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Research Report

Aberrant functional connectivity in autism: Evidence from low-frequency BOLD signal fluctuations

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ABSTRACT

A number of recent studies have examined functional connectivity in individuals with Autism Spectrum Disorders (ASD), generally converging on the finding of reduced interregional coordination, or underconnectivity. Underconnectivity has been reported between many brain regions and across a range of cognitive tasks, and has been proposed to underlie behavioral and cognitive impairments associated with ASD. The current study employed functional connectivity MRI (fcMRI) to examine interregional correlations of low-frequency BOLD signal fluctuations in 10 high-functioning participants with ASD and 10 typically developing control participants. Whole-brain connectivity with three seed regions of interest (left middle frontal, left superior parietal, and left middle occipital cortex) was evaluated using fMRI datasets acquired during performance of a source recognition task. While fcMRI patterns were found to be largely similar across the two groups, including many common areas, effects for the ASD group were generally more extensive. These findings, although inconsistent with generalized underconnectivity in ASD, are compatible with a model of aberrant connectivity in which the nature of connectivity disturbance (i.e., increased or reduced) may vary by region. Taking into consideration methodological factors that might influence measured fcMRI effects, we suggest that ASD is associated with an inefficiency in optimizing network connections to achieve task performance.

1. Introduction

Autism spectrum disorders (ASD) are a group of complex neurodevelopmental disorders defined by impairments in social, behavioral, and communicative functioning (APA, 2000). The precise nature of the neuropathology in ASD is not fully understood. MRI and postmortem studies have identified cellular and volumetric abnormalities of numerous brain regions (Rapin and Katzman, 1998; Sokol and Edwards-Brown, 2004; Trottier et al., 1999), yet with the exception of the relatively consistent finding of early brain overgrowth (Courchesne et al., 2001; Hazlett et al., 2005; Sparks et al., 2002), there is little consensus regarding primary neuroanatomical disturbance. Functional neuroimaging investigations

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have been similarly inconsistent, with reports of atypical brain response in a variety of areas. Nonetheless, evidence of aberrant localization, intensity, and variability of neural activity in ASD suggests widely disrupted functional brain organization (Cody et al., 2002; Courchesne et al., 2004).

Inconsistent reports of regional brain abnormalities are not particularly surprising given the developmental nature of ASD. It is a strongly genetic disorder marked by atypical early brain growth (Courchesne et al., 2001, 2003), abnormal patterns of white matter development (Courchesne et al., 2001), and impairment in numerous cognitive domains by age three (APA, 2000). Such early disturbances undoubtedly alter developmental trajectories for afflicted individuals in diverse and complex ways, and would therefore not be predicted to have circumscribed neural effects. Rather, effects would be widespread, reflecting the ongoing interplay of pathology, normal maturational processes, and experience. Increasingly, research into the neural bases of ASD is moving away from explanations of isolated brain disturbances toward characterization of alterations in neural circuitry.

A number of recent studies have assessed anatomical connectivity in ASD through examination of white matter volume and integrity. On the whole, evidence from volumetric studies suggests atypical white matter growth patterns. That is, the relationship between age and white matter volume is abnormal, such that enlarged volume may be observed relative to typically developing individuals at one age, with relative reductions in volume or no group differences noted at other ages (Carper et al., 2002; Courchesne et al., 2001, 2003; Herbert et al., 2003, 2004). One of the most commonly reported regions of white matter abnormality is the corpus callosum, which has been found to be smaller in ASD in several studies (Boger-Megiddo et al., 2006; Chung et al., 2004; Piven et al., 1997; Vidal et al., 2006; Waiter et al., 2005). Disturbance of this major pathway for interhemispheric information transfer provides compelling evidence of altered connectivity in ASD (Just et al., 2007; Kana et al., 2006). Additional evidence of aberrant anatomical connectivity has emerged from diffusion tensor imaging and transverse relaxation time imaging, which evaluate the integrity rather than volume of cerebral white matter. While the majority of studies employing these methodologies have demonstrated reduced white matter integrity in ASD (Alexander et al., 2007; Barnea-Goraly et al., 2004; Hendry et al., 2006), recent findings from Ben Bashat et al. (2007) suggest that very young children with autism (1.8–3.3 years of age) may show precocious axonal development and myelination.

In addition to investigations of anatomical connectivity, information about patterns of functional connectivity will likely be necessary to further understand the profile of cognitive and behavioral impairments associated with ASD. In particular, functional connectivity approaches can help characterize the neural basis of higher-order integrative processes, believed to be particularly impaired in this population (Hill and Frith, 2003; Minshew et al., 1997, 2002). Functional connectivity MRI (fcMRI) assesses the correlation of BOLD signal fluctuations across brain regions and is based on the observation that interacting regions demonstrate similar BOLD signal profiles (Biswal et al., 1995; Hampson et al., 2002; Xiong et al., 1999). When measured during task performance, functional connectivity may reveal networks of regions coordinating to meet the particular cognitive demands of the task. Resting-state functional connectivity measures, on the other hand, are considered less context-dependent, and have the potential to reveal widespread neuroanatomical networks in the human brain (see Fox and Raichle, 2007 for review). Although several recent studies have investigated task-related functional connectivity in ASD (Just et al., 2004, 2007; Kana et al., 2006, 2007; Kleinhans et al., 2008; Koshino et al., 2005, 2008; Welchew et al., 2005), predominantly showing reduced functional connectivity, or "underconnectivity", evidence of altered connectivity associated with task-free conditions remains limited (Cherkassky et al., 2006; Kennedy and Courchesne, 2008).

