI task; IV) Outcome measures: number and name of the outcome measures, the analysis software, other tests; and V) Findings: results, conclusion, and the suggested biomarkers. As provided in Table 1, the main information extracted from each study was the name of the brain areas which showed an altered (higher or lower) activation between the ASD and control groups during the cognitive tasks.

2.5. Map creation
To provide a visual illustration of the brain structures which showed an altered activation between the normal and ASD groups in the four cognitive functions of interest, we prepared two maps for each of the cognitive functions. The resulting eight maps are illustrated in Figure 1. The maps in warm colors show the brain areas with a higher activation in the ASD group, and the maps with cool colors are illustrating the brain structures with a lower activation in the ASD individuals, compared to normals. The intensity of colors in each map is also in proportion to the number of reports for each structure. In other words, the maps provided in Figure 1 are first illustrating the brain regions which showed a different activation between the ASD and normal individuals, and second, the brightness of the colors in the maps are in proportion to the number of reports on each region; a brighter yellow or a brighter blue shows that higher number of studies had reported changes in the activation of that particular brain area.

Preparing the maps was based on the methods of our previous study (Batouli & Saba, 2017; Razavi, Raminfard, Kalantar, Sisakhti, & Batouli, 2021). Accordingly, first an ROI was created for each brain structure using the AAL (Automated Anatomical Labeling) atlas in the MNI (Montreal Neurologic Institute) space; it was performed using the “wfu pickatlas” toolbox in MATLAB (Maldjian, Laurienti, Kraft, & Burdette, 2003). For those structures whose ROI was not available in the AAL atlas, creation and extraction of the ROIs were performed using the Freeview toolbox of the Freesurfer software package (Freesurfer v5.3a). We excluded the global brain measures as well as the total lobar volumes from these maps, to have a better idea of the single brain areas with an altered activation. Next, the ROIs were added together to make a map,
using codes written in SPM12 toolbox in MATLAB (version R2016a.v9.0), which showed the brain areas with a lower or higher activation in the ASD group in any of those cognitive functions. As stated above, the intensity of colors here were in proportion to the number of reports for each brain structure. The resulting maps are illustrated in Figure 1.

In addition to the maps which showed the areas of the brain with an altered activation, we aimed to identify what ratio of the grey matter of the brain is showing a functional change in the ASD group. In other words, the aim was to estimate and illustrate the amount of overlap between the grey matter tissue of the brain and the brain areas with an altered activation in fMRI. First, normalization of the ROI maps of Figure 1 to the MNI space was performed. Next, the MNI atlas (Montreal Neurologic Institute; MNI152 Template) was segmented into its different tissue types including the grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), and three other tissue types, using the “Segment” toolbox in SPM12. Finally, using a code in MATLAB, the number of voxels in the brain function maps which had an overlap with the grey matter tissue of the brain was counted and reported in proportion to the total number of voxels in the GM map. By this, a ratio was estimated, which illustrated the portion of the GM tissue of the brain which showed an altered activation in the cognitive functions of interest. These maps are illustrated in Figure 2.

3. Results

3.1. Summary of the included studies

There were 131 case-control studies in the four selected cognitive functions. A total number of 2953 patients as well as 2799 typically developing individuals were evaluated; of them around 86% were male, and 35% of the studies included only male participants. Regarding the MR machine, 73% of the studies used a 3 Tesla MR scanner, and the rest used 1.5T, along with using 8, 12, or 32-channel head coils.

Around 79% of the studies were performed in one session. Other researches used 2, 3, 4, or even 5 sessions. The sessions were devoted to preparation, MRI scanning, neurocognitive assessments, behavioral testing, and treatments and interventions. Only 3% of the studies had an intervention, including intranasal administration of oxytocin, pivotal response treatment, taking medications, and visualizing and verbalizing for language comprehension and thinking.
There were different criteria in the studies for inclusion of patients, including receiving a diagnosis of autism or Asperger’s syndrome from an independent clinician based on standard criteria of DSM-IV; the Autism Diagnostic Observational Schedule-Generic (ADOS-G); autism diagnostic interview-revised (ADI-R); the Social Responsiveness Scale (SRS); Childhood Autism Rating Scale; clinical impressions and experienced clinical judgment; and a series of clinical assessments that included a detailed developmental history, clinical interview and observation, medical workup, and cognitive testing. An IQ of 80 or above, measured by the Wechsler Abbreviated Scale of Intelligence, was necessary in some studies. The control groups were mostly composed of typically developing children or adolescents, with no history of psychiatric or neurological disorders, and were matched with the patients in IQ, age, gender, race, and socioeconomic status of the family.

