Resting State fMRI in ASD

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Autism spectrum disorder (ASD) is characterized by a fundamental change in self-awareness including seemingly paradoxical features like increased ego-centeredness and weakened self-referentiality.

mental-self self-reference autism spectrum disorder default-mode network predictive coding weaken central coherence theory of mind

1. Introduction

Autism spectrum disorder (ASD) is a complex psychiatric condition that is characterized by multiple symptoms. Cognitive symptoms like changes in autobiographical/episodic memory [1][2][3][4] are coupled with deficits in social cognition as in theory of mind [5][6][7], affective changes including emotion, empathy, and facial expression [8][9][10], hypersystemizing [11], motor symptoms like difficulty of action imitation [12][13][14], stereotypies and repetitions [15][16][17], and multimodal sensory integration [18][19][20][21][22]. Yet, on a deeper level beneath the various functions, an altered sense of self, i.e., self-awareness, has been described and is a key disturbance of autism [23].

In their original descriptions of autism, Kanner (1943) and Asperger (1944) point out a fundamental or basic disturbance of self: the self in ASD is only himself and self-sufficient [24] and feels neither an integral part of the world nor stands in a lively dynamic relationship with its environment [25]. More recently, Lombardo and Baron-Cohen (2010, 2011) highlighted what they describe as “paradox of self” in ASD [23][26] (see also [27][28][29]). On the one hand, the autistic self is highly centered on itself, showing an abnormally high degree of ego-centeredness as manifest in social isolation and loneliness, inability to read the emotions, feelings, and facial expressions of others [30][31][32], and major deficits in social cognition like theory of mind [5][6][7]. Such high ego-centeredness is, on the other hand, contrasted by weak self-referentiality with decreased use of “I” in language [33][34][35], no mention of own internal states, e.g., own emotion [10][36][37], own theory of mind [27][38][39], changes in time processing like duration estimation of shorter and longer time intervals as deficits in connecting different time points [40][41][42], decreased introspection [43][44], decrease in interoception [45][46][47], and reduced autobiographical memory [1][2][3][4] (see though Markram and Markram, 2012 [48], as well as Lind et al., 2020 [49]).

How is it possible that seemingly two contradictory features like increased ego-centeredness and decreased self-referentiality can co-occur within one and the same person’s self? Lombardo and Baron-Cohen (2010) assume a shared deficit in the neural circuitry that encodes self-representation, including self–other distinction and self–other awareness [26]. Various imaging studies, most often using fMRI, investigated self-reference in ASD. They observed changes in various anterior and posterior regions of the default-mode network (DMN) and outside the DMN during self-referential tasks (see below). At the same time, resting state abnormalities could also be observed in anterior and posterior DMN (and also non-DMN) of ASD, which again showed major changes in DMN (see for recent review Lau et al., 2020 [50] and below). Given that various findings in healthy subjects indicate neural overlap of self and DMN resting state [51][52][53][54][55][56], one may assume a close relationship of resting state and self-specific task-related changes in DMN of ASD. The goal of the present paper is to review recent fMRI findings in ASD during both rest and self-referential task states in order to reconcile the seemingly features of increased ego-centeredness and decreased self-referentiality.

A recent meta-analytic study on the self in healthy subjects suggests a multilayered nested hierarchical model of self with interoceptive self, exteroceptive self, and mental self: neural correlates range from subcortical regions and insula (interoceptive self) over medial prefrontal cortex and temporo-parietal junction (TPJ) (exteroceptive self) to anterior and posterior DMN (mental self) [57][58].

2. Task fMRI in ASD: Task-Related Neural Activity and Functional Connectivity during Self

A total of 19 studies evaluated the neural activity with self-specific tasks in individuals with ASD. Among these studies, 16 studies focused on the psychological self (7 studies with the self-reference task, 2 studies with social reward task, 3 studies with emotional task, and 4 studies with episodic memory task), while the other studies focused more on the physical self (1 study about heartbeat and 2 studies with self-body recognition task) (Table 1). Across these different tasks, decreased activation in DMN regions during self-specific tasks/stimuli was reported, with a particular emphasis on reduction in medial prefrontal cortex (MPFC) (including ventral medial prefrontal cortex (vMPFC) and dorsal medial prefrontal cortex (dMPFC)), anterior cingulate cortex (ACC), media cingulate cortex (MCC), and inferior parietal lobule (IPL) (Figure 1a–f). In contrast to the anterior midline regions, findings in posterior cingulate cortex (PCC)and precuneus (PCUN) are not as consistent among different studies and tasks: decreased activity was observed during the emotional recognition tasks in ASD, whereas they did not show any abnormalities in these regions during the self-reference task (Figure 1b).