Some functional domains, such as theory of mind and face processing, have been extensively studied in ASD with neuroimaging techniques. Much less is known, however, about the functional organization of memory in this population. Within the behavioral literature, numerous studies have reported impairment of higher-order memory abilities. For example, across a series of studies, Minshew and colleagues have shown that while simple memory abilities are typically intact, memory for more complex material is often compromised (Minshew et al., 1997; Minshew and Goldstein, 1998, 2001; Williams et al., 2006). Furthermore, episodic memory has been found to be impaired in ASD relative to control participants when task performance is aided by spontaneous use of organizational strategies (Bennetto et al., 1996; Minshew and Goldstein, 1993, 2001; Tager-Flusberg, 1991). This finding likely reflects impaired higher-order integrative processes in ASD, on which spontaneous organization of items in memory relies. Source memory, a component of episodic memory referring to the ability to recall from which source and in which context an item was encoded into memory, has not been widely studied in ASD. Results from the few published studies have been mixed, providing inconsistent evidence of source memory deficits (Bennetto et al., 1996; Bowler et al., 2004; Hala et al., 2005; O'Shea et al., 2005).

The present study examined functional connectivity in ASD and control participants in the context of a source memory task. Source memory judgments required memory for single words and their encoding context (whether the word had been encountered in the auditory or visual modality). This task is well suited to detect regions involved in higher-order integrative functions, as performance relies on coordination between distributed brain regions to evaluate and integrate information presented across the two modalities. Three regions, identified on the basis of conventional activation analyses, were chosen as seed volumes for functional connectivity analyses. The three seed regions showed distinct profiles of source memory related activation across the two groups; one was engaged during task performance by control participants only (left middle frontal gyrus), one by ASD participants only (left middle occipital gyrus), and one by both groups (left superior parietal lobule).

2. Results

2.1. Behavioral performance

To characterize memory performance, six possible response types were examined: correct source attribution responses (correct identification of the study modality of previously encountered words), correct rejections (correct identification of unstudied words as "new"), source attribution errors (incorrect identification of study modality), false positive errors (incorrect identification of a "new" word as previously studied), miss responses (incorrect identification of a studied word as "new"), and response failures (trials on which no response was made). Relative to the control group, the ASD group showed fewer correct source attribution responses (t_{18}=2.27, p=.04), and a greater number of miss responses (t_{18}=2.87, p=.01) and response failures (t_{18}=2.37, p=.03). The groups did not differ with regard to correct identification of unstudied words, source attribution errors, or false positive errors (ps>.05). Taken together, results from these six behavioral indices suggest poorer general recognition and source recognition performance in the ASD group.

2.2. Activation patterns

Activation results are briefly summarized to document the positioning of seed volumes for fcMRI analyses and to provide a context for interpreting functional connectivity findings. Both ASD and control participants exhibited widespread brain activity during source recognition. Common regions of activation for the two groups included left inferior and superior parietal lobules, left angular gyrus, left supramarginal gyrus, right insula, left cerebellum, right cingulate gyrus, and left precentral gyrus. Significant activation in extrastriate regions (including left middle occipital, lingual, and fusiform gyri) was seen in autism but not control participants. Control participants showed robust activity in bilateral dorsolateral prefrontal regions, while activation in these regions failed to reach significance for ASD participants.

2.3. Functional connectivity with left middle frontal gyrus

The left middle frontal seed volume and its whole-brain pattern of functional connectivity are shown in Fig. 1a. Regions of significant cross-correlation with this seed are summarized in Table 1. In both ASD and control groups, the BOLD signal in left middle frontal gyrus [Brodmann area 9 (BA9)] was significantly correlated with the BOLD signal in multiple brain regions, including the right middle frontal gyrus, posterior left middle frontal gyrus and supplementary motor area, left precentral gyrus, left inferior parietal cortex, left angular gyrus, left middle cingulate cortex, left posterior fusiform gyrus, and left cerebellum. Although the two groups showed similar regions of significant fcMRI effects in the left hemisphere, only the ASD group showed significant fcMRI effects in homologous right hemisphere regions (i.e., right supplementary motor area, precentral gyrus, inferior parietal cortex, angular gyrus, middle cingulate cortex, and cerebellum). Additional regions of connectivity in the ASD group were also found in bilateral postcentral, posterior cingulate, middle temporal, and striate and extrastriate cortex. Direct group comparison revealed greater fcMRI effects for ASD participants in several regions, some of which did not reach significance in either within-group analysis. There were no regions of greater connectivity in control than ASD participants.

2.4. Functional connectivity with left superior parietal lobe

See Table 2 and Fig. 1b for a complete listing of regions of significant cross-correlation with the left superior parietal seed (BA7). Significant connectivity was detected in left inferior and middle frontal gyri, left inferior parietal cortex, bilateral precuneus, and left fusiform gyrus in both groups. Again, while the groups displayed similar fcMRI effects in left hemisphere regions, only the ASD group displayed significant fcMRI effects in homologous right hemisphere regions (i.e., right inferior and middle frontal gyri, right inferior parietal cortex, and right fusiform gyrus). Additional regions of connectivity in the ASD group were also observed in bilateral supplementary motor, posterior cingulate, and striate and extrastriate regions. Between-group analyses revealed significantly greater connectivity for the ASD group in pericentral, perisylvian, and extrastriate regions. Direct group comparison revealed no areas of greater connectivity for the control group.

