Effective Connectivity in Autism

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Abstract

The aim was to go beyond functional connectivity, by measuring in the first large-scale study differences in effective, that is directed, connectivity between brain areas in autism compared to controls. Resting state fMRI was analyzed from the Autism Brain Imaging Data Exchange (ABIDE) dataset in 394 people with autism spectrum disorder and 473 controls, and effective connectivity was measured between 94 brain areas. First, in autism the middle temporal gyrus and other temporal areas had lower effective connectivities to the precuneus and cuneus, and these were correlated with the ADOS total, communication, and social scores. This lower effective connectivity from areas implicated in face expression analysis and theory of mind to the precuneus and cuneus implicated in the sense of self may relate to the poor understanding of the implications of face expression inputs for oneself in autism, and to the reduced theory of mind. Second, the hippocampus and amygdala had higher effective connectivity to the middle temporal gyrus in autism, and these are thought to be backprojections based on anatomical evidence, and are weaker than in the other direction. This may be related to increased retrieval of recent and emotional memories in autism. Third, some prefrontal cortex areas had higher effective connectivity with each other and with the precuneus and cuneus. Fourth, there was decreased effective connectivity from the temporal pole to the ventromedial prefrontal cortex, and there was evidence for lower activity in the ventromedial prefrontal cortex, a brain area implicated in emotion-related decision-making.

Lay summary

To understand autism spectrum disorders better, it may be helpful to understand whether brain systems cause effects on each other differently in people with autism. In this first large scale neuroimaging investigation of effective connectivity in people with autism, it is shown that parts of the temporal lobe involved in face expression identification and theory of mind have weaker effects on the precuneus and cuneus implicated in the sense of self. This may relate to the poor understanding of the implications of face expression inputs for oneself in autism, and to the reduced theory of mind.

Introduction

Autism spectrum disorder (ASD) is a complex developmental disorder that is characterized by difficulties in social communication and social interaction; and restricted and repetitive behavior, interests, or activities (Lai, Lombardo, & Baron-Cohen, 2014). Recently, a great deal of attention has been focused on the delineation of neural systems for brain–behavior relationships in ASD given that ~1% of children are being diagnosed with this disorder (Kim et al., 2011). At the brain circuit level, resting state fMRI studies are contributing to our understanding of brain systems related to autism (Hull et al., 2016; Maximo, Cadena, & Kana, 2014). These studies have suggested abnormality in connectivity between a group of related and partly overlapping brain systems characterized as face processing areas (Cheng, Rolls, Gu, Zhang, & Feng, 2015; Koshino et al., 2008), the default mode network (Padmanabhan, Lynch, Schaer, & Menon, 2017), social brain circuits (Gotts et al., 2012), theory of mind areas (Cheng et al., 2015), self-representation circuitry (Cheng et al., 2015; Lombardo et al., 2010), reward circuitry (Dichter et al., 2012), the salience network (Uddin et al., 2013), and a motor control network (Kenet et al., 2012). In a recent large-scale study (418 people with autism and 509 controls), a key system in the middle temporal gyrus / superior temporal sulcus (STS) region which is implicated in the face expression processing and theory of mind involved in social behavior had reduced functional connectivity with the ventromedial prefrontal cortex which is implicated in emotion and social communication (Cheng et al., 2015). A second key system in the precuneus / superior parietal lobule region which is implicated in spatial functions including of oneself, and of the spatial environment, also had reduced functional connectivity in autism (Cheng et al., 2015).

Resting state functional connectivity, which reflects correlations in the activity between brain areas, is widely used to help understand human brain function in health and disease (Cheng et al., 2016; Deco & Kringelbach, 2014). Here we go beyond functional connectivity to effective connectivity between different brain areas to measure directed influences of human brain regions on each other. Effective connectivity is conceptually very different, for it measures the effect of one brain region on another in a particular direction, and can in principle therefore provide information more closely related to the causal processes that operate in brain function, that is, how one brain region influences another. In the context of disorders of brain function, the effective connectivity may provide evidence on which brain regions may have altered function, and then influence other brain regions, by comparing effective connectivity in individuals with autism and control participants. Effective connectivity is also more powerful, in that it provides a generative model for brain dynamics dynamics – a model that can also generate functional connectivity data features.

In this research we utilize an approach to the measurement of effective connectivity in which each brain area has a simple dynamical model, and known anatomical connectivity is used to provide constraints (Gilson et al., 2018; Gilson, Moreno-Bote, Ponce-Alvarez, Ritter, & Deco, 2016; Rolls et al., 2019; Rolls et al., 2018). This helps the approach to measure the effective connectivity between the 94 automated anatomical atlas (AAL2) (Rolls, Joliot, & Tzourio-Mazoyer, 2015) brain areas using resting state functional magnetic resonance imaging. (The names of the AAL2 areas are shown in Table S1, and the areas can be viewed with the Mricron viewer.) For this we used a large number of autistic people and controls, and were able to use for this analysis data in a large resting state fMRI dataset, the autism brain imaging data exchange (ABIDE http://fcon_1000.projects.nitrc.org/indi/abide/), which has already proved useful (Di Martino et al., 2014).

Methods

Participants

The Autism Brain Imaging Data Exchange (ABIDE) repository is hosted by the 1000 Functional Connectome Project/International Neuroimaging Data-sharing Initiative (INDI) (http://fcon_1000.projects.nitrc.org), and consists of data sets for 1112 individuals (ABIDE I), comprised of 539 individuals with autism and 573 typically developing controls. All data are fully anonymized in accordance with Health Insurance Portability and Accountability (HIPAA) guidelines. All data released were visually inspected by members of the ABIDE project. Details of diagnostic criteria, acquisition, informed consent, and site-specific protocols are available at:

http://fcon_1000.projects.nitrc.org/indi/abide/.