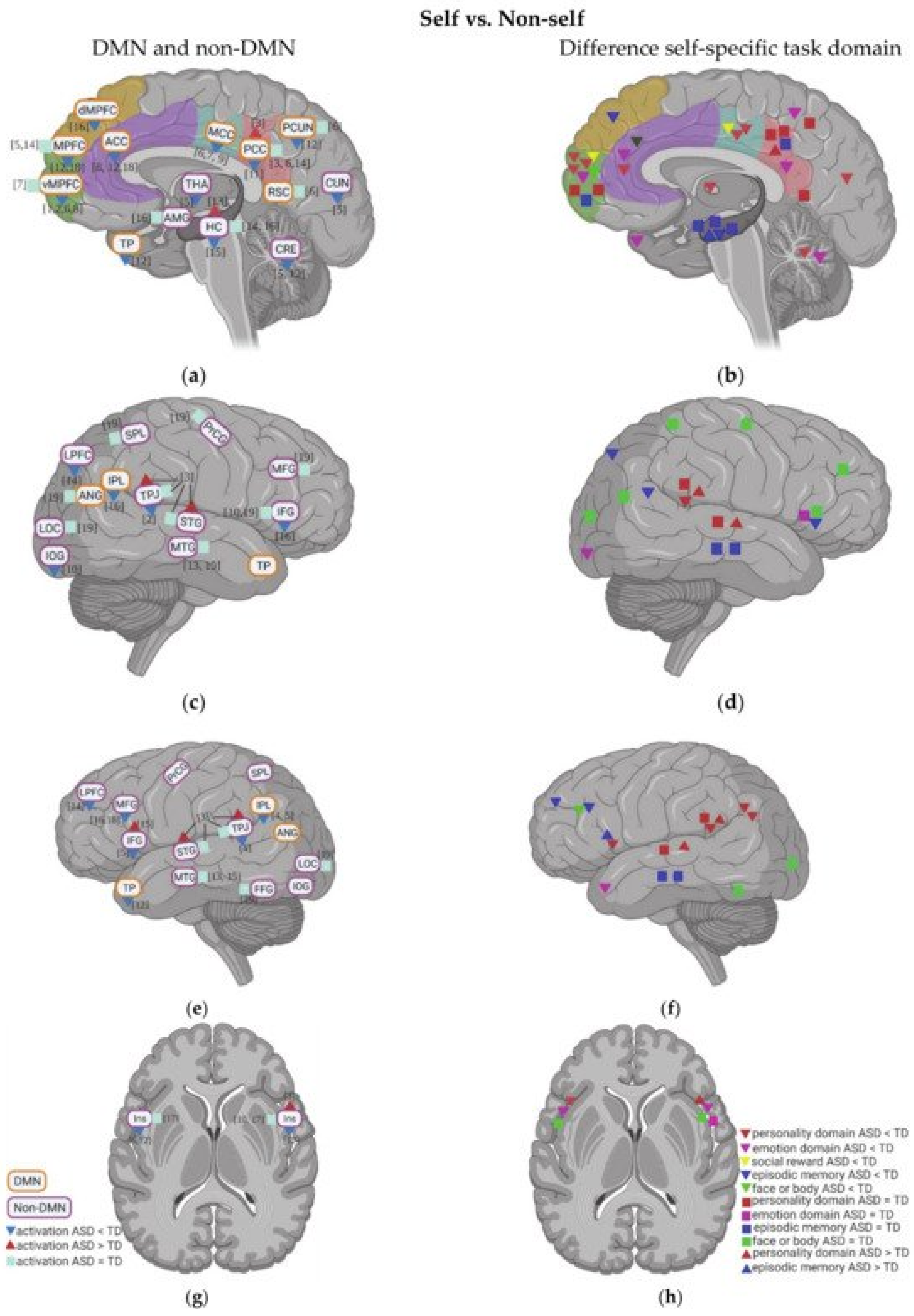

Figure 1. Activation of DMN and non-DMN regions for individuals with ASD compared to TD during self-specific tasks in different studies (left side) and different domains (right side): (**a**,**b**) DMN, subcortical regions and cerebellum (CRE); (**c**,**d**) related regions in right lateral hemisphere; (**e**,**f**) related regions in left lateral hemisphere; (**g**,**h**) insula (Ins). The numbers in the figure correspond to the study numbers in Table 1.

