Brain correlates of cognitive-behavioural manifestations in Autism Spectrum Disorder.

Submitted by

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Under the guidance of

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in partial fulfilment of the requirements for the degree of **Master of Technology in Computational Biology**

to

Department of Computational Biology, **Indraprastha Institute of Information Technology, New Delhi**

August 2022

Certificate

This is to certify that the thesis titled “**Brain correlates of cognitive-behavioural manifestations in Autism Spectrum Disorder.** " is being submitted by **Achyuthanand. K** to the Indraprastha Institute of Information Technology, Delhi, for the award of the Master of Technology is an original research work carried out by him under my supervision. In my opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted in part or full to any other university or institute for the award of any degree/diploma.

11 August, 2022

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Acknowledgement

I would like to express my sincere gratitude and respect towards Dr. Mrinmoy Chakrabarty from Indraprastha Institute of Information Technology, Delhi, for being my supervisor and exposing me to this wonderful research topic and guiding me throughout. Besides my supervisor, I would also like to thank my family, friends and my mentor Mrs. Ranjini Prasanth for providing much-needed support and motivating me from time to time throughout the course of my thesis, which enabled me to pursue my research in an efficient and structured manner.

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List of Abbreviations

ASD :Autism Spectrum disorder

TD :Typical developing

RRB :Restrictive Repetitive Behaviour

fMRI :Functional Magnetic Resonance Imaging

BOLD : Blood-oxygen-level-dependent

PFC : Prefrontal cortex

DMN :Default Mode Network

BDI : Beck's Depression Inventory

ADOS : Autism Diagnostic Observation Schedule

FIQ : Full IQ quotient

sMRI : Structural Magnetic Resonance

R-fMRI : Resting State functional Magnetic Resonance Imaging

MNI : Montreal Neurological Institute

CSF : Cerebrospinal fluid

ROI : Region of Interest

QA : Quality Assurance

FC : Functional Connectivity

rsFC: Resting State Functional Connectivity

MPFC: Medial Prefrontal Cortex

PCC : Posterior cingulate cortex

ACC : Anterior Cingulate Cortex

l&r : Left and Right

SBC : Seed Based Connectivity

SN : Salience Network

CM : Centromedial

LB : Laterobasal

IC l : Insular Cortex Left

SFG r : Superior Frontal Gyrus Right

iLOC l : Lateral Occipital Cortex, inferior division Left

IFG oper l : Inferior Frontal Gyrus, pars opercularis Right

AI l : Anterior Insula Left

sLOC l : Lateral Occipital Cortex, superior division Left

sLOC r : Lateral Occipital Cortex, superior division Right

PostCG l : Postcentral Gyrus Left

ACC : Anterior Cingulate Cortex

Cereb1 r : Cerebelum Crus1 Left

pPaHC r : Parahippocampal Gyrus, posterior division Right

PaCiG l : Paracingulate Gyrus Left

FP r : Frontal Pole Right

AG l : Angular Gyrus Left

sLOC l : Lateral Occipital Cortex, superior division Left

Cereb 45 l : Cerebelum 4 5 Left

Amygdala r : Amygdala Right

PO l : Parietal Operculum Cortex Left

pTFusC l : Temporal Fusiform Cortex, posterior division Left

sLOC r : Lateral Occipital Cortex, superior division Right

MedFC : Frontal Medial Cortex

PreCG l : Precentral Gyrus Left

ACC : Anterior cingulate cortex

Cereb8 l : Cerebellum 8 Left

AC l & r : Cingulate Gyrus, anterior division

PCC : Posterior cingulate cortex

toITG r : Inferior Temporal Gyrus, temporo-occipital part Right

SPL l : Superior Parietal Lobule Left

Cereb8 l : Cerebelum 8 Left

MPFC : Medial prefrontal cortex

Cereb6 l : Cerebelum 6 Left

LPFC l : Lateral prefrontal cortex Left

PostCG l : Postcentral Gyrus Left

pSMG l : Supramarginal Gyrus, posterior division Left

aSMG r : Supramarginal Gyrus, anterior division Right

dACC : dorsal anterior cingulate cortex

DLPFC : dorsolateral prefrontal cortex

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Abstract

Autism spectrum disorder (ASD) is a construct used to describes a cluster of behavioural features that span a range of issues, e.g., decreased social-emotional reciprocity and non-verbal communication in social interactions such as avoiding eye contact, inability to process non-verbal social cues/gestures; stereotyped repetitive movements such as flapping arms, rocking side to side, twirling; narrow spectrum of interests of unusual intensity and focus as well as sensory dysregulation (hyper / hyposensitivity to sensory inputs). These atypical characteristics of behaviour pose various challenges to activities of daily life in ASD, which together manifest as different degrees of clinical severity in this population. The disorder pertains to the development of the brain and nervous system (neurodevelopmental), has a strong genetic underpinning, heterogenous in nature and its cognitive-behavioural features co-occur with other conditions (comorbidities), e.g., depression, anxiety which in turn have been shown to influence cognitive functions. Functional connections between the different underlying structures of the brain generate cognitive functions / behaviours and a wealth of literature has evidenced altered functional connectivity in ASD as compared to their neurotypical peers. However, the evidence is focused majorly on children

and adolescents with ASD. The adult age bracket and the role of comorbidities in modulating the functional connectivity in ASD has relatively been overlooked. Given the neurodevelopmental nature of ASD and a high prevalence of psychiatric comorbidities in this population, investigating the functional connectivity in the adult ASD brain is therefore of relevance. This study explored the differences of seed-to-voxel, resting state functional connectivity within the brain of individuals with ASD and those typically developed (TD), independently and in association with the severity of the psychiatric comorbidity of depression using functional magnetic resonance imaging (fMRI) datasets from the Autism Brain Imaging Data Exchange (ABIDE) repository. Further, the association of the functional connectivity was studied with the severity of the clinical symptomatology in ASD and its interaction with the severity of depression. The results highlight differential functional connectivity of seeds identified in a few key biological neural networks of ASD, i.e., the default mode network, fronto-parietal network, affective salience network and dorsal attention network, with different regions of the brain. The results attempt mechanistic explanations of the adult ASD phenotype offering insights for future research and practice.

Key words: autism spectrum disorder, depression, seed based resting state functional connectivity

Objectives

1. To explore the differences in seed-to-voxel resting state functional brain connectivity between ASD (autism spectrum disorder) and TD (typically developed) adults.

2. To explore the role of the psychiatric comorbidity of depression in # 1.

3. To explore the relationship of seed-to-voxel resting state functional brain connectivity with the clinical severity of core deficits in ASD.

4. To examine the interaction between comorbid depression severity and clinical severity of core deficits towards explaining the seed-to-voxel resting state functional brain connectivity in ASD.

Introduction

Autism Spectrum Disorder (ASD) is a constellation of neurodevelopmental syndromes with a combination of early-onset deficits in social communication and repetitive behaviours, highly narrow range of interests and/or sensory behaviours of abnormal intensity (Messent, 2013).Most individuals with ASD face challenges in daily living crippling independent living and full time work. These difficulties tend to interfere in day to day life of affected individuals to perform social interactions, which include but are not limited to reading emotional cues in social interaction, decreased social-emotional reciprocity, sensory dis-regulation, and often showing hyper and hypo regulations based on the symptomatology and severity (Bryson et al., 1988). Among children with ASD, it has been found that they fail to achieve social communication milestones which are expected of their age, and later diagnosis reveals significant difficulties such as following another person's shift in gaze, smiling at someone who smiles or vocalises at them (Baranek, 1999). Researchers have also found a strong correlation between autism, language deficits, attentional difficulties, and sensory and vestibular systems (Hermelin & O'connor, 1970), which has given a broader definition to autism and is called a 'Pervasive developmental disorder' in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-V) which is used to

categorise current diagnoses. The prevalence of ASD among children was found to be 10 per 1000 (Brugha et al., 2011)and prior literature points to the prevalence of autism across ages varied from 3.3 to 16 per 10,000 among populations in Europe, USA and Japan (Wing, 1993). The diagnosis for autism is usually done between 18-24 months of age and the overall global prevalence across all ages is placed at 1%. Individuals diagnosed with autism are also found to have symptoms such as attention deficits, hyperactivity, anxiety, obsessive-compulsive behaviours, depression, and even psychosis (Pehlivanidis et al., 2020), which are called comorbidities secondary conditions co-occurring with primary ones. These disorders suggest the neuroanatomical functional and genetic overlaps with ASD and other psychiatric disorders (S. H. Kim & Lord, 2013). Understanding the possibility of comorbid mood, anxiety disorders, and depression are essential for improving long-term outcomes for persons with ASD because psychiatric symptoms have been linked to functioning in social, academic, and vocational settings. The ability to determine the population-based risk of related mental disorders might help enhance screening and treatment regimens, thus improving the social life of individuals (Kirsch et al., 2020). Since much of the research on comorbidities associated with autistic individuals is done on a population comprising of children and adolescents, the characteristic differences in functional connectivity among young adults are often

overlooked (Murphy et al., 2016), although clinical studies point toward the prevalence of depression might be expected in adults with ASD as figures from the works of (Gotham et al., 2015; Mazefsky et al., 2008) indicate the range from 20 to 35 %, as opposed to only 7% of depression and 1-12% of reported anxiety among the general population. In this regard, a school of thought proposes that the precipitation of one or more of the core deficits in ASD could be linked with the aforementioned comorbidities, e.g., internal affective/emotional states of the individuals with ASD and there is recent evidence in support of this (Chakrabarty et al., 2021). Consequently, studying the underlying brain correlates that may associate with not only the severity of autism but also the indices of these comorbidities has the potential to offer a better mechanistic understanding of the ASD phenotype thereby paving the way for timely and better management of ASD. However, endeavour along the these lines have challenges due to the lack of measures available to assess mental comorbidities in those with ASD, particularly in adulthood, along with the general variability in diagnostic assessment of ASD, lack of community-based studies and the heterogeneity in the assessment and design of study posits a challenge to integrate and synthesise the literature currently available.

Other challenges include diagnostic overshadowing, where behavioural

similarity is observed between two related comorbidities that could make identification much difficult and the wide range of impairments in intellectual, verbal and adaptive functioning compound the picture.

Our research questions here were aimed at studying differences of seed-to-voxel, resting state functional connectivity within the brain of adults (chosen age bracket 18 – 35 years) with ASD and those typically developed (TD), independently and in association with the severity of the psychiatric comorbidity of depression using functional magnetic resonance imaging (fMRI) datasets from the Autism Brain Imaging Data Exchange (ABIDE) repository. Further, the study aimed to elucidate the association of the functional connectivity with the severity of the clinical symptomatology in ASD and its interaction with the severity of depression. Given the paucity of findings pertaining to the above in the adult ASD population, the potential findings could contribute towards the better understanding of the pathophysiology and subsequent relevant interventions for managing ASD in adults with comorbid depression.

Background and Related works

Language Impairments in ASD

Language disabilities can be ranged from clinically normal to various degrees of impairment among people who have language abilities as opposed to some individuals who do not acquire language abilities ever. The heterogeneity of impairments is diverse, and many minority subgroups are found. Many individuals with ASD tend to use limited gestures without integrating with other nonverbal modes of communication (e.g., eye contact and vocalisation), all of which could retard growth and meaningful social relationships (Dawson et al., 2000). It has been found that some autistic individuals show exceptional abilities, especially in the field of mathematics, music, memorisation, calendar calculations etc (Howlin et al., 2004) and can deliver in-depth monologues on subjects that come under their narrow range of interest but may not able to carry a two-way conversation (Gunn & Delafield-Butt, 2016).

Restrictive Repetitive Behaviour in ASD

Apart from the social and communication deficits that are observed, few other behavioural abnormalities including a very broad category of behaviours such as repetitive sensory-motor/stereotypical behaviours,

ritualistic/insistence on sameness behaviours, compulsive behaviour, restricted/circumscribed interests and self-injurious behaviours as mentioned by (Bishop et al., 2013). The restrictive repetitive behaviours (RRBs) are evident ever since the conceptualisation of ASD by (Kanner & others, 1943) and have been part of the definition and distinctiveness of ASD along with disorders in social communication. Although RRB is a defining feature of ASD, it is not exclusively limited to ASD and is seen in typically developing infants and children; they serve various functions and vary based on skill acquisition and mastery level (Evans et al., 1997). Although various studies are done to organise and categorise expansive and heterogeneous observations, no "gold standard" tool is ever made to measure RRBs in ASD or other neurodevelopment disabilities, which makes it difficult to do cross-comparisons.

Intellectual Impairments in ASD

Intellectual impairments are another class of impairment or intellectual disability characterised by below-average functioning (IQ < 70), which are also prevalent among ASD individuals. Intellectual disability can develop alone or in conjunction with abnormalities, neurological symptoms, and particular senses impairment, seizures, and behavioural problems. In the vast majority of cases, both are present. Seventy per cent of people with

ASDs have some kind of intellectual disability, whereas the remaining 30 per cent have an impairment (speech, behaviour, etc.) (Srivastava & Schwartz, 2014). Spoken language has been identified as one of the most critical factors in predicting improved outcomes in later childhood and adulthood in previous research on ASD (Howlin et al., 2004). Assessments of social, communication, joint attention, and imitation abilities are found significantly compromised in children who have not developed language by the age of five (Thurm et al., 2007). Gender is an important factors associated with the heterogeneity in ASD here. It is found to be more prevalent in males than females and is also found that females are more impaired than males in some earlier studies (Lord et al., 2000).

Sensory and Motor Impairments in ASD

Another common characteristic of autism is sensory and motor impairment which affects people in different ways; the impaired sensory dysregulation observed is due to the hyper and hypo sensitivity which are prevalent among adults and also children (Faras et al., 2010). Some individuals may express abnormalities in visual processing like visually inspecting people or examining things at very close range (Buxbaum & Hof, 2012); other findings include increased temporal resolution (resolution of measurement

with respect to time) to environmental stimuli as reported by (Chakrabarty et al., 2021; Yaguchi et al., 2020) The abnormality in sensory perception extends to all modalities, namely visual, auditory, tactile etc. Auditory hypersensitivity is a category of hypersensitivity that manifests by discomfort or painful response to noises, for example, certain types of noisy environments, human conversation, unexpected loud voices, noises from the kitchen, unpleasant sounds from eating and biting, clinging to silverware, changing of chairs, and people wandering around are all common noises which individuals are having auditory hypersensitivity often are uncomfortable, and that might elicit painful responses. Differences in auditory sensory processing were described by (Kern et al., 2006) which are due to abnormal brain processing; these findings were concreted by further evidence of functional magnetic resonance imaging (fMRI) studies and reported differences in brain activities of the right prefrontal premotor, and the left inferior parietal regions when exposed to acoustic stimuli among ASD samples as opposed to typically developing peers. A frequent sign among children with autism spectrum disorder is a lack of responsiveness to touch stimuli (ASD). In addition, ASD has been linked to problems with filtering or habituation of tactile stimuli. While prior research has found variations in tactile perception and adaptability between ASD and healthy adults with TDC, it's difficult to compare results across studies because of heterogeneity in cohorts examined and

stimulus parameters (Puts et al., 2014). Similar to tactile and auditory stimuli, there is suggestive evidence found in visual perception, particularly for simple stimuli with impairment in more complex tasks (Bertone et al., 2005). Research involving visual evoked potential investigations has found that people with ASD have difficulty detecting object boundaries (Vandenbroucke et al., 2008), and other studies show an increased temporal resolution (resolution of measurement with respect to time) to environmental stimuli as reported by (Yaguchi et al., 2020). Similar to the unimodal sensory processing impairments seen in children with ASD, these people may struggle in situations that require collapsing information from many modalities (multi-modal integration or MSI). The failure to correctly alter or interpret simultaneous channels of visual, aural, and tactile stimuli is thought to be the cause of many of the abnormal perceptual experiences recorded in people with ASD (O'Neill & Jones, 1997). The Electrophysiological studies which probe the neural mechanism of ASD have reported abnormal timing and level of activity within the signal; it was also observed that there is a reduction of response amplitude compared to the typically developing children (Courchesne et al., 1985). Many brain regions are known to integrate multiple sensory inputs including the prefrontal cortex, and associated regions of the temporal lobe, the cerebellum also show a significant change in neuronal density among autistic subjects along with the mirror neuron network were

also identified to play a part in the role of MSI, these sensory difference for autistic individuals could be the cause of core features of autism such as language delay, difficulty in reading emotion etc (Marco et al., 2011). Understanding the neurological foundations of fundamental sensory processing in autism spectrum disorder is critical given the prevalence of sensory and behavioural abnormalities in them. The variability of the disease, as well as the difficulties in devising activities that can precisely test our highly tuned and intricately linked sensory brain networks, have made interpreting pathophysiology difficult.

Neuropsychological disorders in ASD

Autistic individuals have other symptoms co-occurring with the core symptoms; identifying these symptoms is crucial as many symptoms could precipitate abnormal behaviour. These co-occurring conditions are called comorbidities, and the symptoms include anxiety disorders, depression, language impairments, repetitive behaviours, social deficits etc, which are prevalent among autistic individuals than among the general population.