A summary of the findings of the studies is provided in Table 1. This table illustrates the brain areas which had reports on a different activation between cases and controls in the four functions, as well as the number of reports for each area. The areas with more than two reports on their different activation between the two groups are elaborated in below, in the order of their frequency of being reported. References of the selected 131 studies are provided as supplementary data.

[Table 1 about here]

3.2. Findings of the social tasks
Thirty brain areas showed a different activation between cases and controls during the processing of social tasks; 21 of them only showed lower activation in patients, 1 had a higher activation, and 8 areas had both lower and higher reports. The brain areas with a lower activation in patients were temporoparietal junction (13), Inferior Frontal gyrus (IFG) (12), Superior Temporal gyrus (STG) (12), medial prefrontal (8), Supplementary Motor Area (SMA) (6), precuneus (6), anterior cingulate cortex (ACC) (6), posterior cingulate cortex (PCC) (6), inferior parietal lobule (5), anterior insula (5), caudate (4), cuneus (4), medial frontal (3), and insula (3). Post central gyrus (4) was the only brain structure with a higher activation in patients.

3.3. Findings of the face processing tasks
Forty brain regions showed a different activation between cases and controls when processing faces. Sixteen areas only showed a lower activation, 7 areas only a higher activation, and 17
areas showed both lower and higher activations. The areas with a lower activation included fusiform (19), amygdala (19), STG (7), Ventromedial prefrontal cortex (VMPFC) (6), occipital face area (5), IFG (5), inferior occipital (4), middle temporal gyrus (MTG) (4), PCC (4), insula (4), middle frontal gyrus (MFG) (3), cuneus (3), hippocampus (3), and ventral striatum (3). Higher activations in patients were observed in amygdala (6), pulvinar (4), thalamus (3), MFG (3), and precuneus (3).

3.4. Findings of the language tasks

Forty-eight brain regions showed a different level of activation in the language tasks; 22 of them only had lower activation, 6 of them had higher, and 20 had both higher and lower reports. The areas which showed a lower activation in patients in the language tasks were IFG (26), STG (11), cerebellum (9), MTG (8), fusiform (8), ACC (7), superior frontal gyrus (SFG) (6), MFG (5), precentral gyrus (5), SMA (5), precuneus (5), cuneus (5), thalamus (5), occipitotemporal gyrus (4), middle occipital gyrus (MOG) (4), PCC (4), putamen (4), caudate (4), medial frontal gyrus (3), medial prefrontal gyrus (3), amygdala (3), and insula (3). The brain areas with a report on their higher activations in patients were STG (10), fusiform (8), MTG (5), IFG (4), MOG (4), posterior temporal gyrus (PTG) (3), inferior parietal lobule (3), post central gyrus (3), and cuneus (3).

3.6. Findings of the attention tasks

Thirty-nine regions showed differences in brain activations between the cases and controls; 14 areas were only lower in patients, 9 regions were only higher, and 16 areas had both lower and higher reports. The areas with a lower activation in patients were cerebellum (10), STG (9), IFG (6), precentral gyrus (6), SMA (6), post central gyrus (6), insula (6), MFG (4), medial prefrontal (4), superior parietal gyrus (SPG) (4), putamen (4), thalamus (4), caudate (4), and orbito frontal gyrus (3). The brain regions with higher activation in patients were medial prefrontal (7), precuneus (7), IFG (4), cerebellum (4), SMA (3), post central gyrus (3), and amygdala (3).

