Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methodology

Search Strategy

The specific search syntax is provided for PubMed, and was adapted appropriately for each database: "(autis*[Title/Abstract] OR asperger*[Title/Abstract]) AND (fMRI[Title/Abstract] OR "functional MRI"[Title/Abstract] OR "functional magnetic resonance imaging"[Title/Abstract])."

The asterisk represents a wildcard character, allowing for both autism and autistic disorder as well as variations of Asperger (Asperger's, Aspergers).

No additional screening criteria (e.g., "Humans" or "English") were imposed in order to avoid excluding qualified articles that were not MedLine indexed and thus not tagged Human or English. Identification of conference abstracts and dissertations was enabled in Embase and PsycInfo. Authors were asked to provide unpublished data.

The following articles met criteria for inclusion in the reward domain (n=27), but were excluded for the following reasons: task did not involve receiving reward in a domain of interest,[1–7] relevant contrasts between full ASD and TDC groups were not available,[8–11] or subjects overlapped with other included papers.[12–14]

Classification of Studies

Findings were classified by reward type: social, nonsocial, or restricted interest. Stimuli that clearly were neither social (e.g., did not involve a photo or video of another human) nor of restricted interests were classified as nonsocial.

Findings were also classified as anticipation of reward ('wanting') or consumption of reward ('liking') based on the original authors' classification. We classified studies as 'combined' when wanting and liking epochs could not be disentangled either due to block design[15–17] or the analytic approach.[18–21] These studies were included in the primary analysis of domains and excluded from the secondary analysis of 'wanting' and 'liking.'

Data Analysis

Selection of meta-analytic software. We elected to use Seed-based *d* mapping software (SDM)[22] for analysis because SDM offers several advantages over other fMRI meta-analytic methods such as multilevel kernel density analysis (KDA) and activation likelihood estimation (ALE and Ginger ALE), [23] All of these voxel-based methods allow combination of each study's peak activation coordinates, weighted by sample size. SDM further offers inclusion of statistical maps when available, which increases sensitivity to detect real activation.[24] SDM also accounts for the effect size of each peak coordinate by including not only coordinates, but also t-statistics (or maps when available), a capability not yet available in the current version of a commonly used alternative, Ginger ALE, to our knowledge.[23] Furthermore, SDM addresses opposite findings of hypo- and hyperactivation of the same region by creating a single integrated set of maps, while some other approaches handle opposite findings by reporting both positive and negative activation in the same region, rendering interpretation difficult. SDM also offers assessment of both within and between study variance. Finally, SDM alone handles covariates such as IQ and autism severity with meta-regression, which permits exploration of age and IQ differences between the studies' samples.

Peak coordinate extraction. We extracted activation peaks and coordinates from publications when statistical maps were unavailable. Data extraction included only significant

clusters that survived whole brain correction to avoid bias toward regions of interest that were more liberally thresholded, consistent with methods of previous meta-analyses.[25] Nonsignificant and unreported findings were conservatively included as effect sizes of zero across the entire brain so as to avoid bias toward activation by omitting such findings. Coordinates presented in Montreal Neurological Institute (MNI) space were converted to Talairach space with the Brett conversion during analysis in SDM. Effect sizes reported as Z values were converted to *t*-statistics using the *t*-calculator provided by SDM, which accounts for sample size and covariates.[22]

One study did not report individual effect sizes for each of the significant peak coordinates. Schmitz et al.,[21] reported one set of significant peak activation coordinates without a *t*-statistic. The corresponding *t*-statistic (t=1.3) was estimated via the imputation method provided by SDM that utilizes the mean effect sizes of peaks and sample sizes from other studies in the meta-analysis.

Carlisi et al.[20] provided XBAM maps and text files of significant peak coordinates and effect sizes output by XBAM for an unpublished contrast of interest. The effect sizes reported by XBAM for peak coordinates were converted to t statistics using the method described by Sato, 2007.[26]

Recreation of statistical maps from peak coordinates. For each contrast from each study, a statistical map was recreated in SDM using extracted peak coordinates as input. For a detailed description of this method, which uses anisotropic kernels, see Radua et al., 2014.[25] Briefly, this method estimates activation effect sizes in voxels neighboring the peak coordinate using a combination of the effect size at the peak coordinate, the distance of the neighboring voxel from the peak, and a map of correlations between voxels throughout the brain.

Studies presented between one and four contrasts. For example, Delmonte and colleagues[27] presented social wanting, social liking, monetary wanting, and monetary liking. For the domain-general analysis, all contrasts from a study such as Delmonte et al. were combined into a single map with reduced variance using the method implemented in SDM software and described in detail in the supplement of Carlisi et al.[28] Briefly, the method involves averaging the effect sizes in different maps to produce a single new map, then adjusting the variance of the new map by accounting for the correlation between the maps. Combined maps reflect aggregated findings and reduced variance. Thus, the domain-general meta-analysis included 13 maps from 13 studies, collapsing across different domains of reward.

Extraction of other data. We extracted additional data from all articles including reward type, reward epoch, sample sizes, age, IQ, percent male, any measures of ASD severity (SRS, SCQ, AQ, or ADOS scores), participant inclusion and exclusion criteria, analysis program (FSL or SPM), and coordinate space. Numerous other data suspected to contribute to between-study variation were initially extracted, such as scanner type and data acquisition parameters. We chose to use a random effects model to account for such between-study heterogeneity.

Effect sizes. Meta-analytic statistical maps generated by SDM represent effect sizes as SDM Z statistics, which are not necessarily normally distributed. SDM can convert SDM Z statistics to traditional Hedge's d effect sizes for clusters selected for extraction. We utilized this functionality when creating forest and funnel plots for ease of interpretation. Peak coordinate tables in the supplement present effect sizes for all clusters, including those in figures, as SDM Z for ease of reproducibility.

Significance testing. SDM generated significance tests for each voxel based on randomization of voxel location within the standard whole brain template. Specifically,

permutation tests involved repeatedly randomizing all voxels within the full brain to generate a null distribution of activation, then comparing observed activation effect sizes to the null distribution. P values in supplementary tables reflect results of these permutation tests. P values of 0.005 (uncorrected) generated within this context are analogous to corrected P values of 0.05. We employed the combination of thresholds (clusters with Z>1.00, minimum cluster size of 10 voxels, uncorrected $p<0.005$, 20 permutations, and full width at half maximum=20mm) that offer an optimal balance between type I and type II error, as demonstrated by simulation studies.[22]

eTable 1. Analyses Performed and Sample Sizes

Analysis	Study	N ASD	N TDC
Domain general	**N=13**	**259**	**246**
	Assaf et al., 2013[a]	13	14
	Carlisi et al., 2017[a]	20	29
	Cascio et al., 2014[a]	21	23
	Choi et al., 2015[a]	27	12
	Damiano et al., 2015[a]	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Richey et al., 2012	16	20
	Dichter, Felder et al., 2012	15	16
	Kohls et al., 2013[a]	15	17
	Kohls et al., 2018[a]	39	22
	Schmitz et al., 2008	10	10
	Scott-Van Zeeland et al., 2010	16	16
	Solomon et al., 2015[a]	22	25
Social	**N=7**	**158**	**129**
	Choi et al., 2015[a]	27	12
	Damiano et al., 2015[a]	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Richey et al., 2012	16	20
	Kohls et al., 2013[a]	39	22
	Kohls et al., 2018[a]	15	17
	Scott-Van Zeeland et al., 2010	16	16
Nonsocial	**N=10**	**172**	**189**
	Assaf et al., 2013[a]	13	14
	Carlisi et al., 2017[a]	20	29
	Damiano et al., 2015[a]	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Richey et al., 2012	16	20
	Dichter, Felder et al., 2012	15	16
	Kohls et al., 2013[a]	15	17
	Schmitz et al., 2008	10	10
	Scott-Van Zeeland et al., 2010	16	16
	Solomon et al., 2015[a]	22	25
Restricted Interest	**N=3**	**75**	**61**
	Cascio et al., 2014[a]	21	23
	Dichter, Felder et al., 2012	15	16
	Kohls et al., 2018[a]	39	22
Social 'wanting'	**N=3**	**61**	**62**
	Damiano et al., 2015[a]	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Richey et al., 2012	16	20
Nonsocial 'wanting'	**N=6**	**111**	**117**
	Assaf et al., 2013[a]	13	14