Along with the aforementioned typical comorbidities, secondary conditions such as attention deficits, hyperactivity, obsessive-compulsive behaviours, and even psychosis (Pehlivanidis et al., 2020) co-occur with primary ones. These disorders suggest the neuroanatomical, functional and genetic overlaps with ASD and other psychiatric disorders (S. H. Kim & Lord, 2013). Anxiety disorders are frequent in people with ASD, and the total incidence rates for anxiety disorders range between 42 per cent and 79 per cent (Kent & Simonoff, 2017). Individual anxiety disorders have varying prevalence rates, and the most prevalent anxiety disorders are specific phobia, obsessive-compulsive disorder, and social anxiety disorder; however, the rate and kind of anxiety disorders vary by age and skill level. Among children with autism spectrum disorder, anxiety and

poor stress management are common concerns which are found to worsen as young individuals encounter a more complicated social milieu in the later part, especially adolescence and grow more conscious of their distinctions and interpersonal challenges. The anxiety and increased depression are also seen as comorbidity. These findings suggest continued surveillance for mental comorbidities in the ASD community since detecting comorbidities can help with treatments and enhance the quality of life for people with ASD (Kirsch et al., 2020). The significant psychosocial consequences of having ASD, such as difficulty forming and sustaining relationships, difficulties excelling academically and vocationally, and difficult-to-manage behaviours, raise the likelihood of mood and anxiety disorders in these individuals.

One of the challenges in understanding the brain basis of ASD is the fact that it comprises a wide range of abilities and levels of functioning and the disproportionate 4:1 of male to female ratio. Much of the brain works through functional integration of different sets of regions; these regions could be identified by resting-state or from a tasked evoked state based on the pattern of activation during the same; the relationships between the regions are far wider than a simple one to one approach, hence the brain. areas could be labelled as “perceptual”, “motor”, “cognitive”, “emotional”, “motivational”. We could assign functions based on the contribution to a

particular emotion, like amygdala to fear conditioning or dorsal-medial prefrontal cortex for processing response conflict (Pessoa, 2013). The systemic compilation of an anatomical data has shown massive connectivity between cortical areas and subcortical areas (Young et al., 1994), and interconnectedness between subcortical areas (Risold et al., 1997), hence a region that has less connectivity with other regions will have less impact than richly connected region, the region of local connectivity will contribute to local computations, and one with wider connectivity have a broader effect. In addition to the anatomical connection, intrinsic brain connection can be measured by resting-state functional MRI. This is a method where brain mapping is done to evaluate a resting or task-negative state when an explicit task is not being performed.These changes are created as a result of blood oxygen-dependent signal which is observed through changes in blood flow in the brain (Biswal, 2012).Because of the intrinsic nature of brain activity, the BOLD signal is ever-present and spontaneously fluctuates despite any prompted task; hence this approach is apt to examine patients with neurological, mental disorders, intellectual disabilities, pediatric groups etc (Agcaoglu et al., 2019).

Resting-state functional connectivity is increasingly used in the exploring the connectivity present in the ASD individuals. The findings reveal there are patients with ASD expressing under-connectivity and over-connectivity. The under-connectivity theory derived from task-based neuroimaging suggests that behavioural features of ASD stem from reduced inter-regional neural connections in the brain, especially in networks that rely on frontal and posterior integration. A review by (Uddin, 2011) suggested that brain connectivity in autism should be placed in the developmental framework in order to explore the age-related group differences in functional connectivity. Recent evidence pinpointed that younger ages closer to disorder onset have brains with hyper-connectivity as opposed to the TD individuals, especially within the DMN, salience, frontotemporal, motor, and visual networks. Among the adults, functional hypoconnectivity was observed in anterior-posterior connections in adolescents and adults with ASD. In another study by (Kennedy, n.d.) and colleagues, it was demonstrated that disrupted intrinsic connectivity of the DMN but not the dorsal attention network among ASD individuals was observed. This has also been replicated and verified by (Monk et al., 2009) in adults and (Weng et al., 2010) among adolescent ASD population. Recent research using ABIDE data set has shown the origins of functional under-connectivity by investigating both inter and intra-hemispheric connections. The study found global under-connectivity in

the medial prefrontal cortex, posterior cingulate cortex, inferior parietal lobule, and sensorimotor areas when looking at DMN regions (Di Martino et al., 2011). Based on this, Lee and colleagues postulated that social impairments are caused due to the under-connectivity of medial prefrontal cortex and posterior cingulate cortex (Lee et al., 2016). Further exploration of the connectivity, especially of the insula cortex, found a decrease in connectivity of the anterior and posterior insula, as reported by Ebisch and colleagues; the insula is important for a sense of "self", which is also an atypical amongst ASD individuals (Lyons & Fitzgerald, 2013). Autism also presents with over-connectivity, found beyond the DMN. Such evidence was found where over-connectivity was reported between striatum and pons as well as pons and insular cortex (Di Martino et al., 2011).

Since the brain is divided into distributed sets of regions which function in integration during a particular activity, the use of functional networks in understanding and guiding treatment for comorbidities related to autism is of particular interest. The cingulo-opecular network, which includes portions of the bilateral dorsal anterior cingulate cortex (dACC), anterior insula, anterior prefrontal cortex, and anterior thalamus, is also known as the salience network, which is significant in detecting errors or conflict in order to signal the need for cognitive control is demonstrated to have increased sensitivity to errors in individuals with high anxiety or an

anxiety disorder. Further functional connection studies back up the idea that the cingulo-opercular network is disturbed in those who suffer from anxiety disorders. The functional connection between parts of the cingulo-opercular network (dACC) and the frontoparietal network (DLPFC) is reduced. Also findings suggest that the frontoparietal network consisting of inferior parietal lobule, portions of the middle cingulate gyrus, bilateral anterior portions of the dorsolateral prefrontal cortex (DLPFC), and portions of the precuneus, shows a decreased functioning among individuals with high trait anxiety. Such findings are also extended to DMN which includes portions of posterior cingulate cortex, the precuneus, lateral parietal cortex, medial prefrontal cortex, inferior temporal gyrus, parahippocampal gyrus, and the frontal pole/superior frontal cortex and portions of subgenual anterior cingulate cortex (sgACC) (Sylvester et al., 2012). It has been found that there is a decreased functional connectivity between portions of DMN and amygdala in patients with social anxiety disorder and high trait anxiety (M. J. Kim et al., 2011). Apart from the aforementioned findings, in a study by Kleinhans and colleagues (Kleinhans et al., 2016), it was found that ASD individuals who expressed higher levels of anxiety as measured with a Beck Anxiety Inventory (BAI) were associated with reduced right SF (Superficial) - Left superior temporal gyrus connectivity and increased right SF–left temporal pole and right SF hypothalamic connectivity. Similarly, higher scores on Beck

Depression Inventory-II (BDI-II) were correlated with higher connectivity between the LB sub-region and the insular cortex and SF sub region and the parahippocampal gyrus, thalamus, hypothalamus, and the midbrain. ADOS scores from the ADOS test, which is a standardised diagnostic test for autism spectrum disorder (González et al., 2019), correlate a higher social impairment with increased connectivity from the left and right Centromedial (CM) subregion and decreased connectivity from left laterobasal (LB) and inferior frontal gyrus and right SF subregion to the thalamus, cerebellum and occipital cortex (Kleinhans et al., 2016). Considering the aforementioned findings of atypical brain connectivity in behaviour and sensory domain among ASD individuals, it can be affirmed that autism should be investigated and further modelled as a network disorder rather than a localised one.

Methodology

Participants

The participants were selected from the ABIDE-II dataset (Di Martino et al., 2017) as it gave a better phenotypic characterisation of the heterogeneity with respect to comorbidities associated with the ASD population which are largely overlooked. Out of the 1114 samples in the dataset, a subset was chosen for the study in consideration to the key questions to be addressed as follows. Participants were classified into individuals with Autism Spectrum Disorder (ASD) and typically developed (TD) group within the age bracket of 18-35 years (young adults). All ASD individuals were confirmed by a combination of clinical judgement, Autism Diagnostic Observation Scale (ADOS) and revised form of Autism Diagnostic Interview (ADI-R) at the respective sites.

The participants were chosen such that there were relevant ABIDE-II phenotypic information, e.g., ADOS as a metric of clinical autism severity consisting of a standardized assessment of social interaction, play, and imaginative use of material for individuals suspected of having ASD in the age bracket 12 months old to adults ; Beck depression score (BDI) as a metric of assessing symptoms of depression from mood,

pessimism ,sense of failure etc. (Beck et al., 1961); Full-Scale IQ Score (FIQ) that quantifies selected subtest from Wechsler intelligence scale which measures individual's overall level of intellectual and cognitive functioning (Lange, 2011). Consequently, we reached a final sample size of 44 individuals with ASD (mean ± SD: age = 21.34 ± 3.07, FIQ = 110.5 ± 15.27, BDI = 11.78 ± 9.8;40 males, 4 females; male : female=10:1) and 35 TD individuals (mean ± SD: age = 24.02 ± 3.62; FIQ = 111.2 ± 12.84, BDI = 4.6 ± 5.12; 20 males,15 females; male : female = 4:3).

Data acquisition

The dataset was downloaded from the ABIDE-II dataset (Di Martino et al., 2017), which includes data from multiple sites across the world. The imaging data consists of structural MRI (sMRI) and resting state fMRI (rs-fMRI) data. All data were acquired using 3 Tesla scanners. This study contains scans sourced from three sites in United States (Barrow Neurological Institute, Phoenix, Arizona; Indiana University, Bloomington; Olin Neuropsychiatry Research Center, Hartford). The comorbid psychopathologies were assessed according to the International Classification of Disease – 9th edition (Marek & Dosenbach, 2018).

Data Pre-processing and Denoising

The fMRI pre-processing steps were done using a MATLAB based platform - CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012), which uses the Statistical Parametric Mapping software ver. 12 (SPM 12) (Ashburner et al., 2021) for building and assessing spatially applicable statistical procedures to test hypotheses about functional imaging data. The default CONN pipeline has been employed which includes functional realignment, slice-time correction, co-registration, and normalization to the Montreal Neurological Institute (MNI) template as detailed below.

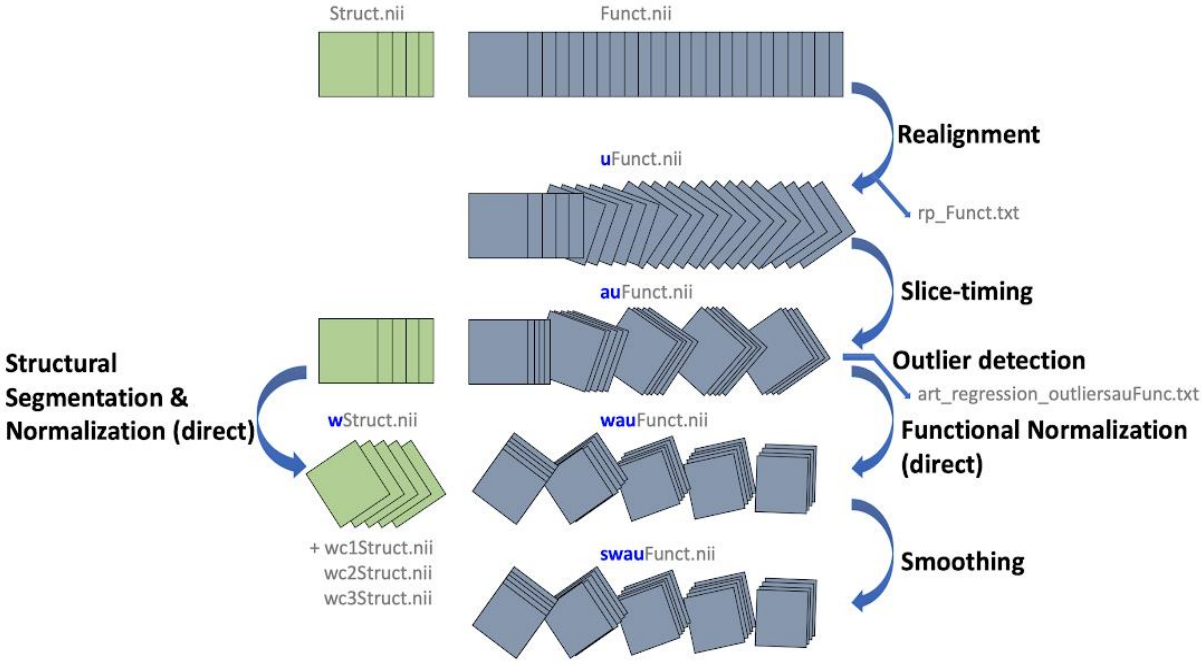

Fig. 1. Illustration of the key pre-processing and de-noising steps in the work flow. Image taken for representational purpose from https://web.conn-toolbox.org/fmri-methods/preprocessing-pipeline

Functional realignment and unwarping:

All scans were co-registered and resampled to the first scan of the first session as a reference image. Thereafter, no outlier scans were confirmed using the observed global signal and the amount of subject motion within the scanner. All scans had frame-wise displacement < 0.9mm. Realignment addresses the potential problems arising out of the interactions between head movements and inhomogeneities in the magnetic field. Unwarping is followed after realignment so as to estimate changes in distortion from movement by measuring distortion field with field map.

Slice-Timing Correction:

This procedure was done by temporally aligning all the slices to a reference point (midpoint of each acquisition time) to correct the temporal misalignment between different slices of functional data that arises due to the sequential nature of image acquisition in fMRI protocol.

Segmentation and Normalisation:

The s-MRI and fMRI scans were segmented and normalised into standard Montreal Neurological Institute (MNI) space. Segmentation was performed on grey matter, white matter, and CSF tissue and both the anatomical and functional data were resampled to default 180 x 216 x

180mm bounding box, with 2mm isotropic voxels for functional data and 1mm for anatomical data.

Functional/anatomical co-registration:

The functional data was first co-registered with the structural data by an affine transformation, and this procedure estimated an optimal transformation between the functional reference image, which is the mean BOLD signal and the reference structural T1-weighted image by maximising the mutual information between the two, based on the mutual information cost function (Collignon et al., 1995).

Smoothing:

The final functional data was smoothed to increase the signal-noise ratio and to reduce the variability across the subjects, and this was implemented by a spatial convolution using a Gaussian kernel of 8 mm full width half maximum (FWHM).

Denoising:

This step was to address the remaining noise in the data in spite of the pre-processing steps, due to various outliers, physiological, subject motion effects, etc., leading to considerable bias in the functional

connectivity measures interfering with the analysis. Thus, to mitigate the influence of such noise components in the data we used the default denoising pipeline that combines linear regression of potential confounding effects in the BOLD signal, and temporal band pass filtering. The confounds used are the five principal components each of White Matter (5) and cerebro-spinal fluid CSF (5), and twelve components of the effect of rest (12), which are derived from the tissue types. After the regression, a temporal bandpass filtering was done with frequency band selection (Slow-4: 0.027–0.073 Hz) as suggested (Liang et al., 2012). At the end of this step, quality assurance (QA) plots generated for each participant were manually inspected to find any errors.

Clinical characterization

ADOS is a standard diagnostic test for autism spectrum disorder . It uses questions and activities that are designed to prompt and observe the peculiar, stereotyped behaviours which are relevant to the characterisation and diagnosis of ASD. It extends to different subscales of ADOS like ADOS G Communication total, ADOS Social Interaction total ADOS-G Sterotyped Behaviours and Restricted Interest Total, ADOS-G Social Affect total. Although impairment levels are measured in terms of language delay, cognitive functioning and behavioural issues, these are

not the core features of an autistic individual. Currently, for the present study, we used ADOS-G Total score, or ADOS-2 calibrated score, all subjects that are filtered are found to have a valid ADOS score, and the ADOS scores are in the range of (range, mean ± SD: [4-18], 9.88 ± 2.8) for ASD, and (range, mean ± SD: [0-5], 2.11 ± 1.4) for TD subjects. The phenotypic file also characterises ASD individuals from TD individuals in a categorical manner from the ADOS score distribution. The phenotypic data associated with the clinical characterisation were taken from the ABIDE-II phenotypic file, (http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html).

Autism is associated with other co-occurring conditions, which are called comorbidities. Depression is a disruptive mood dysregulation disorder which causes persistent feeling of sadness and loss of interest which is due to abnormal functional and structural variations within the brain (Scheepens et al., 2020). Beck's Depression Inventory (BDI) was used to assess the levels of depression. The instrument can be used as an instrument to gauge the severity of depression that meets the clinical diagnostic criteria. It is also used to detect depression onset in the average population. These are calculated based on rating the items which exhibit symptoms and attitudes of depression., i.e., the 21 items reflect a variety of symptoms among clinically depressed individuals which ranges

from self-dislike, social withdrawal to sleep disturbances etc. . The range of scores varies from 0-63. In our present study, the scores are ranged from (range, mean ± SD: [0-43],11.78 ± 9.81) for ASD and (range, mean ± SD: [0-19], 4.60± 5.12) for TD individuals. The phenotypic data associated with the clinical characterisation are taken from the ABIDE-II phenotypic file.

