Altered resting-state dynamics in autism spectrum disorder:

causal to the social impairment?

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Abstract

Autism spectrum disorder (ASD) is characterized by profound impairments in social abilities and by restricted interests and repetitive behaviors. Much work in the past decade has been dedicated to understanding the brain-bases of ASD, and in the context of resting-state functional connectivity fMRI in high-functioning adolescents and adults, the field has established a set of reliable findings: decreased cortico-cortical interactions among brain regions thought to be engaged in social processing, along with a simultaneous increase in thalamo-cortical and striato-cortical interactions. However, few studies have attempted to manipulate these altered patterns, leading to the question of whether such patterns are actually causally involved in producing the corresponding behavioral impairments. We discuss a few such recent attempts in the domains of fMRI neurofeedback and overt social interaction during scanning, and we conclude that the evidence of causal involvement is somewhat mixed. We highlight the potential role of the thalamus and striatum in ASD and emphasize the need for studies that directly compare scanning during multiple cognitive states in addition to the resting-state.

Keywords

ASD, neurofeedback, functional connectivity, hypoconnectivity, hyperconnectivity

Introduction

Autism spectrum disorder (ASD) is a heterogeneous, neurodevelopmental condition characterized by social and communication impairments, restricted interests and repetitive behaviors. Neuroanatomical and physiological studies of the brain bases of ASD suggest that the pathology is not restricted to one region or system but is spatially diffuse, affecting regions in temporal, parietal, and frontal cortex (e.g. Anderson et al., 2011; Cheng et al., 2015; Di Martino et al., 2014; Gotts et al., 2012; Hadjikhani et al., 2006; Raznahan et al., 2010; Scheel et al., 2011; Wallace et al., 2010; 2015). Accordingly, the field has focused on the idea that ASD is the result of altered functional/physiological interactions, referred to as "functional connectivity", among diffuse brain regions (e.g. Belmonte et al., 2004; Castelli et al., 2002; Just et al., 2004). The past decade or so of research on the patterns of altered functional connectivity in ASD has documented a pattern of findings with replication, particularly for those demographic subgroups with the most study coverage, namely high-functioning (i.e. high IQ) adolescent and young adult males in the age ranges of 12 to 30 (for recent reviews, see Mash et al., 2018; Picci et al., 2016). However, much less effort has focused on whether these altered patterns are causally involved in producing the behavioral phenotype of ASD or whether they are merely correlational. In the current review, we first provide an overview of the main theoretical perspectives on connectivity in ASD, and we then review the relevant evidence from resting-state functional connectivity fMRI. We focus the subsequent discussion of causality around two recent studies from our lab that have attempted to manipulate the patterns of functional connectivity, one by neurofeedback (Ramot et al., 2017) and one by altering the task state (Jasmin et al., 2018).

Theoretical models of connectivity in ASD

Most of the initial functional connectivity studies of ASD were conducted not in resting-state scans but in the context of particular tasks (although see Horowitz et al., 1988, for a very early resting-state PET study). For example, in one of the first functional connectivity studies, Castelli et al. (2002) presented 10 ASD and 10 control participants with animated sequences of social situations using abstract shapes (triangles) while scanning with PET. They found that during sequences that elicited mentalizing about intentions, ASD participants gave less accurate descriptions of the events and exhibited reduced activity in medial prefrontal cortex, superior temporal sulcus (STS), temporo-parietal junction (TPJ) and the temporal poles. They further found that extrastriate cortex (active during viewing the animations) had reduced functional connectivity with posterior aspects of the STS near the TPJ (see also Weisberg et al., 2014). Just et al. (2004), in another seminal study, presented written sentences to 17 ASD and 17 control participants and evaluated comprehension performance using probe questions (identifying the agent or recipient of an action) during fMRI. They found increased activity in the left superior temporal gyrus (STG) and reduced activity in the left lateral frontal cortex in ASD relative to controls, along with reduced functional connectivity between these regions and a variety of other areas. Just et al. (2004) then proposed that ASD is characterized by pervasive functional *underconnectivity* among cortical regions, particularly those requiring large-scale coordination with other regions. They further speculated that this underconnectivity was due to white matter abnormalities in ASD.

In the same year, Belmonte et al. (2004) proposed an influential related idea, that perhaps brain regions in ASD have an over-abundance of local excitatory synaptic connections (following Rubenstein & Merzenich, 2003). They argued that this would produce an altered excitatory/inhibitory (E/I) balance in local cortical information processing, first leading to poor local neural selectivity that, in turn, over the course of development would lead to the longer-range hypo-connectivity observed by Just et al. (2004) among distal brain regions. Similar theories of locally altered E/I balance in ASD have since been proposed by Markram et al. (2007) and Vattikuti and Chow (2010). These ideas excited the field and led to dozens of studies examining the patterns of altered functional connectivity in ASD for both local and long-range interactions, first in the context of smaller-scale task-based fMRI studies (usually with fewer than 20 participants per group) and later in much larger resting-state studies (ranging from 30 to 500 participants per group) (see Hull et al., 2017; Picci et al., 2016). In the next section, we briefly review this evidence and show that while these studies have provided support for the idea that functional connectivity is altered in ASD, the precise patterns of altered functional connectivity have not been well anticipated by any of the popular theories.

Resting-state functional connectivity findings

As mentioned above, the first functional connectivity studies in ASD were task-based, with researchers planning more traditional task-based fMRI acquisitions which were then re-purposed as functional connectivity studies. Most of these studies used relatively simple analyses with Pearson correlation after first attempting to regress the average evoked responses out of the data that were due to the task (see Jones et al., 2010, for discussion).