	Damiano et al., 2015[a]	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Felder et al., 2012	15	16
	Dichter, Richey et al., 2012	16	20
	Solomon et al., 2015[a]	22	25
Social 'liking'	**N=3**	**61**	**62**
	Damiano et al., 2015	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Richey et al., 2012	16	20
Nonsocial 'liking'	**N=6**	**111**	**117**
	Assaf et al., 2013[a]	13	14
	Damiano et al., 2015	24	21
	Delmonte et al., 2012[a]	21	21
	Dichter, Felder et al., 2012	15	16
	Dichter, Richey et al., 2012	16	20
	Solomon et al., 2015[a]	22	25

[a]denotes contrasts for which maps were available.

eTable 2. Significant Peak Activations, Jackknife Sensitivity Analysis, and Regressions in Response to Social Stimuli (n=7 studies)

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Voxels	Choi et al., 2015	Damiano et al., 2015	Delmonte et al., 2012	Dichter, Richey et al., 2012	Kohls et al., 2013	Kohls et al., 2018	Scott-Van Zeeland et al., 2010	Age regression
ASD < TDC													
Anterior cingulate gyrus	R,L	0,22,34	-2.118	<0.001	76	x	x	x	x	x	x	x	o
Caudate	R,L	-12,12,16	-2.733	<0.00001	260	x	x	x	x	x	x	x	o
Frontal gyrus (inferior), precentral gyrus	R	46,8,26	-2.499	<0.0001	190	x	x	x	x	x	x	x	o
Frontal gyrus (inferior), precentral gyrus	L	-54,16,6	-2.482	<0.0001	32	x	x	x	x	x	x	x	o
Hippocampus	R	36,-28,-4	-2.336	<0.005	31	x	x	x	x	x	o	x	o
Lateral occipital cortex (inferior), occipital fusiform gyrus	L	-40,-62,-8	-2.152	<0.001	45	o	x	o	x	x	o	x	o
Lateral occipital cortex	L	-6,-88,-34	-2.212	<0.005	49	x	x	o	x	x	o	x	o
Lateral occipital cortex (inferior)	R	48,-58,-22	-2.389	<0.005	129	x	x	x	x	x	o	x	o
Lateral occipital cortex (superior)	R	40,-70,30	-2.197	<0.005	40	x	x	o	x	o	x	x	o
Occipital fusiform gyrus	R	26,-78,-16	-2.233	<0.005	45	x	x	x	x	x	o	x	o
Paracingulate gyrus	R,L	2,48,16	-1.989	<0.005	36	o	x	o	x	o	x	o	o
Superior frontal gyrus	R,L	2,30,58	-2.542	<0.00005	56	x	x	o	x	x	x	x	o
Superior frontal gyrus	R	20,26,36	-2.118	<0.001	26	o	x	o	x	x	x	x	o
ASD > TDC													
Amygdala, hippocampus[a]	L	-26,-2,-26	3.434	<0.00045	264	o	o	x	o	o	o	o	x
Amygdala, hippocampus[a]	R	22,-4,-32	3.904	<0.0001	476	o	o	o	o	o	o	o	x
Frontal pole[a]	L	-20,52,30	3.128	<0.005	61	o	o	o	o	o	o	o	x
Insula, putamen, Heschl's Gyrus, central	R	60,-16,10	2.338	<0.0001	35	x	x	x	x	x	o	x	o

opercular cortex													
Temporal gyrus (inferior) [a]	L	-54,-56,-14	3.374	<0.001	79	x	o	x	o	o	o	o	x
Temporal occipital fusiform cortex	R	36,-56,2	2.335	<0.0001	199	x	x	x	x	x	x	x	x
Middle frontal gyrus/superior frontal gyrus	L	-28,18,42	2.241	<0.0001	43	x	x	x	x	x	o	x	o
Putamen[a]	L	-30,-4,12	2.07	<0.0005	21	x	o	x	o	o	x	x	o
Putamen, insula, Heschl's Gyrus	R	46,-14,8	2.278	<0.0001	125	x	x	x	x	x	x	x	o
Superior temporal gyrus (anterior)	L	-58,-8,-10	1.993	<0.005	26	x	x	o	x	x	x	x	o
Superior temporal gyrus/planum temporale	L	-38,-34,4	2.533	<0.00005	179	x	x	x	x	x	x	x	o
Temporal pole, superior temporal gyrus	L	-50,12,-16	1.902	<0.001	29	x	x	o	x	x	o	x	o

Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".
[a]Superscripts denote regions that did not reach significance in the full meta-analysis, but appeared in several sensitivity analyses and/or regression. Peak coordinates and effect sizes are reported from the age regression, and from the jackknife Scott-Van Zeeland sensitivity analysis when the cluster did not appear significant in the age regression (i.e., left putamen).

eTable 3. Significant Peak Activations, Jackknife Sensitivity Analysis, and Regressions in Response to Nonsocial Stimuli (n=10 studies)

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Vox-els	Assaf et al., 2013	Carlisi et al., 2017	Damiano et al., 2015	Delmonte et al 2012	Dichter, Felder et al., 2012	Dichter, Richey et al., 2012	Kohls et al., 2013	Schmitz et al., 2008	Scott-Van Zeeland et al., 2010	Solomon et al., 2015	Age regression
ASD < TDC																
Accumbens	R,L	-2,16,-4	-2.424	<0.0001	102	x	x	x	x	x	x	x	x	x	x	x
Anterior cingulate, caudate	R,L	-8,2,26	-2.399	<0.0001	582	x	x	x	x	x	x	x	x	x	x	x
Anterior paracingulate gyrus	L	-4,40,-8	-1.877	<0.005	53	x	x	x	o	x	o	o	x	x	x	o
Fusiform gyrus	L	-26,-86,-12	-1.885	<0.005	69	x	x	x	o	x	x	x	x	x	o	o
Insula, central opercular cortex	R	38,-4,16	-1.979	<0.001	58	x	x	x	x	x	x	x	x	x	o	o
Lingual gyrus, Occipital pole, fusiform gyrus	R	10,-88,-2	-2.294	<0.0005	352	x	x	x	x	x	x	x	x	x	x	x
Precentral gyrus	L	-30,-18,66	-2.296	<0.0005	144	x	x	x	x	x	x	x	x	x	x	o
Precentral gyrus	L	-54,-6,32	-2.156	<0.0005	137	x	x	x	x	x	x	x	x	x	o	o
Precentral gyrus	R	62,-4,24	-1.818	<0.005	40	x	x	x	o	x	x	x	x	x	o	o
Temporal occipital fusiform cortex	L	-30,-48,-28	-2.049	<0.0005	54	x	x	x	x	x	x	x	x	x	x	o
Temporal occipital fusiform cortex, lingual gyrus	L	-24,-56,-20	-2.091	<0.0005	125	x	x	x	x	x	x	x	x	x	x	x