In the current study, we employed a dimensional approach in representing clinical scores and examining functional connectivity as opposed to the categorical approach in much of the literature, as it is found to reveal much information about the FC-behaviour relationships that exist in a continuum across typical development and clinical population and also enhanced way to make progress towards customised treatments . The behavioural scores and clinical phenotypic variables, namely the ADOS, BDI, and FIQ, are continuous variables.

Definition of Seeds and Voxels

Default mode network:

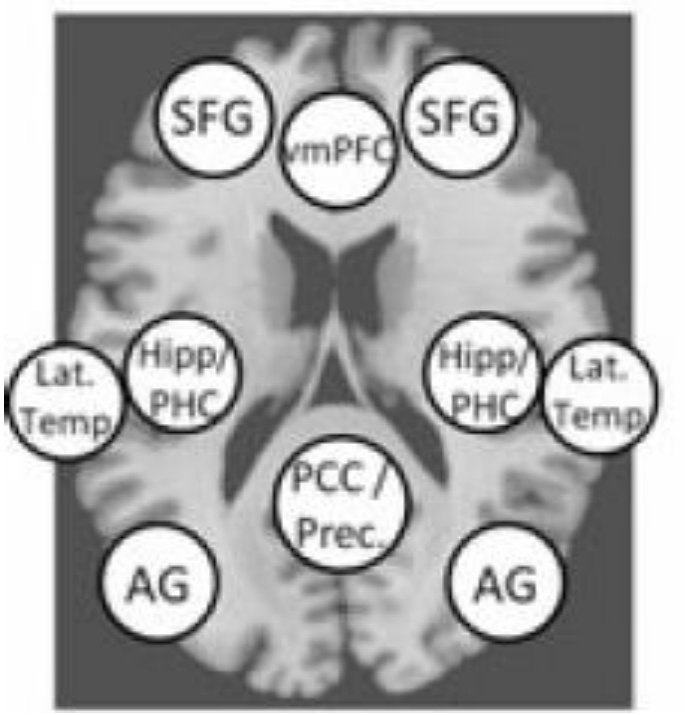

Fig. 2. Key nodes of the default mode network visualized on the axial slice of the brain. SFG Superior Frontal Gyrus, vmPFC Ventro-Medial Prefrontal Cortex, SFG Superior Frontal Gyrus, Hipp/PHC Hippocampus/Para Hippocampal Cortex, Lat. Temp Lateral Temporal Area, PCC/Prec Posterior Cingulate Cortex Precuneus, AG Angular Gyrus. Image taken from Vaidya and Gordon, Brain Connectivity 2013 for representational purpose. Image taken from Vaidya and Gordon, Brain Connectivity 2013 for representational purpose.

The default mode network comprises of regions which are active during the absence of external stimuli and is found to be the network that stays active during the resting state and suppressed when the participant's attention focus on external stimuli (Fischer et al., 2016; Greicius et al., 2003; Raichle et al., 2001). It is an essential network in depression as DMN mediates the internally generated thoughts (Grimm et al., 2009), this network is also involved with the self-referential process, like introspection, and engagement of mental simulations of future, which are

found aberrant in depressed patients resulting in maladaptive rumination of depressive thoughts. The core regions of DMN are the medial prefrontal cortex, posterior cingulate cortex (PCC), precuneus, and lateral and inferior parietal cortices (Fischer et al., 2016). The DMN is found highly interconnected within network in depressed individuals, and it relates to the clinical severity and duration of depression (Price et al., 2017). The regions such as PCC, precuneus, and angular gyrus, which are posterior areas of DMN, are found to have decreased connectivity in depressed and anxious individuals. The posterior DMN areas are associated with autobiographical memory, sensory processing, and social cognition, which are compromised in depressive states, these are also found compromised in autism spectrum disorder as there is evidence of deficits in social cognition. In autistic individuals (Padmanabhan et al., 2017), however, there are inconsistencies in findings. There are both increased and decreased FC in ASD patients relative to TD, while some other studies only detect decreased resting state functional connectivity (rsFC); these are found due to the small sample size and sample selection and the heterogeneity reported within the disorder (L. Wang et al., 2015). In our current study, we have chosen regions of the Medial Prefrontal cortex (MPFC), posterior cingulate cortex, and precuneus from the Default mode network. The rationale for choosing MPFC is that elevated functional connectivity is observed with PCC and angular gyrus in rumination among

depressed individuals, and also it is found to integrate neuronal inputs from different brain regions and sends to several cortical and limbic structures. Hence mPFC is found to act as a hub which modulates depression (Bittar & Labonté, 2021).

Affective Salience network

The affective salience network consists of regions of the amygdala, ventral striatum, dorsal anterior cingulate cortex, and insula as the hub regions. This circuit mostly detects salient changes in the environment encompassing both internal and external stimuli. The amygdala is the critical hub that is identified which is involved in the processing of salient motivational stimuli. In depressed individuals, we see abnormally

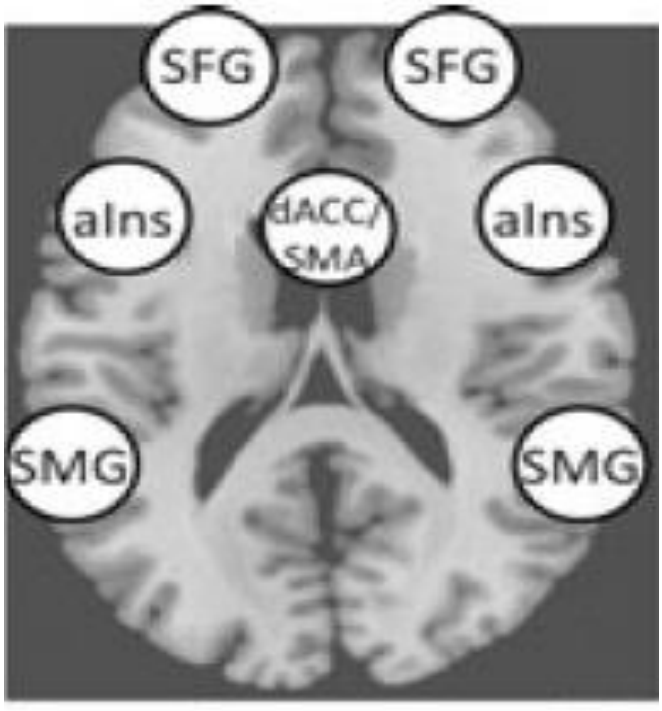

Fig. 3. Key nodes of the affective salience network visualized on the axial slice of the brain. SFG Superior Frontal Gyrus, aIns Anterior insula, SFG Superior Frontal Gyrus , dACC/SMA dorsal anterior cingulate cortex/ supplementary motor area, SMG Supramarginal Gyrus. Image taken from Vaidya and Gordon, Brain Connectivity 2013 for representational purpose.

increased connectivity and heightened activation of the amygdala, ACC, and insula. This was found to be strong evidence for the abnormalities found in the depressed individuals. Also insular hypo-connectivity is evident in comorbidities like social anxiety, panic disorder (Williams, 2016). In depressed individuals, attenuated connectivity was found between the ventral striatum and other regions like dACC, insula and thalamus, which contribute to reward processing (Gabbay et al., 2013). In our study the ROIs, Anterior insula l & r, Anterior cingulate cortex, and Amygdala - l & r are taken since these constitute the salience network, and abnormal FC within SN has been reported that may point to emotional over-reactivity (Liu et al., 2015) rumination (L. Wang et al., 2015) and certain traits of depression (Hamilton et al., 2016).

Fronto-Parietal network

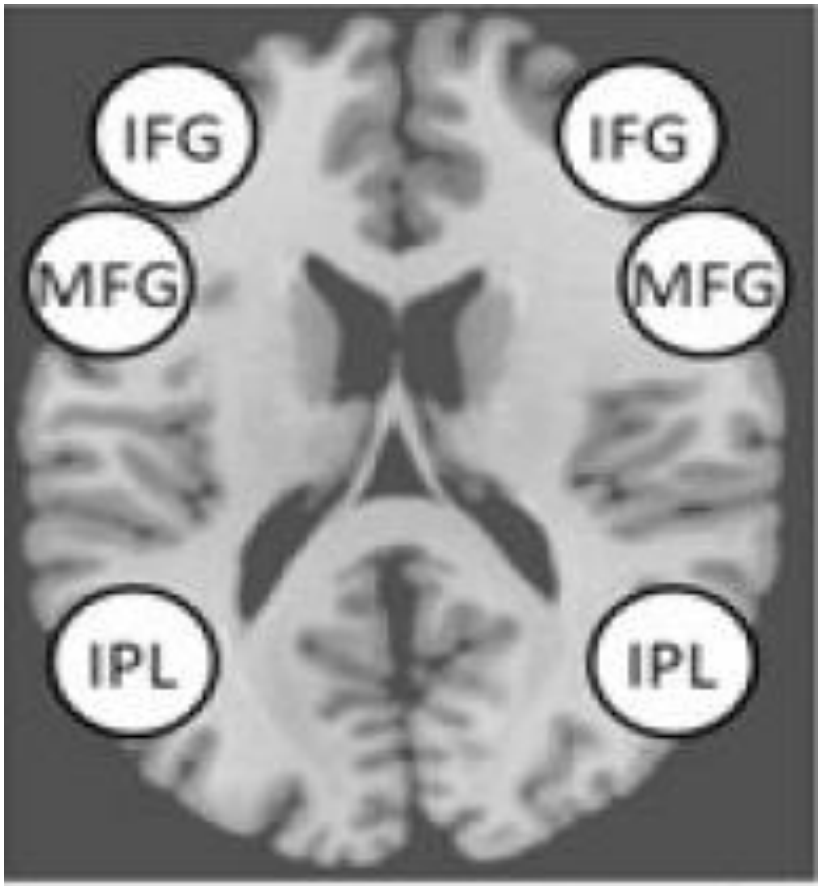

Fig. 4. Key nodes of the Fronto-Parietal network visualized on the axial slice of the brain. IFG Inferior Frontal Gyrus, MFG Middle Frontal Gyrus Right,IPL Inferior parietal lobule. Image taken from Vaidya and Gordon, Brain Connectivity 2013 for representational purpose.

Fronto-parietal network is crucial for our ability to coordinate behaviour in accurate, flexible and goal driven (Marek & Dosenbach, 2018), it has also found to be involved in modulation of task goals by modulating other networks (Zanto & Gazzaley, 2013). It also helps in detection of salient stimuli and help to evade hazards (Silva, 2021). The fronto-parietal network includes lateral prefrontal cortex, posterior parietal cortex and parts of intraparietal sulcus, and an altered network activity results in a

weaker cognitive control that has been observed among ASD individuals (Lin et al., 2019). Also it was also found that major depressive disorders (MDD) are characterized by hypo-connectivity within the fronto-parietal network (Kaiser et al., 2015). Apart from the mentioned regions, we have explored hippocampus l & r, Amygdala l & r, Frontal pole l & r known for learning and memory, emotional evaluation and cognitive control respectively.

Functional connectivity analysis

Denoised and processed time series were extracted from the aforementioned regions as seeds and seed-based-connectivity (SBC) maps (potential paths of connectivity) plotted with the seed region as the ROI and all other voxels in the whole brain as targets, representing the level of functional connectivity within each participant. The individual maps obtained for each individual representing the connectivity within each subject are called SBC maps which were computed as Fisher-transformed bi-variate correlation coefficients between seeds and all other voxels.

$$r(x) = \frac{\int S\,(x,t)R(t)dt}{(\int R^2\,(t)dt \int S^2\,(x,t)dt)^{\frac{1}{2}}} \quad (1)$$

$$Z(x) = tanh^{-1}\big(r(x)\big) \quad (2)$$

where **S** is the BOLD time series at each voxel**, R** is the average BOLD time series within an ROI, ***r*** is a spatial map of Pearson correlation coefficients, ***Z*** is the SBC map of Fisher-transformed correlation coefficients for the ROI, ***x*** and ***t*** are the signal intensity and time respectively of the blood oxygen level dependent (BOLD) time series associated with each voxel. Using the above participant-level whole brain correlation maps, the group-level (second level) analyses were performed with four nuisance covariates – scanning site, mean frame-wise displacement (FD), full-scale intelligence quotient (FIQ) and age employing a voxel-level (cluster-forming) threshold of $p < 0.005$ and a cluster-level (height) threshold of $p < 0.05$, family-wise-error corrected (false discovery rate, FDR) corrected for multiple comparisons.

Results

Difference of functional connectivity between ASD and TD

The first group-level analysis was performed to study the differential patterns of seed-to-voxel functional connectivity between ASD and TD adults. This revealed hyper-connectivity in ASD compared to TD (ASD > TD) between the Caudate Right (r) seed and four clusters – Insular Cortex Left (IC l), Superior Frontal Gyrus Right (SFG r), Lateral Occipital Cortex, inferior division Left (iLOC l); Caudate left (l) seed and Inferior Frontal Gyrus, pars opercularis Right (IFG oper l) cluster; Amygdala left (l) seed and Caudate r cluster; and Anterior Insula Left (AI l) seed and ; Anterior Insula Left (AI l) seed and two clusters-Lateral Occipital Cortex, superior division Left (sLOC l) and Lateral Occipital Cortex, superior division Right (sLOC r);Anterior Insula Right seed and two clusters Lateral Occipital Cortex, superior division Right (sLOC r), Caudate l,Postcentral Gyrus Left (PostCG l); Anterior Cingulate Cortex (ACC) and two clusters Caudate left (l), and Caudate right (r). By contrast a few seeds were hypo-connected with some clusters in ASD than TD (ASD < TD) – between the Caudate Right (r) seed and cluster Cerebelum Crus1 Left (Cereb1 r); Precuneous seed and cluster Parahippocampal Gyrus, posterior division Right

(pPaHC r); Anterior Insula Left (AI l) seed and cluster Paracingulate Gyrus Left (PaCiG l); Anterior Insula Right seed with cluster Frontal Pole Right (FP r). The above seeds and respective clusters are illustrated in Figure 5, 6 and the further detailed in Table 1.

Effect of depression on the difference of functional connectivity between ASD and TD

Further along the study, the effect of depression was tested on the difference of seed-to-voxel functional connectivity to explore the effect of depression on the differential patterns of connectivity between ASD and TD adults. This revealed BDI positively modulated the hyper-connectivity in ASD compared to TD (ASD >TD) between Angular Gyrus Left (AG l) and clusters - Lateral Occipital Cortex, superior division Left (sLOC l), Anterior Insula Right seed with cluster Cerebelum 4 5 Left (Cereb 45 l). By contrast, we found the depression negatively modulated the hypo-connectivity (ASD < TD) – between the seed Amygdala Right (Amygdala r) and Parietal Operculum Cortex Left (PO l) cluster. The above seeds and respective clusters are illustrated in Figure 7 and the further detailed in Table 2.

Effect of ASD clinical severity on functional connectivity:

The study further enquired into the effect of clinical severity of the core deficits in ASD on the connectivity within the ASD group itself. The analysis revealed both positive and negative relationships. A positive correlation (modulation) was found for the connectivity between Anterior Insula Left (l) seed and clusters - Temporal Fusiform Cortex, posterior division Left (pTFusC l), Lateral Occipital Cortex, superior division Right (sLOC r), Anterior Insula Right (r) seed with cluster Precentral Gyrus Left (l) (PreCG l); Frontal Pole Right (FP r) seed as well as clusters Frontal Medial Cortex (MedFC), Lateral Occipital Cortex, superior division Right (sLOC r) ; Caudate Right (r) seed and cluster Precentral Gyrus Left (PreCG l); Anterior cingulate cortex (ACC) seed and cluster Cerebellum 8 Left (Cereb8 l). By contrast we got a negative relationship with seeds- Anterior Insula Left (l) seed and cluster Cingulate Gyrus, anterior division (AC l & r); Posterior cingulate cortex (PCC) seed with cluster Inferior Temporal Gyrus, temporo-occipital part Right (toITG r); Caudate Right (r) seed with three clusters Superior Parietal Lobule Left (SPL l), Frontal Pole Right (r) (FP r); Anterior cingulate cortex (ACC) with Cerebelum 8 Left (Cereb8 l). The above seeds and respective clusters are illustrated in Figure 8,9 and further detailed in Table 3

Effect of ASD clinical severity and depression on functional connectivity:

Finally, to examine the effect of both clinical severity of core ASD deficits and comorbid depression severity on the rsFC within ASD, we set up an ASD clinical severity (ADOS scores)-by-depression severity (BDI scores) interaction term towards explaining the rsFC. The data was split by the median ADOS score (9.5) to have two subsets of participants characterized by the severity of core ASD deficits – mild (ADOS median) and severe (ADOS median). The results revealed that depression modulates the connectivity between seed Medial prefrontal cortex (MPFC) with Cerebelum 6 Left (Cereb6 l);Lateral prefrontal cortex Left (LPFC l) seed with cluster Precentral Gyrus Left (PreCG l);Lateral prefrontal cortex Right (LPFC r) with three clusters Postcentral Gyrus Left (PostCG l), Supramarginal Gyrus, posterior division Left (pSMG l), Supramarginal Gyrus, anterior division Right (aSMG r).(Table 5, Figure 10) differentially in the two subsets of ASD adults. Increasing depression severity in the ASD adult subset with milder clinical severity decreases the rsFC (negative correlation) between the aforementioned seeds and voxels. By contrast, increasing depression severity in the subset of ASD adults with more severe clinical severity increases the rsFC (positive correlation) between the same brain regions. The pattern was similar

across all the aforesaid brain regions and the interactions illustrated in Figure 11.