Perhaps not surprisingly, the small sample sizes typically employed in such studies along with the wide range of tasks employed led to inconsistent results (reviewed in Müller et al., 2011; Picci et al., 2016). While the intent of the task regression during preprocessing was to remove the influences of task on functional connectivity, this was unlikely to have been successful: removing the trial-averaged task response still preserves all of the trial-to-trial variability in the fMRI time series, with much of the observed patterns still likely due to the task modulation of brain activity. Accordingly, studies that employed language-related tasks might observe group differences in the language-related brain regions that are engaged by the task (as in the Just et al., 2004, study), and studies that employed a simple motor coordination task such as finger tapping might instead observe group differences in motor-related regions such as primary motor cortex, supplementary motor cortex and the cerebellum (as in a study by Mostofsky et al., 2009). Between 2005 and 2010, interest in resting-state fMRI exploded (see Fox and Raichle, 2007, for a contemporary review), and these studies soon came to dominate the ASD functional connectivity literature. Resting-state fMRI, in which participants are instructed to lie still and relax -- either with eyes closed or maintaining fixation on a central cross -- became a preferred method for examining brain dynamics in clinical studies, partly because the studies were easy and fast to administer and partly because they didn't require complex task competencies that precluded study of certain participant groups (e.g. infants and patients with severe behavioral impairments). The switch to resting-state fMRI had the added advantage that the sampled cognitive states were more similar across studies, which yielded a notable improvement in the repeatability of results.

The first resting-state fMRI studies of ASD were "seed-based", with the *a priori* choosing of a small number of regions of interest (ROIs), such as the posterior cingulate seed used to identify the "default-mode" network (e.g. Fox et al., 2005; Monk et al., 2009). Researchers would calculate the average time series within a seed ROI for each participant, which would then be correlated across time points during the rest scan in each voxel of the brain, yielding a whole-brain correlation map relative to the seed. Group differences could then be evaluated as relatively simple two-sample t-tests in each voxel. In this way, clusters of voxels that differed in functional connectivity with the seed ROI between ASD and control participants could be identified. Across a set of early studies (e.g. Assaf et al., 2010; Kennedy & Courchesne, 2008; Monk et al., 2009; Weng et al., 2010), ASD participants were found to have reduced functional connectivity among regions of the default-mode network, including the posterior cingulate, medial prefrontal cortex, and the parahippocampal gyrus. Several of these studies presented simultaneous evidence that these disrupted functional connections also predicted the severity of social symptoms in the ASD participants (e.g. Assaf et al., 2010; Monk et al., 2009; Weng et al., 2010). However, while these studies found qualitatively similar alterations within the default-mode network, none of the studies had identical results and all had fewer than 20 participants in each group. Indeed, Di Martino and colleagues (Di Martino et al., 2011) reported qualitatively different effects between the basal ganglia/striatum and sites in the cortex in 20 ASD and 20 control participants, with increased functional connectivity in ASD. These early studies were also conducted prior to awareness of the impact of head motion and other artifacts on functional connectivity measures (e.g. Power et al., 2012, 2014; Satterthwaite et al., 2012, 2013; Van Dijk et al., 2012; see Power et al., 2015, for review).

Later studies employed progressively larger sample sizes, matched groups on variables such as head motion, and conducted much wider-scale investigations over all possible combinations of brain regions. The first of these whole-brain studies was conducted by Anderson et al. (2011), examining functional connectivity differences between 40 ASD and 40 control participants (age range 12-42) at 7266 ROIs sampled over the entire gray matter volume. Using random permutation testing to control for whole-brain comparisons, they found decreased long-range functional connectivity involving the medial prefrontal, posterior cingulate, STS, intraparietal, ventral temporal and insular cortices. Our group then published a voxelwise, whole-brain analysis of functional connectivity differences in 31 ASD and 29 control participants (Gotts et al., 2012). The analysis proceeded in two stages, first identifying voxels/regions with differences in the average functional connectivity with the rest of the brain (termed "connectedness" and similar to degree centrality in graph theory), and then further probing connectivity differences using these regions as seeds to the rest of the brain. Like Anderson et al. (2011), we also observed solely decreased functional connectivity in ASD involving brain regions that had previously been associated with aspects of social processing: ventromedial prefrontal cortex, bilateral STS/STG, anterior temporal cortex, fusiform gyrus, amygdala, anterior hippocampus, left inferior frontal gyrus and anterior insula, left temporo-parietal cortex, as well as parahippocampal gyrus, intraparietal sulcus and occipital regions. Interestingly, these regions were found to organize into three clusters corresponding to limbic-related regions that were associated with more affective aspects of social processing, language related regions, and visuomotor regions, with the most pronounced differences observed between the limbic-related regions and the other two clusters. When examining the severity of

social symptoms in the ASD group using the Social Responsiveness Scale (SRS; Constantino, 2002), we found that these same connections were the ones that related to the patients' social deficits. Importantly, when groups were quantitatively matched for motion through selective removal of high motion frames, all of these results remained unchanged. The decoupling of subgroups of regions within the full set of regions associated with aspects of social processing suggested a basic break-up of dynamics within the "social brain" in ASD (for further discussion, see Adolphs, 2009; Blakemore, 2008; Frith & Frith, 2007; Mitchell, 2009; Olson et al., 2007). Shortly thereafter, a separate study using a completely different statistical approach (ICA) published a similar fractionation of functional connectivity among social brain regions in ASD (von dem Hagen et al., 2013).

While these studies had around twice the sample sizes of previous studies, they were still potentially underpowered and had variation in findings from study to study, although showing common decreases in long-range functional connectivity involving medial prefrontal cortex, STS, left inferior frontal gyrus, somatosensory cortex, and ventral temporal brain regions. Large multi-site data-sharing initiatives, such as the ABIDE database (Di Martino et al., 2014), had a large impact on this picture. ABIDE pooled together data from many sites and allowed researchers to examine differences with sample sizes of several hundred participants per group. The original ABIDE paper itself (Di Martino et al., 2014) reported results from 112 ROIs in 360 ASD and 403 control participants. They found predominantly decreased functional connectivity in ASD among cortico-cortical connections but increases between thalamus/striatum and cortex, particularly with sensorimotor and parietal regions (see also Cerliani et al., 2015). Cheng et al. (2015) further analyzed a larger subset of these data (418 ASD and 509 motion-matched