ASD > TDC																
Caudate	L	-16,-12,26	2.191	<0.0001	49	x	x	o	x	x	x	x	x	x	x	o
Caudate[a]	R	24,-16,22	1.947	<0.0005	48	o	o	o	x	o	x	x	o	o	x	o
Frontal pole	L	-24,58,28	2.56	<0.00001	524	x	x	x	x	x	x	x	x	x	x	o
Hippocampus	R	38,-8,-26	2.095	<0.0005	105	x	x	x	x	x	x	x	x	x	x	x
Hippocampus	R	16,-10,-22	1.78	<0.005	42	o	x	x	o	o	o	x	x	x	x	x
Inferior frontal gyrus	L	-48,14,22	1.798	<0.001	37	x	x	x	x	o	x	x	x	x	x	o
Insula	L	-34,6,6	1.819	<0.001	59	o	x	x	x	x	x	x	x	x	o	o
Middle frontal gyrus; frontal pole (L)	R,L	-36,34,42	1.977	<0.0005	56	x	x	x	x	x	x	x	x	x	o	o
Orbital frontal cortex	R	44,30,-6	1.888	<0.001	37	x	x	x	x	o	x	o	x	x	x	o
Postcentral gyrus	L	-18,-32,40	1.968	<0.0005	38	o	x	x	x	x	x	o	x	x	x	o
Posterior supramarginal gyrus	L	-58,-44,20	2.022	<0.0005	69	x	x	x	x	x	x	x	x	x	x	o
Precuneus cortex	L	-8,-58,54	1.748	<0.005	42	o	x	x	x	o	x	x	x	x	x	o
Precuneus cortex	R	6,-54,50	1.805	<0.001	37	x	x	x	x	x	x	x	x	x	o	o
Superior frontal gyrus	L	-6,24,56	2.143	<0.0005	138	x	x	x	x	x	x	x	x	x	x	o
Superior frontal gyrus	L	0,44,36	2.045	<0.0005	66	x	x	x	x	x	x	x	x	x	x	x

Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".
[a]Superscripts denote regions that did not reach significance in the full meta-analysis, but appeared in several sensitivity analyses and/or regression. Peak coordinates and effect sizes are reported from the jackknife Delmonte sensitivity analysis.

eTable 4. Significant Peak Activations, Sensitivity Analysis, and Regressions in Response to Preferred Interest Stimuli (n=3 studies).

Region	Hemisphere	MNI coordinates	SDM-Z value	p value	Voxels	Cascio et al., 2014	Dichter, Felder et al., 2012	Kohls et al., 2018
ASD < TDC								
Anterior cingulate (superior, posterior)	R,L	4,4,42	-1.873	<0.005	45	x	o	x
Posterior cingulate	R,L	2,6,20	-2.713	<0.00005	61	x	x	x
Central opercular cortex	R	42,8,10	-2.464	<0.0001	466	x	x	x
Hippocampus	L	-18,-44,8	-2.276	<0.0005	41	o	x	o
Middle frontal gyrus	R	34,16,32	-2.079	<0.001	43	o	x	o
Nucleus accumbens, subcallosal cortex	L	-4,6,-12	-2.143	<0.0005	88	o	x	o
Parietal operculum cortex	R	48,-20,24	-2.19	<0.0005	100	o	x	o
Postcentral gyrus	L	-60,-20,24	-1.906	<0.005	32	o	x	o
Precentral gyrus	R	60,2,32	-2.213	<0.0005	97	o	x	o
ASD > TDC								
Angular gyrus	R	38,-54,18	3.066	<0.0005	91	x	x	x
Angular gyrus	R	58,-48,28	3.012	<0.0005	30	x	o	x
Anterior cingulate (inferior, anterior) [a]	R,L	10,30,10	3.827	<0.00005	119	o	x	o
Caudate[a]	L	-12,2,16	3.092	<0.001	57	o	x	o
Caudate, nucleus accumbens	R	14,12,2	2.478	<0.005	29	o	x	o
Frontal pole	L	-28,42,32	4.038	<0.00001	671	x	x	x
Insula, putamen	L	-34,20,-2	2.916	<0.001	104	x	x	x
Precuneus cortex, lateral occipital cortex	L	-12,-66,30	3.324	<0.0005	217	x	x	x

(superior)								
Thalamus	R	14,-12,12	2.473	<0.005	27	o	x	o

Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o". Meta-regressions were not performed due to the small number of studies.

[a]Superscripts denote regions that did not reach significance in the full meta-analysis, but did reach significance in the jackknife Dichter sensitivity analysis. This difference likely occurred because the coordinates-based Dichter study assumed zero activation differences unless nearby peaks were reported, conservatively biasing the full meta-analysis toward null findings.

eTable 5. Significant Peak Activations in 'Wanting' of Social Reward (n=3 studies) and Sensitivity Analysis

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Voxels	Damiano et al., 2015	Delmonte et al., 2012	Dichter, Richey et al., 2012
ASD < TDC								
Anterior cingulate gyrus	R	12,32,38	-1.002	<0.005	29	x	o	o
Anterior cingulate gyrus	R	8,46,12	-1.002	<0.0005	42	x	o	o
Caudate	L	-22,20,16	-1.002	<0.005	25	x	o	o
Frontal pole	L	-14,62,4	-1.002	<0.005	30	x	o	o
Frontal pole	L	-22,44,0	-1.002	<0.0005	27	o	o	o
Insula	R	30,28,2	-1.002	<0.0005	41	x	o	o
Lateral occipital cortex (superior)	R	42,-70,34	-1.002	<0.0005	29	o	o	o
Middle frontal gyrus	R	42,34,38	-1.002	<0.0005	44	x	o	o
Paracingulate gyrus	R	2,34,32	-1.002	<0.0005	37	x	o	o
Parahippocampal gyrus (posterior)	L	-36,-32,-12	-1.002	<0.0005	34	x	o	o
Superior frontal gyrus	L	-26,2,58	-1.002	<0.0005	67	o	o	o
Superior frontal gyrus	R	22,18,54	-1.002	<0.0005	30	x	o	o
ASD > TDC								
Amygdala	R	16,-2,-16	3.22	<0.00005	360	o	x	x
Hippocampus, amygdala	L	-16,-6,-22	1.828	<0.001	25	x	o	o
Intracalcarine cortex, lingual gyrus, lateral occipital cortex (inferior)	R	28,-62,4	1.844	<0.0005	184	x	o	o
Lateral occipital cortex (inferior)	L	-34,-66,14	1.859	<0.0005	181	x	o	o

Parietal operculum cortex	L	-36,-32,24	1.848	<0.0005	58	x	o	o
Planum temporale	L	-30,-32,16	1.792	<0.005	35	x	o	o
Putamen	L	-30,-8,12	1.835	<0.001	62	x	o	o

Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".

eTable 6. Significant Peak Activations in 'Wanting of Nonsocial Reward (n=6 studies) and Sensitivity Analysis

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Voxels	Assaf et al., 2013	Damiano et al., 2015	Delmonte et al., 2012	Dichter, Felder et al., 2012	Dichter, Richey et al., 2012	Solomon et al., 2015
ASD < TDC											
Anterior cingulate gyrus	R,L	-6,2,32	-2.598	<0.00005	729	x	x	x	x	x	x
Insula, central opercular cortex	R	38,-4,18	-1.937	<0.001	46	x	x	o	x	x	o
Lingual gyrus, occipital fusiform gyrus	R	10,-86,-2	-2.122	<0.0005	151	x	x	x	x	x	x
Occipital fusiform gyrus/cerebellum	R	22,-66,-18	-1.714	<0.005	31	o	x	o	x	x	o
Parahippocampal gyrus (posterior)/cerebellum	L	-14,-38,-20	-1.879	<0.001	29	x	x	o	x	x	o
Precentral gyrus	L	-54,-6,32	-1.765	<0.005	29	x	x	o	x	x	o
Precentral gyrus	R	62,-2,28	-1.64	<0.005	25	x	x	o	x	x	o
Subcallosal cortex	R,L	0,16,-4	-2.117	<0.0005	49	x	x	x	x	o	x
Temporal fusiform cortex (posterior)/cerebellum	L	-32,-44,-28	-1.822	<0.005	32	o	x	o	x	x	o
Temporal occipital fusiform/cerebellum	L	-22,-58,-20	-1.98	<0.0005	109	x	x	x	x	x	o
ASD > TDC											
Caudate	L	-22,-14,22	2.405	<0.0005	35	x	o	x	x	x	x
Frontal pole	L	-24,58,28	2.537	<0.0005	252	x	x	x	x	x	x
Hippocampus	L	-24,-20,-8	2.108	<0.005	55	x	x	o	x	x	o
Middle frontal gyrus	L	-48,12,34	2.185	<0.001	64	x	x	x	x	x	x
Parahippocampal gyrus, amygdala	R	28,-8,-26	2.795	<0.0001	329	x	x	x	x	x	x
Precuneus cortex	L	-8,-64,50	2.296	<0.001	84	x	x	x	o	x	x