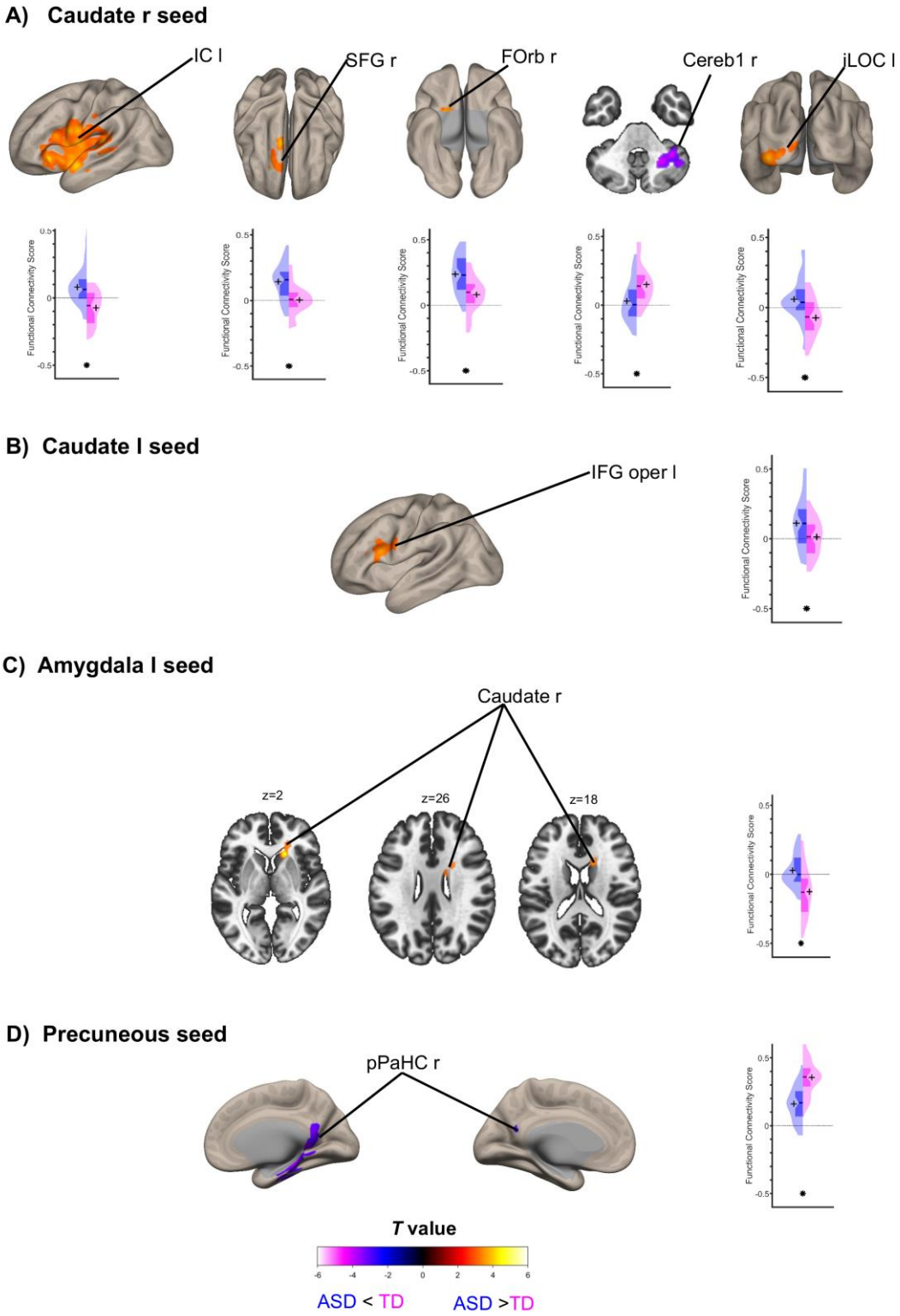

Figure 5. Difference of seed-to-voxel connectivity between ASD and TD. (A-D) Seeds showing significant hyper-connectivity (ASD > TD) and hypo-connectivity (ASD < TD) with respective clusters at p < 0.05, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and axial slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed *r* values) in ASD (blue) and TD (magenta). The edges of the box plots show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * p < 0.05; IC l Insular Cortex Left, SFG r Superior Frontal Gyrus Right, FOrb r Frontal Orbital Cortex Right, Cereb1 r Cerebellum Crus1 Right, iLOC l Lateral Occipital Cortex, IFG oper l Inferior Frontal Gyrus pars opercularis Left, Caudate r, pPaHC r Parahippocampal Gyrus

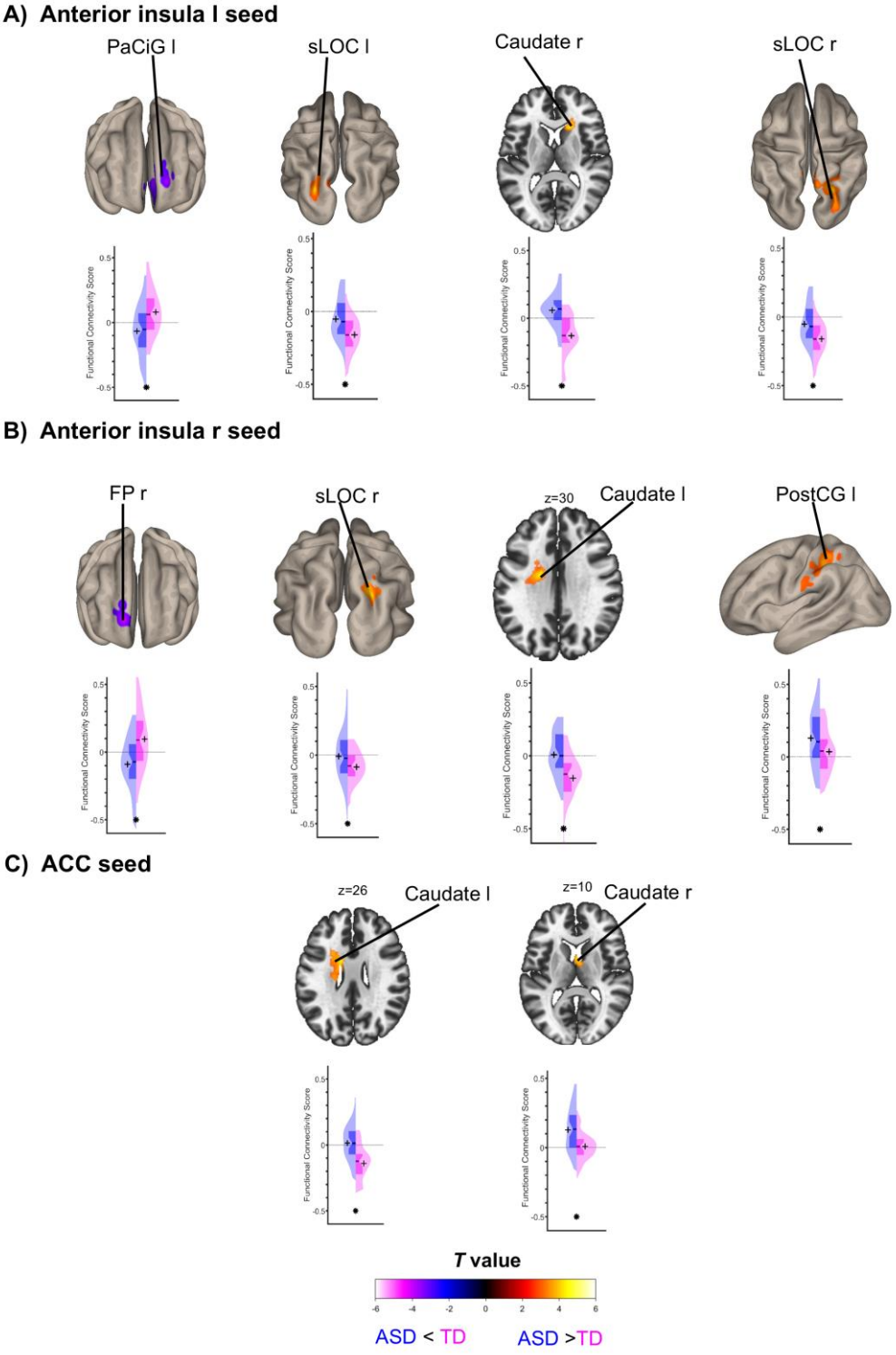

Figure 6. Difference of seed-to-voxel connectivity between ASD and TD. (A-C) Seeds showing significant hyper-connectivity (ASD > TD) and hypo-connectivity (ASD < TD) with respective clusters at $p < 0.05$, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and axial slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed *r* values) in ASD (blue) and TD (magenta). The edges of the box plots show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * $p < 0.05$; PaCiG l Paracingulate Gyrus Left, sLOC l Lateral Occipital Cortex superior division Left, Caudate r, Lateral Occipital Cortex superior division Right, FP r Frontal Pole Right, sLOC r Lateral Occipital Cortex superior division Right, Caudate l, Post CG l Postcentral

Table 1. Difference of seed-to-voxel connectivity between ASD and TD

Seed	Voxels of the Brain area	Hemisphere (Left =L, Right=R)	Size (Voxels)	Size (*p*-FDR)	MNI coordinates			Effect size (beta value)
					X	Y	Z	
Caudate right	Insular Cortex (Cluster 1)	L	5261	0.00	-32	-04	+02	5.49
	Cerebelum Crus1 (Cluster 2)	R	602	0.00	+26	-54	-40	-5.00
	Superior Frontal Gyrus (Cluster 3)	R	582	0.00	+08	+28	+64	5.41
	Lateral Occipital Cortex (Cluster 4)	L	579	0.00	-32	-86	-06	4.70
	Frontal Orbital Cortex (Cluster 5)	R	397	0.01	+16	+08	-12	5.89
Caudate left	Inferior Frontal Gyrus (Cluster 1)	L	497	0.01	-52	+16	+20	4.42
Amygdala left	Caudate (Cluster 1)	R	407	0.03	+18	+22	+00	5.10
Precuneous	Parahippocampal Gyrus (Cluster 1)	R	834	0.00	+20	-30	-20	-6.35
Anterior Insula left	Lateral Occipital Cortex (Cluster 1)	R	1391	0.00	+24	-58	+34	5.54
	Paracingulate Gyrus (Cluster 2)	L	1014	0.00	-14	+52	+10	-4.84
	Caudate (Cluster 3)	R	936	0.00	+22	+16	+18	6.03
	Lateral Occipital Cortex (Cluster 4)	L	368	0.02	-28	-74	+18	4.10
Anterior Insula right	Postcentral Gyrus (Cluster 1)	L	586	0.00	-40	-32	+38	4.56
	Caudate (Cluster 2)	L	414	0.02	-20	-06	+30	4.43
	Frontal Pole (Cluster 3)	R	401	0.02	+14	+54	+12	-4.54
	Lateral Occipital Cortex (Cluster 4)	R	315	0.03	+24	-60	+34	4.70
	Cerebelum 8 (Cluster 5)	L	314	0.03	-28	-72	-56	4.69
Anterior Cingulate Cortex	Caudate (Cluster 1)	L	538	0.00	-14	+04	+24	-5.03
	Caudate (Cluster 2)	R	510	0.00	+02	+00	+12	5.53

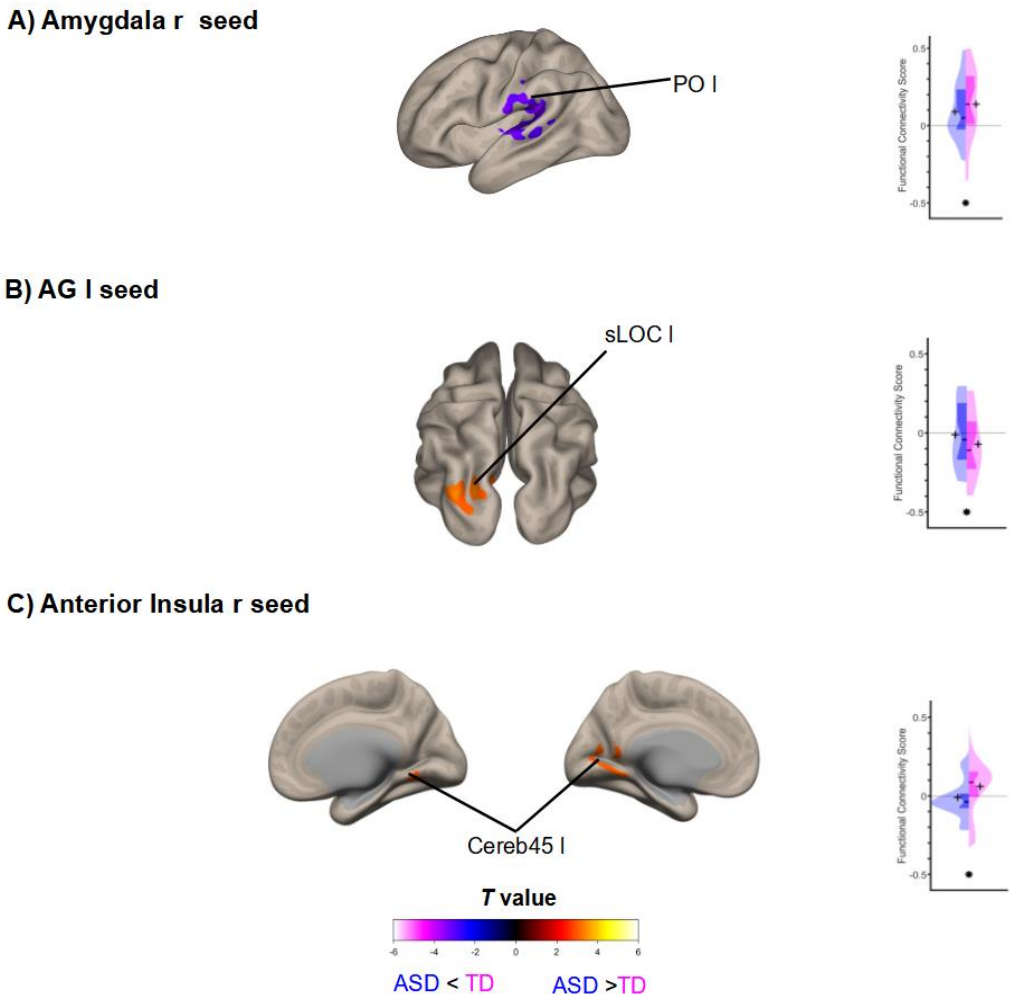

Figure 7. Effect of depression on the difference of seed-to-voxel connectivity between ASD and TD. (A-C) Seeds showing significant hyper-connectivity (ASD > TD) and hypo-connectivity (ASD < TD) with respective clusters at $p < 0.05$, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and axial slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed *r* values) in ASD (blue) and TD (magenta). The edges of the box plots show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * p < 0.05; PO l Parietal Operculum Cortex Left, sLOC l Lateral Occipital Cortex superior division Left, Cereb45 l Cerebelum 4 5 Left.