controls from 16 sites), examining all possible voxelwise combinations for functional connectivity differences and correcting for multiple comparisons with False Discovery Rate (FDR). They also included covariates to model nuisance variables such as mean Framewise Displacement (a measure of transient head motion, Power et al., 2012) and scanning site, and they included a replication analysis across two independent subsets of the data. Cheng et al. (2015) observed decreased long-range functional connectivity in ASD involving medial prefrontal, posterior cingulate, bilateral STS/MTG, and bilateral sensorimotor cortices, along with increased functional connectivity between the medial thalamus and the right SMA, left STS and superior frontal gyrus (see Figure 1A). A re-analysis of our own data with approximately twice the original sample sizes and age- and motion-matched groups (56 ASD, 62 control; see Figure 1 in Ramot et al., 2017) provides yet another replication of this overall pattern, with particularly strong decreases involving bilateral STS and somatosensory cortex, as well as increased functional connectivity between thalamus/striatum and these same regions of cortex (Figure 1B; see Gotts et al., 2017, for further discussion). This correspondence holds true despite differences in data preprocessing and overall analysis approaches (see Gotts et al., 2013; Saad et al., 2013; for further discussion). It is also worth noting that this overall pattern does not depart qualitatively from many of the earlier resting-state functional connectivity studies that were conducted with smaller sample sizes and without rigorous control of factors such as motion (e.g. Di Martino et al., 2011; Kennedy & Courchesne, 2008; Mizuno et al., 2006; Weng et al., 2010). This is not to say, though, that numerous discrepant reports haven't also been published (see Hull et al., 2017, for review). Cortico-cortical "overconnectivity" in ASD has been reported using a variety of individual seed locations (although often outside the set of "social"

brain regions discussed above), with sample sizes ranging from 15 to 50 (e.g. Alaerts et al., 2014; Chien et al., 2015; Fishman et al., 2014; 2015; Nebel et al., 2014a, 2014b; Redcay et al., 2013). The larger-sample studies (several hundred participants in each group) conducting whole brain searches often require more stringent statistical thresholding, which may have led to some Type II statistical errors (failing to detect an effect when it should be detected), potentially permitting some of these discrepancies. However, the apparent conflict with much larger-sample studies with higher statistical power suggests that these discrepant reports should certainly be re-examined with efforts at establishing replication.

The consistent pattern of altered functional connectivity in adolescent and adult ASD males discussed above has some similarities with the Just et al. (2004) proposal in that cortico-cortical alterations are often decreases. However, Just et al. (2004) (and the E/I balance theories of Belmonte et al., 2004; Markram et al., 2007; Vattikuti & Chow, 2010) failed to anticipate that these changes would follow a basic systems neuroscience distinction between "social" and "non-social" regions (see Gotts et al., 2012, for further discussion). Similarly, none of these theories foresaw a shift from cortico-cortical functional connectivity to subcortico-cortical in ASD (although see a very early empirical observation in Mizuno et al., 2006). Attempts to find the inverse relationship between local and long-range functional connectivity predicted by Belmonte et al. (2004) have also failed to observe such a pattern (e.g. Di Martino et al., 2014; Gotts et al., 2013; Maximo et al., 2013; see Picci et al., 2016, for review). All of this suggests that a new understanding of the ASD phenotype may want to ground proposals in consistent and replicated systems-level neuroscience results.

Altered ASD resting-state dynamics: Correlation versus causation

The documented agreement between group differences in functional connectivity and correlations with symptoms within the ASD group (e.g. Gotts et al., 2012; Cheng et al., 2015) suggests that the changes in functional connectivity are at least correlated with core aspects of the ASD phenotype. Recent magnetoencephalography (MEG) findings performing a similar data-driven analysis to the centrality-based approach of Gotts et al. (2012) have further established that decreased functional connectivity among social brain regions such as medial prefrontal, STS and ventral anterior temporal cortices is present in more rapid electrophysiological activity (alpha-band phase-locking), indicating that this pattern is not an artifact of BOLD fMRI measurement (Ghuman et al., 2017). However, it remains possible that the altered dynamics, perhaps in part or in total, are a *result* rather than a cause of the underlying behavioral disorder in ASD.

Recently, we have set out to examine this issue in two different ways. In the first, we have attempted to manipulate the aberrant pattern of functional connectivity in ASD to make it more like the control pattern, observing whether the behavioral impairment is also remedied (Ramot et al., 2017). In the other, we have manipulated task state by engaging ASD and control participants in a demanding or less-demanding social task, comparing the patterns of task-based functional connectivity with that observed in resting-state data (Jasmin et al., 2018). Below, we discuss these studies and their implications for our understanding of the role of altered resting-state functional connectivity in producing the behavioral phenotype of ASD.

fMRI Neurofeedback to change ASD functional connectivity

There is growing interest in the online use of non-invasive brain measures to study and treat various clinical disorders, techniques referred to here as "neurofeedback". Previous studies have examined neurofeedback in a variety of sensory and motor domains (e.g. Birbaumer et al., 2006; Hui et al., 2014; Cohen et al., 2014), for cortical plasticity and attention (e.g. Bagdasaryan et al., 2013; deBettencourt et al., 2015; Robineau et al., 2014; Scharnowski et al., 2012; Seitz, 2013), and for the treatment chronic pain, depression, and mood control (e.g. deCharms et al., 2005; Grone et al., 2015; Lawrence et al., 2013; Yuan et al., 2014). Advances in fMRI hardware and timing have recently made fMRI a viable approach to neurofeedback studies, with superior spatial resolution to less expensive methods such as EEG (e.g. Weiskopf et al., 2007). Enhanced localization permits the use of not only activity in small patches of neural tissue, but also of differential activity patterns in multiple regions (e.g. Koush et al., 2013; Ramot et al., 2016; Robineau et al., 2014; Shibata et al., 2011), permitting feedback based on larger network states. Participants also appear to be able to use neurofeedback to perform a task without explicit instruction (i.e. "covert"; e.g. Scharnowski et al., 2012; Shibata et al., 2011), which can greatly enhance the flexibility for therapeutic intervention when no specific explicit strategies are known.