Putamen	L	-26,6,6	2.146	<0.005	173	x	x	o	x	x	o
Superior frontal gyrus	L	-6,26,56	2.213	<0.001	44	x	x	x	o	x	x
Supramarginal gyrus (posterior)	L	-52,-46,22	2.418	<0.0005	87	x	x	o	o	x	x
Thalamus	R	20,-26,-2	2.104	<0.005	72	x	x	o	x	x	o

Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".

eTable 7. Significant Peak Activations in 'Liking' of Social Reward (n=3 studies) and Sensitivity Analysis

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Voxels	Damiano et al., 2015	Delmonte et al., 2012	Dichter, Richey et al., 2012
ASD < TDC								
Precuneus cortex	L	-26,-54,12	-1.029	<0.000005	30	o	o	o
ASD > TDC								
Angular gyrus, lateral occipital cortex (superior)	R	52,-58,20	1.817	<0.0005	119	x	o	o
Insula	R	38,14,-4	1.847	<0.00005	389	x	o	o
Insula, putamen, amygdala, accumbens, caudate, frontal orbital cortex	L	-30,16,-14	1.859	<0.00001	1021	x	o	o
Lingual gyrus	R	10,-48,0	1.847	<0.00005	252	x	o	o
Superior temporal gyrus (anterior)	R	52,4,-16	1.854	<0.00005	225	x	o	o

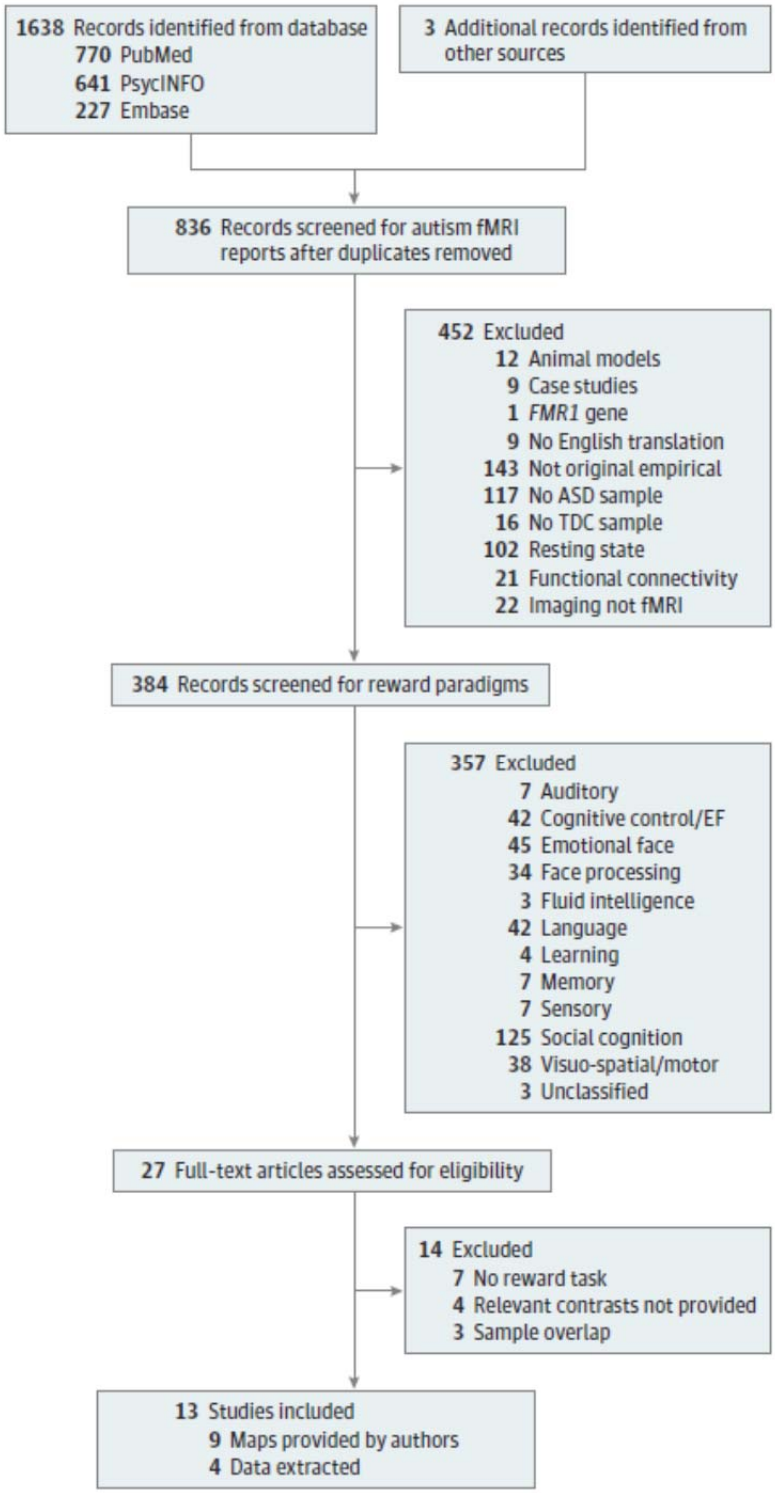
Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".

eTable 8. Significant Peak Activations in 'Liking' of Nonsocial Reward (n=6 studies) and Sensitivity Analysis

Region	Hemi-sphere	MNI coordinates	SDM-Z value	p value	Voxels	Assaf et al., 2013	Damiano et al., 2015	Delmonte et al., 2012	Dichter, Felder et al., 2012	Dichter, Richey et al., 2012	Solomon et al., 2015
ASD < TDC											
Anterior cingulate gyrus	R,L	-6,-6,28	-1.116	<0.001	57	x	x	o	x	x	o
Caudate, posterior cingulate gyrus	R	18,-34,20	-1.475	<0.0001	259	x	x	o	x	x	o
Frontal pole	L	-14,62,10	-1.519	<0.00005	94	x	x	o	x	x	x
Insula	R	42,-4,-4	-1.633	<0.00005	106	x	x	o	x	x	x
Orbital frontal cortex, frontal pole	R	44,32,-18	-1.374	<0.0005	207	x	x	x	o	x	x
Pallidum, putamen	L	-18,0,-4	-1.657	<0.00005	103	x	x	o	x	x	x
ASD > TDC											
Amygdala	R	26,-2,-16	2.855	<0.00005	298	x	x	x	x	x	x
Central opercular cortex	R	46,-10,14	2.305	<0.005	30	x	x	o	x	o	x
Frontal pole	L	-42,46,18	2.869	<0.00005	104	x	x	x	x	o	x
Lingual gyrys	R	10,-54,4	2.757	<0.0001	453	x	x	x	x	o	x
Lingual gyrys, intracalcarine cortex	R	28,-64,2	2.763	<0.0001	118	x	x	x	x	o	x
Precentral gyrus	R	20,-14,70	2.379	<0.001	48	x	x	o	x	x	x
Precentral gyrus (lateral)	R	54,4,40	2.502	<0.0005	42	x	x	x	x	x	o
Superior parietal lobule	L	-26,-50,62	2.321	<0.001	28	o	x	o	x	x	o