Table 2. Effect of depression on the difference of seed-to-voxel connectivity between ASD and TD

					MNI coordinates			
Seed	**Voxels of the Brain area**	**Hemisphere (Left =L, Right=R)**	**Size (Voxels)**	**Size (*p* -FDR)**	**X**	**Y**	**Z**	**Effect size (beta value)**
Anterior Insula Left	Cingulate Gyrus (Cluster 1)	L & R	591	0.00	+06	+32	+22	-4.67
	Lateral Occipital Cortex (Cluster 2)	L	388	0.02	-40	-50	+50	5.03
	Temporal Fusiform Cortex (Cluster 3)	L	315	0.03	-36	-34	-24	5.00
Anterior Insula right	Precentral Gyrus (Cluster 1)	L	692	0.00	-58	-10	+38	4.48
Frontal Pole right	Frontal Medial Cortex (Cluster 1)	L & R	393	0.02	+12	+40	-16	5.06
	Lateral Occipital Cortex (Cluster 2)	R	317	0.04	+36	-66	+26	5.33
Anterior Cingulate Cortex	Cerebelum 8 (Cluster 1)	L	1082	0.00	+20	-60	-34	-5.89
Posterior Cingulate Cortex	Inferior Temporal Gyrus (Cluster 1)	R	523	0.00	+46	-44	-12	-5.57
Caudate right	Superior Parietal Lobule (Cluster 1)	L	465	0.01	-16	-54	+50	-5.36
	Precentral Gyrus (Cluster 3)	L	386	0.01	-30	-10	+74	4.39
	Frontal Pole (Cluster 4)	R	339	0.01	+44	+52	+08	-4.30

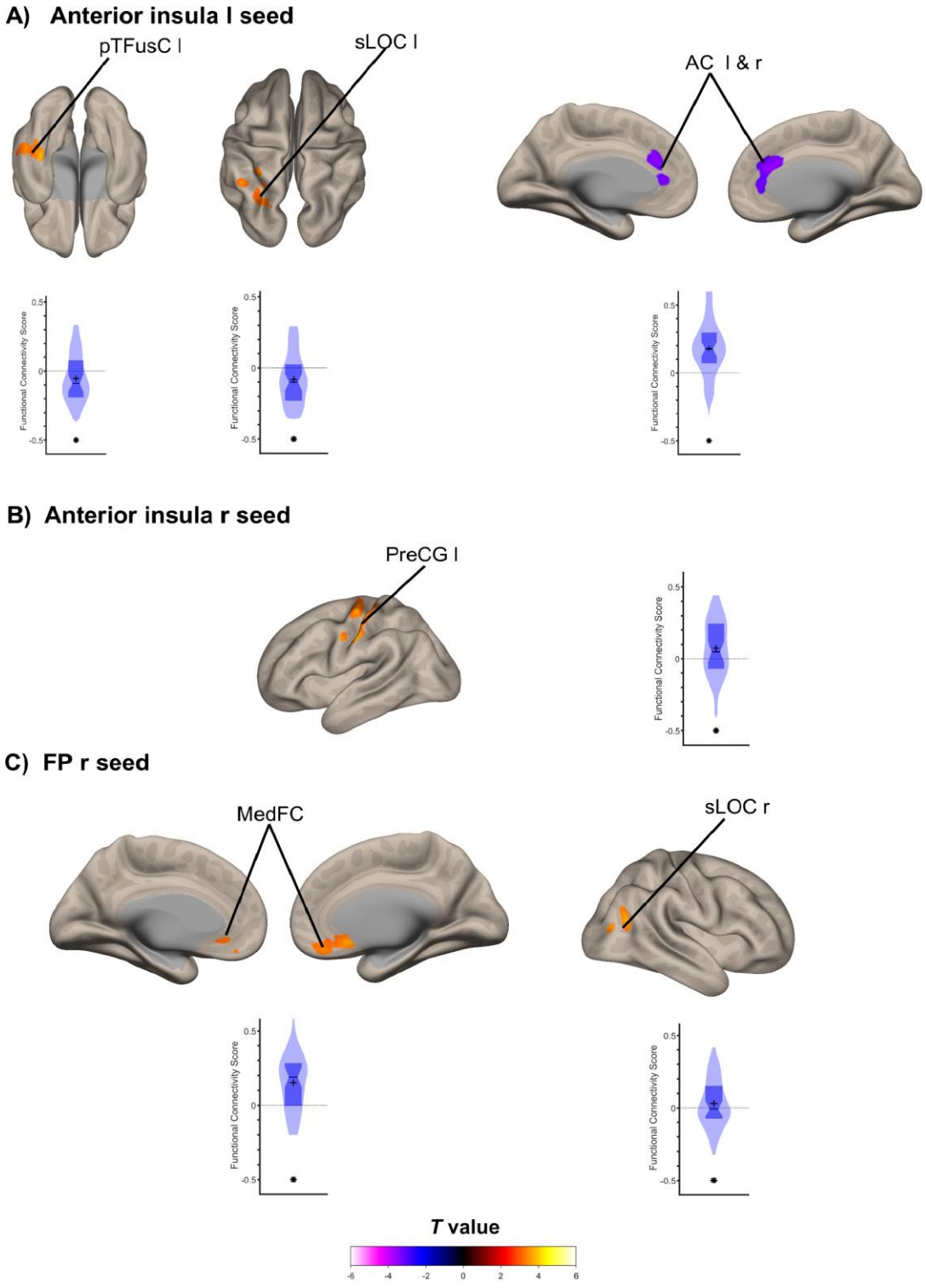

Figure 8. Effect of clinical severity on seed-to-voxel connectivity in ASD. (A-C) Seeds showing significant connectivity within ASD with respective clusters at p < 0.05, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed *r* values) within ASD (blue). The edges of the box plots show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * p < 0.05; pTFusC l Temporal Fusiform Cortex, posterior division Left, sLOC l Lateral Occipital Cortex superior division Left, AC Cingulate Gyrus, anterior division, PreCG l Precentral Gyrus Left, MedFC Frontal Medial Cortex, sLOC r Lateral Occipital Cortex,

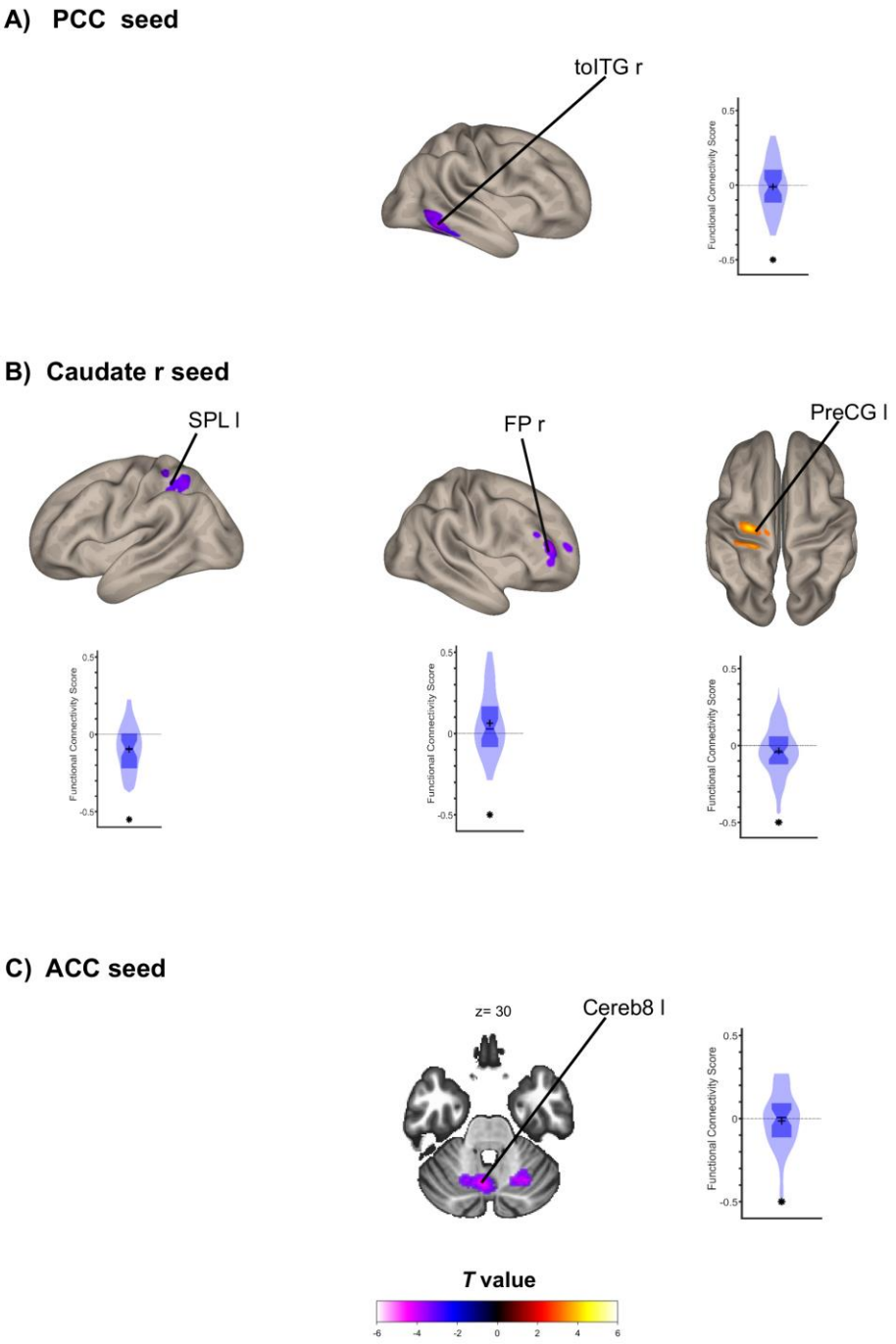

Figure 9. Effect of clinical severity on seed-to-voxel connectivity in ASD. (A-C) Seeds showing significant connectivity within ASD with respective clusters at $p < 0.05$, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and axial slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed *r* values) within ASD (blue). The edges of the box plot show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * $p < 0.05$; toITG r Inferior Temporal Gyrus temporooccipital part Right, SPL l Superior Parietal Lobule Left, FP r Frontal Pole Right, PreCG l Precentral Gyrus Left, Cereb8 l Cerebelum 8 Left.

Table 3. Effect of clinical severity on seed-to-voxel connectivity in ASD

Seed	Voxels of the Brain area	Hemisphere (Left =L, Right=R)	Size (Voxels)	Size (*p* -FDR)	MNI coordinates X	Y	Z	Effect size (beta value)
Anterior Insula Left	Cingulate Gyrus (Cluster 1)	L & R	591	0.00	+06	+32	+22	-4.67
	Lateral Occipital Cortex (Cluster 2)	L	388	0.02	-40	-50	+50	5.03
	Temporal Fusiform Cortex (Cluster 3)	L	315	0.03	-36	-34	-24	5.00
Anterior Insula right	Precentral Gyrus (Cluster 1)	L	692	0.00	-58	-10	+38	4.48
Frontal Pole right	Frontal Medial Cortex (Cluster 1)	L & R	393	0.02	+12	+40	-16	5.06
	Lateral Occipital Cortex (Cluster 2)	R	317	0.04	+36	-66	+26	5.33
Anterior Cingulate Cortex	Cerebelum 8 (Cluster 1)	L	1082	0.00	+20	-60	-34	-5.89
Posterior Cingulate Cortex	Inferior Temporal Gyrus (Cluster 1)	R	523	0.00	+46	-44	-12	-5.57
Caudate right	Superior Parietal Lobule (Cluster 1)	L	465	0.01	-16	-54	+50	-5.36
	Precentral Gyrus (Cluster 3)	L	386	0.01	-30	-10	+74	4.39
	Frontal Pole (Cluster 4)	R	339	0.01	+44	+52	+08	-4.30

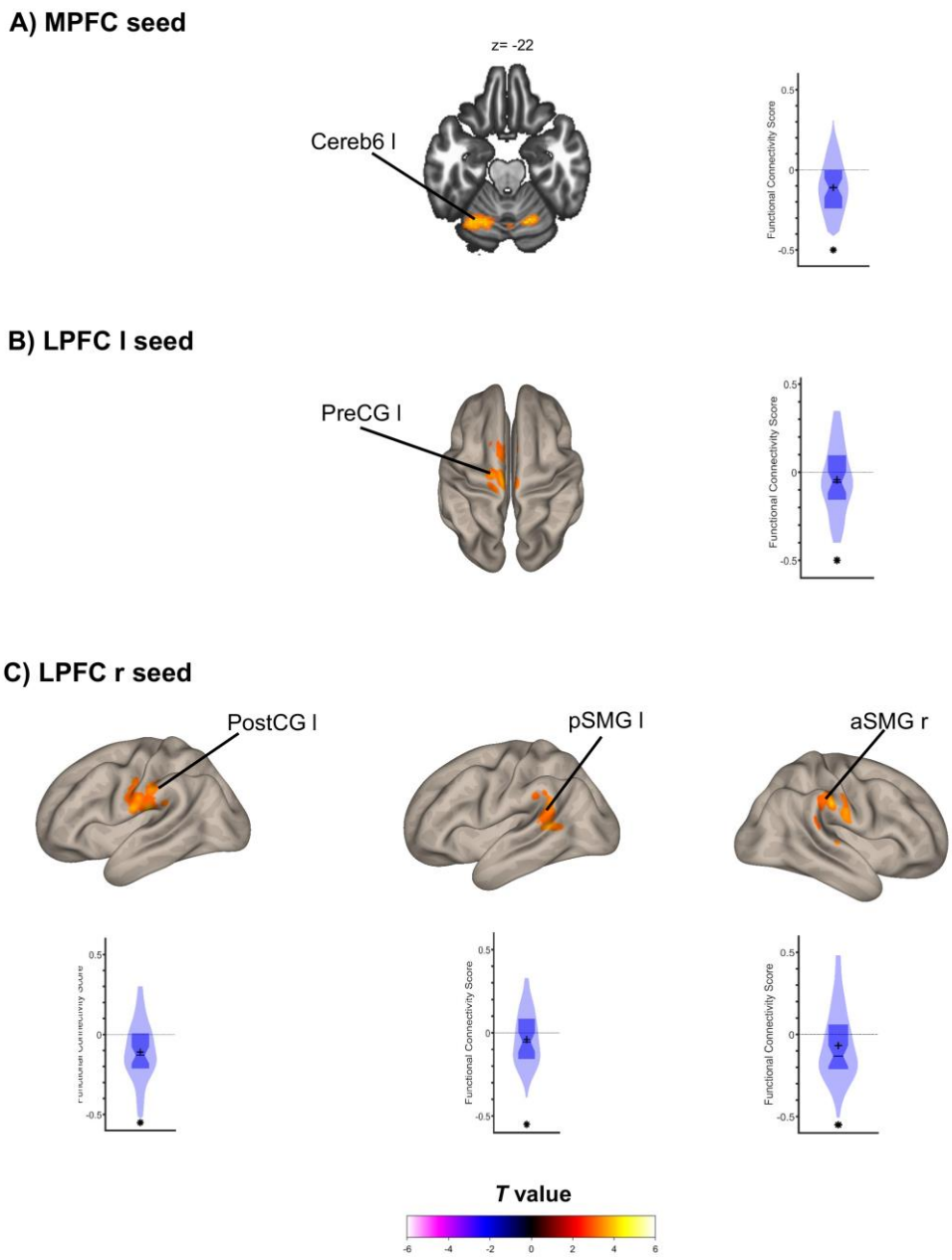

Figure 10. Effect of interaction between clinical severity and depression on seed-to-voxel connectivity in ASD. (A-C) Seeds showing significant connectivity within ASD with respective clusters at $p < 0.05$, FDR-corrected cluster-wise threshold are overlaid on inflated surface maps and axial slices. Violin and overlapping box plots show the distribution of functional connectivity scores / values (z- transformed r values) within ASD (blue). The edges of the box plots show 25%, 50% and 75% percentiles of the distribution. + mean of the distribution, * $p < 0.05$; Cereb6 l Cerebellum 6 Left, PreCG l Precentral Gyrus Left, PostCG l Postcentral Gyrus Left, pSMG l Supramarginal Gyrus, posterior division Left, aSMG r Supramarginal Gyrus, anterior division Right.

