The functional neural architecture of dysfunctional reward processing in autism

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ABSTRACT

Functional imaging studies have found differential neural activation patterns during reward-paradigms in patients with autism spectrum disorder (ASD) compared to neurotypical controls. However, publications report conflicting results on the directionality and location of these aberrant activations. We here quantitatively summarized relevant fMRI papers in the field using the anatomical likelihood estimation (ALE) algorithm.

Patients with ASD consistently showed hypoactivations in the striatum across studies, mainly in the right putamen and accumbens. These regions are functionally involved in the processing of rewards and are enrolled in extensive neural networks involving limbic, cortical, thalamic and mesencephalic regions.

The striatal hypo-activations found in our ALE meta-analysis, which pooled over contrasts derived from the included studies on reward-processing in ASD, highlight the role of the striatum as a key neural correlate of impaired reward processing in autism. These changes were present for studies using social and non-social stimuli alike. The involvement of these regions in extensive networks associated with the processing of both positive and negative emotion alike might hint at broader impairments of emotion processing in the disorder.

1. Introduction

The diagnosis of autism spectrum disorder (ASD) is based on two core symptoms – persistent deficits in social interaction and restricted, repetitive patterns of behavior - although the clinical presentation can be very heterogeneous and the intensity of symptoms can vary significantly between individuals (APA, 2000; Masi et al., 2017). Impairments of reward processing and reward anticipation have been proposed as a major common pathomechanism shared across this phenotypical heterogeneity. This idea was initially focused on the processing of social cues during critical periods of development, resulting in deficient social interaction in ASD (Botini, 2018; Chevallier et al., 2012). However, other studies have pointed to a broader dysfunction of the reward system that extends into the processing of non-social reinforcers (Kohls et al., 2018), which is in line with recent evidence that regions processing social and non-social rewards overlap (Lin et al., 2012).

Given the potentially pivotal role of reward circuit dysfunction on ASD symptoms, multiple functional magnetic resonance imaging (fMRI) studies have tried to elucidate the neural correlates of reward processing deficits in ASD. Reward processing is a complex process that involves a large neural network, including the striatum, ventral tegmental area (VTA), thalamus, insula, frontocortical regions, anterior cingulate cortex (ACC) and amygdala. Two hubs within that circuitry have been repeatedly implicated in ASD pathophysiology: the striatum (Carlisi et al., 2017a; Delmonte et al., 2012; Dichter et al., 2012b, 2012c; Kohls et al., 2013; Lassalle et al., 2017; Mikita et al., 2016; Murphy et al., 2017; Rahko et al., 2012; Schwarz et al., 2020) and the amygdala (Dichter et al., 2012c; Kim et al., 2015; Kohls et al., 2013; Lassalle et al., 2017; Murphy et al., 2017). These regions are linked to reward prediction and motivation (ventral striatum) (Delmonte et al., 2012; Fareri

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https://doi.org/10.1016/j.nicl.2021.102700
Received 2 January 2021; Received in revised form 10 May 2021; Accepted 11 May 2021
Available online 28 May 2021
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Moreover, the development of functional networks in ASD seems to differ from healthy controls (HC) (Rudie et al., 2012; Weng et al., 2011). Inconsistent findings have not only been reported for these regions, but also for other key parts of the reward circuitry, such as the orbitofrontal cortex (OFC) (Carlisi et al., 2017a; Choi et al., 2015; Dichter et al., 2012c; Lassalle et al., 2017; Murphy et al., 2017; Solomon et al., 2015), and the ventromedial prefrontal cortex (vmPFC) (Carlisi et al., 2017a; Damiano et al., 2014; Dichter et al., 2012b, 2012c).

A previous neuroimaging meta-analysis by Clements and colleagues (Clements et al., 2018) provided a first insight into altered striatal activations associated with reward in ASD. However, at that time only 13 studies met inclusion criteria, whereas recent literature recommends a minimum of 17 studies for coordinate-based meta-analysis (Eickhoff et al., 2016). Therefore, we conducted a new meta-analysis to potentially corroborate and extend these findings.