In Ramot et al. (2017), we used real-time fMRI and covert neurofeedback training in an attempt to bring ASD resting-state functional connectivity between the STS and somatosensory cortex closer to the level seen in control participants. We used our previously acquired resting-state data (56 ASD, 62 age-, motion-, and IQ-matched controls; see Figure 1B) to choose three regions for neurofeedback training, two with strongly decreased functional connectivity in ASD (one in the left STS, the other in left somatosensory cortex; see Figure 2) and a third region to

serve as a control (a region in right parietal cortex with seed-based functional connectivity that was relatively uncorrelated with either STS or somatosensory cortex in controls). Importantly, individual variability of the functional connectivity values between left STS and somatosensory cortex in ASD was also correlated with the severity of social symptoms as measured by the SRS. Seventeen ASD participants participated in the training, which consisted of 4 days of scanning sessions. On each day, two rest runs were acquired first, followed by 4 neurofeedback training runs, with another two rest runs at the end (all runs 9 minutes in length). The first two training sessions were conducted on consecutive days, and after a week delay, two more training sessions followed (also on consecutive days).

For the covert neurofeedback training task itself, participants began with a blank screen. They were told that they were trying to solve a puzzle task and were asked to try to reveal the picture hidden underneath. Each moment that the magnitude of the BOLD signal in their left STS and somatosensory regions jointly changed in the same direction (either a joint increase or decrease, sampled every two seconds), along with a simultaneous opposite change in the parietal control region (e.g. if joint increases in STS/somatosensory, a decrease), a piece of the hidden picture was revealed. The use of the parietal control region was essential in order to guard against non-selective, global changes in functional connectivity. The training was 'covert' in the sense that participants were not directly informed that it was their brain activity that was being used reveal the picture, and they were not provided with any guidance about how to solve the puzzle. Parents filled out behavioral questionnaires before the beginning of training, as well as two weeks after the last training session. An additional follow-up study was also

carried out in 15 of the 17 ASD participants to examine how long the training effects lasted, with delays ranging from 5 to 56 weeks post-training.

We found that, indeed, ASD participants were able to change their functional connectivity patterns toward the control pattern through covert neurofeedback over the four days of training sessions (see Figure 2). These changes were also long-lasting, showing little or no attenuation with delay between training and the later follow-up session (up to 56 weeks later). Interestingly, there was also a positive correlation between the training-related changes in resting-state functional connectivity and the pre- versus post-training changes in the SRS behavioral score (rated by the parents), indicating that changes toward the control pattern were related to decreases in social symptoms. However, while the pre- versus post-training changes were correlated between brain and behavior, the overall SRS values changed very little and still indicated high levels of social impairment (mean SRS post-training total score of 71.6, with control scores on this measure typically lower than 40). While overall, these preliminary results are exciting, they suggest that simply training functional connectivity values in ASD to match control levels may not fully remediate the behavioral phenotype (although it remains possible that our behavioral measure was simply not sensitive to this change). It appears that there are also limits on the modifiability of individual neural connections with this method, as ten healthy control participants failed to show consistent changes when the assignment of the same regions was altered (training to increase STS-Parietal ROI correlations, with the somatosensory ROI used as control region; Ramot et al., 2017; Supplementary Figure 3).

Core versus context-sensitive differences in ASD functional connectivity

A different way to probe the causal nature of cortico-cortical resting-state functional connectivity decreases in ASD is to manipulate behavioral and neural states through explicit task demands. For example, we can ask ASD participants to engage in the highly demanding social task of spontaneous conversation, which requires language comprehension, sensitivity to non-verbal aspects of communication such as emotion and prosody, formulation and execution of a socially and informationally appropriate response, as well as appropriate turn taking. Would functional connectivity in this context still show the same profile of altered functional connectivity observed in resting-state?

We recently addressed this question in a task-based functional connectivity study with 19 ASD and 20 age- and IQ-matched control participants (Jasmin et al., 2018). Each participant engaged in three spontaneous conversations with the experimenter during fMRI, two on topics related to the participant's interests (e.g. music, games, etc.) and one related to either work or school life, depending on the participant's age. As a task-based control with lower social demand, participants also repeated nursery rhymes spoken by the experimenter. Participants' speech during fMRI was transcribed, periods of experimenter versus participant speech were marked, and eye movements during the video feed with the experimenter were monitored. Differences in functional connectivity patterns were examined between ASD and control participants during conversation, as well as during nursery rhyme repetition, and these were also examined relative to patterns of differences during rest for our larger set of resting-state data (56 ASD, 62 age-, motion-, and IQ-matched controls; shown in Figure 1B).

In terms of behaviors measured during conversations and rhyme repetition, ASD and control participants did not differ in the number of words uttered, overall durations of speaking

versus listening time, number of speaking turns, or number of words per sentence. Using the centrality-based analysis approach of Gotts et al. (2012) discussed earlier, we identified a number of social brain regions involved in group differences that did not interact with task condition (conversation versus repetition), including the bilateral somatomotor cortex, STS/STG, temporal pole, posterior cingulate, right inferior frontal gyrus, as well as thalamus, ventral striatum, parahippocampal cortex and the superior frontal gyrus. However, in marked contrast to our resting state data, these differences corresponded to *increased* rather than decreased functional connectivity in ASD, a subset of which also simultaneously showed a correlation with social symptoms measured by SRS score (greater functional connectivity corresponded to a higher level of social impairment). We also identified regions involved in functional connectivity differences that exhibited a group-by-task-condition interaction (ASD/Control X Conversation/Repetition). These involved the right fusiform gyrus, bilateral STS/STG, ventromedial prefrontal cortex, right somatomotor cortex, right inferior frontal gyrus, along with striate and extrastriate cortex, with a similar pattern observed for the main effect of Group: greater functional connectivity during conversation for ASD participants, with smaller or reversed differences during nursery rhyme repetition.

The seeming lack of agreement -- or even qualitative reversal -- of both group differences and symptom correlations in conversation/repetition relative to the resting state led us to quantitatively compare the task-based and resting-state patterns. This comparison verified that, indeed, cortico-cortical increases were unique to the ASD task-based data, whereas the cortico-cortical decreases were unique to the ASD resting-state data (i.e., the effect on the direction of correlation was context-sensitive). Importantly, however, both task-

based and resting-state data had common functional connectivity *increases* involving subcortical regions (thalamus and striatum) and select regions of the cortex (thalamus to somatomotor cortex and STS/STG; ventral striatum to parahippocampal gyrus, superior frontal gyrus and medial somatomotor regions; see Figure 3). This led us to suggest that the "core" ASD functional connectivity pattern may actually have more to do with the thalamo-cortical and striato-cortical increases than with the cortico-cortical decreases observed during rest -- despite their simultaneous correlation with social symptoms.