In non-DMN regions, hypoactivity of cerebellum (CRE) and middle frontal gyrus (MFG) is reported for individuals with ASD compared to TD in a few studies (Figure 1c–f). Contradictory results were found for the activity of inferior frontal gyrus (IFG) (Figure 1c–f), TPJ (Figure 1c–f), insula, and hippocampus (HC) across different tasks (Figure 1g,h).

Few studies also evaluated the task-related deactivation of DMN in ASD. In anterior regions of DMN, individuals with ASD show either reduced deactivation (e.g., vMPFC, MPFC, and ACC) or "normal" levels of deactivation (e.g., ACC and dMPFC). Although one study reports reduced deactivation in PCC and PCUN in ASD, two studies could now show group difference in deactivation of PCC, PCUN, and retrosplenial cortex (RSC) (Figure 2a).

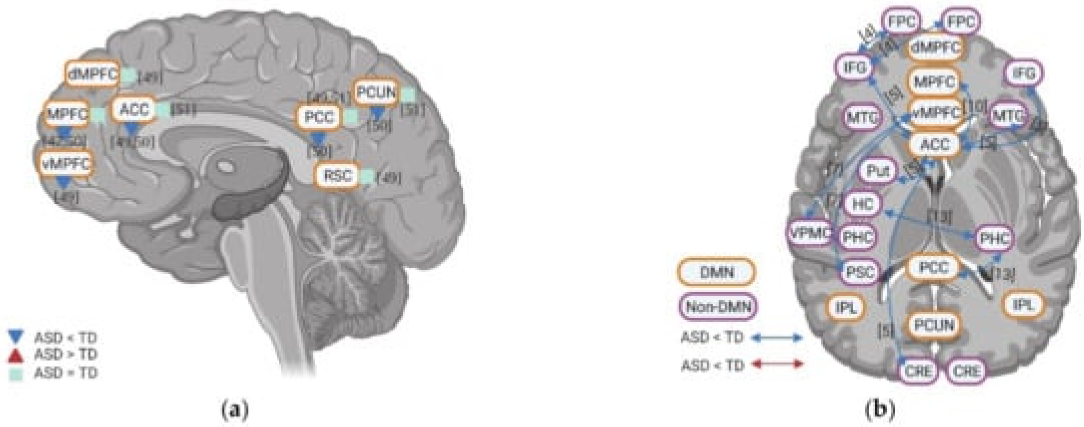

Figure 2. (**a**) Deactivation of DMN for individuals with ASD compared to TD during self-specific tasks in contrast with resting states. The numbers in the figure correspond to the study numbers in Table 2. (**b**) Functional connectivity within DMN and between DMN and non-DMN regions for individuals with ASD compared to TD during self-specific tasks. The numbers in figure correspond to the study numbers in Table 1.

Finally, few studies investigated the functional connectivity among different brain regions during self-specific tasks. With the few results available, hypoconnectivity between DMN regions (e.g., vMPFC, ACC, and PCC) and non-DMN regions (e.g., IFG, medial temporal gyrus (MTG), CRE, putamen (Put), parahippocampal cortex (PHC), ventral premotor cortex (VPMC), and primary somatosensory cortex (PSC)), as well as within the DMN itself (e.g., MPFC-ACC) were reported (Figure 2b).

Taking together, unlike the inconsistent results of most of the non-DMN regions, individuals of ASD show decreased activity, i.e., amplitude or magnitude in DMN, especially in the anterior parts across different self-specific tasks, i.e., domain-general. Decreased self-specific activity in these regions is further supported by observations that individuals of ASD also exhibit reduced deactivation and hypoconnectivity within DNM and of DMN with non-DMN regions during various self-specific tasks.