Multiple factors could be the cause for the above mentioned heterogeneity of imaging findings. A considerable number of ASD patients receive antidepressive medications, antidepresants or stimulants to treat comorbid conditions (Lord et al., 2018). These medications can influence the activity of the striatum and other hubs of the reward circuitry (Abler et al., 2007; Stoy et al., 2012; Vollm et al., 2004). The percentage of patients on those medications in a given sample can, thus, influence the findings of individual fMRI studies. Also, multiple paradigms and contrasts that are used to assess reward-associated brain activations might increase variation between publications. Researchers have applied different methods to elicit reward in fMRI studies. For example, they used paradigms that involve social rewards (Caria et al., 2011; Choi et al., 2015; Delmonte et al., 2012; Dichter et al., 2012c; Kohls et al., 2013; Monk et al., 2010; Weng et al., 2011), monetary rewards (Carlisi et al., 2017b; Delmonte et al., 2012; Dichter et al., 2012b; Kohls et al., 2013; Murphy et al., 2017; Schmitz et al., 2008), object rewards (Dichter et al., 2012b), candy (Mikita et al., 2016), pleasant textures (Cascio et al., 2012b) and happy music (Caria et al., 2011). Moreover, they delineated neural activations during different phases of reward processing, such as the anticipation or the delivery of a reward (Dichter et al., 2012b, 2012c; Mikita et al., 2016). Depending on the chosen paradigm and/or contrast, different neural networks might be involved. Another frequent methodological problem are small sample sizes that can lead to false positive findings. Besides these rather general parameters, more disease-specific factors might also come into play. Altered trajectories of brain growth and maturation in patients, among other factors, could explain divergent results across publications. Differential growth patterns of distinct brain regions have been well documented in ASD (Greimel et al., 2013; Nickl-Jockschat et al., 2012). Moreover, the development of functional networks in ASD seems to differ from healthy controls (HC) (Rudie et al., 2012; Weng et al., 2010). Given the changes in reward processing during development (Lasking et al., 2016), the alterations in growth patterns and network development might affect the development and subsequent impairment of the reward system in ASD. The enormous variety of clinical phenotypes that are subsumed under the broad umbrella of ASD could constitute another obstacle to identify commonalities between neural signatures. As mentioned above, both the constellation of individual symptoms and their severity can vary significantly across affected individuals and heterogeneity inside patient samples could reduce the detectability of each specific phenotype (Lord et al., 2018).

Coordinate-based meta-analysis provides a powerful tool to delineate brain regions that are consistently implicated in a given brain function across publications. Given this, we chose the activation likelihood estimation (ALE) approach (Eickhoff et al., 2012, 2016), a well-established algorithm for coordinate-based meta-analysis, to test the hypothesis that there is a common neural pattern of dysfunctional reward processing in ASD. We first identified 29 papers on fMRI, 23 of those reporting whole-brain results of individuals with ASD vs. HC for reward paradigms (Eickhoff et al., 2012, 2009), and tested the convergence of the reported results.

The function of a brain region largely depends on its connectivity. Therefore, the premise for understanding the impact of regionally altered connectivity on pathophysiology and psychopathology is to understand the connectivity and function of this specific region in healthy individuals. Based on these considerations, we conducted follow-up analyses on the functional connectivity pattern and the associated brain functions of the clusters ensuing from our ALE meta-analysis in separate datasets with healthy subjects using a data-driven approach relying on the BrainMap data base and the enhanced NIKI-Rockland sample. The BrainMap approach (Laird et al., 2011, 2009) pools over neuroimaging experiments in healthy subjects. It allows an observer-independent assignment of functional properties to a given cluster (functional decoding). We have also used the BrainMap database to detect task-dependent co-activation patterns (MACM) of the clusters retrieved. Task-independent (resting-state) connectivity was assessed with the enhanced NIKI-Rockland sample that pools over resting state fMRIs of healthy subjects.

The insights gained from this subsequent analysis allow to generate data-driven hypotheses on the possible impact of alterations of these clusters on pathophysiology and psychopathology beyond their involvement in reward processing.

In sum, the approaches applied in this paper allowed us to robustly identify and characterize the neural signature of the clusters showing dysfunctional reward processing in autism spectrum disorder.

2. Methods

2.1. Literature search and selection

We performed a literature search for functional magnetic resonance imaging (fMRI) papers reporting reward-paradigms in ASD compared to HC using PubMed (https://www.ncbi.nlm.nih.gov/pubmed), and Google Scholar (https://scholar.google.de) (search strings see inline supplementary table 1) and reference tracking. A total of 29 publications were included. 6 did not report significant results for whole-brain analyses (see Fig. 1). Inclusion criteria were: (1) human fMRI papers published until December 2nd 2019 in original peer-reviewed journals, (2) using reward-paradigms with a comparison of contrasts between populations with ASD and healthy controls, (3) reporting whole-brain results with peak coordinates for all clusters in MNI or Talairach stereotactic space. Case-reports, reviews and publications with restricted inference spaces were excluded. If we found that two publications used overlapping patient-populations, we still included all coordinates reported in those papers, but treated them as if they came from one publication.

Our search identified a total of 347 articles in PubMed, Google Scholar and by reference tracking for screening. Book chapters and thesis/dissertations and posters were not screened.