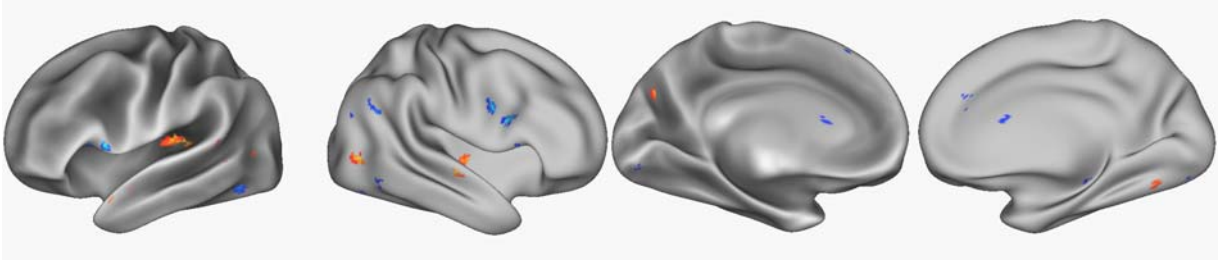
Peak coordinates are reported for clusters ≥25 voxels. In sensitivity analysis, the study 'left out' is indicated by the name of the first author. Results that replicated without a study are noted with an "x" and results that were no longer significant are noted with an "o".

eFigure 1. Study Flow Diagram
PRISMA flow diagram depicting systematic review process and results. ASD indicates autism spectrum disorder; EF, executive function; fMRI, functional magnetic resonance imaging; and TDC, typically developing controls.

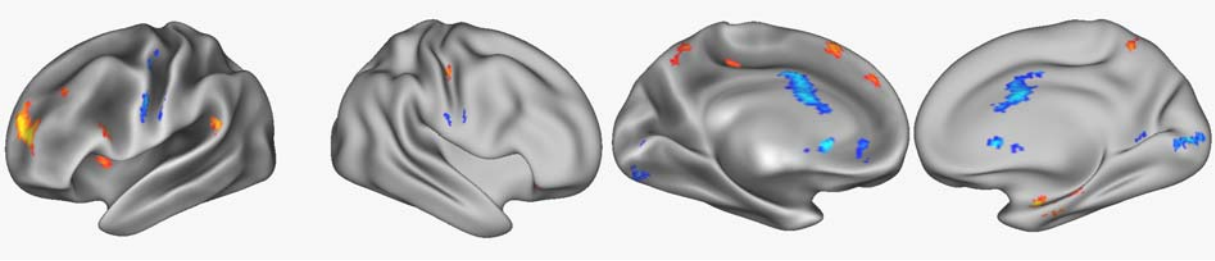


eFigure 2. Whole-Brain Images, by Meta-analysis

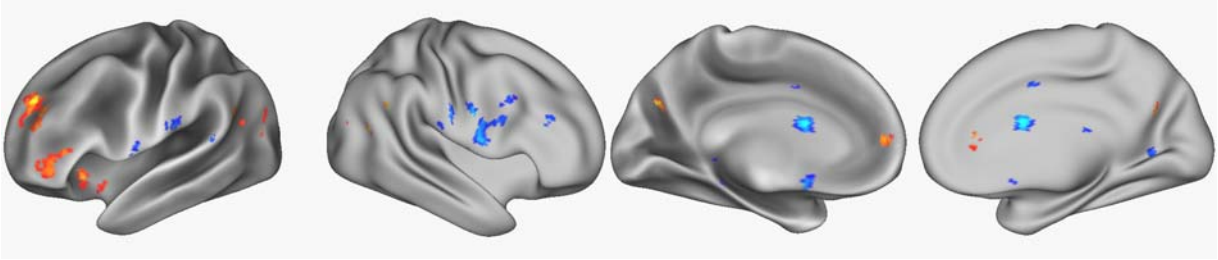
a. Social meta-analysis (n=7 studies)



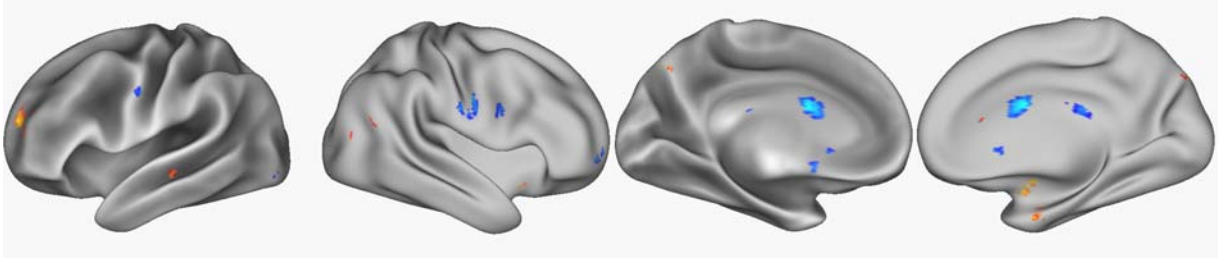
b. Nonsocial meta-analysis (n=10 studies)



c. Restricted Interest meta-analysis (n=3 studies)