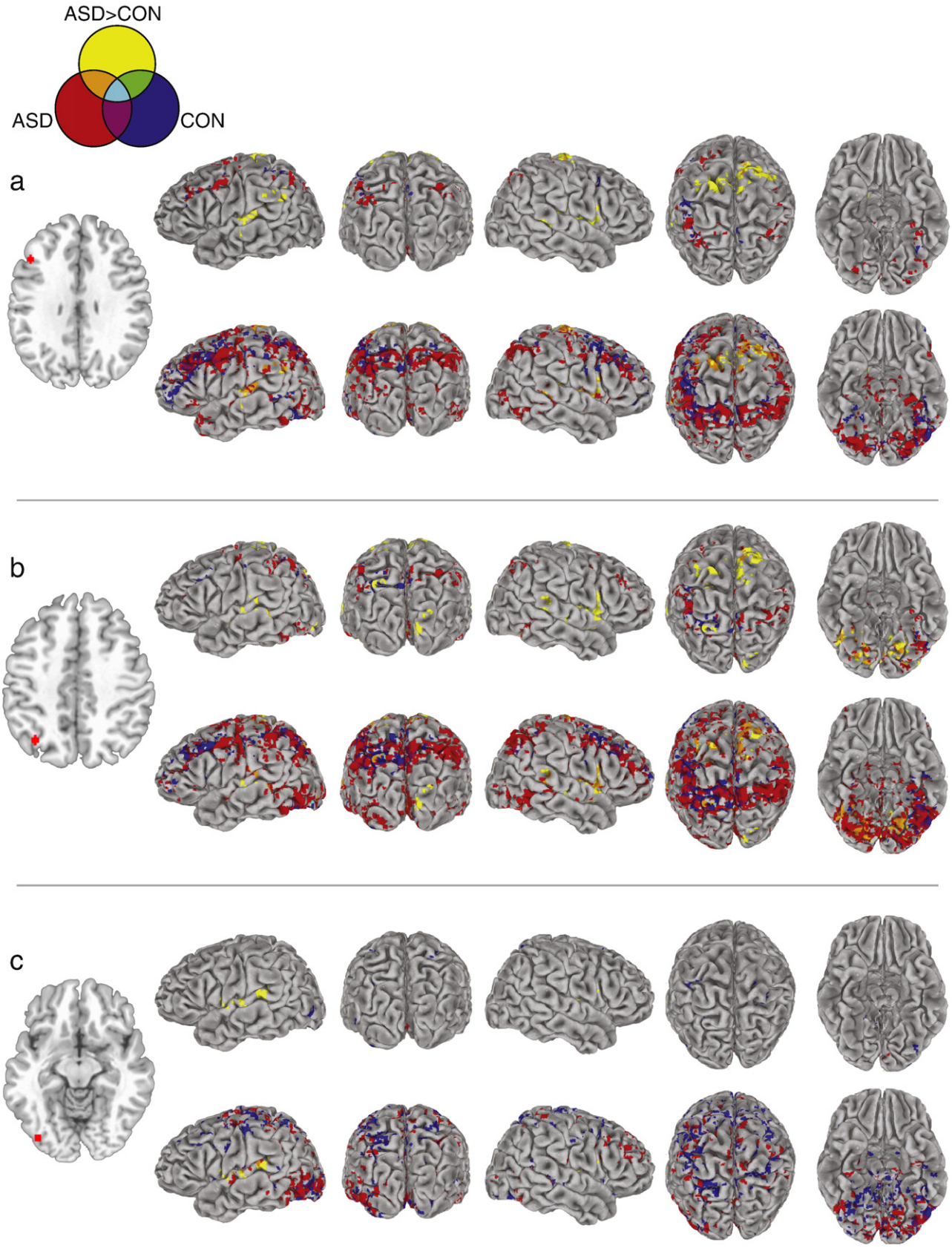
2.5. Functional connectivity with left middle occipital gyrus

See Table 3 and Fig. 1c for a complete listing of regions of significant cross-correlation with the left middle occipital seed (BA18). In contrast to results from the other two seed volumes, the control group displayed a greater number of regions of significant cross-correlation with the left middle occipital seed. These regions included right superior and middle frontal gyri, left pre- and postcentral gyri, bilateral supplementary motor area, left inferior parietal cortex, bilateral superior parietal cortex, and right lingual gyrus. For the ASD group, significant functional connectivity with the left middle occipital seed was limited to bilateral regions in the calcarine sulcus. While the control group showed more regions of functional connectivity in within-group analyses, direct group comparison yielded only clusters with greater fcMRI effects in the ASD group, located in bilateral inferior frontal and superior temporal gyri.

Fig. 1 – Seed volumes and corresponding functional connectivity maps. (a) Original and low-threshold results for the left middle frontal gyrus (–43, 23, 30), (b) left superior parietal cortex (–33, –63, 42), and (c) left middle occipital gyrus (–37, –79, –8). Original threshold images show regions in which BOLD timeseries are significantly correlated with seed volume timeseries; that is, regions surpassing the α=.05 corrected voxel-cluster significance threshold. In low-threshold images, individual voxel intensity thresholds for within-group comparisons are less stringent ($p_{voxel} \leq .001$, versus $p_{voxel} \leq .0001$ for original maps) allowing less strongly correlated regions to emerge.

2.6. *Post-hoc correlation analyses*

Although no significant group differences in IQ were detected (see Table 4), negative findings could well be a reflection of the small sample sizes, which might limit statistical power to detect such differences. Post-hoc correlation analyses were thus performed to assure that fcMRI findings are minimally influenced by potential group disparities in IQ. To examine the



relationship between intellectual functioning and fcMRI effects in the ASD group, correlations between connectivity strength (z′ values) and FSIQ were computed for each of the 19 regions showing between-group fcMRI differences (as detailed in Tables 1, 2 and 3). The results for each region were evaluated at the $\alpha = .01$ level, to mitigate the consequences of inflated Type-1 error associated with multiple comparisons. This approach balances the risk of identifying spurious relationships with the risk of failing to identify potentially meaningful relationships through use of more conservative Type-1 error controls (e.g., Bonferroni correction). From the 19 regions evaluated, only one significant correlation emerged. In the right superior temporal region (centered at 53, −11, 8), an inverse relationship was detected between FSIQ and functional connectivity with the left middle occipital seed ($r = -.81$, $p = .005$), suggesting that higher FSIQ was associated with reduced connectivity strength.