The inclusion criteria for sample selection include: (1) functional MRI data were successfully preprocessed with manual visual inspection of normalization to MNI space; (2) any data with a mean framewise displacement exceeding 0.5mm were excluded; (3) subjects were excluded if the percentage of 'bad' points (framewise displacement>0.5mm) was over 0.35 in volume censoring; (4) data collection centres were only included if they have at least 19 individuals and they have the IQ of the individuals recorded. After quality control, a total of 867 subjects (394 people with autism, and 473 controls) met all inclusion criteria. The demographic and clinical characteristics of participants satisfying the inclusion criteria are summarized in Supplementary Table S2.

Effective connectivity measurement

Neuroimaging preprocessing was performed with standard techniques by the Preprocessed Connectomes Project (http://preprocessed-connectomes-project.github.io/abide/index.html). No temporal band-pass filtering was applied. This ensures that fast fluctuations in the signal remained available for an efficient connectivity analysis (but the linear drifts in the BOLD signal timeseries were regressed out to remove any linear trends in the data). After preprocessing, the whole brain (gray matter) was parcellated into 94 regions of interest (ROI) using the AAL2 atlas (Rolls et al., 2015) which includes a useful parcellation of the orbitofrontal cortex. The time series were extracted in each ROI by averaging the signals of all voxels within that region. The names of the ROIs are listed in Supplementary Table 1.

We used a method that provides efficient calculation of maximum-likelihood Effective Connectivity (EC) estimates for a large number (94) of nodes (Gilson et al., 2018; Gilson et al., 2016; Rolls et al., 2019; Rolls et al., 2018). The method uses transitions of fMRI measurements across successive repetition times (volumes) and takes into account known anatomical connections. The effective connectivity model captures and uses this information via the covariances with nonzero time shifts. Both the EC in the model and the local input variance in a parameter Σ are optimized such that the model best reproduces statistics of the observed fMRI signals. The resting state analysis described here can be thought of as probing the connectivities between brain regions by analyzing the effects on the system of perturbations produced by noise related to the random spiking times of neurons (Rolls & Deco, 2010). A description of the EC method follows, and full details of the EC method and statistical analysis are provided in the Supplementary Material.

A classical approach to measuring effective connectivity is dynamic causal modelling (DCM) (Bajaj, Adhikari, Friston, & Dhamala, 2016; Friston, 2009; Valdes-Sosa, Roebroeck, Daunizeau, & Friston, 2011). DCM is often used with circuits consisting of a-priori selected brain regions to test hypotheses on the interactions between the considered regions. Here we instead use a network model with simpler assumptions than those typically used in DCM to perform a large scale connectivity analysis involving many brain areas (Gilson et al., 2016). This allows for the very efficient calculation of maximum-likelihood EC estimates for a large number (94) of nodes, individually for a large cohort of participants. In this way we target significant EC differences for all existing connections (as determined by DTI) that characterize autism with FDR correction and without preliminary knowledge, expecting a distributed pattern of abnormal EC links across the brain. Our estimation procedure (Gilson et al., 2016) iteratively optimizes a network model such that it reproduces the empirical cross-covariances between ROIs, which are canonically related to the cross spectral density used in recent studies that apply DCM to resting state fMRI data (Friston, Kahan, Biswal, & Razi, 2014; Razi et al., 2017). Our model uses an exponential approximation of BOLD autocovariance (locally over a few TRs) and discards very slow-frequency fluctuations. Because we are dealing with broadband (slow) fluctuations in neuronal signals, we can simplify our modelling of effective connectivity by using an adiabatic approximation (in which we can ignore the effects of the haemodynamic response function) and treat the measured signals as a direct reflection of underlying neuronal activity. Finally, we place positivity constraints on extrinsic or between node connections - in line with known neuroanatomy and previous modeling studies (Marreiros, Kiebel, & Friston, 2008), for the reasons described below. A last simplification compared to DCM includes a fixed (but plausible) form of endogenous neuronal fluctuations (Σ – i.e. sigma in our model) that were characterized by a single (variance) parameter in each region or node. In spite of these differences, we still borrow the term "effective connectivity" from the DCM literature as our connectivity estimates relate to directional interactions between ROIs in the brain network. This model-based approach has been successfully applied to identify changes in the cortical coordination between rest and movie viewing (Gilson et al., 2018), and to effective connectivity in depression (Rolls et al., 2018) and in schizophrenia (Rolls et al., 2019).

Compared to DCM the new method used here (Gilson et al., 2016) is computationally more efficient and thus can analyze larger networks because it limits the degrees of freedom for each brain region by utilizing a simpler model of each brain region, and because it uses some structural connectivity information from for example diffusion tensor imaging to reduce the number of nodes between which effectivity connectivity needs to be computed. Further, the new effective connectivity method focuses on transitions between fMRI "activity states" across successive time points (Mitra, Snyder, Tagliazucchi, Laufs, & Raichle, 2015) and does not include details about hemodynamics like the Balloon model (Friston, Mechelli, Turner, & Price, 2000). The estimated effective connectivity measures the strengths of causal interactions from one brain area to another, via the proxy of BOLD fluctuations: it provides a single number that lumps together the effects of the strength of the synapse, and neurotransmitter release, etc. The synaptic conductivity interpretation also relates to our earlier neuron-level models in which the synaptic conductivity between modules is a key parameter that specifies how much one module influences another module (Rolls, Webb, & Deco, 2012). The new method has the additional advantage that each brain region or module has its own Σ parameter which specifies the variance of the module's activity, which may be related to the intrinsic excitability of the region. In relation to our integrate-and-fire models, the parameter *w+* that defines the strength of the recurrent collateral synapses within the attractor network (Rolls, 2016; Rolls & Deco, 2010; Rolls et al., 2012) may relate to the Σ parameter in the current effective connectivity approach (Gilson et al., 2016), because the local feedback influenced by w+ influences the fluctuations of the activity, for example how readily an area will transition to a high firing rate state. That is, Sigma corresponds in the model to the spontaneous activity (its variance) of a region, and this propagates via the effective connectivities to the other nodes in the recurrent network. A higher value for Sigma relative to controls indicates more fluctuating activity, which could reflect an increase of activity.