Summary and conclusions

In the current paper, we have reviewed the resting-state fMRI literature in autism with a focus on replicated findings in high-functioning adolescent and adult males. These studies have shown reliable cortico-cortical decreases in functional connectivity involving regions of the "social brain", such as STS/STG (anterior and posterior), somatosensory, ventromedial prefrontal, left IFG, posterior cingulate, and ventral temporal cortices. These decreases have also shown reliable correlations with the severity of social symptoms (e.g. Cheng et al., 2015; Gotts et al., 2012; Ramot et al., 2017). Simultaneously, increased functional connectivity in ASD has been observed between the thalamus and striatum and many of the same social brain regions that exhibit cortico-cortical decreases (e.g. Di Martino et al., 2011; 2014; Cerliani et al., 2015; Cheng et al., 2015). Despite the agreement of group differences and symptom correlations, recent evidence from fMRI neurofeedback and task-based functional connectivity in overt conversation (Ramot et al., 2017; Jasmin et al., 2018) suggests the need to carefully consider the role of subcortico-cortical connectivity in producing the ASD behavioral phenotype.

The recent results of Jasmin et al. (2018) suggest that the shift from cortico-cortical to subcortico-cortical connectivity in ASD may be central to a wider range of task- and behavioral states. Indeed, the widespread nature of inputs and outputs between the cortex, thalamus, and striatum may be indicating that ASD is a problem of large-scale cortical gating. The presence of group differences in one condition, such as rest, that are absent in another condition administered just a few minutes apart in time, such as overt conversation, certainly rules out more simple, anatomical bases to the differences in connectivity, such as axonal degradation.

Currently, the functional connectivity literature in ASD is still quite focused on resting-state studies in a variety of domains. There is some question as to whether the patterns of resting-state differences are qualitatively different over development, with a period of potential cortico-cortical "overconnectivity" in younger ages (e.g. Supekar et al., 2013; Uddin et al., 2013a). Researchers are also currently exploring the sex-linked nature of ASD, with an emergence of comparisons of male and female ASD participants (e.g. Alaerts et al., 2016; Floris et al., 2018; Jamison et al., 2017; Lai et al., 2017). There has been an ongoing interest in the potential for "sub-typing" of ASD and other patient groups, as well using machine-learning classification models to differentially classify ASD, Schizophrenia, and other disorders relative to controls (e.g. Anderson et al., 2011; Drysdale et al., 2017; Feczko et al., 2018; Mastrovito et al., 2018; Nielsen et al., 2013; Plitt et al., 2015; Uddin et al., 2013b). In our opinion, these are all interesting pursuits. However, it would also be helpful for future studies to examine a wider range of task conditions and mental states than simply focusing on the resting state. These should include task domains of clear impairment in ASD (e.g. social), as well as domains that are

relatively spared. As shown above, perturbing brain dynamics with tasks and interventions can teach one a great deal about the relevance or central nature of resting-state patterns. This will be challenging, as it is difficult (and expensive) to acquire larger sample sizes in task-based studies such that demonstrations of replication and stability are possible. However, it may be the only pathway to understanding what is causal in producing the phenotype of ASD and what is merely correlational.

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References

Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annual Review of Psychology 60*, 693-716.

Alaerts, K., Swinnen, S.P., & Wenderoth, N. (2016). Sex differences in autism: a resting-state fMRI investigation of functional brain connectivity in males and females. *Social, Cognitive, and Affective Neuroscience 11*, 1002-16.

Alaerts, K., Woolley, D.G., Steyaert, J., Di Martino, A., Swinnen, S.P., & Wenderoth, N. (2014). Underconnectivity of the superior temporal sulcus predicts emotion recognition deficits in autism. *Social Cognitive and Affective Neuroscience 9*, 1589–1600.

Anderson, J.S., Nielsen, J.A., Froehlich, A.L., DuBray, M.B., Druzgal, T.J., Cariello, A.N., et al. (2011). Functional connectivity magnetic resonance imaging classification of autism. *Brain 134*, 3742-54.

Assaf, M., Jagannathan, K., Calhoun, V.D., Miller, L., Stevens, M.C., Sahl, R., et al. (2010). Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. *Neuroimage 53*, 247-56.

Bagdasaryan, J., & Quyen, M.V. (2013). Experiencing your brain: Neurofeedback as a new bridge between neuroscience and phenomenology. *Frontiers in Human Neuroscience* 7:680.

Belmonte, M.K., Allen, G., Beckel-Mitchener, A., Boulanger, L.M., Carper, R.A., & Webb, S.J. (2004). Autism and abnormal development of brain connectivity. *Journal of Neuroscience 24*, 9228-31.

Birbaumer, N. (2006). Breaking the silence: Brain-computer interfaces (BCI) for communication and motor control. *Psychophysiology 43*, 517-32.

Blakemore, S.J. (2008). The social brain in adolescence. *Nature Reviews Neuroscience 9*, 267-77.

Castelli, F., Frith, C., Happé, F., & Frith, U. (2002). Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. *Brain 125*, 1839-49.

Cheng, W., Rolls, E.T., Gu, H., Zhang, J., & Feng, J. (2015). Autism: reduced connectivity between cortical areas involved in face expression, theory of mind, and the sense of self. *Brain 138*, 1382-93.

Chien, H.-Y., Lin, H.-Y., Lai, M.-C., Gau, S.S.-F., & Tseng, W.-Y.I. (2015). Hyperconnectivity of the Right Posterior Temporo-parietal Junction Predicts Social Difficulties in Boys with Autism Spectrum Disorder. *Autism Research 8*, 427–41.

Cohen, O., Koppel, M., Malach, R., & Friedman, D. (2014). Controlling an avatar by thought using real-time fMRI. *Journal of Neural Engineering 11(3)*:035006.