3. Discussion

3.1. *General remarks*

The present study aimed to further characterize the neural bases of complex integrative functions and their breakdown in ASD through evaluating whole-brain fcMRI patterns in 10 high-functioning participants with ASD and 10 typically developing control participants. Three seed regions for functional connectivity analyses were identified from conventional activation analysis of a source memory dataset. One region showed significant response during source memory performance in the control group only (left middle frontal), one showed significant response in both groups (left superior parietal), and one showed significant response in the ASD group only (left middle occipital). Across the three seed regions, the general pattern of fcMRI findings was remarkably consistent. Specifically, although the two groups displayed many similarities, ASD was associated with increased functional connectivity that was apparent on two levels. First, the ASD group demonstrated a greater number of regions of significant functional connectivity in within-group analyses for both the left middle frontal and left superior parietal seeds. Second, all between-group comparisons revealed regions of significantly greater correlation with seed volume timeseries for the ASD group, whereas no regions showing greater connectivity for the control group were identified.

Interestingly, many regions of increased fcMRI effects in ASD relative to control participants upon direct group comparison did not reach significance in either within-group comparison. This pattern suggests that while the groups showed differences in connectivity with these areas, these regions may not constitute primary network components for either group. Greater functional connectivity with these regions in the ASD group likely represents low-level (i.e., sub-threshold) synchronization that is not present in the control group. Indeed, inspection of within-group data at a more lenient statistical threshold revealed that many regions showing significant between-group effects (i.e., greater connectivity in the ASD group) were characterized by moderate fcMRI effects in the ASD but not control group (see Fig. 1). The ASD group thus not only displayed a greater number of regions of significant connectivity, but also showed additional regions of weaker sub-threshold connectivity. Taken together, these findings suggest more diffuse patterns of connectivity in this population.

3.2. *Relation to previous findings*

Our results appear to be inconsistent with the hypothesis of generalized underconnectivity in ASD, put forth by Just et al. (2004) and supported by several recent fcMRI studies. This hypothesis proposes that ASD is characterized by a dysfunction of integrative circuitry, with decreased cortical connectivity underlying documented cognitive difficulties with complex integrative processing. While our behavioral findings of impaired source memory performance support disruption of higher-order integrative processes, the fcMRI findings suggest that this disruption may in part reflect overabundant or diffuse, rather than reduced, functional connectivity. Our results also point toward the potential influence of various methodological decisions on measured fcMRI effects, such as statistical procedures for allowing or disallowing task-related effects, and choice of seed volumes or regions of interest (ROIs).

One of the primary methodological differences between the current study and those that have reported underconnectivity in ASD involves our decision to partial task-related effects from the fMRI timeseries prior to assessing interregional correlations. This approach, which aims to isolate task-independent low-frequency BOLD signal fluctuations, was motivated by the pioneering fcMRI studies of Biswal et al. (1995) showing BOLD signal correlation within the motor network during rest. Such system-specific correlations in the resting state have also been confirmed for auditory and visual (Cordes et al., 2000), language (Cordes et al., 2000; Hampson et al., 2002), attention (Fox et al., 2006a), and episodic memory networks (Vincent et al., 2006). While our study did not utilize true resting-state data, it parallels resting studies in its focus on intrinsic, rather than task-driven, temporal synchronization across brain regions. It thereby differs from studies that have examined task-related functional connectivity in ASD [using tasks such as sentence comprehension (Just et al., 2004; Kana et al., 2006), working memory (Koshino et al., 2005; Koshino et al., 2008), inhibitory control (Kana et al., 2007), planning and problem solving (Just et al., 2007), and face processing (Kleinhans et al., 2008; Welchew et al., 2005)].

Given the growing evidence that patterns of interregional correlation are modulated by task-evoked activation (Fox and Raichle, 2007; Fransson, 2006; Hampson et al., 2002, 2004; Jiang et al., 2004; Lowe et al., 2000; Newton et al., 2007; Nir et al., 2006), it is not surprising that our findings diverge from those of previous studies. In general, correlations between activated regions are thought to increase during cognitive task performance. Thus, one explanation that might reconcile the current findings with those of task-related underconnectivity would be a failure of typical network upregulation. That is, if the normal pattern of increasing interregional coordination with task performance

Table 1 – Regions of significant cross-correlation with the left middle frontal seed

ASD						Control						ASD>Control					
Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates		
			x	y	z				x	y	z				x	y	z
Frontal																	
R precentral gyrus	4	5.0	33	−29	58	L precentral and L middle frontal gyrus	6/9	4.9	−41	−3	42	B precentral gyrus and B SMA	4/6	3.9	28	−19	63
L middle frontal gyrus and L SMA	6	4.9	−29	−13	62	R inferior frontal and R middle frontal gyrus	6/9	4.6	31	9	30						
R inferior frontal gyrus	9/44	4.9	31	7	28												
R SMA and R superior frontal gyrus	6	4.5	7	−19	70												
L SMA and L superior frontal gyrus	6	4.5	−5	7	54												
Temporal																	
L angular gyrus and L inferior parietal lobule	39/7	4.5	−37	−70	33							R superior temporal and R Heschl's gyrus	22/41	4.4	53	−10	8
R inferior temporal and R middle temporal gyrus	37	4.4	41	−65	−4							L superior temporal gyrus	41/42	3.8	−57	−27	12
												R parahippocampal gyrus	34	3.6	19	0	−15
												L middle temporal gyrus	21/22	3.5	−55	−36	−1
Parietal																	
L inferior parietal lobule	40	5.1	−49	−45	42	L inferior parietal lobule	40	5.4	−41	−43	44	L supramarginal gyrus	40	3.6	−50	−46	27
L supramarginal gyrus and L middle temporal gyrus	40/22	5.0	−49	−52	28	B precuneus	7	4.6	7	−77	44	L postcentral gyrus	1/2	3.5	−23	−31	64
R superior parietal lobule and R angular gyrus	7/39	5.0	29	−71	42	L angular gyrus	39	4.5	−34	−61	33	L precuneus	7	3.1	−12	−44	58
R inferior parietal lobule and R supramarginal gyrus	40	4.9	45	−43	44												
L postcentral and L precentral gyrus	3/4	4.6	−39	−33	52												
L postcentral gyrus	3	4.4	−45	−17	34												
Occipital																	
R lingual gyrus and B calcarine sulcus	18/17	4.9	9	−79	−10												
L fusiform gyrus and L cerebellum	19	4.8	−11	−65	−12												
Cingulate																	
B posterior cingulate	23/31	5.0	5	−39	28	L middle cingulate cortex and L SMA	32/6	4.5	−9	19	40						
R middle cingulate cortex	23	4.7	3	−19	30												
L middle cingulate cortex and L precuneus	31/7	4.6	−5	−31	46												
Cerebellar																	
R cerebellum		4.4	9	−35	−18	L cerebellum and L fusiform gyrus	37	4.5	−35	−51	−22						