The effective connectivity model and algorithm used here is closely related to the linearized version of the dynamic causal model (DCM) that is used for the resting state (Frassle et al., 2017; Friston et al., 2014) and for task-related fMRI (Gilson et al., 2018). Although the hemodynamics of the filtering is modeled for DCM, the complex nonlinearity is simplified in the effective connectivity algorithm used here (Gilson et al., 2016), which enables it to be applied to a whole-brain parcellation with many nodes (in this case, the 94 nodes of the AAL2 atlas). Instead of the model comparison used by DCM to find the best network topology, the current algorithm uses structural data (from DTI) to specify possible connections in the model, thereby simplifying the operation of the model because some links with no known anatomical connection are excluded. (However, the algorithm settles similarly in practice with typical fMRI data even when these anatomical constraints are removed.) The implication is that significant differences of effective connectivity identified with this algorithm (here autism versus controls) are expected to reflect significant changes in the corresponding DCM. The results were thresholded at $p<0.05$, correcting multiple comparisons using False Discovery Rate (FDR, $q<0.05$).

Forward vs backward effective connectivity: The connections between adjacent cortical areas in a sensory hierarchy can usually be classified as forward (from the sensory input) vs backward (from an upper region in the hierarchy to the preceding region) (Rolls, 2016). Forward connectivity is often characterized by connections from layer 2-3 pyramidal cells forwards to layers 4, and 2 and 3, of the next cortical area. Backprojections between adjacent cortical areas in a hierarchy typically arise from the deep layers of the cerebral cortex, mainly layer 5, and project back mainly to layer 1 of the preceding cortical area (Markov et al., 2013; Markov et al., 2014a; Markov & Kennedy, 2013; Markov et al., 2014b; Rolls, 2016). Given the termination on the apical dendrites in layer 1, far from the cell bodies, the backward projections are generally found to be modulatory or weaker, relative to driving forward connections, with effects reducing the backprojecting efficacy including shunting on the dendrites produced by other inputs to pyramidal cells. It is also crucial for attention and memory recall that the top-down or backprojections are weaker than the forward connections, so that attentional biasing and memory recall does not dominate over bottom-up forward inputs (Deco & Rolls, 2005; Fuster, 2015; Rolls, 2016; Rolls & Deco, 2002; Turova & Rolls, 2019). In areas of the brain apart from sensory hierarchies there may also be similar asymmetries for systems level functional reasons, for example that short term memory processing in prefrontal cortical areas does not dominate perceptual processing in the temporal and parietal areas that utilize the prefrontal cortex for short-term memory (Goldman-Rakic, 1996). Because this asymmetry of the strength of the connectivity between brain regions is so important functionally, and usually has an anatomical basis, we conceptualize some of the effective connectivities analyzed in this investigation as forward or backward based on the strengths in each direction, as well as information about the anatomy of the different brain areas being connected (Rolls, 2016). It is at the same time the case that the effective connectivities can change to some extent based on whether sensory inputs vs memory recall (for example) is being performed, but nevertheless the forward and backward connectivity difference between many brain areas is large (as shown in the Results). In this paper, we refer to the strengths of the connectivities in each direction as 'stronger direction' or 'weaker direction', but the concepts in this paragraph provide some insight into how this may relate to cortical structure and function (Rolls, 2016).

Clinical correlates

We also investigated whether differences in effective connectivity (EC) among individuals with autism were correlated with symptoms assessed by the Autism Diagnostic Observational Schedule (ADOS) total, communication, social and stereotyped behavior scores. We used the Liptak-Stouffer z-score method (Liptak, 1958) to combine the data from the different neuroimaging sites for this analysis, for this provides a principled way to take into consideration possible differences in these measures between sites. Specifically, we calculated the partial correlation between the normalized effective connectivities and the clinical scores, with head motion, age, sex and IQ as covariates so that they did not contribute to the correlation between the ECs and the clinical scores, in each individual centre. Then we used the Liptak-Stouffer z-score method to combine the results from the individual datasets (Liptak, 1958).

Results

Differences of effective connectivity between individuals with autism and controls

Table 1 shows the top 41 links with the most significant differences in effective connectivity between individuals with autism and controls. Links are considered here if there was a significant difference for a link between individuals with autism and controls using FDR correction for multiple comparisons ($p<0.05$), for which the significance level must be $p<0.00081$. (In addition, to focus on links with a reasonable strength of effective connectivity that is likely to be meaningful in value (Rolls et al., 2019; Rolls et al., 2018) as well as significantly different in autism, links are shown if their effective connectivity value in either direction exceeds the threshold of 0.02 Hz.) Fig. 1 shows similar information in diagrammatic form, and includes all links that satisfy the two criteria just described. Fig. 2A shows these links between AAL2 nodes shown on views of the brain. Fig. 2B shows the main areas with on average increases or decreases in their effective connectivity directed to or from them in autism.

We now describe some of the main changes in effective connectivity in autism, using the summaries in Table 2, and also illustrated in Fig. 3. Table 2a summarises links *from* a brain region (region 1) that have different EC in autism, and Table 2b summarises links *to* a brain region (region 2) that have different EC in autism. In addition, in Table 2 we indicate for the ECs, the stronger direction as S defined as the direction in which the effective connectivity from Region 1 to Region 2 is stronger in the controls; W as the direction in which the EC is weaker from region 1 to region 2; and Bid (bidirectional) in which the ECs between Region 1 and Region 2 are similar. We note that all the information in Table 2 is from the 41 links shown in Table 1.

First, the middle temporal gyrus (Temporal_Mid) and some other temporal cortical areas have lower EC to the precuneus and cuneus in the ASD group, as summarized in Table 2b. These effective connectivities are in the stronger direction. In addition, the Temporal Pole has lower EC to FrontalMedOrb, which is ventromedial prefrontal cortex (VMPFC) BA 10, and these are in the stronger direction. In addition, there is an EC link from the middle temporal gyrus to the hippocampus that is increased, and this is the stronger direction (Table 1). Thus the pattern for the temporal cortex in autism is decreased effective connectivity to the precuneus and cuneus; and to the VMPFC; and increased EC to the hippocampus.