[Figure 1 about here]

Figure 1. Illustration of the brain areas with an altered activation between the ASD and normal individuals, in the four cognitive functions of interest. Colors are in proportion to the number of reports for each structure. Warm and cool colors respectively show the brain areas with a higher or lower activation in the ASD, compared to normal individuals.
3.7. Overlap with the Grey Matter
As mentioned above, the aim in this work was to evaluate if fMRI is able to reveal a considerable amount of data on the ASD; a positive answer to this question would introduce fMRI as a potential diagnostic tool for the ASD in the future works. For this aim, we assessed the overlap of the brain maps obtained for the four cognitive functions (illustrated in Figure 1) with the grey matter tissue of the brain, as explained in Methods. Figure 2 shows these overlaps, as well as the percentage of the overlap.

The highest coverage of the GM was observed in the language tasks-low condition (69%); other estimates were attention tasks-low (64%), social tasks-low (55%), and face processing tasks-low (48%). These findings showed that a larger area of the brain showed a lower activation in the ASD individuals versus normal, compared to a higher activation. On the other hand, both attention tasks-high and language tasks-high maps showed 44% coverage of the GM, with 36% in the face processing-high, and 19% in social tasks-high maps.

When all eight brain maps in the four cognitive tasks were combined, 83% of the brain GM was covered, which suggests that fMRI is a strong tool in revealing signs of ASD.

[Figure 2 about here]

Figure 2. The overlap of the brain areas with an altered activation between the ASD and normal individuals, in the four cognitive functions of interest, with the grey matter tissue of the brain. a) the combination of the maps of the four cognitive functions; b) social tasks-low; c) social tasks-high; d) face processing-low; e) face processing-high; f) language tasks-low; g) language tasks-high; h) attention tasks-low; i) attention-tasks-high. The percentages show the overlap of each map with the grey matter tissue of the brain.

4. Discussion
4.1. Summary of the results
This study reviewed the task-based fMRI studies on ASD, with the aim of assessing the potential of fMRI in terms of predicting or diagnosing ASD in the future. The severity of the difference between the fMRI measures of the normal and ASD groups could suggest the fMRI to be a useful method for this aim. By initially recruiting 292 studies, and reviewing the results of 131 fMRI works in the four cognitive abilities of interest, 73 brain structures were identified which
showed an altered brain function between the two groups. In addition, a combination of the results of the four cognitive functions showed that about 83% of brain GM shows an altered activation in the ASD, compared to normal individuals. Future works with the aim of diagnosing ASD using the automatic algorithms, such as machine learning, would benefit from the findings of this study.

4.2. ASD Diagnosis

The prevalence of Autism Spectrum Disorders (ASD) is 1 person in 59 in the United States (Baio et al., 2018), and 1 in 132 globally (Baxter et al., 2015), which are much higher than previously reported. This data reflects the growing knowledge about ASD, as well as innovations in the diagnostic approaches which enhanced evaluation of its clinical symptoms (Sandin et al., 2014). The main characteristics of autism’s clinical manifestations is its significant heterogeneity; no two autism patients are alike, which means that each autistic individual shows unique phenotypic heterogeneity in the combination of symptom severity and comorbid conditions [e.g. anxiety, depression, social communication disorder, ADHD, epileptic disorders] (Jones & Lord, 2013). Early diagnosis would facilitate decisions for the selection of the best therapeutic method, would improve the quality of life of children with ASD and their families (Pagnozzi et al., 2018), and would lead to prevent notable economic and emotional costs to the autistic people and their families. Despite all these, early diagnosis is a challenge (Fein et al., 2013; Zwaigenbaum et al., 2015).

There are lots of undetermined questions about the causes and the pathophysiology of ASD (D. Li et al., 2017). To date, diagnostic evaluation of ASD is based on clinical observation and interview with the caregivers using some standardized instruments including Autism Diagnostic Observational schedule (ADOS) (Steiner, Koegel, Koegel, & Ence, 2012). The lack of knowledge on the exact neural basis of autism spectrum disorder, and the absence of validated measures of diagnosis throughout development, are challenging. To date, diagnostic evaluation for autism requires a team of professionals from different disciplines, usually including a physician, speech-therapist, cognitive therapist, and occupational therapist.