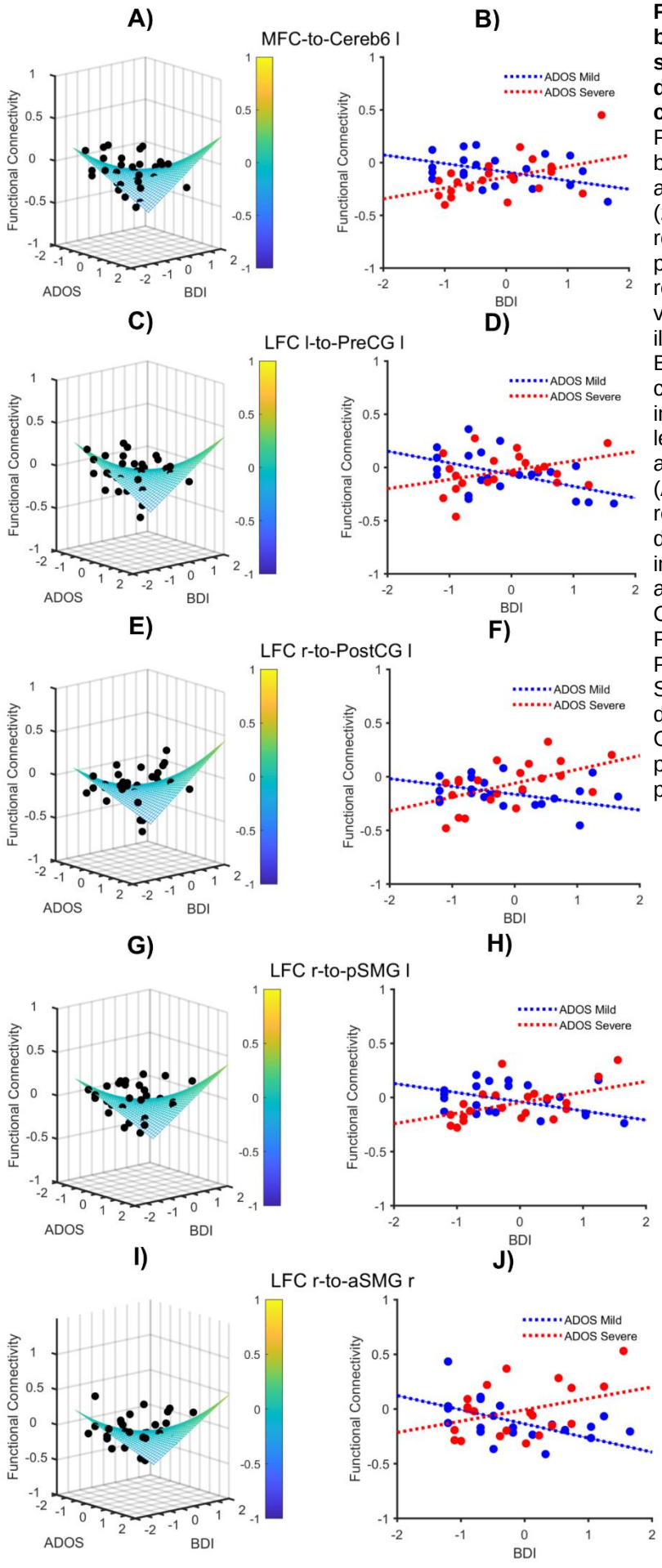

Figure 11. Pattern of interaction between clinical severity of ASD symptoms (ADOS) and depression (BDI) on seed-to-voxel connectivity in ASD. (A, C, E, G, I) Plots showing the interaction between ADOS (x-axis) and BDI (y-axis) on the functional connectivity (z-axis) between seeds and respective voxels. The regression planes capture the trend in the relationships between the three variables. (B, D, F, H, J) Plots illustrating the relationship between BDI (x-axis) and functional connectivity (y-axis) when the individuals with ASD are split by lesser (ADOS mild; blue markers and regression line) and greater (ADOS severe; red markers and regression line) severity of core ASD deficits. Note the evident interaction in all. The z-scores of the variables are plotted in all panels. Cereb6 l Cerebellum 6 Left, PreCG l Precentral Gyrus Left, PostCG l Postcentral Gyrus Left, pSMG l Supramarginal Gyrus, posterior division Left, aSMG r Supramarginal Gyrus, anterior division Right.Medial prefrontal cortex (MPFC), Lateral prefrontal cortex (LPFC).

Table 4. Effect of interaction between clinical severity and depression on seed-to-voxel

					MNI coordinates			
Seed	Voxels of the Brain area	Hemisphere (Left =L, Right=R)	Size (Voxels)	Size (*p* -FDR)	X	Y	Z	Effect size (beta value)
Medial Prefrontal Cortex	Cerebelum 6 (Cluster 1)	L	443	0.01	+12	-64	-20	4.99
Lateral Prefrontal Cortex left	Precentral Gyrus (Cluster 1)	L	433	0.02	-10	-22	+74	4.84
Lateral Prefrontal Cortex right	Postcentral Gyrus (Cluster 1)	L	646	0.00	-50	-20	+26	4.87
	Supramarginal Gyrus, posterior division (Cluster 2)	L	353	0.03	+66	-22	+24	4.57
	Supramarginal Gyrus, anterior division (Cluster 3)	R	309	0.03	-50	-44	+10	5.09

Discussion

In this study, we explored the seed-to-voxel resting state functional connectivity in ASD and matched TD adults using resting-state fMRI datasets taken from the ABIDE repository. One arm of the analyses was aimed at elucidating the differences of resting-state functional connectivity between ASD and TD per se and in association with the severity of the psychiatric comorbidity of depression. Another arm of the analyses focussed on examining the relationship of the clinical severity of ASD with intrinsic functional connectivity as well as the modulation of this relationship by the severity of comorbid depression. Consequently, our analyses revealed not only differential intrinsic functional connectivity (both hyper- and hypo-connectivity) between ASD and their typically developed peers but also clarified the role of the severity of core ASD features and its interaction with the severity of comorbid depression respectively with resting-state functional connectivity in ASD. These results inform a better brain-based functional understanding of the adult ASD phenotype, which is not frequently reported in the literature at this moment and is of import given the developmental trajectory of the brain in ASD.

We focussed on the seed regions within a few principal networks which have been implicated earlier in ASD as well as various affective disorders pertaining to the social and cognitive domains – the default mode network known to be involved in various aspects of cognitive and social processing such as perception of emotions, empathy, theory of mind, and morality (Li et al., 2014); the cingulo-opercular network known for effort driven processes required to maintain available cognitive resources for processing the demands of the tasks at hand (Sadaghiani & D'Esposito, 2015) effortful process of maintaining cognitive faculties available for current processing requirements; the salience network which parses multiple sources of environmental stimuli and determines the relative salience of these stimuli for these inputs to be processed elaborately (Menon & Uddin, 2010); finally the fronto-parietal network which computes the priority map by collating sensory features and top-down representations of behavioural goals and expectations, towards serving attention-mediated sensory selection (Ptak, 2012). The dynamic functional coupling across the regions of the brain has been found to model the interactions of the brain with the external environment, and has explained behavioural phenotypes (Liégeois et al., 2019; Vaidya & Gordon, 2013), which we discuss below in the adult ASD sample vis-à-vis a comparable TD sample.

Firstly, upon examining the differences in functional connectivity in ASD compared to TD, we found that the caudate which partakes in cognitive and emotional processing (Mendez et al., 1989); reward-related decision making and goal-directed behaviour (Balleine et al., 2007; Via et al., 2021)); suppression of pain (Borsook et al., 2010) is hyper-connected in ASD with the insular cortex which is also known for pain perception (Jensen et al., 2016), which could be linked with altered pain (Gu et al., 2018) and reward processing (Jones et al., 2010) . An aberrant hyper-connectivity of caudate with SFG could be associated with social, communication deficits reported in ASD (Assaf et al., 2010) and that with Frontal Orbital Cortex Right (FOrb r), which also processes emotions and coordinates with caudate for the prediction of reward/punishment error (Finger et al., 2011) may result in prediction errors (Van de Cruys et al., 2014). These prediction errors which the brain generates from models to infer prediction of sensory inputs and update accordingly to update sensory output will lead to a suboptimal updating among ASD individuals and leads to enhanced sensations of surprise (Sapey-Triomphe et al., 2021) and failure to attenuate sensory precision (Lawson et al., 2014). The Lateral Occipital Cortex which is related to the increasing amount of visual information and that corresponds to object identification (Grill-Spector et al., 2001) was also found to be hyper-connected among ASD individuals which could be associated with the affect biased attention and

atypical selective attention (Caplette et al., 2016). The caudate-IFG oper l hyper-connectivity could further explain the enhanced value associated with learning in non- social domain. An aberrant hyper-connectivity associated between caudate l and IFG oper l that is responsible for language and communication abilities (Tremblay & Dick, 2016) in the brain could also shed light on the impairments observed among ASD individuals following the same . Amygdala left which was found to partake in sustained stimulus evaluation and associated with increased correlation to fearful responses and emotional processing (Jung et al., 2018) was found to be hyper-connected with caudate r which is a part of amygdalofugal pathway that can influence responses; this coincides with the reports of increased levels of anxiety (Mingins et al., 2021) and highly typical fear learning in Pavlovian conditioning task (Bertone et al., 2005). Anterior insula which was found to be involved in motor action and social interaction and related to the processing of salient, autonomic function, and pain processing, was also found to be hyper-connected to LOC l & r which could explain atypical selective attention to objects (Q. Wang et al., 2020) as opposed to the social setting which is supported by evidence of LOC l underpinning the function related to the naming of objects and LOC r to matching object task (Large et al., 2007). The connectivity between caudate and anterior insula could also explain the differences in pain responsivity among ASD individuals (Failla et al., 2020) as it has been

observed during painful task (Emmert et al., 2014) and it may seem due to the role of caudate and insula on pain processing (Ghaziri et al., 2018). Furthermore, enhanced negative affect such as anger, anxiety and fear (Vasa & Mazurek, 2015) among autistic individuals observed could be related to the aberrance in the connectivity between Anterior Insula r and Post CG l. In addition to this Anterior cingulate cortex which is involved in affect regulation by its connections to the limbic system and prefrontal cortex observed a hyper-connectivity with caudate l & r which could potentially suggest abnormal reward behaviour among ASD individuals, comparing with prior studies the current findings may be specific to adults and not among children (Delmonte et al., 2013) as it was not observed among children (Di Martino et al., 2011).

In comparison to TD individuals, the caudate r which partake in cognitive, emotional and goal-directed decisions was found to be hypoconnected to the region Cereb1 r, and this may explain the reduced goal-directed action control among ASD individuals (Alvares et al., 2016) since prior research underpinned the role of the cerebellum as a modulator to change of errors in movement and thought and forms (Duan et al., 2015) and forms closed circuits that are related to social, language, and movement processing. Cerebellar dysfunction may have an effect on the primary ASD symptoms of social and communication difficulties as well as repetitive and

stereotyped behaviours (D'Mello & Stoodley, 2015). The precuneus which is a part default mode network that is implicated in recollection, memory and integration of information, sense of self and processing of self-relevant information (Cullen et al., 2014) was found hypoconnected with aPaHC r, which is involved in spatial navigation, memory encoding and retrieval etc (Mouga et al., 2022); the findings may explain the atypical self-perception and related activities that are reported in autism (Lyons & Fitzgerald, 2013), the current findings are also supported by prior findings by (Assaf et al., 2010) which showed reduced connectivity within DMN subregions. The left paracingulate cortex which is more activated during word generation and showed greater activation among ASD than in TD for signed prediction errors which indicate the extent to which an outcome is better or worse than expected, was also found to be hypo-connected to the anterior insula left, similarly, hypo-activation between the anterior insula which is also involved in response switching, attention and control (Dambacher et al., 2015) and frontal pole right, a region that is implicated in higher cognitive operations, decision making, evaluation of reward, action selection, directed action and tracking value could explain the reduced goal-directed action control among ASD (Alvares et al., 2016) based on our findings of the hypo-connectivty between Anterior insula right and Frontal Pole right.

The differential functional connectivity between ASD and TD was then examined in association with the comorbidity of depression. Our findings suggest that with increasing severity of depression, the hyperconnectivity between angular gyrus and lateral occipital cortical regions observed can be explained as it was evident from previous studies for its role in pathophysiology for depressed individuals (J. H. Kim et al., 2019), a similar trend is also observed for connectivity between the Anterior insula right and Cereb45 l, since cerebellum is not only limited to motor function but also involved in emotion and cognition (Alalade et al., 2011) and damages related to cerebellum might result in difficulty of depressed patients in recognising their mood state awareness (depression disorder in patients). As opposed to the aforementioned trend we found with increasing severity of depression the hypoconnectivity between the amygdala right and Parietal operculum which is associated with multisensory integration, perception of body and interoceptive awareness (Van de Winckel et al., 2020), could explain the altered self-representation of ASD (Uddin, 2011).

The third objective was to find if the clinical severity, i.e. ADOS scores modulated the connectivity within the ASD population. Firstly we found that the connectivity between anterior insula left which is involved and found to be activated in all valence categories (Gu et al., 2013), ability to

recognise facial emotion expression, and also crucial role in distinguishing primordial emotions like disgust, happiness etc (Uddin et al., 2017) with fusiform gyrus which a part of the temporal fusiform cortex that is highly implicated in high-level visual processing, face processing (Ho et al., 2014) and object recognition and naming, was found to be positively modulated by ADOS scores, along with this ADOS was also found to positively modulate the connectivity with Lateral Occipital cortex , superior division Left which could explain the atypical selective attention to objects which is considered as key clinical feature of ASD (Q. Wang et al., 2020) while the positive modulation of Anterior insula r and precentral gyrus left connectivity would explain atypical motor functioning which is prevalent among ASD and known to be linked with social, communicative impairments since precentral gyrus is a key component of the motor control networks (Nebel et al., 2014). Apart from the aforementioned findings it was also found that an increasing clinical severity modulated positively the connectivity between frontal pole right and medial prefrontal cortex, which is found to be sensitive to deviations from expected outcome and updating of expectations after prediction errors (van Noordt et al., 2017), these findings may posits to the aberrant reward value system and prevalence of RRBs among ASD individuals (Kohls et al., 2018), similar trend between frontal pole right and lateral occipital cortex right might explain the reduced activation compared to controls during the reception

of social rewards as opposed to non-social rewards (Delmonte et al., 2013). Caudate r which was involved in cognitive, goal directed decision making was also found to be positively modulated by ADOS in its connectivity with the precentral gyrus left which could explain atypical motor functioning and social and communicative impairments that is prevalent and strength of which is correlated with clinical severity (Baranek, 1999; Nebel et al., 2014) . As opposed to positive regulation, increasing clinical severity also modulated decreased connectivity between different brain regions; for anterior insula left and with Cingulate Gyrus, anterior division a negative correlation reveals the under-connectivity between DMN and Salience network which are previously reported by (Duan et al., 2015) and also explain the atypical characteristics in the motivation, reward and movement (Heimer et al., 2008; Posner et al., 2007). In continuation to the aforementioned analysis the clinical severity was also found to negatively correlated for seed region posterior cingulate cortex with region Inferior Temporal Gyrus ,inferior temporal gyrus is known to be involved in high cognitive functions, including emotional regulation, visual and language comprehension (Lin et al., 2019) ,these may point to why ASD individuals are generally poor in word reading and oral language predict reading (Davidson et al., 2018), seed caudate r with regions SPL l, FP r also followed similar trend as; the Caudate r/SPL l connectivity modulation may

be possible since the Superior parietal lobule is an area of default mode network and involved in the recall of personal experiences, mental imagery and prior studies point to alterations in visual perception and mental imagery (Maróthi et al., 2019) that occur among ASD individuals, and caudate r/FP r negative correlation might also explain the reduced correlation between caudate and frontal regions that are reported among autistic children and is associated with the stereotyped behaviour in autism (atypical diffuse). In autistic individuals, there is a general trend of non-regulation of emotion or emotional control (Mazefsky et al., 2008). This might be attributed to the negative correlation of clinical severity between the Anterior cingulate cortex and Cereb 8 l, as the cerebellum is also found to have an essential role in affect regulation and to manage negative emotions (Gross & Muñoz, 1995; Schutter & van Honk, 2009),

Lastly, we checked for interaction between clinical severity and depression scores within the ASD population to check if the clinical severity and depression scores have any interaction effect and the underpinning findings are that there is an interaction. It was found that interaction term correlates positively with the connectivity between the seed region and Medial prefrontal cortex, which is associated with the integration of information from different input structures and updates to different structures. It is also found to be sensitive to deviation expected

outcomes and linked to rapid updation of the following and plays an important role in in cognition, emotion regulation, sociability (van Noordt et al., 2017) and also top-down regulation (Lawther et al., 2020), with region Cereb6 l,which explains and associate to representation of mental states of other or forming theory of mind of other human beings (Han et al., 2005), these pieces of evidence along with prior research could points to the impaired mentalisation among ASD individuals, also impaired emotional regulation (Mazefsky et al., 2013) and in mouse models of ASD MPFC mediated cerebellum regulated repetitive behaviour (Kelly et al., 2020). For the positive regulation of seed region Lateral prefrontal cortex Left with region Prec CG l may be due to the functions of Pre CG l in social and motor impairments and functions associated with LPFC l in cognitive control and planning (Wallis, 2019). For connectivity between the Lateral prefrontal cortex Right and Post CG l, the left postcentral gyrus was found to distinguish positive and negative affect from face-body and body-the whole person on a task-based study. It was also found to have been involved in emotional processing of face and body (Cao et al., 2018), this finding may also shed light on the deficits in facial, body emotional processing that are found in autism spectrum disorders (Philip et al., 2010), another possible explanation for the connectivity could be that altered somatic brain network could play a major role in trait anxiety (Philip et al., 2010) which is one of the comorbidities associated with ASD. Since

it was found that greater cognitive control was needed for anxious individuals to cope with anxiety, thus a greater activity is seen between the postcentral gyrus and regions of LPFC to mitigate it and finally the interaction also showed a positive correlation between LPFC r and Supramarginal Gyrus (pSMG l & aSMG r); this may be due to the role of SPL that may play an important role in motor learning and repetitive behaviour in ASD (Travers et al., 2015), and altered functional connectivity pattern that may reflect underlying deficits associated with ASD individuals during a task related to behavioural learning.

Taken together, the study highlights the differential resting state functional brain networks between ASD and TD adults and its relationship with the severity of depression. Moreover, the interaction between ASD symptomatic severity and depression towards explaining the resting state functional connectivity in the ASD brain is elucidated. These results add a leaf on the resting state brain functional architecture in ASD to the existing body of knowledge.