Second, the hippocampus and amygdala have increased effective connectivity to the middle temporal gyrus in autism, and this is mainly in the weaker direction (with the macaque neuroanatomy providing evidence that these are backprojections (Amaral & Price, 1984; Lavenex & Amaral, 2000; Rolls, 2016; Van Hoesen, 1982)), though there is also an increase in the stronger direction (Tables 2 and 1). (In addition, the parahippocampal gyrus has decreased effective connectivity to early visual cortical areas such as the calcarine cortex in autism.)

Third, some frontal cortical areas (FrontalSup and Supmedial) have increased EC to the middle frontal gyrus, and decreased EC to the superior frontal gyrus.

Correlation between the effective connectivities and the autism symptom scores

The correlations of the effective connectivities with the autism symptom scores are shown in Tables S5 and S4. The ECs from the middle temporal gyrus to the precuneus were negatively correlated with the ADOS total, communication, and social score (Table S5). Thus the weaker this EC value the greater was the autism score, in line with the finding that the ECs from the temporal cortex to the precuneus were decreased in autism (Tables 1 and 2).

The ECs from the hippocampus to the temporal cortex were positively correlated with the ADOS stereotyped behaviour score (Table S5). Thus the stronger this EC value the greater was the autism score, in line with the finding that the ECs from the hippocampus to the temporal cortex were increased in autism (Tables 1 and 2).

Differences in Sigma in Autism

Sigma (i.e. Σ – the amplitude of endogenous neuronal fluctuations) was lower in the ventromedial prefrontal cortex (BA 10) in the group with autism (z=-4.12, p=3.8e-5). This implies less activity in the ventromedial prefrontal cortex in people with autism (see Supplementary Material).

Comparison with Functional Connectivity

For completeness, the functional connectivity differences between participants with autism and controls found in the same dataset and using the AAL2 parcellation are shown in Table S3. (This is different from our previous work, which was a voxel-level study, and was with a somewhat larger group of participants (Cheng et al., 2015).) It will be seen that only some of the areas with different functional connectivity have significantly different effective connectivity, and this is to be expected, as they measure different properties of the connectivity. It is also of interest that all the top 25 functional connectivities (those significant after Bonferroni correction $p<0.05$) were lower in autism than in controls (Table S3), whereas for the effective connectivities, some higher effective connectivities were found (Fig. 1). With FDR correction ($p<0.05$), 836 functional connectivity links were significantly different in autism, and of these 825 were lower in autism.

This is of interest, for this elucidates one way in which effective connectivities can provide information that is not available from the functional connectivities.

Robustness of the effective connectivity results

The results described here were with a relatively large dataset of 394 people with autism spectrum disorder and 473 controls, and should be robust with this sample size. However, as a check on whether similar results would be obtained with a smaller sample as a form of internal validation, we performed a split data analysis, in which the autism and control group were split into independent datasets. From the ABIDE1 dataset from which data from 16 neuroimaging sites were used in the main analyses, the data from 8 neuroimaging sites formed one data split, and from the other 8 sites the second data split. The numbers of participants in each split were similar. Overall, for the results shown in Tables 1 and 2, consistent results were found in each of the two data splits, with the correlations with the presented results (of the t values of the differences of all ECs between the autism and control groups) 0.83 for the first split, and 0.78 for the second split. Further, most of the EC links with significant differences in the whole dataset were also significant ($p<0.05$) in both of the split datasets (67/80). Further, all the significant differences in EC between the autism and control groups shown in Fig. 3 were also significant in each of the two data splits, apart from two which were significant in one of the data splits. These analyses confirm the robustness of the results presented here with the full dataset; but also make the point that large sample sizes are needed for resting state connectivity analyses to obtain robust results.

Discussion

Figure 3 summarizes some of the differences in effective connectivity in autism found in this investigation, with further details in Tables 1 and 2. These differences are discussed next.

First, the middle temporal gyrus (Temporal_Mid) and some other temporal cortical areas have decreased ECs to the precuneus and cuneus (Tables 1 and 2), and these are correlated with the ADOS total, communication, and social score (Table S5). These findings are supported by the decrease in functional connectivity between these areas described previously (Cheng et al., 2015), but the new findings provide evidence on the directionality of the effect, with the effective connectivity in the reverse direction from the precuneus to the temporal lobe being both very much weaker, and less significantly differently between people with autism and controls (Table 2). This is important new evidence. These temporal lobe areas, especially the parts of the middle temporal gyrus identified in the voxel-level functional connectivity study, are implicated in face expression analysis and in theory of mind (Cheng et al., 2015; Critchley et al., 2000; Hasselmo, Rolls, & Baylis, 1989). Further, in autism poor face recognition performance predicted smaller activation in the right anterior temporal lobe to faces (Scherf, Elbich, Minshew, & Behrmann, 2015), further implicating these temporal lobe areas in the problems in face processing in autism (Deutsch & Raffaele, 2019). The precuneus and cuneus region are implicated in the sense of self, in autobiographical memory retrieval, and of spatial processing that is relevant to that (Cavanna & Trimble, 2006; Freton et al., 2014; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012). The implication of the new effective connectivity results is that the face expression analysis, which is important in social interactions, and theory of mind, important in understanding others' behaviour, have reduced effects in autism on parts of the brain involved in representing the self in the world. Thus this reduced effective connectivity from temporal cortex areas to the precuneus and cuneus may be related to the poor understanding of the implications of face expression inputs for oneself in autism.