Since the first description of the disease in the early 1940s, researchers always have been intensively trying to identify biological markers for ASD (Szpir, 2006). As mentioned before, the crucial challenges are the underlying biological heterogeneity of ASD. Nowadays, we can only
reliably diagnose the ASD based on the current standardized behavioral observations and psychometric tools (Steiner et al., 2012). Precise diagnostic assessments are required, as finding specific biomarkers for autism may reduce the variability of ASD diagnosis. Such methods are also helpful for evaluating treatment effects on the neurodevelopmental disorders.

Neuroimaging has already provided a pivotal role in the ASD characterization, by the in vivo monitoring of the brain structure and function during the disorder (Retico, Tosetti, Muratori, & Calderoni, 2014). MRI is a safe, non-invasive, and powerful diagnostic tool for observing alterations in the structure and the function of the brain. Moreover, fMRI techniques role as an important opportunity in forming these diagnostic assessments (D. Li et al., 2017). fMRI is considered to provide the required biomarkers for exploring and diagnosing the severity of neurodevelopmental disorders, such as autism (Castellanos, Di Martino, Craddock, Mehta, & Milham, 2013). Current researches on the structural and functional brain MRI indicate that identifying general biological alterations in most of ASD patients requires large cohort sizes, and they often lead to numerous overlapping markers with those of other conditions and of the public population, rather than a single marker (Voineagu & Yoo, 2013). As a result, more reliable algorithms are needed to use neuroimaging for purposes such as ASD diagnosis. Neuroimaging could be combined with the machine learning methods for disease diagnosis or prediction purposes (Andrews, Marquand, Ecker, & McAlonan, 2018). These methods are already used for the ASD diagnosis, and as an example, classification approaches using a support vector machine (SVM) was used to characterize the structural changes of the brain in adults with ASD, to discriminate them from normal population (Ecker et al., 2010). These methods have been reviewed recently (Andrews et al., 2018). These classifiers, in addition to being able to separate patients and controls, are also applicable on a single subject basis to aid in the diagnosis. This is done by assigning an abnormality score to each subject which quantifies the degree of pathology (Ingalhalikar, Parker, Bloy, Roberts, & Verma, 2011). The current study aimed to initially show the potential of fMRI to be used for ASD diagnosis along with machine learning algorithms, and also to provide the biomarkers for fMRI in such works.

4.3. Face processing stimuli

Fusiform gyrus, as well as the amygdala, STG, VMPFC, occipital face area, IFG, IOG, MTG, PCC, insula, MFG, cuneus, hippocampus, and striatum, showed lower activation in the ASD
group when processing faces. Striatum is involved in processing rewards, and for individuals with high autistic traits, facial mimicry is associated with lower reward-related neural response(Hsu, Neufeld, & Chakrabarti, 2018). Amygdala showed a lower activation during the attentional orienting triggered by eye gaze(Klapwijk et al., 2016), suggesting that impairments associated with gaze-triggered attentional orienting could be modified by treatments directed at amygdala activity(Sato, Kochiyama, Uono, Yoshimura, & Toichi, 2017). The decline of activation in the hippocampus also suggests problems in integrating emotional information with declarative memory(Klapwijk et al., 2016).

Fusiform is vital in face processing(Grill-Spector, Knouf, & Kanwisher, 2004), and its activation is associated with one’s face discrimination performance(Jiang et al., 2013). It is suggested that the phenotypic heterogeneity in face processing in ASD is mediated by neuronal selectivity to faces in this area(Jiang et al., 2013). Moreover, it is proposed that training on tasks which recruit the face representation in this area could remediate face-processing differences(Jiang et al., 2013). Another study hypothesized that the abnormal activity of this area in autism could be due to inappropriate information acquisition during eye scanning(Pelphrey, Morris, McCarthy, & Labar, 2007). Besides, ASD children differently recognize faces, as they more focus on feature-based than configural analyses, and the fusiform gyrus is associated with configural processing(Pelphrey et al., 2007). Also, FFA activation depends on orientation towards the eyes during stimulus presentation(Zürcher et al., 2013), and therefore, this reduced activation may be caused by atypical eye-gaze patterns towards faces.