Constantino, J.N. (2002). *The Social Responsiveness Scale*. Los Angeles: Western Psychological Services.

deBettencourt, M.T., Cohen, J.D., Lee, R.F., Norman, K.A., & Turk-Browne, N.B. (2015). Closed-loop training of attention with real-time brain imaging. *Nature Neuroscience 18*, 470-5.

deCharms, R.C., Maeda, F., Glover, G.H., Ludlow, D., Pauly, J.M., et al. (2005). Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci USA 102*, 18626-31.

Di Martino, A., Kelly, C., Grzadzinski, R., Zuo, X.N., Mennes, M., Mairena, M.A., et al. (2011). Aberrant striatal functional connectivity in children with autism. *Biological Psychiatry 69*, 847-56.

Di Martino, A., Yan, C.G., Li, Q., Denio, E., Castellanos, F.X., Alaerts, K., et al. (2014). The autism brain imaging data exchange: towards a large-scale evaluation of the intrinsic brain architecture in autism. *Molecular Psychiatry 19*, 659-67.

Drysdale, A.T., Grosenick, L., Downar, J., Dunlop, K., Mansouri, F., Meng, Y., et al. (2017). Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine 23*, 28-38.

Feczko, E., Balba, N.M., Miranda-Dominguez, O., Cordova, M., Karalunas, S.L., Irwin, L., et al. (2018). Subtyping cognitive profiles in Autism Spectrum Disorder using a functional random forest algorithm. *Neuroimage 172*, 674-88.

Fishman, I., Datko, M., Cabrera, Y., Carper, R.A., & Müller, R.-A. (2015). Reduced integration and differentiation of the imitation network in autism: A combined functional connectivity magnetic resonance imaging and diffusion-weighted imaging study. *Annals of Neurology 78*, 958–69.

Fishman, I., Keown, C.L., Lincoln, A.J., Pineda, J.A., & Müller, R.-A. (2014). Atypical Cross Talk Between Mentalizing and Mirror Neuron Networks in Autism Spectrum Disorder. *JAMA Psychiatry 71*, 751–10.

Floris, D.L., Lai, M.-C., Nath, T., Milham, M.P., & Di Martino, A. (2018). Network-specific sex differentiation of intrinsic brain function in males with autism. *Molecular Autism 9*: 17. doi:10.1186/s13229-018-0192-x.

Fox, M.D., & Raichle, M.E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience 8*, 700-11.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., & Raichle, M.E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences, U.S.A. 102*, 9673-8.

Frith, C.D., & Frith, U. (2007). Social cognition in humans. *Current Biology 17*, R724-32.

Gotts, S.J., Gilmore, A.D., & Martin, A. (2017). Brain networks, dimensionality, and global signal averaging in resting-state fMRI: hierarchical network structure results in low-dimensional spatiotemporal dynamics. *bioRxiv*. doi:10.1101/229567.

Gotts, S.J., Saad, Z.S., Jo, H.J., Wallace, G.L., Cox, R.W., & Martin, A. (2013). The perils of global signal regression for group comparisons: a case study of Autism Spectrum Disorders. *Frontiers in Human Neuroscience* Jul 12; 7:356. doi:10.3389/fnhum.2013.00356.

Gotts, S.J., Simmons, W.K., Milbury, L.A., Wallace, G.L., Cox, R.W., & Martin, A. (2012). Fractionation of social brain circuits in autism spectrum disorders. *Brain 135*, 2711-25.

Ghuman, A.S., van den Honert, R.N., Huppert, T.J., Wallace, G.L., & Martin, A. (2017). Aberrant oscillatory synchrony is biased toward specific frequencies and processing domains in the autistic brain. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2*, 245-52.

Gröne, M., Dyck, M., Koush, Y., Bergert, S., Mathiak, K.A., et al. (2015). Upregulation of the rostral anterior cingulate cortex can alter the perception of emotions: fMRI-based neurofeedback at 3 and 7T. *Brain Topogr. 28*, 197-207.

Hadjikhani, N., Joseph, R.M., Snyder, J., & Tager-Flusberg, H. (2006). Anatomical differences in the mirror neuron system and social cognition network in autism. *Human Brain Mapping 28*, 441-449.

Horowitz, B., Rumsey, J.M., Grady, C.L., & Rapoport, S.I. (1988). The cerebral metabolic landscape in autism: intercorrelations of regional glucose utilization. *Archives of Neurology 45*, 749-55.

Hui, M., Zhang, H., Ge, R., Yao, L., & Long, Z. (2014). Modulation of functional network with real-time fMRI feedback training of right premotor cortex activity. *Neuropsychologia 62*, 111-23.

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. doi:10.3389/fpsyt.2016.00205.

Jamison, R., Bishop, S.L., Huerta, M., & Halliday, A.K. (2017). The clinician perspective on sex differences in autism spectrum disorders. *Autism 21*, 772-84.

Jasmin, K., Gotts, S.J., Xu, Y., Liu, S., Riddell, C., Ingeholm, J., et al. (2018). Overt social interaction and resting state in autism: core and contextual neural features. *bioRxiv*. doi: 10.1101/332213.

Jones, T.B., Bandettini, P.A., Kenworthy, L., Case, L.K., Milleville, S.C., Martin, A., & Birn, R.M. (2010). Sources of group differences in functional connectivity: an investigation applied to autism spectrum disorder. *Neuroimage 49*, 401-14.

Just, M.A., Cherkassky, V.L., Keller, T.A., & Minshew, N.J. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: evidence of underconnectivity. *Brain 127*, 1811-21.

Kennedy, D.P., & Courchesne, E. (2008). The intrinsic functional organization of the brain is altered in autism. *Neuroimage 39*, 1877-85.

Koush, Y., Rosa, M.J., Robineau, F., Heinen, K., Rieger S., et al. (2013). Connectivity-based neurofeedback: dynamic causal modeling for real-time fMRI. *Neuroimage 81*, 422-30.

Lai, M.C., Lerch, J.P., Floris, D.L., Ruigork, A.N., Lombardo, M.V., & Baron-Cohen, S. (2017). Imaging sex/gender and autism in the brain: etiological implications. *Journal of Neuroscience Research 95*, 380-97.