Another interesting decreased effective connectivity is from the temporal cortex (Mid-Pole) to the ventromedial prefrontal cortex, which latter is implicated in reward evaluation, emotion, and decision-making (Du et al., 2019; Rolls, 2014, 2018a, 2019a, 2019b, 2019c). This may be related to poor reward and punishment decoding of face expression, and thus to difficulty with social behaviour. Interestingly, the sigma value for this ventromedial prefrontal cortex region, reflecting in the EC analysis the signal variance value Sigma, was lower for autistic people compared to controls. This may reflect reduced processing in the ventromedial prefrontal cortex if there is reduced input from face expression and theory of mind middle temporal gyrus areas. This ventromedial prefrontal cortex region has been reported to be more active in response to self- compared with other-referential processing, with this difference attenuated in people with autism (Lombardo et al., 2010), further implicating this ventromedial prefrontal cortex area in autism.

Second, the hippocampus and amygdala have increased effective connectivity to the middle temporal gyrus in autism, and this is mainly in the weaker direction (with the macaque neuroanatomy providing evidence that these are backprojections (Amaral & Price, 1984; Lavenex & Amaral, 2000; Rolls, 2016; Van Hoesen, 1982)), though there is also an increase in the stronger direction (Tables 2 and 1), and this increase is positively correlated with the ADOS stereotyped behaviour score (Table S5). The usual understanding of the connections from the hippocampus back to neocortex is that they are backprojections involved in episodic memory retrieval (Kesner & Rolls, 2015; Rolls, 2016, 2018b; Rolls & Wirth, 2018; Treves & Rolls, 1994). The usual understanding of the connections from the amygdala to the neocortex is that they are backprojections (Amaral & Price, 1984), which might be involved in retrieving emotion-related memories (Rolls, 2014, 2016). An implication is that the increased effective connectivity in these pathways may be related to increased retrieval of recent and emotional memories in autism, which may contribute to the state if these are unpleasant memories. In addition, the increased top-down effects from the amygdala and hippocampus on the temporal cortical areas may contribute to the reduced activations of temporal cortex areas to bottom up inputs produced by faces (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2007; Koshino et al., 2008; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001).

Third, some frontal cortical areas (FrontalSup and FrontalSupMedial) have increased EC to the middle frontal gyrus, and decreased EC to the superior frontal gyrus. From our functional connectivity study, we know that some of these prefrontal cortex areas have increased functional connectivity with the precuneus and cuneus (Cheng et al., 2015). Given that the prefrontal cortex is implicated in executive functions, working memory, and planning (Passingham & Wise, 2012), the alterations in effective connectivity in these prefrontal cortex areas may be related to increased executive function devoted to the precuneus and cuneus in trying to make sense of the self in the world. They may also relate to the increased spatial processing in which many people with autism excel. Also of potential interest is that activations in the precuneus and posterior cingulate cortex were found to be greater to the faces of familiar people compared to strangers, and that this activation was reduced in people with autism (Pierce, Haist, Sedaghat, & Courchesne, 2004). In the same study, activation to familiar faces was reported to be greater in medial prefrontal cortex areas than in people with autism (Pierce et al., 2004).

We also note that some subcortical effects on cortical areas involved in touch and movement are increased, for example from the thalamus and putamen to precentral, post-central, and mid-cingulate cortex (Table 1). Autistics are oversensitive to being touched (Lundqvist, 2015; Riquelme, Hatem, & Montoya, 2016). These increased effective connectivities may be related to this.

In the results described, there were 347 males and 47 females in the autistic group (Table S2), consistent with the increased prevalence of autism spectrum disorders in males, and the effects of sex were regressed out. If the analysis was restricted to only males in the autism and control groups, then some of the main differences in effective connectivity described here remained, including reduced effective connectivity from the middle temporal gyrus to the cuneus and precuneus, and increased effective connectivity from the amygdala and hippocampus to the middle temporal gyrus. The female-only groups were insufficiently large to obtain FDR-corrected significant differences in effective connectivity.

It would be of interest in future investigations to analyze whether subtypes of EC in autism could be found; and to investigate these differences in an even larger group of females and in people with a wider range of age. Further, as effective connectivity is an approach to causal analysis, it would be of interest in future studies to investigate possible associations between genes and the differences in effective connectivity described here. The present findings make a significant step towards causality, by going beyond functional connectivity, which reflects correlations, to effective connectivity, which reflects directed effects of one brain region on another.

In conclusion, this is the first large-scale study of effective connectivity in people with autism. The investigation provided important new evidence on directed connectivity in autism, which help to reveal the underlying differences in connectivity in people with autism. One new set of findings was that directed connectivity *from* the middle temporal gyrus areas implicated in face expression processing and theory of mind *to* the precuneus and cuneus implicated in processing about the self was reduced; and that connectivity *from* these middle temporal gyrus areas *to* the ventromedial prefrontal cortex, involved in emotion and emotion-related decision-making (Rolls, 2019b), was reduced in autism. Another set of findings was that effective connectivity *from* memory and emotion related areas, the hippocampus and amygdala respectively, *to* the middle temporal gyrus was increased in autism. Another set of findings was that effective connectivity *from* the basal ganglia *to* the pre- and post-central gyrus and midcingulate cortex was increased in people with autism.

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Table 1. Effective connectivity (EC) links that are different between individuals with autism and controls. Links are shown if their EC value in either direction exceeds the threshold of 0.02 Hz, and if there is a significant difference using FDR correction for multiple comparisons between individuals with autism and controls, for which the significance level must be p<0.00081. A negative value for z indicates a weaker effective connectivity link in individuals with autism. All 41 links with these EC differences are shown. ('*' indicates this direction is significant; 'Strong/Weak' indicates the ratio of the EC from 1 to 2 in terms of the strong direction / the weak direction.)