MTG in involved in the processing of facial features and expressions(H. Critchley et al., 2000), but it is also strongly modulated by ‘top-down’ attentional mechanisms, and therefore different attentional mechanisms concerning faces(H. D. Critchley et al., 2000) in ASD could be a reason for its declined activation. STG is active in tasks involving the attribution of intentions to moving geometric figures, as well as in social dysfunction in autism(Pelphrey et al., 2007). Other brain areas with a declined activation in ASD are also involved in face processing, such as the insula, a driving node in the salience network(Sridharan, Levitin, & Menon, 2008); PCC in acquiring facial familiarity(Kosaka et al., 2003); and IFG consistently being active during imitation, action observation, and intention understanding(Iacoboni, 2005).
Higher activations in individuals with ASD while processing faces were observed in amygdala, pulvinar, thalamus, MFG, and precuneus. Pulvinar nucleus and amygdala have roles in rapid face processing (Hadjikhani et al., 2017). Higher activation in the subcortical areas, such as amygdala, in children with ASD when looking at the eyes, is possibly related to their eye avoidance in daily life (Hadjikhani et al., 2017). It seems that the subcortical system in ASD overreacts to stimuli that should be considered as positively engaging and socially rewarding (Hadjikhani et al., 2017), and for example, the amygdalar hyper-responsiveness to direct gaze shows a neural indicator for heightened emotional arousal triggered by eye contact (Dalton et al., 2005). The thalamic hyperactivation is also hypothesized as one of the substrates of social cognition deficits in ASD, through its dysregulatory impact on the dorsolateral prefrontal cortex (Hadjikhani et al., 2017). The activation of precuneus is modulated depending on attentional demands, and therefore its increased activation in ASD could be a compensatory mechanism (Wang, Dapretto, Hariri, Sigman, & Bookheimer, 2004). Amygdala has reports on higher, lower, and no difference in activation between the ASD and healthy individuals in face processing. The reasons for the inconsistent findings could be due to the differences in attention to the faces (Klapwijk et al., 2016) or the type of tasks and stimuli (Pinal, Zurrón, & Díaz, 2014).

4.4. Language stimuli

The language function is impaired in ASD children. They have difficulty in generating words that are relevant to a context or topic (Kenworthy et al., 2013), and in the processing of mental states and words related to emotions (Moseley et al., 2015). This impairment is also observed in patients with a lesion in the motor system (Moseley et al., 2013). In general, there is altered recruitment of reading-related neural resources in ASD children, weaknesses in the top-down modulation of semantic processing (Karten & Hirsch, 2015), as well as difficulties in the use of context to predict the final word of sentences (Catarino et al., 2011). Executive functions are critical for selecting, generating, and organizing words into sentences, and for sustaining meaningful conversations, and there are reports on impaired executive control of language in ASD (Kenworthy et al., 2013).

Twenty-two brain structures showed a declined activation in language processing in the ASD children, including IFG, STG, cerebellum, MTG, fusiform, ACC, SFG, MFG, precentral gyrus, SMA, precuneus, cuneus, thalamus, MOG, PCC, putamen, caudate, medial frontal gyrus,
amygdala, and insula. These structures are involved in different aspects of the language processing. The putamen and ventral lateral nucleus of the thalamus is involved in fluency-related activity (Kenworthy et al., 2013), whereas temporal regions are important in auditory processing (Belin, Zatorre, Lafaille, Ahad, & Pike, 2000) particularly emotional prosody (Wildgruber et al., 2005), and the ACC is activated in the explicit evaluation of emotions (Bach et al., 2008). Thalamus has a role in language and verbal memory (Hebb & Ojemann, 2013), as well as visual attention (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005), suggestive of serial visual scanning during the initial steps of reading (Koyama et al., 2011). The left putamen has also been implicated in reading and language comprehension, especially in sublexical and lexical processing (Oberhuber et al., 2013).