3. Resting State fMRI in ASD: Resting State Functional Connectivity (rsFC) within DMN

The fMRI studies investigating rsFC in individuals with ASD highlight abnormal activity within DMN. Although few studies showed hyperconnectivity of dMPFC with RSC and right IPL, left temporal pole (TP) with RSC and PCC, a decrease in rsFC between anterior DMN (e.g., MPFC/vMPFC and ACC) and posterior DMN (e.g., PCC, PCUN, and IPL) is a consistent finding across various studies (Figure 3a,b). Within anterior DMN regions, hypoconnectivity among vMPFC, dMPFC, ACC, and bilateral TP was observed, with the exception of one of study that reported hyperconnectivity between the MPFC and ACC (Figure 3a,b). Within the posterior DMN regions, both hypoconnectivity and hyperconnectivity between PCC and PCUN, PCC and bilateral IPL, and PCUN and bilateral IPL has been observed by a few studies, while decreased rsFC was reported between RSC and PCC, PCUN in one study. When it comes to the whole-brain rsFC, both anterior and posterior DMN regions show decreased rsFC (with only one study showing increased rsFC in ACC and PCC) (Figure 3c).

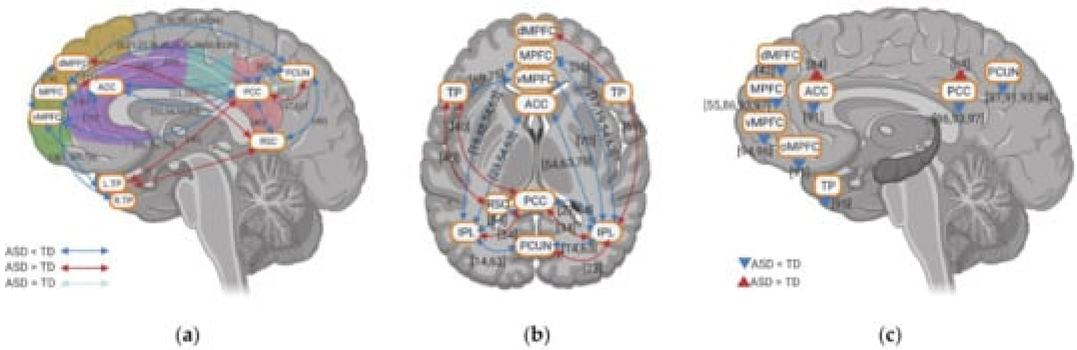

Figure 3. Inter-regional functional connectivity (**a**,**b**) and whole-brain resting state functional connectivity (**c**) of DMN for individuals with ASD compared to TD. The numbers in the figure correspond to the study numbers in Table 2.

Unlike the results of static rsFC, the few studies on dynamic rsFC show contradictory rsFC results between anterior DMN (vMPFC and ACC) and posterior DMN (PCC and PCUN) in ASD including weaker, equal, and stronger rsFC, respectively (Figure 4a). A few studies investigating the dynamic whole-brain rsFC of DMN also report contradictory results, with two studies showing increased rsFC and two studies reporting decreased rsFC for individuals with ASD. More consistent is a decrease of dynamic rsFC within anterior DMN (e.g., vMPFC, ACC, and TP) in ASD (Figure 4a).

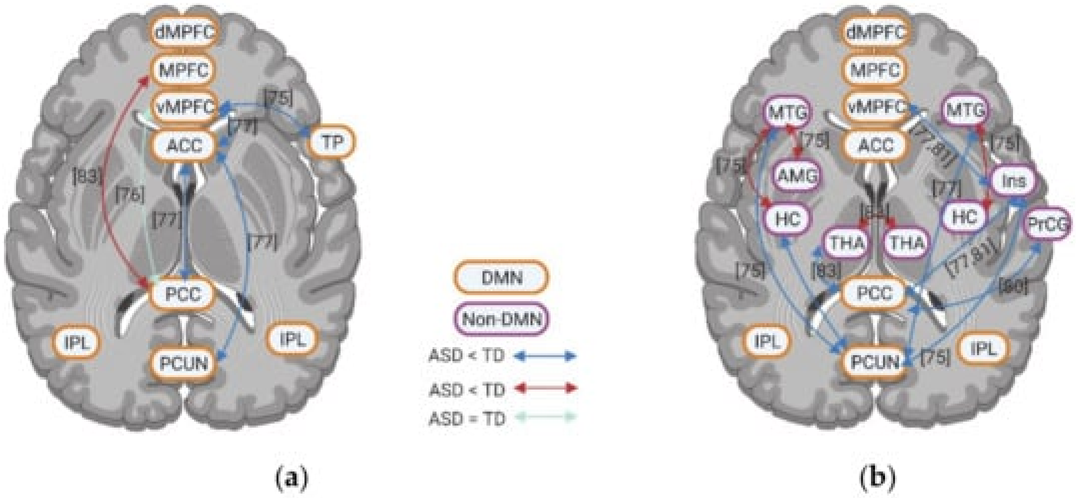

Figure 4. Dynamic functional connectivity between regions within DMN regions (**a**) as well as between DMN and non-DMN regions (**b**) for individuals with ASD compared to TD. The numbers in the figure correspond to the study numbers in Table 2.