Region1 AAL2 Name	Region2 AAL2 Name	z Value (1 to 2)	*p* Value (1 to 2)	Z Value (2 to 1)	*p* Value (2 to 1)	EC in HC (1 to 2)	EC in AUT (1 to 2)	EC in HC (2 to 1)	EC in AUT (2 to 1)	EC Ratio in HC **(Strong / Weak)**
Temporal_ Mid_R	Cuneus_R (S)	-5.556	2.76e-08*	-3.222	1.27E-03	0.031	0.029	0.010	0.010	3.077
Temporal_ Mid_L	Cuneus_L (S)	-5.092	3.54e-07*	-3.031	2.44E-03	0.040	0.030	0.011	0.010	3.630
Paracentral_ Lobule_R	Postcentral_L (W)	-4.836	1.32e-06*	-2.125	3.36E-02	0.027	0.021	0.066	0.070	2.453
Temporal_ Mid_L	Hippocampus_L (S)	4.449	8.65e-06*	4.244	2.20e-05*	0.021	0.029	0.017	0.022	1.228
Temporal_ Mid_L	Cuneus_R (S)	-4.411	1.03e-05*	-3.274	1.06E-03	0.025	0.023	0.009	0.009	2.789
Temporal_ Mid_R	Lingual_R (S)	-4.327	1.51e-05*	-1.738	8.22E-02	0.033	0.028	0.016	0.015	2.142
Hippocampus_L	Temporal_ Mid_L (W)	4.244	2.20e-05*	4.449	8.65e-06*	0.017	0.022	0.021	0.029	1.228
Frontal_ Sup_Medial_R	Frontal_ Sup_2_L (W)	-4.187	2.83e-05*	-1.548	1.22E-01	0.033	0.030	0.038	0.036	1.136
Putamen_R	Postcentral_R (S)	4.040	5.35e-05*	1.439	1.50E-01	0.030	0.038	0.016	0.020	1.901
Paracentral_ Lobule_R	Precentral_R (W)	-4.025	5.71e-05*	-1.473	1.41E-01	0.027	0.023	0.085	0.090	3.121
ParaHippocampal_L	Calcarine_L (S)	-3.930	8.48e-05*	-0.415	6.78E-01	0.041	0.044	0.016	0.015	2.532
Putamen_R	Paracentral_ Lobule_R (S)	3.865	1.11e-04*	0.997	3.19E-01	0.025	0.033	0.009	0.011	2.671
Thalamus_L	Temporal_ Sup_L (S)	3.855	1.16e-04*	2.759	5.80E-03	0.022	0.028	0.022	0.027	1.018
Hippocampus_L	Temporal_ Inf_L (W)	3.822	1.32e-04*	3.004	2.67E-03	0.016	0.023	0.025	0.030	1.603
Temporal_Mid_L	Postcentral_L (S)	-3.804	1.42e-04*	-1.614	1.07E-01	0.024	0.023	0.020	0.021	1.186
ParaHippocampal_R	Calcarine_R (S)	-3.794	1.48e-04*	-0.092	9.27E-01	0.033	0.032	0.017	0.021	1.956
Caudate_L	Frontal_ Inf_Orb_2_L (S)	3.745	1.81e-04*	2.302	2.13E-02	0.023	0.030	0.012	0.014	1.910
ParaHippocampal_R	Lingual_R (S)	-3.739	1.85e-04*	-1.104	2.70E-01	0.049	0.046	0.018	0.021	2.655
Frontal_ Sup_Medial_L	Frontal_ Mid_2_R (W)	3.709	2.08e-04*	1.960	5.01E-02	0.009	0.014	0.024	0.028	2.744

Amygdala_L	Temporal_Mid_L (W)	3.687	2.27e-04*	3.349	8.10E-04	0.015	0.018	0.034	0.048	2.271
Temporal_Mid_R	Precuneus_L (S)	-3.682	2.31e-04*	0.974	3.30E-01	0.059	0.053	0.009	0.010	6.616
Parietal_Sup_R	Cuneus_R (S)	-3.645	2.67e-04*	-1.079	2.81E-01	0.024	0.027	0.021	0.031	1.146
Putamen_R	Precentral_R (S)	3.627	2.87e-04*	-0.013	9.90E-01	0.034	0.043	0.022	0.026	1.511
Thalamus_R	Fusiform_R (W)	3.610	3.06e-04*	1.411	1.58E-01	0.013	0.019	0.026	0.035	1.974
Precentral_L	Supp_Motor_Area_L (S)	-3.608	3.09e-04*	-1.287	1.98E-01	0.071	0.069	0.034	0.035	2.101
Frontal_Sup_2_L	Frontal_Mid_2_R (W)	3.604	3.14e-04*	2.121	3.39E-02	0.016	0.025	0.023	0.029	1.474
Temporal_Pole_Mid_R	Cuneus_R (S)	-3.599	3.20e-04*	-2.627	8.61E-03	0.023	0.021	0.008	0.007	2.971
Paracentral_Lobule_R	Postcentral_R (W)	-3.595	3.24e-04*	-0.390	6.96E-01	0.031	0.027	0.067	0.072	2.158
Temporal_Pole_Mid_R	Frontal_Med_Orb_R (S)	-3.576	3.49e-04*	-2.003	4.52E-02	0.055	0.049	0.022	0.022	2.439
Thalamus_L	Frontal_Inf_Orb_2_L (S)	3.560	3.71e-04*	1.645	1.00E-01	0.020	0.028	0.015	0.017	1.379
Temporal_Pole_Mid_R	Lingual_R (S)	-3.556	3.77e-04*	-2.004	4.51E-02	0.035	0.031	0.012	0.012	2.863
Hippocampus_R	Temporal_Mid_R (W)	3.543	3.96e-04*	1.220	2.23E-01	0.018	0.024	0.020	0.023	1.120
Pallidum_L	Postcentral_L (S)	3.483	4.96e-04*	2.269	2.33E-02	0.020	0.029	0.017	0.022	1.177
Occipital_Inf_L	Occipital_Inf_R (S)	-3.482	4.98e-04*	-1.180	2.38E-01	0.083	0.077	0.065	0.068	1.268
Temporal_Mid_R	Heschl_R (S)	-3.447	5.68e-04*	-2.057	3.97E-02	0.036	0.030	0.021	0.021	1.691
Putamen_L	Cingulate_Mid_R (S)	3.432	6.00e-04*	-1.298	1.94E-01	0.028	0.038	0.024	0.025	1.201
SupraMarginal_L	SupraMarginal_R (S)	-3.425	6.15e-04*	-2.133	3.30E-02	0.090	0.094	0.081	0.084	1.105
Frontal_Sup_2_L	Frontal_Mid_2_L (W)	3.413	6.42e-04*	0.898	3.69E-01	0.054	0.064	0.064	0.069	1.187
Frontal_Sup_Medial_R	Olfactory_R (W)	3.402	6.70e-04*	0.729	4.66E-01	0.016	0.021	0.024	0.025	1.512
Putamen_L	Cingulate_Mid_L (S)	3.377	7.34e-04*	-0.525	6.00E-01	0.033	0.043	0.020	0.020	1.669
Putamen_L	Temporal_Sup_L (S)	3.359	7.82e-04*	1.809	7.05E-02	0.042	0.054	0.020	0.023	2.125