Lawrence, E.J., Su, L., Barker, G.J., Medford, N., Dalton, J., et al. (2014). Self-regulation of the anterior insula: Reinforcement learning using real-time fMRI neurofeedback. *Neuroimage 88*, 113-24.

Markram, H., Rinaldi, T., & Markram, K. (2007). The intense world syndrome -- an alternative hypothesis for autism. *Frontiers in Neuroscience* Oct 15;1(1), 77-96. doi:10.3389/neuro.01.1.1.006.2007.

Mash, L.E., Reiter, M.A., Linke, A.C., Townsend, J., & Müller, R.A. (2018). Multimodal approaches to functional connectivity in autism spectrum disorders: An integrative perspective. *Developmental Neurobiology 78*, 456-73.

Mastrovito, D., Hanson, C., & Hanson, S.J. (2018). Differences in atypical resting-state effective connectivity distinguish autism from schizophrenia. *Neuroimage Clinical 18*, 367-76.

Maximo, J.O., Keown, C.L., Nair, A., & Müller, R.A. (2013). Approaches to local connectivity in autism using resting state functional connectivity MRI. *Frontiers in Human Neuroscience* Oct 8; 7:605. doi:10.3389/fnhum.2013.00605.

Mitchell, J.P. (2009). Social psychology as a natural kind. *Trends in Cognitive Sciences 13*, 246-51.

Mizuno, A., Villalobos, M.E., Davies, M.M., Dahl, B.C., & Müller, R.A. (2006). Partially enhanced thalamocortical functional connectivity in autism. *Brain Research 1104*, 160-74.

Monk, C.S., Peltier, S.J., Wiggins, J.L., Weng, S.J., Carrasco, M., Risi, S., et al. (2009). Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *Neuroimage 47*, 764-72.

Mostofsky, S.H., Powell, S.K., Simmonds, D.J., Goldberg, M.C., Caffo, B., & Pekar, J.J. (2009). Decreased connectivity and cerebellar activity in autism during motor task performance. *Brain 132*, 2413-25.

Müller, R.A., Shih, P., Keehn, B., Deyoe, J.R., Leyden, K.M., & Shukla, D.K. (2011). Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cerebral Cortex 21*, 2233-43.

Nebel, M.B., Eloyan, A., Barber, A.D., & Mostofsky, S.H. (2014a). Precentral gyrus functional connectivity signatures of autism. *Front. Syst. Neurosci.* 8: 1524.

Nebel, M.B., Joel, S.E., Muschelli, J., Barber, A.D., Caffo, B.S., Pekar, J.J., & Mostofsky, S.H. (2014b). Disruption of functional organization within the primary motor cortex in children with autism. *Human Brain Mapping 35*, 567-80.

Nielsen, J.A., Zielinski, B.A., Fletcher, P.T., Alexander, A.L., Lange, N., Bigler, E.D., et al. (2013). Multisite functional connectivity MRI classification of autism: ABIDE results. *Frontiers in Human Neuroscience* 7 (September), p.599. doi:10.3389/fnhum.2013.00599.

Olson, I.R., Plotzker, A., & Ezzyat, Y. (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain 130*, 1718-31.

Picci, G., Gotts, S.J., & Scherf, K.S. (2016). A theoretical rut: revisiting and critically evaluating the generalized under/over-connectivity hypothesis of autism. *Developmental Science 19*, 523-48.

Plitt, M., Barnes, K.A., & Martin, A. (2014). Functional connectivity classification of autism identifies highly predictive brain features but falls short of biomarker standards. *Neuroimage Clinical 7*, 359-66.

Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage 59*, 2142-54.

Power, J.D., Mitra, A., Laumann, T.O., Snyder, A.Z., Schlaggar, B.L., & Petersen, S.E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *Neuroimage 84*, 320-41.

Power, J.D., Schlaggar, B.L., & Petersen, S.E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage 105*, 536-51.

Ramot, M., Grossman, S., Friedman, D., & Malach, R. (2016). Covert neurofeedback without awareness shapes cortical network spontaneous connectivity. *Proc Natl Acad Sci USA 113*, E2413-20.

Ramot, M., Kimmich, S., Gonzalez-Castillo, J., Roopchansingh, V., Popal, H., White, E., et al., (2017). Direct modulation of aberrant brain network connectivity through real-time NeuroFeedback. *Elife* Sep 16; 6. pii: e28974. doi:10.7554/eLife.28974.

Raznahan, A., Toro, R., Daly, E., Robertson, D., Murphy, C., Deeley, Q., et al. (2010). Cortical anatomy in autism spectrum disorder: an in vivo MRI study on the effect of age. *Cerebral Cortex 20*, 1332-40.

Redcay, E., Moran, J.M., Mavros, P.L., Tager Flusberg, H., Gabrieli, J.D.E., & Whitfield-Gabrieli, S. (2013). Intrinsic functional network organization in high-functioning adolescents with autism spectrum disorder. *Front. Hum. Neurosci.* 7: 573. doi:10.3389/fnhum.2013.00573.

Robineau, F., Rieger, S.W., Mermoud, C., Pichon, S., Koush, Y., et al. (2014). Self-regulation of inter-hemispheric visual cortex balance through real-time fMRI neurofeedback training. *Neuroimage 100*, 1-14.

Rubenstein, J.L., & Merzenich, M.M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior 2*, 255-67.

Saad, Z.S., Reynolds, R.C., Jo, H.J., Gotts, S.J., Chen, C., Martin, A., et al. (2013). Correcting brain-wide correlation differences in resting-state FMRI. *Brain Connectivity 3*, 339-52.

Satterthwaite, T.D., Elliot, M.A., Gerraty, R.T., Ruparel, K., Loughead, J., Calkins, M.E., et al. (2013). An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data. *Neuroimage 64*, 240-56.

Satterthwaite, T.D., Wolf, D.H., Loughead, J., Ruparel, K., Elliott, M.A., Hakonarson, H., et al. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *Neuroimage 60*, 623-32.