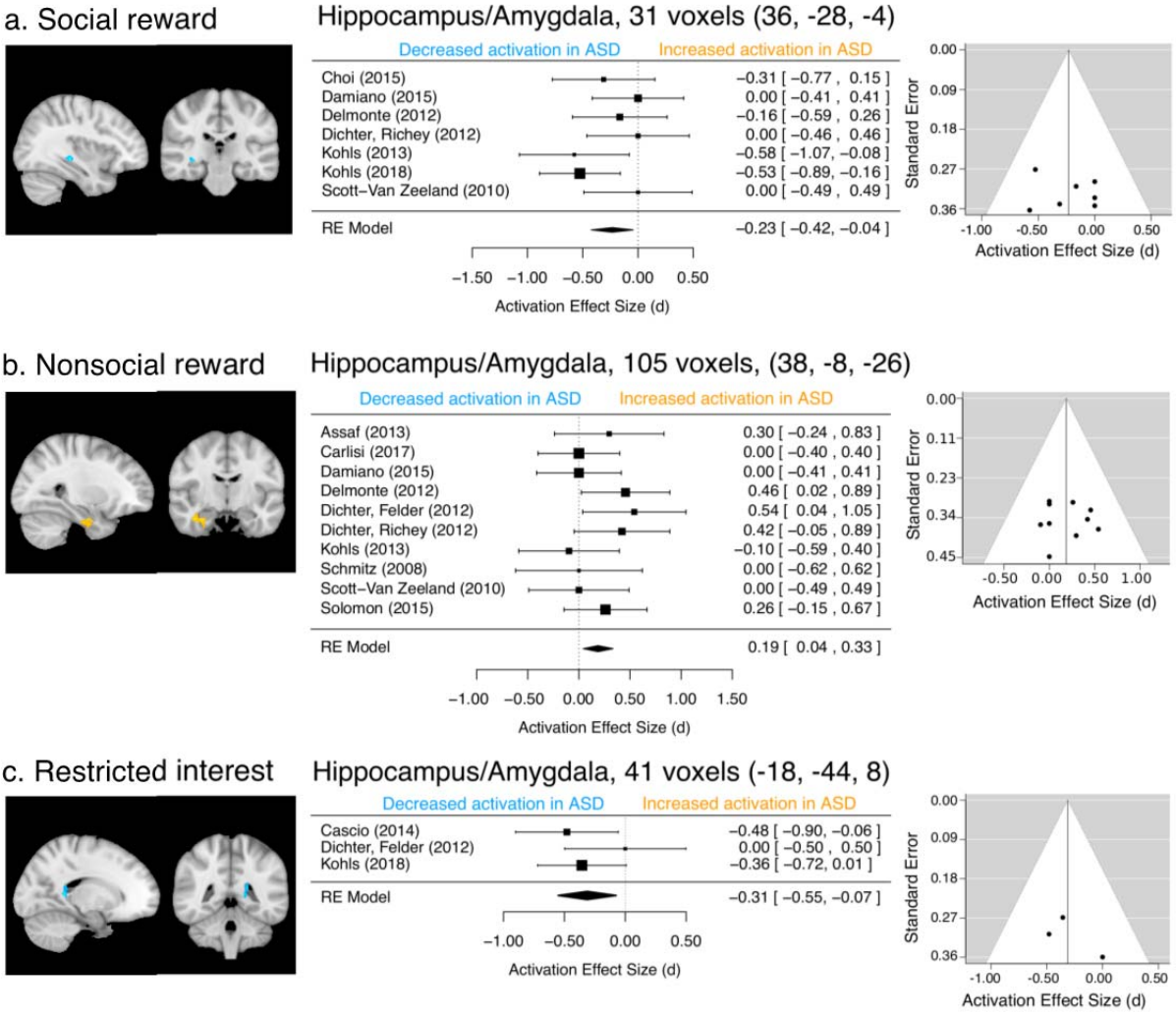


d. Domain general meta-analysis (n=13 studies)



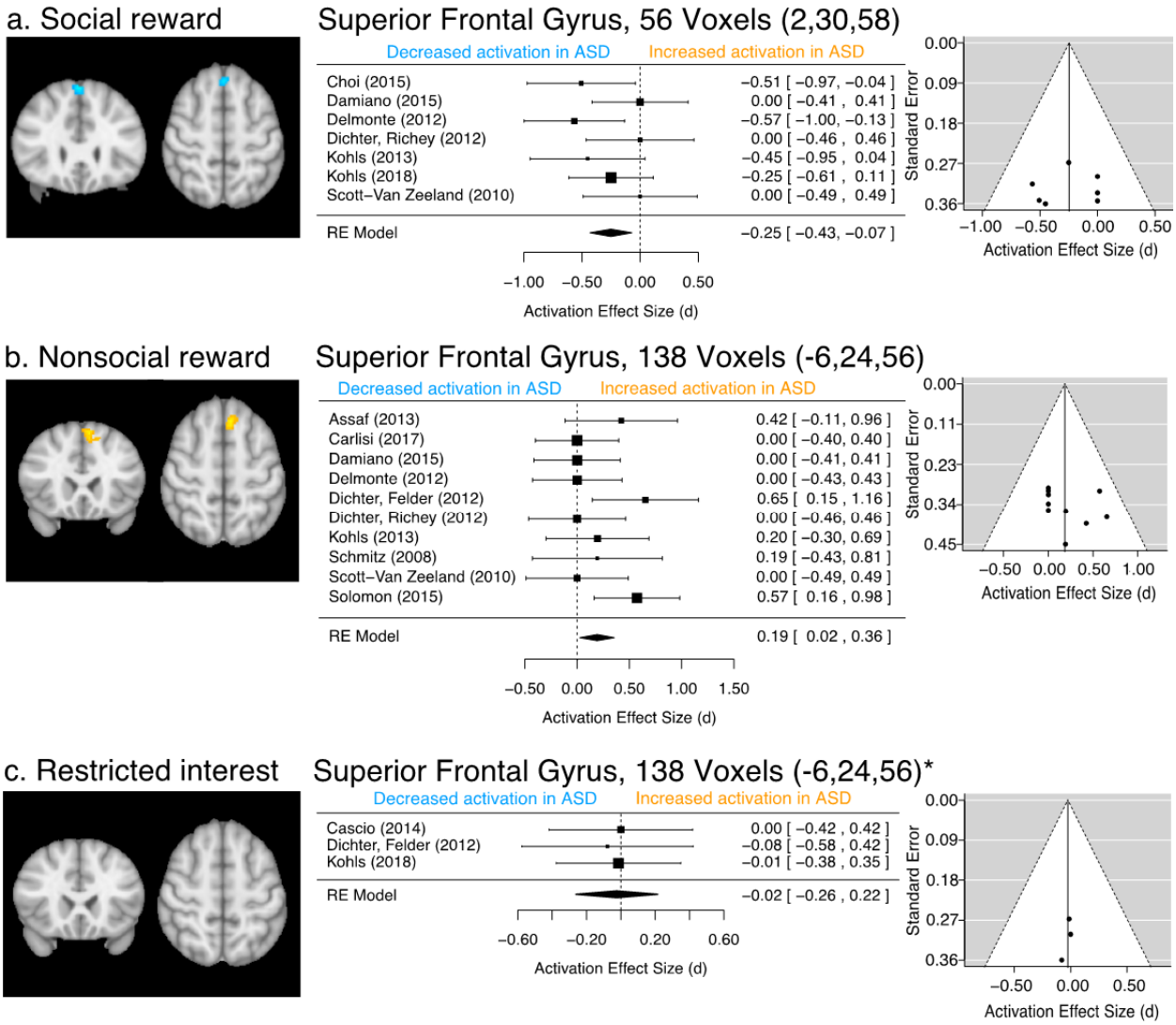
eFigures 2a-d depict significant activation differences between ASD and control samples across three types of reward (a-c), and all types of reward meta-analyzed together (d). Cool colors show hypoactivation in the meta-analytic ASD sample compared to controls, and hot colors depict hyperactivation; the right hemisphere is shown on the right.

eFigure 3. Differences Between ASD and Control Samples in the Hippocampus and Amygdala