Overall, individuals with ASD show decreased static rsFC between anterior DMN and posterior DMN as well as reduced whole-brain hypoconnectivity of the DMN. In contrast, results on dynamic rsFC are more inconsistent, though they consistently also show decreased variability in anterior DMN rsFC.

4. Resting State fMRI in ASD: Resting State Functional Connectivity between DMN and Non-DMN

The various resting state fMRI studies examined also underline altered rsFC between DMN and non-DMN regions in individuals with ASD. In the lateral frontal regions (Figure 5a,b), superior frontal gyrus (SFG) especially in the right hemisphere is reported to have altered rsFC with posterior DMN (e.g., PCC, PCUN, and IPL) with a tendency towards hypoconnectivity: six studies report decreased rsFC, while three studies observed increased rsFC. IFG showed hyperconnectivity with posterior DMN (e.g., PCC, PCUN, and RSC), and MFG also exhibited predominant increased rsFC with posterior DMN: three studies show increased rsFC and two studies report decreased rsFC. Unlike posterior DMN, there are less studies investigating the rsFC between anterior DMN and lateral frontal regions. For IFG, weaker rsFC with anterior DNM was found in two studies while stronger rsFC was found in one study. For SFG, both decreased and increased rsFC with anterior DMN were found in one study. In temporal lobe (TL) (Figure 5a,b), studies reported hyperconnectivity with PCC when considering TL as whole region. However, different subregions of temporal lobe showed distinct rsFC patterns with posterior DMN. Hypoconnectivity was observed for superior temporal gyrus (STG) with PCUN and IPL, MTG with PCUN and IPL, and inferior temporal gyrus (ITG) with PCC, whereas hyperconnectivity was reported for fusiform gyrus (FFG) with PCC. As opposed to the posterior DMN, the anterior DMN, especially the MPFC/vMPFC, exhibits relatively consistent hypoconnectivity with temporal lobe subregions, including decreased rsFC for the whole TL, a decrease in rsFC for STG, and weaker rsFC for MTG, but also sees increased rsFC MTG. There is also hypoconnectivity of TPJ with both anterior, i.e., MPFC, and posterior DMN, i.e., PCC, PCUN, and IPL (Figure 5c). Finally, bilateral insula was observed to have decreased rsFC with anterior DMN (MPFC and ACC) and increased rsFC with posterior DMN (PCC, RSC and IPL); there is also higher rsFC with PCUN (Figure 5c).