References

1. Agcaoglu, O., Wilson, T. W., Wang, Y.-P., Stephen, J., & Calhoun, V. D. (2019). Resting-state connectivity differences in eyes open versus eyes closed conditions. Human Brain Mapping, 40(8), 2488–2498.
2. Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. Journal of Autism and Developmental Disorders, 29(3), 213–224.
3. Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. Archives of General Psychiatry, 4(6), 561–571.
4. Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. Brain, 128(10), 2430–2441.
5. Bishop, S. L., Hus, V., Duncan, A., Huerta, M., Gotham, K., Pickles, A., Kreiger, A., Buja, A., Lund, S., & Lord, C. (2013). Subcategories of restricted and repetitive behaviors in children with autism spectrum disorders. Journal of Autism and Developmental Disorders, 43(6), 1287–1297.
6. Biswal, B. B. (2012). Resting-state fMRI: a personal history. Neuroimage, 62(2), 938–944.
7. Bittar, T. P., & Labonté, B. (2021). Functional Contribution of the Medial Prefrontal Circuitry in Major Depressive Disorder and Stress-Induced

Depressive-Like Behaviors. Frontiers in Behavioral Neuroscience, 15, 699592. https://doi.org/10.3389/fnbeh.2021.699592

8. Bryson, S. E., Clark, B. S., & Smith, I. M. (1988). First report of a Canadian epidemiological study of autistic syndromes. Journal of Child Psychology and Psychiatry, 29(4), 433–445.
9. Butcher, J. N., Taylor, J., & Fekken, G. C. (1998). Objective personality assessment with adults.
10. Buxbaum, J. D., & Hof, P. R. (2012). The neuroscience of autism spectrum disorders. Academic Press.
11. Chakrabarty, M., Atsumi, T., Kaneko, A., Fukatsu, R., & Ide, M. (2021). State anxiety modulates the effect of emotion cues on visual temporal sensitivity in autism spectrum disorder. European Journal of Neuroscience.
12. Collignon, A., Maes, F., Delaere, D., Vandermeulen, D., Suetens, P., & Marchal, G. (1995). Automated multi-modality image registration based on information theory. Information Processing in Medical Imaging, 3(6), 263–274.
13. Courchesne, E., Lincoln, A. J., Kilman, B. A., & Galambos, R. (1985). Event-related brain potential correlates of the processing of novel visual and auditory information in autism. Journal of Autism and Developmental Disorders, 15(1), 55–76.
14. Dawson, G., Osterling, J., Meltzoff, A. N., & Kuhl, P. (2000). Case study of the development of an infant with autism from birth to two years of age. Journal of Applied Developmental Psychology, 21(3), 299–313.
15. Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.-N., Mennes, M., Mairena,

M. A., Lord, C., Castellanos, F. X., & Milham, M. P. (2011). Aberrant striatal functional connectivity in children with autism. Biological Psychiatry, 69(9), 847–856.

16. Di Martino, A., O'Connor, D., Chen, B., Alerts, K., Anderson, J. S., Assaf, M., Balsters, J. H., Baxter, L., Beggiato, A., Bernaerts, S., & others. (2017a). Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. Scientific Data, 4(1), 1–15.

17. Di Martino, A., O'Connor, D., Chen, B., Alerts, K., Anderson, J. S., Assaf, M., Balsters, J. H., Baxter, L., Beggiato, A., Bernaerts, S., & others. (2017b). Enhancing studies of the connectome in autism using the autism brain imaging data exchange II. Scientific Data, 4(1), 1–15.

18. Easson, A. K., Fatima, Z., & McIntosh, A. R. (2019). Functional connectivity-based subtypes of individuals with and without autism spectrum disorder. Network Neuroscience, 3(2), 344–362.

19. Edwards, R. L., Moore, B. E., & Fine, B. (n.d.). American Psychiatric Association. Diagnostic Criteria of DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000. American Psychological Association. Dictionary of Psychology. Washington, DC: American Psychological Association.

20. Evans, D. W., Leckman, J. F., Carter, A., Reznick, J. S., Henshaw, D., King, R. A., & Pauls, D. (1997). Ritual, habit, and perfectionism: The prevalence and development of compulsive-like behavior in normal young children. Child Development, 58–68.

21. Faras, H., Al Ateeqi, N., & Tidmarsh, L. (2010). Autism spectrum disorders.

Annals of Saudi Medicine, 30(4), 295–300.

22. Fischer, A. S., Keller, C. J., & Etkin, A. (2016). The clinical applicability of functional connectivity in depression: Pathways toward more targeted intervention. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 1(3), 262–270.

23. Gabbay, V., Ely, B. A., Li, Q., Bangaru, S. D., Panzer, A. M., Alonso, C. M., Castellanos, F. X., & Milham, M. P. (2013). Striatum-Based Circuitry of Adolescent Depression and Anhedonia. Journal of the American Academy of Child & Adolescent Psychiatry, 52(6), 628-641.e13. https://doi.org/10.1016/j.jaac.2013.04.003

24. González, M. C., Vásquez, M., & Hernández Chávez, M. (2019). Autism spectrum disorder: Clinical diagnosis and ADOS test.

25. Gotham, K., Risi, S., Pickles, A., & Lord, C. (2007). The Autism Diagnostic Observation Schedule: Revised algorithms for improved diagnostic validity. Journal of Autism and Developmental Disorders, 37(4), 613–627.

26. Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. Proceedings of the National Academy of Sciences, 100(1), 253–258. https://doi.org/10.1073/pnas.0135058100

27. Grimm, S., Boesiger, P., Beck, J., Schuepbach, D., Bermpohl, F., Walter, M., Ernst, J., Hell, D., Boeker, H., & Northoff, G. (2009). Altered Negative BOLD Responses in the Default-Mode Network during Emotion Processing in Depressed Subjects. Neuropsychopharmacology, 34(4), 932–943.

https://doi.org/10.1038/npp.2008.81

28. Gunn, K. C., & Delafield-Butt, J. T. (2016). Teaching children with autism spectrum disorder with restricted interests: A review of evidence for best practice. Review of Educational Research, 86(2), 408–430.

29. Hamilton, J. P., Glover, G. H., Bagarinao, E., Chang, C., Mackey, S., Sacchet, M. D., & Gotlib, I. H. (2016). Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder. Psychiatry Research: Neuroimaging, 249, 91–96. https://doi.org/10.1016/j.pscychresns.2016.01.016

30. Hao, Z. Y., Zhong, Y., Ma, Z. J., Xu, H. Z., Kong, J. Y., Wu, Z., Wu, Y., Li, J., Lu, X., Zhang, N., & Wang, C. (2020). Abnormal resting-state functional connectivity of hippocampal subfields in patients with major depressive disorder. BMC Psychiatry, 20(1), 71. https://doi.org/10.1186/s12888-020-02490-7

31. Hermelin, B., & O'connor, N. (1970). Psychological experiments with autistic children.

32. Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2004). Adult outcome for children with autism. Journal of Child Psychology and Psychiatry, 45(2), 212–229.

33. Hull, J. V., Dokovna, L. B., Jacokes, Z. J., Torgerson, C. M., Irimia, A., & Van Horn, J. D. (2017). Resting-state functional connectivity in autism spectrum disorders: A review. Frontiers in Psychiatry, 7, 205.

34. ICD - ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification. (2021, November 3).

https://www.cdc.gov/nchs/icd/icd9cm.htm

35. Kanner, L. & others. (1943). Autistic disturbances of affective contact. Nervous Child, 2(3), 217–250.

36. Kennedy, D. (n.d.). Courchesne E (2008b) The intrinsic functional organisation of the brain is altered in autism. Neuroimage, 39(4), 1877–1885.

37. Kent, R., & Simonoff, E. (2017). Prevalence of anxiety in autism spectrum disorders. Anxiety in Children and Adolescents with Autism Spectrum Disorder, 5–32.

38. Kern, J. K., Trivedi, M. H., Garver, C. R., Grannemann, B. D., Andrews, A. A., Savla, J. S., Johnson, D. G., Mehta, J. A., & Schroeder, J. L. (2006). The pattern of sensory processing abnormalities in autism. Autism, 10(5), 480–494.

39. Kim, M. J., Gee, D. G., Loucks, R. A., Davis, F. C., & Whalen, P. J. (2011). Anxiety dissociates dorsal and ventral medial prefrontal cortex functional connectivity with the amygdala at rest. Cerebral Cortex, 21(7), 1667–1673.

40. Kim, S. H., & Lord, C. (2013). The behavioral manifestations of autism spectrum disorders. The Neuroscience of Autism Spectrum Disorders, 25–37.

41. Kirsch, A. C., Huebner, A. R., Mehta, S. Q., Howie, F. R., Weaver, A. L., Myers, S. M., Voigt, R. G., & Katusic, S. K. (2020). Association of comorbid mood and anxiety disorders with autism spectrum disorder. JAMA Pediatrics, 174(1), 63–70.

42. Kleinhans, N. M., Reiter, M. A., Neuhaus, E., Pauley, G., Martin, N., Dager, S., & Estes, A. (2016). Subregional differences in intrinsic amygdala hyperconnectivity and hypoconnectivity in autism spectrum disorder: Subregional

amygdala connectivity in autism. Autism Research, 9(7), 760–772. https://doi.org/10.1002/aur.1589

43. Lee, J. M., Kyeong, S., Kim, E., & Cheon, K.-A. (2016). Abnormalities of inter-and intra-hemispheric functional connectivity in autism spectrum disorders: A study using the autism brain imaging data exchange database. Frontiers in Neuroscience, 10, 191.

44. Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. Journal of Autism and Developmental Disorders, 37(5), 894–910.

45. Liang, X., Wang, J., Yan, C., Shu, N., Xu, K., Gong, G., & He, Y. (2012). Effects of Different Correlation Metrics and Preprocessing Factors on Small-World Brain Functional Networks: A Resting-State Functional MRI Study. PLoS ONE, 7(3), e32766. https://doi.org/10.1371/journal.pone.0032766

46. Liu, C.-H., Ma, X., Song, L.-P., Tang, L.-R., Jing, B., Zhang, Y., Li, F., Zhou, Z., Fan, J., & Wang, C.-Y. (2015). Alteration of spontaneous neuronal activity within the salience network is partially remitted depression. Brain Research, 1599, 93–102. https://doi.org/10.1016/j.brainres.2014.12.040

47. Lord, C., Schopler, E., & Revicki, D. (1982). Sex differences in autism. Journal of Autism and Developmental Disorders, 12(4), 317–330.

48. Lyons, V., & Fitzgerald, M. (2013). Atypical sense of self in autism spectrum disorders: A neurocognitive perspective. In Recent Advances in Autism Spectrum Disorders-Volume I. IntechOpen.

49. Marco, E. J., Hinkley, L. B., Hill, S. S., & Nagarajan, S. S. (2011). Sensory

processing in autism: A review of neurophysiologic findings. Pediatric Research, 69(8), 48–54.

50. Mazefsky, C. A., Folstein, S. E., & Lainhart, J. E. (2008). Overrepresentation of mood and anxiety disorders in adults with autism and their first-degree relatives: What does it mean? Autism Research, 1(3), 193–197.

51. Monk, C. S., Peltier, S. J., Wiggins, J. L., Weng, S.-J., Carrasco, M., Risi, S., & Lord, C. (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders. Neuroimage, 47(2), 764–772.

52. Murphy, C. M., Wilson, C. E., Robertson, D. M., Ecker, C., Daly, E. M., Hammond, N., Galanopoulos, A., Dud, I., Murphy, D. G., & McAlonan, G. M. (2016). Autism spectrum disorder in adults: Diagnosis, management, and health services development. Neuropsychiatric Disease and Treatment.

53. O'Neill, M., & Jones, R. S. (1997). Sensory-perceptual abnormalities in autism: A case for more research? Journal of Autism and Developmental Disorders, 27(3), 283–293.

54. Organisation, W. H. & others. (1996). International Classification of Diseases. 10th Revision World Health Organization. Geneva, Switzerland.

55. Padmanabhan, A., Lynch, C. J., Schaer, M., & Menon, V. (2017). The Default Mode Network in Autism. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2(6), 476–486. https://doi.org/10.1016/j.bpsc.2017.04.004

56. Pehlivanidis, A., Papanikolaou, K., Mantas, V., Kalantzi, E., Korobili, K., Xenaki, L.-A., Vassiliou, G., & Papageorgiou, C. (2020). Lifetime co-occurring psychiatric disorders in newly diagnosed adults with attention deficit hyperactivity

disorder (ADHD) or/and autism spectrum disorder (ASD). BMC Psychiatry, 20(1), 1–12.

57. Pessoa, L. (2013). The cognitive-emotional brain: From interactions to integration. MIT press.

58. Puts, N. A., Wodka, E. L., Tommerdahl, M., Mostofsky, S. H., & Edden, R. A. (2014). Impaired tactile processing in children with autism spectrum disorder. Journal of Neurophysiology, 111(9), 1803–1811.

59. Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. Proceedings of the National Academy of Sciences, 98(2), 676–682.

60. Risold, P., Thompson, R., & Swanson, L. (1997). The structural organisation of connections between hypothalamus and cerebral cortex. Brain Research Reviews, 24(2–3), 197–254.

61. Scheepens, D. S., van Waarde, J. A., Lok, A., de Vries, G., Denys, D. A., & van Wingen, G. A. (2020). The link between structural and functional brain abnormalities in depression: A systematic review of Multimodal Neuroimaging Studies. Frontiers in Psychiatry, 11, 485.

62. Snow, A. V., Lecavalier, L., & Houts, C. (2009). The structure of the Autism Diagnostic Interview-Revised: Diagnostic and phenotypic implications. Journal of Child Psychology and Psychiatry, 50(6), 734–742.

63. Studholme, C., Hawkes, D. J., & Hill, D. L. (1998). Normalised entropy measure for multimodality image alignment. Medical Imaging 1998: Image Processing, 3338, 132–143.

64. Sylvester, C. M., Corbetta, M., Raichle, M., Rodebaugh, T., Schlaggar, B., Sheline, Y., Zorumski, C., & Lenze, E. (2012). Functional network dysfunction in anxiety and anxiety disorders. Trends in Neurosciences, 35(9), 527–535.

65. Thurm, A., Lord, C., Lee, L.-C., & Newschaffer, C. (2007). Predictors of language acquisition in preschool children with autism spectrum disorders. Journal of Autism and Developmental Disorders, 37(9), 1721–1734.

66. Uddin, L. Q., Supekar, K., & Menon, V. (2013). Reconceptualising functional brain connectivity in autism from a developmental perspective. Frontiers in Human Neuroscience, 7, 458.

67. Vandenbroucke, M. W., Scholte, H. S., van Engeland, H., Lamme, V. A., & Kemner, C. (2008). A neural substrate for atypical low-level visual processing in autism spectrum disorder. Brain, 131(4), 1013–1024.

68. Wang, Q., Li, H.-Y., Li, Y.-D., Lv, Y.-T., Ma, H.-B., Xiang, A.-F., Jia, X.-Z., & Liu, D.-Q. (2021). Resting-state abnormalities in functional connectivity of the default mode network in autism spectrum disorder: A meta-analysis. Brain Imaging and Behavior, 15(5), 2583–2592. https://doi.org/10.1007/s11682-021-00460-5

69. Weng, S.-J., Wiggins, J. L., Peltier, S. J., Carrasco, M., Risi, S., Lord, C., & Monk, C. S. (2010). Alterations of resting-state functional connectivity in the default network in adolescents with autism spectrum disorders. Brain Research, 1313, 202–214.

70. Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain

Connectivity, 2(3), 125–141. https://doi.org/10.1089/brain.2012.0073

71. Williams, L. M. (2016). Precision psychiatry: A neural circuit taxonomy for depression and anxiety. The Lancet Psychiatry, 3(5), 472–480.

72. Yaguchi, A., Atsumi, T., Fukatsu, R., & Ide, M. (2020). Temporal resolution relates to sensory hyperreactivity independently of stimulus detection sensitivity in individuals with autism spectrum disorder. BioRxiv.

73. Young, M. P., Scanneil, J. W., Burns, G. A., & Blakemore, C. (1994). Analysis of connectivity: Neural systems in the cerebral cortex. Reviews in the Neurosciences, 5(3), 227–250.

74. Alalade, E., Denny, K., Potter, G., Steffens, D., & Wang, L. (2011). Altered Cerebellar-Cerebral Functional Connectivity in Geriatric Depression. PLoS ONE, 6(5), e20035. https://doi.org/10.1371/journal.pone.0020035

75. Alvares, G. A., Balleine, B. W., Whittle, L., & Guastella, A. J. (2016). Reduced goal-directed action control in autism spectrum disorder. Autism Research: Official Journal of the International Society for Autism Research, 9(12), 1285–1293. https://doi.org/10.1002/aur.1613

76. Assaf, M., Jagannathan, K., Calhoun, V. D., Miller, L., Stevens, M. C., Sahl, R., O'Boyle, J. G., Schultz, R. T., & Pearlson, G. D. (2010). Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. NeuroImage, 53(1), 247–256. https://doi.org/10.1016/j.neuroimage.2010.05.067

77. Balleine, B. W., Delgado, M. R., & Hikosaka, O. (2007). The role of the dorsal striatum in reward and decision-making. The Journal of Neuroscience:

The Official Journal of the Society for Neuroscience, 27(31), 8161–8165. https://doi.org/10.1523/JNEUROSCI.1554-07.2007

78. Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. Journal of Autism and Developmental Disorders, 29(3), 213–224.