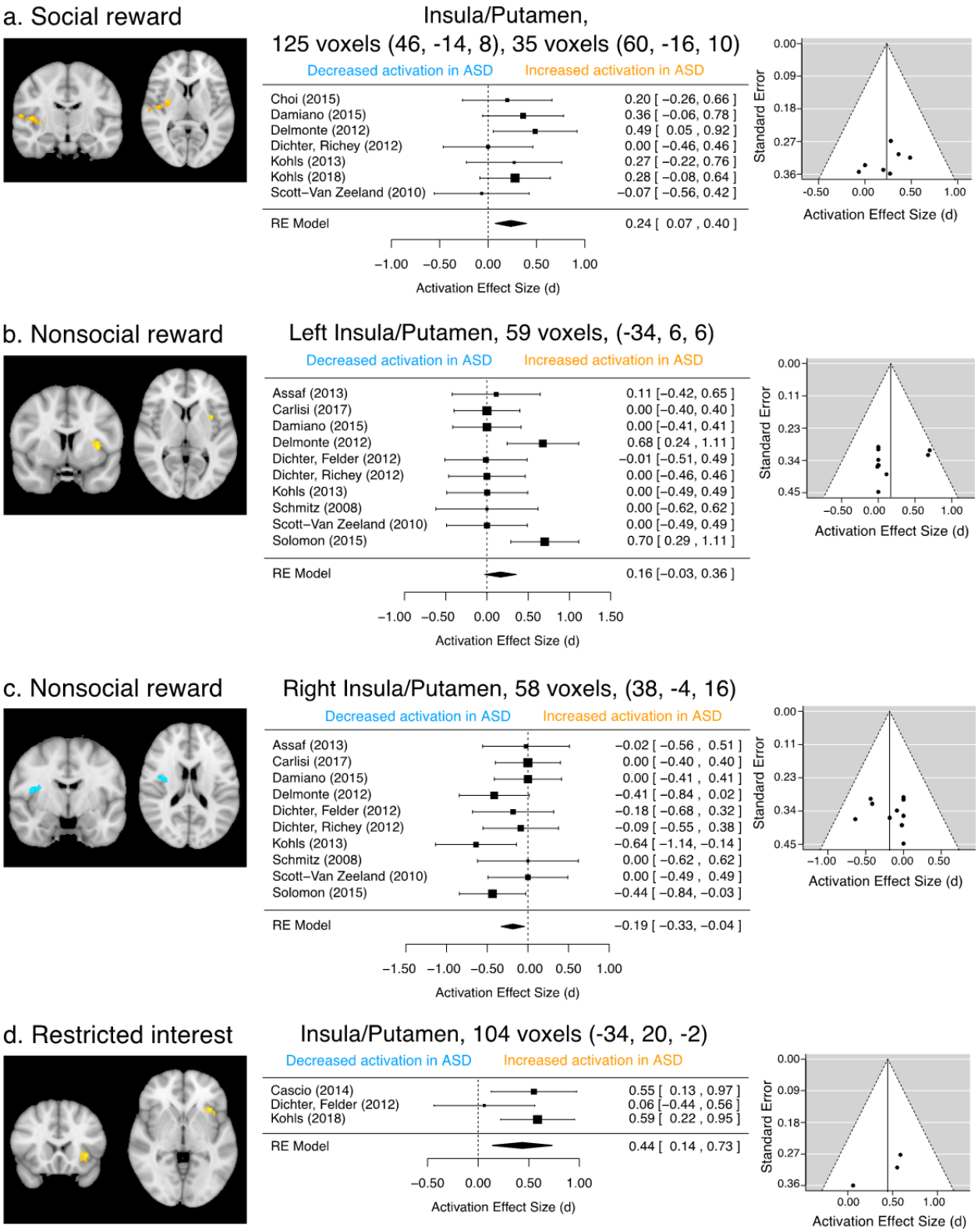
eFigure 3 depicts significant activation differences between ASD and control samples across three types of reward in the hippocampus and amygdala. These structures are presented together because significant clusters included parts of both of these reward circuitry structures. Plots depict the overall effect size of all voxels in the cluster that showed significance in permutation testing (see eTables 2-4). Compared to the control sample, the ASD sample showed significant hypoactivation (cool colors) to social rewards and restricted interests, and hyperactivation (hot colors) to nonsocial rewards. All effect sizes were small. In coronal slices, the left hemisphere is depicted on the right.

eFigure 4. Differences Between ASD and Control Samples in the Superior Frontal Gyrus



eFigure 4 depicts significant activation differences between ASD and control samples across three types of reward in the superior frontal gyrus. Plots depict the overall effect size of all voxels in the cluster that showed significance in permutation testing (see eTables 2-4). Compared to the control sample, the ASD sample showed significant hypoactivation (cool colors) to social rewards and hyperactivation (hot colors) to nonsocial rewards. *We observed no significant clusters including the superior frontal gyrus in the restricted interests domain. Instead, we present the null group activation differences within the cluster that was significant in the nonsocial condition, demonstrating differences across conditions; the ASD sample showed significant superior frontal gyrus hyperactivation to nonsocial reward, but few activation differences in any studies to restricted interest rewards. In coronal slices, the left hemisphere is depicted on the right.

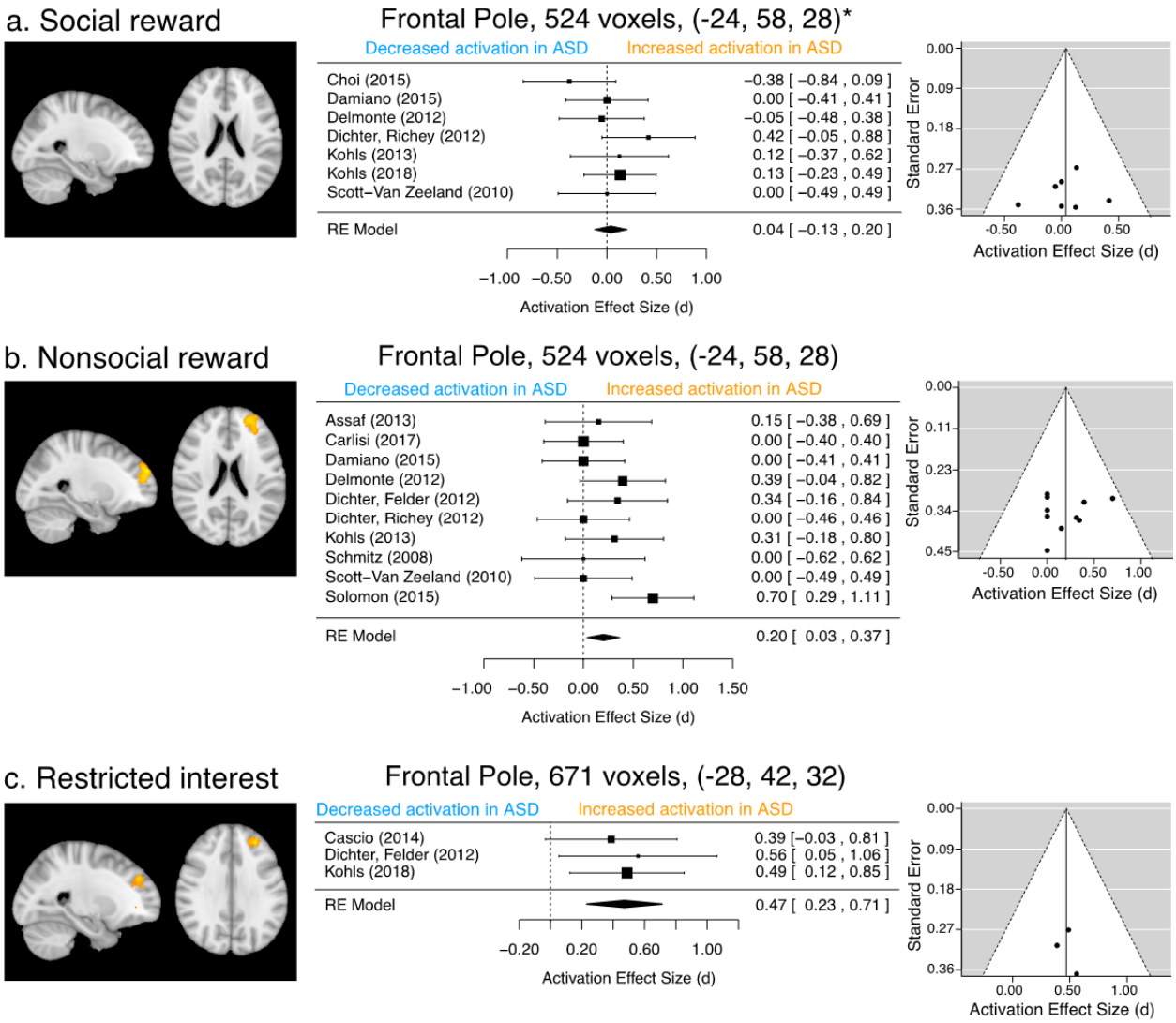
eFigure 5. Differences Between ASD and Control Samples in the Insula And Putamen



eFigure 5 depicts significant activation differences between ASD and control samples across three types of reward in the insula and putamen. These structures are presented together because

significant clusters included parts of both of these reward circuitry structures. Plots depict the overall effect size of all voxels in the cluster that showed significance in permutation testing (see eTables 2-4). The ASD sample showed significant hyperactivation (hot colors) compared to the control sample in the insula and/or hippocampus in response to all three types of rewards: social, nonsocial, and restricted interests. We observed heterogeneity in the nonsocial domain, in which hypoactivation was observed in the right hemisphere, and hyperactivation in the left. In coronal slices, the left hemisphere is depicted on the right.