While some articles could be included after the authors provided additional information, 318 articles had to be excluded. 29 publications were included in the meta-analysis. Reasons for exclusion were: no fMRI study, no ASD group, no healthy controls, no comparison between ASD and HC for a reward paradigm, review/essay or comment, no humans, no whole-brain analysis, case-reports, or language neither English nor German.

For details on publication selection and an overview of the papers enrolled in this meta-analysis see Fig. 1 and table 1.
The included papers were published in peer-reviewed journals and diagnosed autism by DSM-IV or ICD-10 and/or by ADOS (Autism Diagnostic Observation Schedule) (Lord et al., 2000), ADI-R (Autism Diagnostic Interview – revised) (Lord et al., 1994), the ASD-section of the Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000), Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers et al., 1999), Structured Clinical Interview for DSM-IV (SCID) (First et al., 2001). The following tests were additionally used for diagnostic confirmation: Asperger Gilliam Asperger’s Disorder Scale (GADS) (Gilliam, 2001), Krug Asperger’s Disorder Index (KADI) (Krug and Arick, 2003), Social Communication Questionnaire (SCQ) (Rutter et al., 2003).

For demographic and clinical information see Table 2.

Given that altered reward processing is thought to be a major pathomechanism of ASD, which results in core symptoms that undergo quantitative, but not qualitative changes during development (Lai et al., 2014), we aimed to find functional correlates of impaired reward processing irrespective of age. We primarily relied upon the same definition of social and non-social reward as given by the included publications. In a second step, two experienced researchers (H.J., R.S.) went over the original studies to make sure that no studies were erroneously included in the groups pooling over social and non-social reward.

2.2. Activation likelihood estimation (ALE)

For our ALE, we extracted the whole-brain peak coordinates of the included studies, reporting comparisons of neural activations between individuals with ASD and HC during reward paradigms. The directionality of the respective contrast was identified, where applicable.

We used a revised version (Eickhoff et al., 2012; 2009) of the activation likelihood estimation (ALE) approach (Laird et al., 2005). This analysis treats the respective coordinates as centers of a Gaussian 3D probability distribution, which reflects the spatial uncertainty associated with each set of reported coordinates (Eickhoff et al., 2009; Turkeltaub et al., 2012) and allows to determine brain regions with a spatial
convergence of results across different publications which is higher than expected under a spatially random association. For each of our analyses convergence between studies was greater than it would be expected by chance (i.e., to separate true convergence from noise). The yielded statistical parametric maps were thresholded at p < 0.05 (cluster level FWE, corrected for multiple comparisons, cluster forming threshold at voxel level p < 0.001) (Eickhoff et al., 2012).

The ALE algorithm allows to subcategorize experiments. This enabled us to specify the contribution of experiments with distinct reward types (monetary, non-monetary, social, non-social), age distributions (adults only or also including minors) and medication status (medicated, non-medicated) to the ALE clusters.

Our main analysis pooled over all contrasts reporting hypervactivations. Additional analyses pooled over clusters reporting hyperactivations and over all contrasts, irrespective of their directionality. In order to evaluate, if the clusters derived from our ALE analysis overlapped with the results of a prior ALE meta-analysis on structural