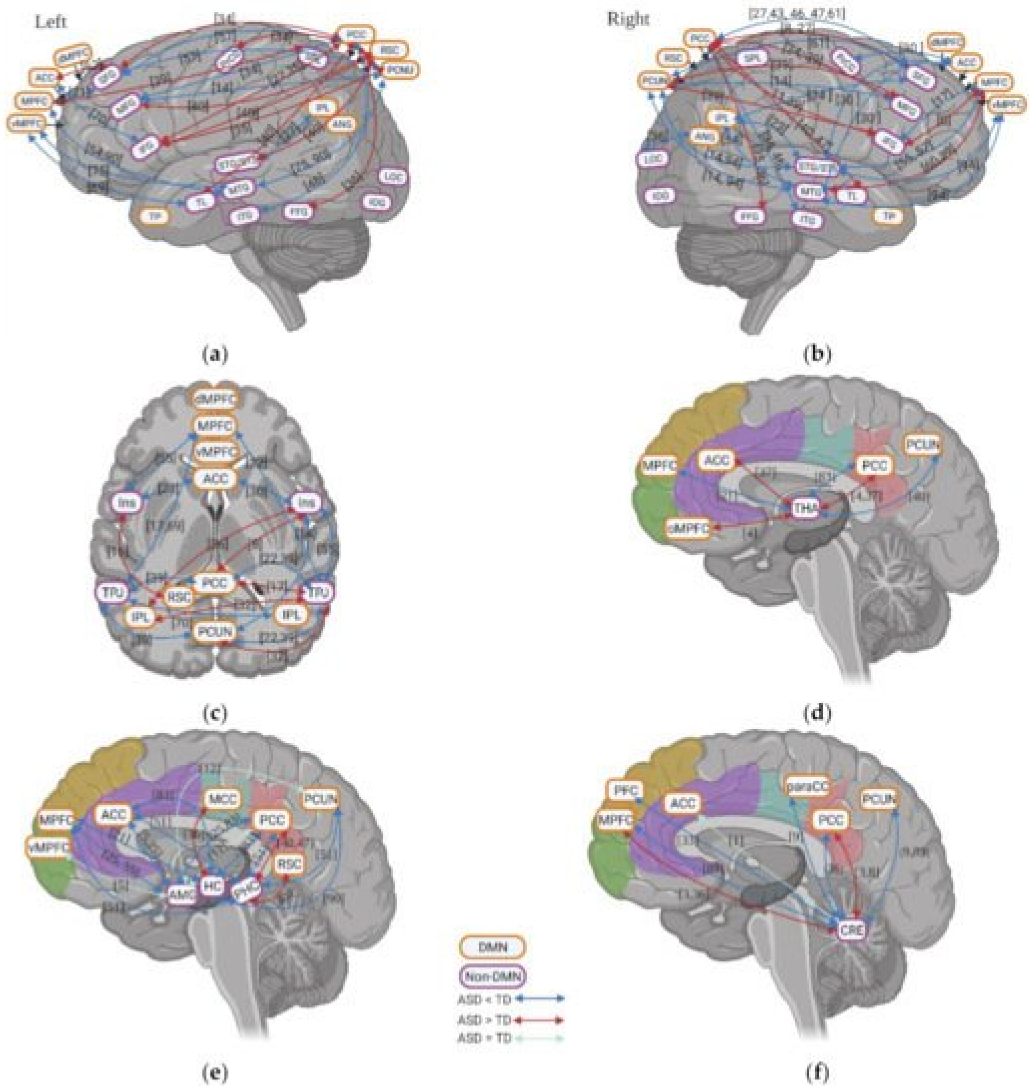

Figure 5. Functional connectivity between DMN and non-DMN regions for individuals with ASD compared to TD. In this figure, (**a**,**b**) shows the functional connectivity between DMN and non-DMN regions in left and right hemisphere; (**c**) shows functional connectivity between DMN and Insular (Ins), temporo-parietal junctions (TPJ); (**d**) shows the functional connectivity between thalamus (THA) and DMN; (**e**) shows the functional connectivity between DMN and amygdala (AMG), hippocampus cortex (HC), and parahippocampal cortex (PHC); (**f**) shows the functional connectivity between cerebellum (CRE) and DMN. The numbers in the figure correspond to the study numbers in Table 2.

Compared to the static rsfMRI studies, dynamic rsfMRI studies showed relatively consistent weaker rsFC of DMN, especially the posterior DMN with cortical non-DMN regions, i.e., MTG, precentral gyrus (PrCG), and insula (Figure 4b).

In general, individuals with ASD showed decreased rsFC between SFG and posterior DMN regions as well as hypoconnectivity of STG, MTG, ITG, TPJ, and insular with both anterior and posterior DMN during resting states. Weaker dynamic rsFC of DMN with non-DMN regions was also found for individuals with ASD. However, they had predominant hyperconnectivity of IFG, MFG, and FFG with posterior DMN during resting states.