eFigure 6. Differences Between ASD and Control Samples in the Frontal Pole



eFigure 6 depicts significant activation differences between ASD and control samples across three types of reward in the frontal pole, also seen clearly in eFigure 2. Plots depict the overall effect size of all voxels in the cluster that showed significance in permutation testing (see eTables 2-4). Compared to the control sample, the ASD sample showed significant hyperactivation (hot colors) to nonsocial and restricted interest rewards. *We observed no significant clusters that included the frontal pole in the social condition. Instead, we present the null group activation differences within the cluster that was significant in the nonsocial condition, demonstrating differences across conditions; the ASD sample showed significant frontal pole hyperactivation to nonsocial and restricted interest rewards that was consistent across all included studies. In contrast, individual social domain studies reported both hyper- and hypo-activation (n=3 and n=2, respectively), resulting in an aggregate null effect. In coronal slices, the left hemisphere is depicted on the right.

eReferences

1. Caria A, de Falco S. Anterior insular cortex regulation in autism spectrum disorders. *Front Behav Neurosci*. 2015;9:38. doi:10.3389/fnbeh.2015.00038

2. Hoffmann F, Koehne S, Steinbeis N, Dziobek I, Singer T. Preserved self-other distinction during empathy in autism is linked to network integrity of right supramarginal gyrus. *J Autism Dev Disord*. October 2015. doi:10.1007/s10803-015-2609-0

3. Ventola P, Yang DYJ, Friedman HE, et al. Heterogeneity of neural mechanisms of response to pivotal response treatment. *Brain Imaging Behav*. 2015;9(1):74-88. doi:10.1007/s11682-014-9331-y

4. Whyte EM, Behrmann M, Minshew NJ, Garcia NV, Scherf KS. Animal, but not human, faces engage the distributed face network in adolescents with autism. *Dev Sci*. 2016;19(2):306-317. doi:10.1111/desc.12305

5. Pierce K. The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. *Brain*. 2004;127(12):2703-2716. doi:10.1093/brain/awh289

6. Cascio CJ, Foss-Feig JH, Heacock JL, et al. Response of neural reward regions to food cues in autism spectrum disorders. *J Neurodev Disord*. 2012;4(1):9. doi:10.1186/1866-1955-4-9

7. Cascio CJ, Moana-Filho EJ, Guest S, et al. Perceptual and neural response to affective tactile texture stimulation in adults with autism spectrum disorders. *Autism Res*. 2012;5(4):231-244. doi:10.1002/aur.1224

8. Chantiluke K, Barrett N, Giampietro V, et al. Inverse effect of fluoxetine on medial prefrontal cortex activation during reward reversal in ADHD and autism. *Cereb Cortex*. 2015;25(7):1757-1770. doi:10.1093/cercor/bht365

9. Chantiluke K, Christakou A, Murphy CM, et al. Disorder-specific functional abnormalities during temporal discounting in youth with Attention Deficit Hyperactivity Disorder (ADHD), Autism and comorbid ADHD and Autism. *Psychiatry Res*. 2014;223(2):113-120. doi:10.1016/j.pscychresns.2014.04.006

10. Duerden EG, Lee M, Chow S, Sato J, Mak-Fan K, Taylor MJ. Neural Correlates of Reward Processing in Typical and Atypical Development. *Child Neurol Open*. 2016;3:2329048X16667350. doi:10.1177/2329048X16667350

11. van Hulst BM, de Zeeuw P, Bos DJ, Rijks Y, Neggers SFW, Durston S. Children with ADHD symptoms show decreased activity in ventral striatum during the anticipation of reward, irrespective of ADHD diagnosis. *J Child Psychol Psychiatry*. 2017;58(2):206-214. doi:10.1111/jcpp.12643

12. Kohls G, Thönessen H, Bartley GK, et al. Differentiating neural reward responsiveness in autism versus ADHD. *Dev Cogn Neurosci*. 2014;10:104-116. doi:10.1016/j.dcn.2014.08.003

13. Richey JA, Rittenberg A, Hughes L, et al. Common and distinct neural features of social and non-social reward processing in autism and social anxiety disorder. *Soc Cogn Affect Neurosci*. 2014;9(3):367-377. doi:10.1093/scan/nss146

14. Damiano CR. *Neural mechanisms of uncertainty processing in children with autism spectrum disorders* [dissertation]. The University of North Carolina at Chapel Hill; 2015.

15. Kohls G, Schulte-Rüther M, Nehrkorn B, et al. Reward system dysfunction in autism spectrum disorders. *Soc Cogn Affect Neurosci*. 2013;8(5):565-572. doi:10.1093/scan/nss033

16. Kohls G, Antezana L, Mosner MG, Schultz RT, Yerys BE. Altered reward system reactivity for personalized circumscribed interests in autism. *Mol Autism*. 2018;9:9. doi:10.1186/s13229-018-0195-7

17. Cascio CJ, Foss-Feig JH, Heacock J, et al. Affective neural response to restricted interests in autism spectrum disorders. *J Child Psychol Psychiatry*. 2014;55(2):162-171. doi:10.1111/jcpp.12147

18. Scott-Van Zeeland AA, Dapretto M, Ghahremani DG, Poldrack RA, Bookheimer SY. Reward processing in autism. *Autism Res Off J Int Soc Autism Res*. 2010;3(2):53-67. doi:10.1002/aur.122

19. Choi U-S, Kim S-Y, Sim HJ, et al. Abnormal brain activity in social reward learning in children with autism spectrum disorder: an fMRI study. *Yonsei Med J*. 2015;56(3):705-711. doi:10.3349/ymj.2015.56.3.705

20. Carlisi CO, Norman L, Murphy CM, et al. Comparison of neural substrates of temporal discounting between youth with autism spectrum disorder and with obsessive-compulsive disorder. *Psychol Med*. 2017;47(14):2513-2527. doi:10.1017/S0033291717001088

21. Schmitz N, Rubia K, van Amelsvoort T, Daly E, Smith A, Murphy DGM. Neural correlates of reward in autism. *Br J Psychiatry*. 2008;192(1):19-24. doi:10.1192/bjp.bp.107.036921

22. Radua J, Mataix-Cols D, Phillips ML, et al. A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *Eur Psychiatry*. 2012;27(8):605-611. doi:10.1016/j.eurpsy.2011.04.001

23. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT. Activation likelihood estimation meta-analysis revisited. *NeuroImage*. 2012;59(3):2349-2361. doi:10.1016/j.neuroimage.2011.09.017

24. Radua J, Mataix-Cols D. Meta-analytic methods for neuroimaging data explained. *Biol Mood Anxiety Disord*. 2012;2:6. doi:10.1186/2045-5380-2-6

25. Radua J, Rubia K, Canales-Rodríguez EJ, Pomarol-Clotet E, Fusar-Poli P, Mataix-Cols D. Anisotropic Kernels for Coordinate-Based Meta-Analyses of Neuroimaging Studies. *Front Psychiatry*. 2014;5. doi:10.3389/fpsyt.2014.00013

26. Sato JR. Computational Statistics for fMRI Data Analysis using XBAM v3.4. May 2007. https://www.ime.usp.br/~jsato/nif/Manual.pdf. Accessed August 10, 2017.

27. Delmonte S, Balsters JH, McGrath J, et al. Social and monetary reward processing in autism spectrum disorders. *Mol Autism*. 2012;3(1):7. doi:10.1186/2040-2392-3-7

28. Carlisi CO, Norman LJ, Lukito SS, Radua J, Mataix-Cols D, Rubia K. Comparative Multimodal Meta-analysis of Structural and Functional Brain Abnormalities in Autism Spectrum Disorder and Obsessive-Compulsive Disorder. *Biol Psychiatry*. 2017;82(2):83-102. doi:10.1016/j.biopsych.2016.10.006