Scharnowski, F., Hutton, C., Josephs, O., Weiskopf, N., & Rees, G. (2012). Improving visual perception through neurofeedback. *Journal of Neuroscience 32*, 17830-41.

Scheel, C., Rotarska-Jagliela, A., Schilbach, L., Lehnhardt, F.G., Krug, B., & Vogeley, K., et al. (2011). Imaging derived cortical thickness reduction in high-functioning autism: key regions and temporal slope. *Neuroimage 58*, 391-400.

Seitz, A.R. (2013). Cognitive neuroscience: Targeting neuroplasticity with neural decoding and biofeedback. *Current Biology 23*, R210-2.

Shibata, K., Watanabe, T., Sasaki, Y., & Kawato, M. (2011). Perceptual learning incepted by decoded fMRI neurofeedback without stimulus presentation. *Science 334*, 1413-5.

Supekar, K., Uddin, L.Q., Khouzam, A., Phillips, J., Gaillard, W.D., Kenworthy, L.E., et al. (2013). Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Reports 5*, 738-47.

Uddin, L.Q., Supekar, K., & Menon, V. (2013a). Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Frontiers in Human Neuroscience* Aug 7; 7:458. doi:10.3389/fnhum.2013.00458.

Uddin, L.Q., Supekar, K., Lynch, C.J., Khouzam, A., Phillips, J., Feinstein, C., et al. (2013b). Salience network-based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry 70*, 869-79.

Van Dijk, K.R., Sabuncu, M.R., & Buckner, R.L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage 59*, 431-8.

Vattikuti, S., & Chow, C.C. (2010). A computational model for cerebral cortical dysfunction in autism spectrum disorders. *Biological Psychiatry 67*, 672-8.

von dem Hagen, E.A., Stoyanova, R.S., Baron-Cohen, S., & Calder, A.J. (2013). Reduced functional connectivity within and between 'social' resting state networks in autism spectrum conditions. *Social, Cognitive, and Affective Neuroscience 8*, 694-701.

Wallace, G.L., Dankner, N., Kenworthy, L., Giedd, J.N., & Martin, A. (2010). Age-related temporal and parietal cortical thinning in autism spectrum disorders. *Brain 133*, 3745-54.

Wallace, G.L., Eisenberg, I.W., Robustelli, B., Dankner, N., Kenworthy, L., Giedd, J.N., et al., (2015). Longitudinal cortical development during adolescence and young adulthood in autism spectrum disorder: increased cortical thinning but comparable surface area changes. *Journal of American Academy of Childhood Adolescent Psychiatry 54*, 464-9.

Weisberg, J., Milleville, S.C., Kenworthy, L., Wallace, G.L., Gotts, S.J., Beauchamp, M.S., et al. (2014). Social perception in autism spectrum disorders: impaired category selectivity for dynamic but not static images in ventral temporal cortex. *Cerebral Cortex 24*, 37-48.

Weiskopf, N., Sitaram, R., Josephs, O., Veit, R., Scharnowski, F., et al. (2007). Real-time functional magnetic resonance imaging: methods and applications. *Magn. Reson. Imaging 25*, 989-1003.

Weng, S.J., Wiggins, J.L., Peltier, S.J., Carrasco, M., Risi, S., Lord, C., et al. (2010). Alterations of resting state functional connectivity in the default network in adolescents with autism spectrum disorders. *Brain Research 1313*, 202-14.

Yuan, H., Young, K.D., Phillips, R., Zotev, V., Misaki, M., & Bodurka, J. (2014). Resting-state functional connectivity modulation and sustained changes after real-time functional magnetic resonance imaging neurofeedback training in depression. *Brain Connectivity 4*, 690-701.

Figure Captions

Figure 1. Resting-state functional connectivity in ASD shows a mixture of cortico-cortical decreases and subcortico-cortical increases. (A) Summary of results from Cheng et al. (2015) using data from the ABIDE database (418 ASD and 509 matched control participants). Decreased functional connectivity in ASD (blue) involved bilateral STS/STG and somatomotor cortex, posterior cingulate and ventromedial prefrontal cortex. Increased functional connectivity in ASD (red) involved connections between bilateral thalamus and left STS, left middle frontal gyrus, and right somatomotor cortex (reproduced from Figure S3, C, in Cheng et

al., 2015; permission pending). (B) Resting-state data from our lab published in Ramot et al. (2017; see also Gotts et al., 2012) with 56 ASD and 62 matched control participants. Data thresholded at P<.001 (FDR-corrected to q<.003) show decreases in ASD involving bilateral STS/STG, somatomotor cortex, left TPJ and left frontal cortex, whereas data thresholded lower (P<.05, q<.03) also show increases in ASD from bilateral thalamus and the caudate nucleus to most of the cortex exhibiting decreases, replicating pattern seen in Cheng et al. (2015).

Figure 2. fMRI neurofeedback study of Ramot et al. (2017). (A) Study design (see text for further description) and location of regions used during training (see also Figure 1B). Increases in correlation in ASD were trained between target 1 (left STS) and target 2 (left somatomotor cortex), with decreases between these two regions and a third control region (right parietal) (reproduced from Figure 2A and 2B, Ramot et al., 2017; permission pending). (B) The impact of neurofeedback training on functional connectivity during the neurofeedback runs among the three regions of interest. The upper left panel shows the functional connectivity between targets 1 and 2, the upper right and lower left panels show the relationships between targets 1 and 2 and the control region, and the lower right panel shows the impact of training on a composite measure involving all relationships. The correlation between targets 1 and 2 and the composite measure show increases in functional connectivity across the four sessions, as well as sustained improvement lasting through the follow-up session (ranging from 5-56 weeks post-training) (reproduced from Figure 3, Ramot et al., 2017; permission pending).

Figure 3. Summary figure of results from Jasmin et al. (2018). Regions showing increased functional connectivity in ASD during conversation and nursery rhyme repetition are shown in red. Regions showing decreased functional connectivity in ASD during rest (from the Ramot et al., 2017, data; see also Figure 1B) are shown in blue. The thalamus and ventral striatum (shown in green) exhibited increased functional connectivity in ASD to cortex in both contexts, suggesting that these relationships may be invariant to behavioral state and core to the condition of ASD.