Table 2 – Regions of significant cross-correlation with the left superior parietal seed

ASD						Control						ASD>Control					
Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates		
			x	y	z				x	y	z				x	y	z
Frontal																	
R SMA and R superior frontal gyrus	6	5.5	5	−23	70	L inferior frontal and L middle frontal gyrus	9/46	4.8	−51	29	26	B SMA and L postcentral gyrus	6/1	5.4	5	−23	70
R inferior frontal and R middle frontal gyrus	9/8	5.0	39	15	20							R inferior frontal gyrus	44	3.4	54	3	18
L middle frontal and L inferior frontal gyrus	9	4.9	−37	21	36												
L precentral gyrus	6	4.7	−25	1	60												
R middle frontal and R inferior frontal gyrus	9/44	4.7	33	5	26												
L SMA	6	4.7	−11	−11	52												
R middle frontal and R superior frontal gyrus	10	4.5	27	45	8												
R middle frontal and R superior frontal gyrus	8/6	4.3	27	13	47												
Temporal																	
L fusiform gyrus	37/19	4.7	−34	−60	−18							L superior temporal gyrus	22	4.0	−35	−13	−4
R fusiform and R inferior temporal gyrus	37/19	4.6	42	−53	−13							R superior temporal gyrus and R middle temporal gyrus	22/38	4.0	51	−13	8
												L middle temporal gyrus	22/21	3.7	−55	−37	0

Parietal																
R inferior parietal lobule and R angular gyrus	7/39	5.0	46	−57	40	B precuneus	7	5.1	7	−72	40	L superior parietal lobule and L inferior parietal lobule	7	4.0	−25	−81	40
L inferior pariteal lobule	40	4.8	−47	−44	43	L inferior parietal lobule	40	4.5	−44	−36	45						
B precuneus	7	4.3	−3	−71	33												
Occipital																
L superior occipital and L middle occipital gyrus	18	4.6	−19	−75	20							L fusiform gyrus, L lingual gyrus, and L cerebellum	19/18	4.2	−17	−67	−12
B calcarine sulcus	17	4.5	4	−82	−4												
B cuneus	18	4.2	3	−74	15												
Cingulate																
R middle cingulate cortex	23	4.6	9	−23	30												
B cingulate gyrus	31	4.4	0	−37	34												
Cerebellar																
R cerebellum and R lingual gyrus	37/19	4.8	18	−66	−13	L cerebellum and L fusiform gyrus	37/19	4.2	−35	−51	−22						
Subcortical																
B thalamus		4.9	−11	−1	6												
R hippocampus and R parahippocampal gyrus	27	4.8	21	−27	−2												
L putamen		4.3	−23	−3	4												

Table 3 – Regions of significant cross-correlation with the left middle occipital seed

ASD						Control						ASD>Control					
Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates			Location	BA	Peak z	Talairach coordinates		
			x	y	z				x	y	z				x	y	z
Frontal																	
						L precentral and L postcentral gyrus	4/3	4.9	−39	−17	42	R inferior frontal gyrus	44	3.5	44	−4	20
						B SMA	6	4.8	7	3	50	L inferior frontal gyrus	44	2.9	−47	−1	13
						R superior frontal and R middle frontal gyrus	6	4.8	23	13	50						
Temporal																	
												R superior temporal and R Heschl's gyrus	22/41/42	4.6	53	−11	8
												L superior temporal and L Heschl's gyrus	22/41/42	4.0	−63	−35	14
Parietal																	
						R superior parietal lobule	7	4.8	23	−59	56						
						L superior parietal and L inferior parietal lobule	40	4.4	−38	−43	50						
						L inferior parietal lobule and L middle occipital gyrus	19	4.2	−39	−73	0						
Occipital																	
B calcarine sulcus	17	4.7	3	−89	0	R lingual gyrus	18/19	4.5	9	−51	2						

Table 4 – Participant characteristics

Group	Diagnosis	Age	IQ			ADI-R subscales		
			VIQ	PIQ	FSIQ	Soc	Verb	Behav
ASD	Aut	21	63	72	65	18	17	6
ASD	Aut	15	76	89	80	27	19	7
ASD	Aut	43	86	115	100	22	19	6
ASD	Aut	14	108	108	108	26	19	6
ASD	Aut	26	80	81	79	30	16	11
ASD	Aut	38	98	114	104	21	22	10
ASD	Asp	19	111	99	106	21	20	7
ASD	Asp	19	97	105	101	13	12	3
ASD	Asp	20	116	109	114	7	11	10
ASD	Asp	15	102	117	109	18	11	6
ASD Mean:		23.0	93.7	100.9	96.7	20.3	16.6	7.2
SD:		9.9	17.0	15.4	16.1	6.8	4.0	2.4
Control Mean:		25.8	109.2	108.5	110.0			
SD:		9.9	15.1	12.8	15.8			

Notes. Aut = Autism, Asp = Asperger's Syndrome. VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full-Scale IQ. Soc = Social communication subscale (min. cutoff = 10), Verb = Verbal communication subscale (min. cutoff = 8), Behav = Restricted Behavior subscale (min. cutoff = 3). Control age range = 19–40; FSIQ = 88–129; VIQ = 89–120; PIQ = 93–139. Control group IQ estimates based on scores from five randomly selected control participants. Control and ASD participants did not differ with respect to age ($t_{18} = 0.63$, $p = 0.54$), FSIQ ($t_{13} = 1.52$, $p = 0.15$), PIQ ($t_{13} = 0.95$, $p = 0.36$), or VIQ ($t_{13} = 1.72$, $p = 0.11$).

did not hold in ASD, task-driven functional connectivity would likely appear deficient, while intrinsic connectivity might not. Thus, rather than indicating an absence or restriction of connections, task-related underconnectivity may instead reflect an inefficiency in optimizing network connections to achieve task performance (e.g., increasing coherence between task-relevant regions).