5. Resting State fMRI in ASD: Subcortical–Cortical Resting State Functional Connectivity

Subcortical regions also had changes in their rsFC with DMN. The amygdala (AMG) exhibits hypoconnectivity with both anterior (e.g., MPFC and ACC) and posterior DMN (e.g., PCC) for individuals with ASD; although some studies did not show any group difference (Figure 5e). Similar to AMG, HC shows weaker rsFC both with anterior (e.g., MPFC and ACC) and with posterior DMN (e.g., PCC and PCUN) with the exception of higher rsFC with MCC (Figure 5e). However, PHC exhibits decreased rsFC with anterior DMN whereas it showed increased rsFC with posterior DMN (e.g., PCC and RSC) (Figure 5e). Few studies focused on thalamus (THA) rsFC with DMN and showed contradictory results: two studies observed increased rsFC with ACC/orbital MPFC and PCC, while one reports decreased rsFC with MPFC, PCC, and PCUN (Figure 5d). Furthermore, the cerebellum was observed to have increased rsFC with MPFC and PCC, whereas it shows decreased rsFC with PCUN (Figure 5f). Finally, in contrast to the static rsfMRI studies, dynamic rsfMRI studies showed relatively consistent weaker rsFC of DMN, especially the posterior DMN with subcortical regions, i.e., HC and THA (Figure 4b).

In sum, AMG and HC show hypoconnectivity with both anterior and posterior DMN in static and dynamic rsFC. In contrast, the CRE exhibits predominant hyperconnectivity with DMN during resting states. The THA shows a contradictory rsFC pattern across the studies.

6. Resting State fMRI in ASD: ALFF and REHO in DMN Regions

Few studies investigated the intraregional resting state activity using amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo), in individuals with ASD compared to TD controls. In these studies, relatively consistent results of the intraregional activity of the DMN were reported. Anterior DMN regions (e.g., MPFC, ACC, and TP) have reduced activity in ReHo. Meanwhile, although two studies reported hyperactivity in PCUN in ReHo, the posterior DMN regions (e.g., PCC and PCUN) show decreased activity in both ALFF and ReHo in ASD (Figure 6). In general, findings show decreased intraregional resting state activity in anterior and posterior DMN regions in ASD.

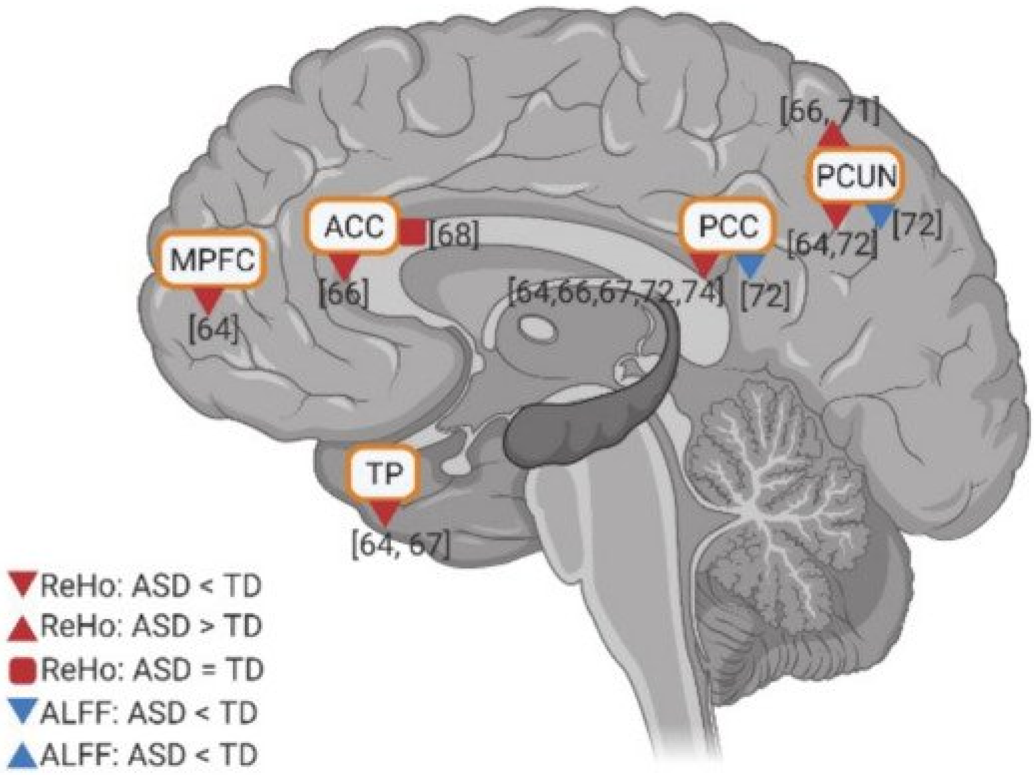

Figure 6. Intraregional resting state activity (ALFF and REHO) in DMN for individuals with ASD compared to TD. The numbers in the figure correspond to the study numbers in Table 2.

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