The middle and superior frontal gyri are involved in executive functions (Moreno-López et al., 2012), attention, and working memory (Boisgueheneuc et al., 2006), therefore be related to the cognitive evaluation of the emotional content (Gebauer, Skewes, Hørlyck, & Vuust, 2014). LMFG is also reported to be a region involved in word retrieval during language production (Bednarz, Maximo, Murdaugh, O’Kelley, & Kana, 2017), and there are numerous reports on the activation of the LMFG during single-word reading, sentence reading, and lexical retrieval (Bednarz et al., 2017). This region is shown to be underactive in children with reading difficulty (Barquero, Davis, & Cutting, 2014). Lack of activation of the LMOG is previously shown in reading dysfunction, due to its role in reading intervention (Barquero et al., 2014). Frishkoff et al. (Frishkoff, Tucker, Davey, & Scherg, 2004) also suggested that the anterior cingulate cortex discriminates congruous and incongruous words, and its activity is sustained over time during the processing of semantic incongruities. Besides, the cerebellum has direct connections to Broca’s area, which enables it to facilitate verbal abilities (Harris et al., 2006).

Nine brain structures also showed an elevated activation in ASD individuals, including STG, fusiform, MTG, IFG, MOG, PTG, inferior parietal lobule, post central gyrus, and cuneus. The increased activation of brain areas in ASD is suggested to be a compensatory mechanism to aid in language comprehension (Murdaugh, Deshpande, & Kana, 2016). There are some evidence of recruiting more cortical resources during word generation, in both males and females with ASD (Beacher et al., 2012). An elevated activation of fusiform has been shown in individuals with ASD in order to interpret the meaning of emotional words (Han, Yoo, Kim, McMahon, &
Renshaw, 2014). Greater activation of the cuneus in line with the evidence of atypical reliance on the visual cortex in individuals with ASD (Chen, Gau, Lee, & Chou, 2016) as the cuneus activation is related to visual perception and retrieving stored mental imagery of word stimuli (Kim et al., 2013). It seems that individuals with ASD tend to recruit more visual cortex compared to IFG for word processing (Samson, Mottron, Soulières, & Zeffiro, 2012).

Another finding is the use of right hemisphere language-analogous regions in ASD to assist reading. This finding supports the idea that autism is related to early left-hemisphere dysfunction (Takeuchi, Harada, Matsuzaki, Nishitani, & Mori, 2004). Studies suggest that ASD children are more likely to show right-hemisphere lateralization for language (Harris et al., 2006). As an example, the right IFG has been more strongly implicated in emotional prosody processing than its contralateral homologues (Schirmer & Kotz, 2006). However, there are still disputes on whether the reversal of Broca’s asymmetry in the language is a predisposing factor toward language-impairment, or a compensatory neurodevelopmental response to language dysfunction in the left-hemisphere (Harris et al., 2006), although the increased right hemisphere activity for the ASD group is mostly interpreted as reflecting more effortful processing (Tesink et al., 2009).

The LIFG, commonly referred to as Broca’s area, is involved in affective aspects of language processing, semantics, and visual memory (Beacher et al., 2012), in word processing and controlled retrieval and selection of semantic knowledge (Weikum et al., 2007), in unification operations required for binding single word information into larger structures (Fitzpatrick & Indefrey, 2009), in representing social knowledge and abstract social concepts (Zahn et al., 2007), and in attributing personality traits (Heberlein & Saxe, 2005). It also subserves verbal working memory by maintaining semantic representations (Bednarz et al., 2017). This area had 26 reports on decreased and 4 reports on higher activation in ASD. The activation of this area has been shown to be dependent on the stimuli, for example, elevated activation of in letter fluency vs. category (Kenworthy et al., 2013), and attenuation of responsiveness to manipulations of semantic congruity (Beacher et al., 2012). In addition, the different activation of this region in ASD could be linked to other perceptual and expressive deficits in affective communication (Beacher et al., 2012).
4.5. Attention tasks

The neural mechanism of attention is different in ASD. The failure to orient attention towards salient stimuli is a fundamental problem in ASD, which impairs the development of social skills and learning (Klin, Jones, Schultz, & Volkmar, 2003). It could be due to the abnormalities in their functional brain maturation (C. M. Murphy et al., 2014), which is associated with clinical symptoms of ASD and inattention (C. M. Murphy et al., 2014). Neural circuitry of attention is driven by hyper-responsivity to salience (E. R. Murphy et al., 2017), and the observed differences may reflect compensatory mechanisms enabling normal behavioral performance (Rahko et al., 2015). Besides, over-focused attention in ASD is the result of hyperarousal, which is seen as disinhibition of the competing sensory information that generally leads to attentional shifts (Liss, Saulnier, Fein, & Kinsbourne, 2006). There are evidence showing that arousal regulation in ASD results from early deficits in disengaging attention (Rahko et al., 2015). In general, it seems that ASD children are under-reactive to behaviorally-relevant stimuli. There are also findings of atypical functions of both top-down and bottom-up attention networks in these individuals, and they are unable to filter irrelevant information (Kechn, Nair, Lincoln, Townsend, & Müller, 2016).