To date, only two studies have explicitly examined functional connectivity in ASD during rest (Cherkassky et al., 2006; Kennedy and Courchesne, 2008). Cherkassky et al. (2006) analyzed data from fixation blocks of blocked-design fMRI paradigms, and reported reduced functional connectivity in ASD between selected cortical ROIs. This study focused exclusively on functional connectivity between default mode regions (defined as regions showing task-related "deactivation", or significantly greater BOLD response during fixation than task blocks). Activity in default mode regions during rest is considered to be associated with self-reflective and inwardly guided thought (Buckner et al., 2008; Mason et al., 2007) or a state of ready alertness (Gilbert et al., 2007), which is interrupted when an individual engages in a demanding task. In this sense, paradoxically, the "active" state for default regions is in fact rest. Functional connectivity in the default network has been shown to be stronger during rest than during cognitive task performance (Fransson, 2006), further indicating that these regions are more highly coordinated and commonly directed during rest. If, as hypothesized, ASD is characterized by an inefficiency in organizing network components to accomplish a given function (in this case, inwardly guided thought or watchfulness), functional connectivity between default mode regions would be predicted to be reduced at rest.

Kennedy and Courchesne (2008) also reported reduced resting-state functional connectivity in ASD between default mode regions (referred to as regions of the Task-Negative Network). They found a different pattern of results, however, when they examined resting coordination between regions that commonly activate during task performance (i.e., regions of the Task-Positive Network). In contrast to findings of reduced connectivity between Task-Negative regions, functional connectivity between Task-Positive regions did not differ between ASD and control participants. While the authors discuss these findings in terms of the different functions performed by the two networks (characterized as socioemotional processing vs. goal-directed cognition), they also fit well within a framework of disrupted network optimization/upregulation in ASD.

The foregoing discussion highlights the importance of considering both the contribution of task-evoked activation to functional connectivity measures, and the nature of the brain regions chosen for analysis. Seed-based connectivity analyses, such as those employed in the present study, examine correlations with seed region timeseries across all other voxels in the brain. ROI-based approaches, in contrast, restrict examination of correlational effects to a selected group of brain regions. The majority of fcMRI studies in ASD have used ROI-based analyses, and have often limited investigation to a subset of regions showing significant task-related activation (e.g., Cherkassky et al., 2006; Just et al., 2007; Kana et al., 2006, 2007; Koshino et al., 2008). This could explain why our observed pattern of over-extensive cortical connectivity in ASD has not previously been reported; by not imposing such limitations, our connectivity analyses were likely more sensitive to distributed effects. Consistent with this suggestion, two recent studies from our group utilizing similar analysis techniques to examine functional connectivity with subcortical seed volumes also found more extensive fcMRI effects in ASD than control groups (Mizuno et al., 2006; Turner et al., 2006).

3.3. *Global vs. regional connectivity alterations*

Regardless of the contribution of methodological differences across studies, our findings of regionally increased fcMRI effects are not necessarily incompatible with findings of regionally reduced fcMRI effects. It is certainly plausible that early developmental disruptions in ASD do not affect all regions and functions of the developing brain in a uniform manner. Rather, a dynamic system adapting to pathological, maturational, and experiential influences likely reorganizes in more complex and intricate ways, potentially resulting in increased coordination between certain regions, and reduced or unaltered coordination between others. The findings from Kennedy and Courchesne (2008) discussed above support this notion of region-specific rather than global connectivity alterations in ASD. Moreover, regional differences in functional connectivity can be appreciated within the present study by comparing the three seed volumes chosen for analysis.

As mentioned above, the three regions chosen as seed volumes showed distinct patterns of activation during performance of the source memory task. One might reasonably expect that differing activation profiles would correspond to different patterns of functional connectivity. Yet, contrary to this expectation, results of direct group comparisons showed consistently greater fcMRI effects in the ASD group across all three seed regions. A particularly interesting pattern was observed for the left extrastriate seed. In contrast to within-group results from the other two seeds (for which the ASD group showed a greater number of functionally connected regions), a greater number of significantly coordinated regions were identified for the control group. This finding may appear somewhat surprising given that only the ASD group showed activation in this region during source recognition. That is, on the basis of activation results, one might expect left extrastriate cortex to be more coordinated with other regions involved in source memory performance in ASD. However, because our analysis assesses interregional correlations after accounting for task-evoked BOLD signal fluctuations, the unique connectivity profile observed for this region may instead relate more generally to its function as a lower-order perceptual processing region (versus the higher-order associative functions of the other seed regions). Such a divergence of patterns between early developing lower-order regions and later developing higher-order regions fits well within a developmental model of ASD, as pathological events may differentially affect regions with restricted vs. protracted developmental courses (Courchesne et al., 2007).