Table 2a. Summary of the main differences in Effective Connectivity (EC) **from** one brain region (1) to other brain regions (2) in autism. A positive value for z indicates a higher EC in autism (AUT). Each link is followed by S if it is in the Strong direction; by W if it is in the Weak direction; and by Bid if the EC is similar in both directions.

Region 1	Region 2 (a set of regions)	z value of region 1 to 2 EC	z value of region 2 to 1 EC	EC of region 1 to 2 in HC	EC of region 1 to 2 in AUT	EC of region 2 to 1 in HC	EC of region 2 to 1 in AUT
Temporal	Hippocampus_L (S),	4.448	4.244	0.021	0.029	0.017	0.022
	Heschl_R (Bid), Post_central_L (Bid), Cuneus_R (S), Cuneus_L(S), Precuneus_L (S), Lingual_R(S), Frontal_Med_Orb_R (S),	-4.105	-2.060	0.036	0.032	0.014	0.014
Hippocampus	Temporal_Mid_L (Bid), Temporal_Mid_R, (Bid) Temporal_Inf_L (W)	3.870	2.891	0.017	0.023	0.022	0.027
Amygdala	Temporal_Mid_L, (W),	3.687	3.349	0.015	0.018	0.034	0.048
Parahippocampal	Lingual_R (S), Calcarine_L (S), Calcarine_R (S)	-3.821	-0.537	0.041	0.041	0.017	0.019
FrontalSup and SupMedial	Frontal_Mid_2_L (W), Frontal_Mid_2_R (W), Olfactory_R (W)	3.532	1.427	0.023	0.031	0.034	0.038
	Frontal_Sup_2_L (Bid),	-4.187	-1.548	0.033	0.030	0.038	0.036

Table 2b. Summary of the main differences in Effective Connectivity (EC) **to** one brain region (2) from other brain regions (1) in autism. A positive value for z indicates a higher EC in autism (AUT). Entries in Tables 2a and 2b are not mutually exclusive.

Region 1 (a set of regions)	Region 2	z value of region 1 to 2 EC	z value of region 2 to 1 EC	EC of region 1 to 2 in HC	EC of region 1 to 2 in AUT	EC of region 2 to 1 in HC	EC of region 2 to 1 in AUT
Temporal_Mid_L (S), Temporal_Mid_R (S), Temporal_Pole_Mid_R (S), Parietal_Sup_R (Bid)	Cuneus	-4.461	-2.647	0.029	0.026	0.012	0.013
Caudate_L(S), Thalamus_L(S)	FrontalInfOrb_L	3.652	1.974	0.021	0.029	0.013	0.016
Temporal_Pole_Mid_R (S)	FrontalMedOr_R	-3.576	-2.003	0.055	0.049	0.022	0.022
Frontal_Sup_2_L (W), Frontal_Sup_Medial_L (W)	FrontalMid	3.576	1.660	0.026	0.034	0.037	0.042
Temporal_Mid_R (S),	Precuneus	-3.682	0.974	0.059	0.053	0.009	0.010
Amygdala_L (W), Hippocampus (Bid), Putamen_L (S), Thalamus_L(Bid)	Temporal	3.752	2.765	0.022	0.028	0.024	0.030

Figure Legends

Figure 1. The matrices of differences in effective connectivity between individuals with autism and controls. The axes are the AAL2 areas, shown in their numbered order and with their names in Table S1. The effective connectivity matrix has the index j for the columns and the index i for the rows. The matrix is thus non-symmetric, and the effective connectivity is always from j to i. The effective connectivity between any pair of links is shown in one direction in the upper right of the matrix, and in the opposite direction in the lower left. The table includes only AAL2 areas between which there is a significant different in effective connectivity.