Fourteen brain structures have been showed to have lower activation in patients with ASD, including cerebellum, STG, IFG, precentral gyrus, SMA, post central gyrus, insula, MFG, medial prefrontal, SPG, putamen, thalamus, caudate, and orbito frontal gyrus. The cerebellum plays an essential role in attentional processes (Kechn et al., 2016), and is implicated in the neuropathology of ASD (Fatemi et al., 2012). Caudate, STG, and SPG are involved in joint attention, and they facilitate attentional regulatory processes (J. H. G. Williams, Waiter, Perra, Perrett, & Whiten, 2005), which show deficits in ASD. STG also plays a role in utilizing social cues to orient attention, but in ASD, this area may not be sensitive to the social meaning conveyed by eye gaze (Pelphrey, Morris, & McCarthy, 2005). Finally, putamen responds when a stimulus is important, but not when the behavioral significance is removed (Greene et al., 2011).

On the contrary, seven brain areas showed an elevated activation in ASD, including the medial prefrontal, precuneus, IFG, cerebellum, SMA, post central gyrus, and amygdala. The activation of visual cortex, and in particular precuneus, was significantly correlated with the severity of autistic symptoms (Ohta et al., 2012). Precuneus is implicated in spatial attention and anticipation.
of motor responses (Cavanna & Trimble, 2006), and the deficits in this area were positively correlated with the severity of social reciprocity and communication problem (Christakou et al., 2013). The increased response in children with ASD may reflect hyper-responsivity of bottom-up processing of salient visual stimuli (E. R. Murphy et al., 2017). This increase may be attributable to differences in the visual receptive fields in ASD. There is evidence of increased perifoveal population receptive fields in extrastriate cortex, associated with hyper-excitability of the visual cortex or poor peripheral spatial attention in individuals with ASD (Schwarzkopf, Anderson, de Haas, White, & Rees, 2014).

Studies have indicated that the medial rostral PFC plays a role in attentional selection between stimulus-oriented and stimulus-independent thought (Gilbert et al., 2007). This region is also implicated in multitasking and prospective memory (Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006). One suggestion based on these findings is that healthy individuals were able to modulate activity in their visual cortex according to the attentional demands of the task to a higher degree than the ASD group (Gilbert, Bird, Brindley, Frith, & Burgess, 2008). This finding also suggests functional underconnectivity in ASD (Just, Keller, Malave, Kana, & Varma, 2012), leading to a decrease in top-down modulation of sensory areas according to attentional demands (Gilbert et al., 2008). Moreover, the medial rostral PFC is involved in mentalizing (Gilbert et al., 2007), and its higher activation in ASD raises the possibility that these individuals recruit brain regions typically associated with mentalizing to perform other tasks, such as for face perception (Pierce, Müller, Ambrose, Allen, & Courchesne, 2001). As an example, the inability to suppress task-related activation of the medial prefrontal cortex is linked to distractibility in ADHD (Fassbender et al., 2009), and because of the high comorbidity of ADHD and autism (Simonoff et al., 2008), this may indicate a particular difficulty with distraction during the global condition (Gadgil, Peterson, Tregellas, Hepburn, & Rojas, 2013).

4.6. Limitations
Despite our endeavors, there are a few limitations with our work. A number of studies may be missing during our database searches. Our inferences were based on 131 studies from the 292; including a larger number of works could result in more comprehensive deductions. Also, the methodology and participants of the selected studies were not identical, the factors which could have associations with the findings of a study. More detailed discussions could be provided on
our findings, and finally, practically using the reported biomarkers for ASD diagnosis would be helpful as a validation algorithm.