3.4. *Implications of increased functional connectivity*

In considering potential implications of over-extensive connectivity in ASD, we suggest that reports of regional "over-connectivity" or "underconnectivity", while seemingly at odds, may both be reflections of widely aberrant connectivity in ASD and may in fact have comparable consequences. Specifically, deficits in complex integrative processing could arise from either over-abundant or insufficient coordination between brain regions. An expected functional outcome of abnormal neural connectivity is a disruption of the signal-to-noise balance in cortical processing (Belmonte et al., 2004). In signal-to-noise terms, diffusely increased functional connectivity may impair cognitive processing by increasing noise in the system. That is, coordination with nonessential regions may introduce low-level crosstalk, thereby obscuring signal across primary network components. In the case of reduced functional connectivity, lack of coordination across primary components may result in diminished signal. Thus, whether the signal-to-noise balance is disrupted by increased noise (increased connectivity) or decreased signal (restricted connectivity), the outcome is reduced efficiency of information transfer. Functions that rely on integration across distributed networks of regions will likely be most affected by this loss of efficiency.

3.5. *Study limitations*

One important limitation of the current study concerns the potential influence of task performance on intrinsic BOLD signal fluctuations. Despite the measures taken to isolate intrinsic fluctuations (e.g., applying a lowpass filter to remove higher frequency signal components, partialling task-evoked contributions to signal variance), data were collected in the context of a source memory experiment and the cognitive state of participants cannot simply be subtracted. Thus, while we consider our findings to be less task-dependent than those of studies that have not taken such measures, our approach clearly differs from studies of resting connectivity.

Low-frequency BOLD signal fluctuations have been shown to persist during task performance (Bianciardi et al., in press; Fox et al., 2006b, 2007), however there is continuing debate as to the whether task-evoked and spontaneous fluctuations can be reliably separated (Arfanakis et al., 2000; Fair et al., 2007; Fox et al., 2006b, 2007). A study by Fair et al. (2007) directly compared connectivity patterns in task-regressed data from an event-related paradigm (employing methods similar to our own) with connectivity patterns in true resting-state data. While fcMRI patterns derived from task-regressed data were similar overall to those derived from true resting-state data, some regional differences were found.

Such findings suggest that non-linear task effects, which survive task regression, might influence fcMRI results (see above for discussion of task-evoked activation effects on interregional correlations). Although incomplete removal of task effects represents an inherent limitation of our approach with regard to approximating resting connectivity, we have interpreted our results primarily in comparison with studies of task-driven connectivity. Thus, our speculation that ASD may be associated with reduced task-related upregulation of functional connections rests more on the ability of our approach to diminish the influence of task-evoked signal fluctuations, than on its ability to completely remove them.

A further limitation of the current study is our modest sample size, which may impact both statistical power and generalizability of findings. The issue of statistical power is perhaps most relevant in the case of negative findings. For example, group differences on IQ measures were not significant despite sizeable mean differences (see Table 4). Acknowledging that group differences in intellectual functioning could pose difficulty for interpretation of fcMRI results, we performed post-hoc correlation analyses to examine the extent to which

between-group fcMRI findings were influenced by level of general intellectual functioning. These analyses investigated the association between functional connectivity strength and FSIQ within the ASD sample. Overall, the lack of a significant association in 18 of the 19 regions evaluated indicates that fcMRI effects in the ASD group are not systematically related to IQ. It is therefore unlikely that the present findings can be attributed to group differences in general intellectual functioning.

Although performance on the source memory task was clearly above chance in all ASD participants, it was overall lower than in control participants. The question of whether performance differences might have affected fcMRI findings relates to the more general issue of task effects discussed above. Since we removed linear task effects in our fcMRI analyses, our results are presumably less sensitive to group differences in performance than those from previous fcMRI studies that have not regressed out task effects. However, given the likely complex interrelationship between task performance, regional brain activation, and functional connectivity, subtle effects of task and behavioral performance cannot be ruled out.

3.6. *Future directions*

The current findings raise the possibility that intrinsic and task-driven connectivity patterns may differ in ASD, but further studies that directly contrast active and resting conditions will be required for definitive confirmation. In addition, our results suggest that whole-brain fcMRI studies are needed for a comprehensive characterization of connectivity disturbances in ASD. Nearly all studies to date have focused solely on task-driven functional connectivity between ROIs identified based on task-evoked activation. Although assessing functional connectivity between co-activated regions provides important information about task-related coordination of those regions, such a focus cannot reveal regions that are functionally connected but not significantly modulated by task performance. Furthermore, given that functional connectivity between task-relevant regions increases during task performance, it is unclear whether between-group differences in task-related functional connectivity represent true differences in underlying connectivity, or simply differences in the modulation of connectivity strength accompanying task performance.

3.7. *Summary*

Functional connectivity patterns across ASD and control participants in the current study were found to be largely similar, including many common areas. Functional networks identified for the ASD group were generally more extensive, however, containing additional correlated regions (for both left middle frontal and left superior parietal seeds), as well as regions of weaker sub-threshold correlation (for all three seeds). Although these findings are inconsistent with suggestions of generalized underconnectivity, they are compatible with a model of aberrant connectivity in which the nature of connectivity disturbance (i.e., increased or reduced) may vary by region. A number of methodological factors may reconcile the present findings with previous reports of regionally reduced connectivity in ASD, most importantly, consideration of whether task-driven or intrinsic effects are examined, and whether analyses are limited to selected ROIs. Taking the potential influence of such factors into consideration, our results suggest that ASD may be associated with atypically diffuse low-threshold ("noisy") connectivity between certain brain regions, and inefficient modulation of functional connectivity during task performance.

4. Experimental procedures

4.1. *Participants*

Ten high-functioning male ASD participants (six diagnosed with autism, four with Asperger's Disorder) and 10 healthy male comparison participants were tested. ASD diagnoses were based on criteria from the DSM-IV (APA, 2000), Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), and Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000). ASD participants meeting criteria for Autistic Disorder on each of the three diagnostic measures were diagnosed with autism. A diagnosis of Asperger's Disorder was given to individuals meeting criteria for Autistic Disorder or ASD on the ADI-R and ADOS, and DSM-IV criteria for Asperger's Disorder. IQ estimates were obtained through administration of either the WAIS-R (Wechsler, 1981), the WAIS-III (Wechsler, 1997), or the WASI (Wechsler, 1999). There were no significant group differences in age, Full-Scale IQ, Performance IQ, or Verbal IQ (see Table 4). All subjects were right-handed, with no reported history of major medical illness, head trauma, substance abuse, neurological disorder, or psychiatric disorder. The experimental protocol was approved by the Institutional Review Board of the University of California, San Diego. Written informed consent was obtained from each subject prior to participation.