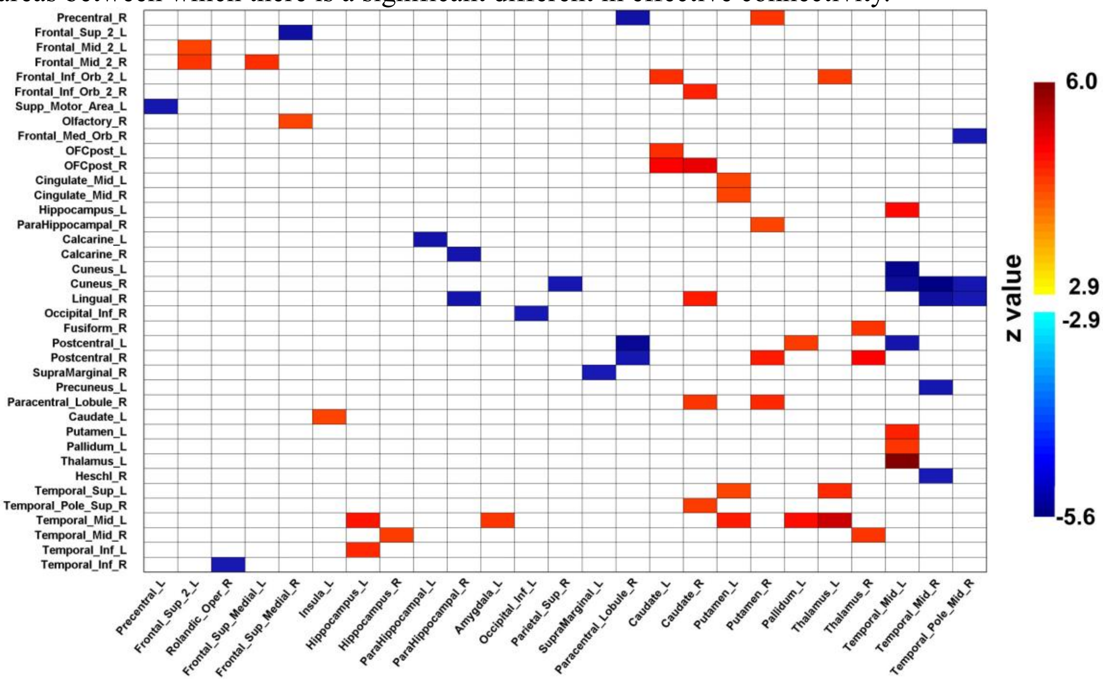

Figure 2. A) Differences in effective connectivity between individuals with autism and controls. The links shown are those with significantly different effective connectivity after FDR $p<0.05$ correction. Red indicates that the effective connectivity is increased in individuals with autism, and blue that it is decreased. There were 41 such links significant with FDR correction, $p<0.05$, and with effective connectivity values in at least one direction that were greater than 0.02 Hz. The glass brains were generated using the BrainNet Viewer (Xia, Wang, & He, 2013).
B) The AAL2 atlas areas with effective connectivities that were significantly different in individuals with autism. An area is shown if it has effective connectivities either from it or to it that are different in autism.

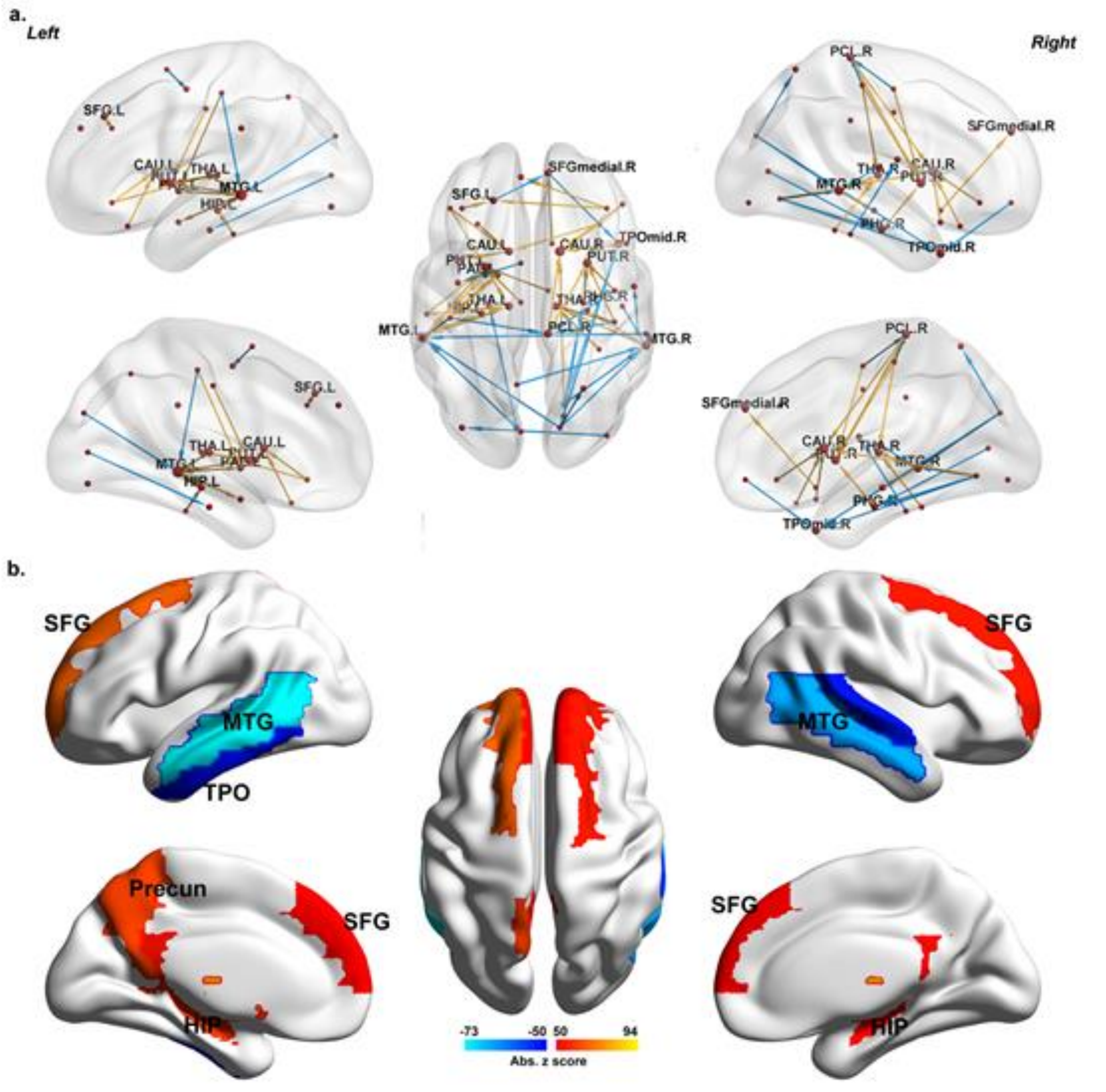

Figure 3. Summary of some of the main changes in Effective Connectivity in autism. The increased effective connectivities in autism are shown in red; and decreased in blue. A blue circle indicates a decrease in Sigma in autism. For details of the effective connectivities, see Tables 1 and 2, and Fig. 1.