79. Bertone, A., Mottron, L., Jelenic, P., & Faubert, J. (2005). Enhanced and diminished visuo-spatial information processing in autism depends on stimulus complexity. Brain, 128(10), 2430–2441.

80. Borsook, D., Upadhyay, J., Chudler, E. H., & Becerra, L. (2010). A key role of the basal ganglia in pain and analgesia—Insights gained through human functional imaging. Molecular Pain, 6, 27. https://doi.org/10.1186/1744-8069-6-27

81. Cao, L., Xu, J., Yang, X., Li, X., & Liu, B. (2018). Abstract Representations of Emotions Perceived From the Face, Body, and Whole-Person Expressions in the Left Postcentral Gyrus. Frontiers in Human Neuroscience, 12. https://www.frontiersin.org/articles/10.3389/fnhum.2018.00419

82. Caplette, L., Wicker, B., & Gosselin, F. (2016). Atypical Time Course of Object Recognition in Autism Spectrum Disorder. Scientific Reports, 6(1), 35494. https://doi.org/10.1038/srep35494

83. Cullen, K. R., Westlund, M. K., Klimes-Dougan, B., Mueller, B. A., Houri, A., Eberly, L. E., & Lim, K. O. (2014). Abnormal Amygdala Resting-State Functional Connectivity in Adolescent Depression. JAMA Psychiatry, 71(10), 1138–1147. https://doi.org/10.1001/jamapsychiatry.2014.1087

84. Dambacher, F., Sack, A. T., Lobbestael, J., Arntz, A., Brugman, S., & Schuhmann, T. (2015). Out of control: Evidence for anterior insula involvement in motor impulsivity and reactive aggression. Social Cognitive and Affective Neuroscience, 10(4), 508–516. https://doi.org/10.1093/scan/nsu077

85. Davidson, M. M., Kaushanskaya, M., & Weismer, S. E. (2018). Reading Comprehension in Children With and Without ASD: The Role of Word Reading, Oral Language, and Working Memory. Journal of Autism and Developmental Disorders, 48(10), 3524–3541. https://doi.org/10.1007/s10803-018-3617-7

86. Delmonte, S., Gallagher, L., O'Hanlon, E., McGrath, J., & Balsters, J. H. (2013). Functional and structural connectivity of frontostriatal circuitry in Autism Spectrum Disorder. Frontiers in Human Neuroscience, 7, 430. https://doi.org/10.3389/fnhum.2013.00430

87. Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.-N., Mennes, M., Mairena, M. A., Lord, C., Castellanos, F. X., & Milham, M. P. (2011). Aberrant striatal functional connectivity in children with autism. Biological Psychiatry, 69(9), 847–856. https://doi.org/10.1016/j.biopsych.2010.10.029

88. D'Mello, A. M., & Stoodley, C. J. (2015). Cerebro-cerebellar circuits in autism spectrum disorder. Frontiers in Neuroscience, 9. https://www.frontiersin.org/articles/10.3389/fnins.2015.00408

89. Duan, M., Chen, X., He, H., Jiang, Y., Jiang, S., Xie, Q., Lai, Y., Luo, C., & Yao, D. (2015). Altered Basal Ganglia Network Integration in Schizophrenia. Frontiers in Human Neuroscience, 9, 561. https://doi.org/10.3389/fnhum.2015.00561

90. Duan, X., Chen, H., He, C., Long, Z., Guo, X., Zhou, Y., Uddin, L. Q., & Chen, H. (2017). Resting-state functional under-connectivity within and between large-scale cortical networks across three low-frequency bands in adolescents with autism. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 79(Pt B), 434–441. https://doi.org/10.1016/j.pnpbp.2017.07.027

91. Emmert, K., Breimhorst, M., Bauermann, T., Birklein, F., Van De Ville, D., & Haller, S. (2014). Comparison of anterior cingulate vs. Insular cortex as targets for real-time fMRI regulation during pain stimulation. Frontiers in Behavioral Neuroscience, 8, 350. https://doi.org/10.3389/fnbeh.2014.00350

92. Failla, M. D., Gerdes, M. B., Williams, Z. J., Moore, D. J., & Cascio, C. J. (2020). Increased pain sensitivity and pain-related anxiety in individuals with autism. Pain Reports, 5(6), e861. https://doi.org/10.1097/PR9.0000000000000861

93. Finger, E. C., Marsh, A. A., Blair, K. S., Reid, M. E., Sims, C., Ng, P., Pine, D. S., & Blair, R. J. R. (2011). Disrupted Reinforcement Signaling in the Orbitofrontal Cortex and Caudate in Youths With Conduct Disorder or Oppositional Defiant Disorder and a High Level of Psychopathic Traits. American Journal of Psychiatry, 168(2), 152–162. https://doi.org/10.1176/appi.ajp.2010.10010129

94. Ghaziri, J., Tucholka, A., Girard, G., Boucher, O., Houde, J.-C., Descoteaux, M., Obaid, S., Gilbert, G., Rouleau, I., & Nguyen, D. K. (2018). Subcortical structural connectivity of insular subregions. Scientific Reports, 8(1), 8596. https://doi.org/10.1038/s41598-018-26995-0

95. Grill-Spector, K., Kourtzi, Z., & Kanwisher, N. (2001). The lateral occipital complex and its role in object recognition. Vision Research, 41(10–11), 1409–1422. https://doi.org/10.1016/s0042-6989(01)00073-6

96. Gross, J. J., & Muñoz, R. F. (1995). Emotion regulation and mental health. Clinical Psychology: Science and Practice, 2(2), 151–164. https://doi.org/10.1111/j.1468-2850.1995.tb00036.x

97. Gu, X., Hof, P. R., Friston, K. J., & Fan, J. (2013). Anterior Insular Cortex and Emotional Awareness. The Journal of Comparative Neurology, 521(15), 3371–3388. https://doi.org/10.1002/cne.23368

98. Gu, X., Zhou, T. J., Anagnostou, E., Soorya, L., Kolevzon, A., Hof, P. R., & Fan, J. (2018). Heightened brain response to pain anticipation in high-functioning adults with autism spectrum disorder. European Journal of Neuroscience, 47(6), 592–601. https://doi.org/10.1111/ejn.13598

99. Han, S., Jiang, Y., Humphreys, G. W., Zhou, T., & Cai, P. (2005). Distinct neural substrates for the perception of real and virtual visual worlds. NeuroImage, 24(3), 928–935. https://doi.org/10.1016/j.neuroimage.2004.09.046

100. Heimer, L., Van Hoesen, G. W., Trimble, M., & Zahm, D. S. (2008). 4—THE GREATER LIMBIC LOBE. In L. Heimer, G. W. Van Hoesen, M. Trimble, & D. S. Zahm (Eds.), Anatomy of Neuropsychiatry (pp. 69–100). Academic Press. https://doi.org/10.1016/B978-012374239-1.50007-5

101. Ho, T. C., Yang, G., Wu, J., Cassey, P., Brown, S. D., Hoang, N., Chan, M., Connolly, C. G., Henje-Blom, E., Duncan, L. G., Chesney, M. A., Paulus, M. P., Max, J. E., Patel, R., Simmons, A. N., & Yang, T. T. (2014). Functional

connectivity of negative emotional processing in adolescent depression. Journal of Affective Disorders, 155, 65–74. https://doi.org/10.1016/j.jad.2013.10.025

102. Jensen, K. B., Regenbogen, C., Ohse, M. C., Frasnelli, J., Freiherr, J., & Lundström, J. N. (2016). Brain activations during pain: A neuroimaging meta-analysis of patients with pain and healthy controls. Pain, 157(6), 1279–1286. https://doi.org/10.1097/j.pain.0000000000000517

103. Jung, Y. H., Shin, J. E., Lee, Y. I., Jang, J. H., Jo, H. J., & Choi, S. H. (2018). Altered amygdala resting-state functional connectivity and hemispheric asymmetry in patients with social anxiety disorder. Frontiers in Psychiatry, 9(APR), 164. https://doi.org/10.3389/FPSYT.2018.00164/BIBTEX

104. Kelly, E., Meng, F., Fujita, H., Morgado, F., Kazemi, Y., Rice, L. C., Ren, C., Escamilla, C. O., Gibson, J. M., Sajadi, S., Pendry, R. J., Tan, T., Ellegood, J., Basson, M. A., Blakely, R. D., Dindot, S. V., Golzio, C., Hahn, M. K., Katsanis, N., … Tsai, P. T. (2020). Regulation of autism-relevant behaviors by cerebellar–prefrontal cortical circuits. Nature Neuroscience, 23(9), 1102–1110. https://doi.org/10.1038/s41593-020-0665-z

105. Kim, J. H., Suh, S., Lee, H.-J., Lee, J., & Lee, M.-S. (2019). Cortical and subcortical gray matter alterations in first-episode drug-naïve adolescents with major depressive disorder. NeuroReport, 30(17), 1172–1178. https://doi.org/10.1097/WNR.0000000000001336

106. Kohls, G., Antezana, L., Mosner, M. G., Schultz, R. T., & Yerys, B. E. (2018). Altered reward system reactivity for personalized circumscribed interests in autism. Molecular Autism, 9(1), 9. https://doi.org/10.1186/s13229-018-0195-7

107. Large, M.-E., Aldcroft, A., & Vilis, T. (2007). Task-related laterality effects in the lateral occipital complex. Brain Research, 1128(1), 130–138. https://doi.org/10.1016/j.brainres.2006.10.023

108. Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. Frontiers in Human Neuroscience, 8. https://www.frontiersin.org/articles/10.3389/fnhum.2014.00302

109. Lawther, A. J., Hale, M. W., & Lowry, C. A. (2020). Chapter 29—Serotonin and the neurobiology of anxious states. In C. P. Müller & K. A. Cunningham (Eds.), Handbook of Behavioral Neuroscience (Vol. 31, pp. 505–520). Elsevier. https://doi.org/10.1016/B978-0-444-64125-0.00029-3

110. Li, X., Zhang, M., Li, K., Zou, F., Wang, Y., Wu, X., & Zhang, H. (2019). The Altered Somatic Brain Network in State Anxiety. Frontiers in Psychiatry, 10. https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00465

111. Lin, Y.-H., Young, I. M., Conner, A. K., Glenn, C. A., Chakraborty, A. R., Nix, C. E., Bai, M. Y., Dhanaraj, V., Fonseka, R. D., Hormovas, J., Tanglay, O., Briggs, R. G., & Sughrue, M. E. (2020). Anatomy and White Matter Connections of the Inferior Temporal Gyrus. World Neurosurgery, 143, e656–e666. https://doi.org/10.1016/j.wneu.2020.08.058

112. Lyons, V., & Fitzgerald, M. (2013). Atypical Sense of Self in Autism Spectrum Disorders: A Neuro- Cognitive Perspective. https://doi.org/10.5772/53680

113. Maróthi, R., Csigó, K., & Kéri, S. (2019). Early-Stage Vision and Perceptual Imagery in Autism Spectrum Conditions. Frontiers in Human Neuroscience, 13.

https://www.frontiersin.org/articles/10.3389/fnhum.2019.00337

114. Mazefsky, C. A., Herrington, J., Siegel, M., Scarpa, A., Maddox, B. B., Scahill, L., & White, S. W. (2013). The Role of Emotion Regulation in Autism Spectrum Disorder RH: Emotion Regulation in ASD. Journal of the American Academy of Child and Adolescent Psychiatry, 52(7), 679–688. https://doi.org/10.1016/j.jaac.2013.05.006

115. Mendez, M. F., Adams, N. L., & Lewandowski, K. S. (1989). Neurobehavioral changes associated with caudate lesions. Neurology, 39(3), 349–349. https://doi.org/10.1212/WNL.39.3.349

116. Mingins, J. E., Tarver, J., Waite, J., Jones, C., & Surtees, A. D. (2021). Anxiety and intellectual functioning in autistic children: A systematic review and meta-analysis. Autism, 25(1), 18–32. https://doi.org/10.1177/1362361320953253

117. Mosner, M. G., McLaurin, R. E., Kinard, J. L., Hakimi, S., Parelman, J., Shah, J. S., Bizzell, J., Greene, R. K., Cernasov, P. M., Walsh, E., Addicott, M. A., Eisenlohr-Moul, T., Carter, R. M., & Dichter, G. S. (2019). Neural Mechanisms of Reward Prediction Error in Autism Spectrum Disorder. Autism Research and Treatment, 2019, e5469191. https://doi.org/10.1155/2019/5469191

118. Mouga, S., Duarte, I. C., Café, C., Sousa, D., Duque, F., Oliveira, G., & Castelo-Branco, M. (2022). Parahippocampal deactivation and hyperactivation of central executive, saliency and social cognition networks in autism spectrum disorder. Journal of Neurodevelopmental Disorders, 14(1), 9. https://doi.org/10.1186/s11689-022-09417-1

119. Nebel, M. B., Eloyan, A., Barber, A. D., & Mostofsky, S. H. (2014). Precentral gyrus functional connectivity signatures of autism. Frontiers in Systems Neuroscience, 8, 80. https://doi.org/10.3389/fnsys.2014.00080

120. Philip, R. C. M., Whalley, H. C., Stanfield, A. C., Sprengelmeyer, R., Santos, I. M., Young, A. W., Atkinson, A. P., Calder, A. J., Johnstone, E. C., Lawrie, S. M., & Hall, J. (2010). Deficits in facial, body movement and vocal emotional processing in autism spectrum disorders. Psychological Medicine, 40(11), 1919–1929. https://doi.org/10.1017/S0033291709992364

121. Posner, M. I., Rothbart, M. K., Sheese, B. E., & Tang, Y. (2007). The anterior cingulate gyrus and the mechanism of self-regulation. Cognitive, Affective, & Behavioral Neuroscience, 7(4), 391–395. https://doi.org/10.3758/CABN.7.4.391

122. Sapey-Triomphe, L.-A., Temmerman, J., Puts, N. A. J., & Wagemans, J. (2021). Prediction learning in adults with autism and its molecular correlates. Molecular Autism, 12(1), 64. https://doi.org/10.1186/s13229-021-00470-6

123. Schutter, D. J. L. G., & van Honk, J. (2009). The cerebellum in emotion regulation: A repetitive transcranial magnetic stimulation study. Cerebellum (London, England), 8(1), 28–34. https://doi.org/10.1007/s12311-008-0056-6

124. Travers, B. G., Kana, R. K., Klinger, L. G., Klein, C. L., & Klinger, M. R. (2015). Motor learning in individuals with autism spectrum disorder: Activation in superior parietal lobule related to learning and repetitive behaviors. Autism Research: Official Journal of the International Society for Autism Research, 8(1), 38–51. https://doi.org/10.1002/aur.1403

125. Tremblay, P., & Dick, A. S. (2016). Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain and Language, 162, 60–71. https://doi.org/10.1016/j.bandl.2016.08.004

126. Uddin, L. Q. (2011). The self in autism: An emerging view from neuroimaging. Neurocase, 17(3), 201–208. https://doi.org/10.1080/13554794.2010.509320

127. Uddin, L. Q., Nomi, J. S., Hebert-Seropian, B., Ghaziri, J., & Boucher, O. (2017). Structure and function of the human insula. Journal of Clinical Neurophysiology : Official Publication of the American Electroencephalographic Society, 34(4), 300–306. https://doi.org/10.1097/WNP.0000000000000377

128. Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: Predictive coding in autism. Psychological Review, 121(4), 649–675. https://doi.org/10.1037/a0037665

129. van Noordt, S., Wu, J., Venkataraman, A., Larson, M. J., South, M., & Crowley, M. J. (2017). Inter-trial Coherence of Medial Frontal Theta Oscillations Linked to Differential Feedback Processing in Youth and Young Adults with Autism. Research in Autism Spectrum Disorders, 37, 1–10. https://doi.org/10.1016/j.rasd.2017.01.011

130. Vasa, R. A., & Mazurek, M. O. (2015). An update on anxiety in youth with autism spectrum disorders. Current Opinion in Psychiatry, 28(2), 83–90. https://doi.org/10.1097/YCO.0000000000000133

131. Via, E., Calvo, A., de la Serna, E., Blázquez, A., Lázaro, L., Andrés-

Perpiñá, S., Plana, M. T., Flamarique, I., Martínez, E., Pariente, J., Moreno, E., Bargallo, N., & Castro-Fornieles, J. (2021). Longitudinal study in adolescent anorexia nervosa: Evaluation of cortico-striatal and default mode network resting-state brain circuits. European Child & Adolescent Psychiatry. https://doi.org/10.1007/s00787-021-01880-w

132. Wallis, J. D. (2019). Chapter 15—Reward. In M. D'Esposito & J. H. Grafman (Eds.), Handbook of Clinical Neurology (Vol. 163, pp. 281–294). Elsevier. https://doi.org/10.1016/B978-0-12-804281-6.00015-X

133. Wang, Q., Chang, J., & Chawarska, K. (2020). Atypical Value-Driven Selective Attention in Young Children With Autism Spectrum Disorder. *JAMA Network Open*, *3*(5), e204928. https://doi.org/10.1001/jamanetworkopen.2020.4928