4.2. *Task design*

A set of 216 English nouns, each three to nine letters in length with a frequency of usage between 10 and 250 occurrences per million in written language (Coltheart, 1981), was used to create three 72-word lists. The three lists were equated for frequency, imageability, and concreteness. One list was presented in the visual study condition, another in the auditory study condition, and the remaining list was presented as unstudied words during the source memory test.

Participants underwent functional magnetic resonance imaging (fMRI) during performance of both study and test conditions. Prior to scanning they were instructed that a memory test for the presented words would immediately follow the study condition. During the study condition subjects pressed one of two buttons on a modified mouse device to indicate whether each word represented something that could be touched. An iconic depiction of these instructions remained on-screen throughout. The study condition consisted of four runs, two in which words were presented visually and two in which words were presented aurally. Each

run contained 72 word trials presented in a pseudorandomized order. In addition, 52 null trials (i.e., trials during which no stimuli were presented) were randomly interspersed for temporal jittering. Each trial lasted 2600 ms, for a total duration of 5 min 22 s. The word stimuli in the two visual study runs were identical, though presented in different order, as were those in the two auditory study runs. Each word was thus encountered twice in the same modality during study. The order of study runs and study modality were counterbalanced across participants.

Similar to the study condition, the recognition condition consisted of two runs of visually presented words and two runs of aurally presented words. Participants were instructed to press one of three buttons on a mouse device to indicate whether each word had been previously encountered during visual study, during auditory study, or not at all ("new" items). As in the study condition, an iconic depiction of these instruction remained on-screen throughout. Each recognition run contained 54 memory trials and 40 null trials, presented in a pseudorandomized order. The 54 memory trials in each run included 18 auditory study words (i.e., words that had been previously presented in the auditory study condition), 18 visual study words, and 18 unstudied "new" words. The order of recognition runs and recognition modality was counterbalanced across participants. In the present study, functional connectivity analyses were performed on ROIs derived from the visual recognition runs.

4.3. *fMRI acquisition*

All scans were performed on a 1.5 T Siemens Symphony MR scanner (Erlangen, Germany) using a standard clinical head coil. During each of the four runs, 141 whole-brain T2*-weighted axial images were acquired using a single-shot gradient-echo EPI sequence (28 contiguous slices, 4 mm thickness, TR=2600 ms, TE=36 ms, flip angle=90°, FOV=256 mm, 64×64 matrix, in-plane resolution=4 mm^2). A high-resolution 3D MPRAGE structural scan was also acquired for anatomical localization and overlay of statistical maps (180 slices, resolution=1 mm^3, TR=11.08 ms, TE=4.3 ms, flip angle=45°, FOV=256 mm, 256×256 matrix).

4.4. *Activation analyses*

All analyses were conducted using Analysis of Functional NeuroImages (AFNI; Cox and Hyde, 1997). Image preprocessing included motion correction and 3D volume registration, spatial smoothing with an 8-mm FWHM Gaussian kernel, and landmark-based spatial normalization to Talairach space. A deconvolution approach was used for analysis of data from individual participants. Within-group analyses examined BOLD signal change for correct source recognition trials (i.e., trials in which participants correctly identified the study modality of "old" words) relative to null trials, within ASD and control groups separately. For these analyses, results of the deconvolution analysis for each participant were entered into a two-way ANOVA including subject (random effect) and test modality (fixed effect) as factors. A combined voxel-cluster threshold was used to correct for multiple comparisons (Forman et al., 1995), resulting in a corrected significance level of $\alpha=.05$.

4.5. *Functional connectivity analyses*

Three regions identified from BOLD activation analyses were selected as seed volumes for the functional connectivity analyses (Fig. 1). Each seed volume consisted of a spherical region of interest with a radius of 3.5 mm centered at the peak activation coordinates of the cluster: left middle frontal gyrus (−43, 23, 30), left superior parietal cortex (−33, −63, 42), and left middle occipital gyrus (−37, −79, −8). These three regions showed distinct profiles of activation across the two groups. The left middle frontal and superior parietal regions chosen as seed volumes showed robust activation in control participants during source recognition performance, and have been reported in numerous other source memory studies (Cansino et al., 2002; Dobbins et al., 2002, 2004; Kahn et al., 2004; Ranganath et al., 2000; Rugg et al., 1999; Wilding, 1999). The ASD group also showed significant BOLD response in the left superior parietal region, while activation in the left middle frontal gyrus was weaker than in the control group and did not surpass the cluster corrected threshold. The left middle occipital region selected as the third seed volume showed significant activation in the ASD group only, possibly reflecting an increased reliance on lower-level visual processing during memory performance.

Data preprocessing included removing the linear trend in each task run and applying a 0.1 Hz lowpass filter to isolate low-frequency components of the BOLD signal. The mean timeseries of each seed volume was then computed for each individual. Multiple regression analysis was performed to partial effects due to head motion and task presentation prior to cross-correlation of each seed volume timeseries with all other voxels in the brain. Positive correlation coefficients from individual analyses were transformed to normally distributed z-scores using Fisher's z' transformation, and subsequently entered into one-sample *t*-tests for within-group comparisons and two-sample *t*-tests for between-group comparisons. Thus, two statistical maps of within-group fcMRI effects (ASD and control) and one group difference map were generated for each of the three seed volumes. All statistical maps were corrected for multiple comparisons using voxel-cluster Monte-Carlo-type alpha simulations (Forman et al., 1995) for a corrected significance threshold of $\alpha=.05$.

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