4.7. Summary
This study, by initially including 292 papers and studying 131 of them in detail, first showed which cognitive domains are currently mostly studied in the ASD individuals. The mostly studied domains are the best candidates for diagnosis/prediction purposes. Also, the less studied cognitive functions could be suggestions for the future works. Second, the study showed that a large part of the brain show abnormalities in fMRI in ASD individuals compared to normal, which suggests the application of fMRI in ASD diagnosis. For this aim, the study provided a comprehensive list of biomarkers for using task-based fMRI in the diagnosis/prediction of ASD, which included the brain structures that showed an altered activation in ASD, as well as the frequency of reports for each structure. All the 73 brain areas illustrated in Figure 2 are ideal candidates for this purpose, with the brighter areas being stronger neuromarkers. FMRI imaging of an individual, and evaluating these biomarkers in methods such as machine-learning, could help assess the risk of an individual to be in the ASD spectrum.

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Grill-Spector, K., Knouf, N., & Kanwisher, N. (2004). The fusiform face area subserves face


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<th>Attention</th>
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<td>B:2;L:1</td>
<td>B:1;R:3</td>
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| Temporal lobe |
|---------------------|---------------------|---------------------|
| Sup. temporal G. | B:6 | B:2 | B:3;R:1 | B:1 | B:5;L:1 | B:3;L:4 | B:4;R:1 | L:1 |
| Mid. temporal G. | -- | -- | B:1 | -- | -- | -- | -- | -- |
| Fusiform | -- | -- | B:2;L:1 | B:4 | B:2;L:1 | B:1 | -- | -- |
| Inf. temporal | -- | -- | B:5;R:9 | L:1 | B:3;L:2 | B:4 | B:1 | -- |
| Ant. temporal | -- | -- | R:1 | -- | R:1 | -- | -- | -- |
| Temporal pole | B:1 | B:1 | B:1 | -- | -- | -- | B:1 |
| Heschl’s G. | -- | -- | -- | -- | -- | -- | -- | B:1 |
| Temporal operculum | -- | -- | -- | -- | B:1;L:2 | -- | -- | -- |

| Parietal Lobe |
|-------------------|-------------------|-------------------|
| Sup. parietal | -- | -- | -- | -- | R:1 | B:2 | -- | -- |
| Inf. parietal lobule | B:1;L:3 | L:1 | -- | -- | B:1 | B:1;L:1 | -- | -- |
| Supramarginal gyrus | -- | -- | -- | -- | R:1 | -- | B:1 | -- |
| Angular gyrus | -- | -- | L:2 | -- | R:1 | -- | B:1 | -- |
| Precuneus | B:3 | -- | B:1;R:1 | B:2;L:1 | B:1 | B:3;L:1 | -- | -- |
| Post central gyrus | -- | B:2 | L:1 | L:1 | R:2 | B:1;L:1 | B:3 | B:1;L:1 |
| Med. parietal | -- | -- | -- | -- | -- | B:1 | -- | -- |
| Post. parietal | -- | -- | -- | -- | -- | B:1 | -- | -- |
| Temporal parietal | B:4;R:3 | L:1 | -- | -- | R:1 | -- | -- | -- |
| Occipito parietal | -- | -- | -- | -- | B:1 | L:1 | -- | -- |
### Occipital Lobe

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### Cingulate Gyrus

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<td>L:1</td>
<td>R:1</td>
<td>B:2:R:3</td>
<td>R:1</td>
<td>B:1</td>
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### Subcortical Areas

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### Cerebellum

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<td>Ant. cerebellum</td>
<td>--</td>
<td>--</td>
<td>B:3:R:3</td>
<td>B:2</td>
</tr>
<tr>
<td>Post. cerebellum</td>
<td>--</td>
<td>--</td>
<td>B:1</td>
<td>--</td>
</tr>
</tbody>
</table>

**Table 1.** The brain areas which showed an altered activation between the ASD and normal individuals in the four cognitive functions of interest; numbers represent the number of studies which reported a similar finding.

B= Bilateral; R= Right; L= Left; G= gyrus; Sup= superior; Med= middle; Inf= inferior; Pref= prefrontal; Ant= anterior; Post= posterior; J= junction;