| Paper                  | Subjects | Comparison ASD vs TDC | Comparison group × reward type interaction | Task                                      |
|------------------------|----------|-----------------------|--------------------------------------------|------------------------------------------|
| Assaf et al. 2013      | 27       | Gains versus losses   | Domino task: Guessing paradigm, computer versus human opponent |
| Caria et al. 2011      | 22       | [Standard & Favorite] versus baseline; Favorite versus baseline | Music listening paradigm: block design |
| Carlisi et al. 2017a   | 44       | Wins versus losses    | Iowa gambling task                          |
| Carlisi et al. 2017b   | 49       | Delayed versus immediate; Immediate versus delayed | Temporal discounting paradigm (choices between immediate and delayed monetary rewards) |
| Cascio et al., 2012a, 2012b | 27 | Pleasant touch versus baseline rest | Tactile paradigm, with different levels of pleasantness (brush/burlap/mesh) |
| Choi et al. 2015       | 20       | Feedback phase versus baseline phase | Auditory discrimination paradigm with social feedback (facial expressions) |
| Decley et al. 2007     | 18       | Main effect of group on happy faces versus fixation contrast | Viewing of emotional facial expressions (sad/fear/happy), at three intensity levels (intense, mild, neutral). |
| Delmonte et al. 2012   | 42       | Correct feedback versus baseline | Monetary Incentive Delay paradigm; Social Incentive Delay paradigm |
| Dichter et al. 2012c   | 36       | Monetary reward anticipation; monetary reward outcome; social reward anticipation; social reward outcome | Monetary Incentive Delay paradigm; Social Incentive Delay paradigm (positive/neural emotional face outcomes) |
| Dichter et al. 2012c   | 31       | Monetary reward anticipation; monetary reward outcome; object reward anticipation; object reward outcome | Monetary Incentive Delay paradigm; Object Incentive Delay paradigm (valued objects) |
| Hsu et al. 2018        | 56       | Group by Mimicry/anti-mimicry interaction | Facial mimicry paradigm – hypothesized by authors to be rewarding |
| Kim et al. 2015        | 41       | Group by Happy face interaction | Emotional face presentation (happy, fear, neutral) |
| Kohls et al. 2013      | 32       | Go monetary reward blocks versus go neutral blocks; Go social reward blocks versus go neutral blocks | Incentivized go/no-go paradigm, including monetary and social rewards (block design) |
| Lassalle et al., 2017  | 48       | 100% intensity happy faces versus neutral faces | Emotional face viewing paradigm (fear, happy, angry, neutral), with high (100%) intensity emotional faces. |
| Mikita et al. 2016     | 1472     | Reward anticipation (large win versus no win anticipation); Positive feedback (large hit win versus no hit win) | Monetary Incentive Delay paradigm |
| Monk et al. 2010       | 24       | Happy/neural trials versus neutral/neural trials | Probe detection paradigm including emotional face pairs (happy, sad, angry, neutral) |
| Murphy et al. 2017     | 78       | Delayed versus immediate choice | Temporal discounting paradigm (choices between delayed and immediate options). |
| Rahko et al., 2012     | 52       | Happy faces versus mosaic | Dynamic emotional face viewing (happy, fear), contrasted with mosaic images |
| Richey et al. 2015     | 30       | Application of (pretrained) positive reappraisal to face cue (‘Enhance positive’) versus pre-regulation baseline | Cognitive reappraisal paradigm. 40 neutral faces were shown, participants were instructed to reappraise the picture positively or negatively or to just look at the picture. |
| Schmitz et al. 2008    | 20       | Successful response for rewarded target versus successful response for non-reward target | Continuous performance task (CPT), including monetary incentives for one of the targets |
| Solomon et al. 2015    | 47       | Association between neural activation coupled to early-stage stimuli and behavioral performance (learning on high probability stimuli) differs between groups; Stimulus (high probability)-coupled neural activation during early/late stages of the task; Feedback coupled neural activation during early/late task stages | Probabilistic selection task: 3 stimulus pairs of Hiragana characters (probabilistically rewarded). 4 runs of 72 trials: run 1 2 early learning, run 3 4 later learning) |
| Schwarz et al., 2020   | 135      | Reward cue (social & monetary reward) versus reward control cue | Social/Monetary Incentive Delay paradigm (collapsed) |
| Weng et al. 2011       | 42       | Happy faces versus baseline | Emotional face viewing (happy, fearful, sad, neutral). |

Summary of the number of subjects, comparison and task used to compare reward processing in typically developing controls (TDC) and participants with autism spectrum disorder (ASD). As listed above, mostly faces were used as social rewards and monetary rewards as non-social rewards. The study, which used pleasant touch as social reward (Cascio et al., 2012) did not contribute to our ALE clusters. Amongst the studies with alternative non-social rewards, only the study by Dichter and colleagues (Dichter et al., 2012b), which also included monetary rewards, contributed to our ALE clusters.
| Paper                  | Subjects | TDC | ASD | Minimum IQ ASD | Age TDC | Age ASD | Age range ASD - unless otherwise specified | Diagnostic system used | Tests to confirm diagnosis | Medication status                                                                 | Relevant comorbidities of individuals with ASD |
|-----------------------|----------|-----|-----|----------------|---------|---------|--------------------------------------------|------------------------|---------------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------|
| Assaf et al. 2013     | 27       | 14  | 13  | ≥70            | 17.4 ± 3.6 | 17.3 ± 3.3 | 12–24                                     | NA                     | ADOS, ADI-R                      | 8 of 13 medicated (information on 1 was missing), 5 psychostimulants, 3 antipsychotics, 4 antidepressants, 6 with >1 drug | NA                                              |
| Caria et al. 2011     | 22       | 14  | 8   | NA             | 24.30 ± 3.02 | 23.40 ± 3.02 | 19–37                                     | DSM-IV, ICD-10         | ADOS, GADS, KADI                | NA                                                                                |                                                  |
| Carlisi et al. 2017a  | 44       | 20  | 24  | ≥70            | 15.1 ± 2.0  | 14.6 ± 1.6  | 11–17                                     | ICD-10                 | ADOS, ADI-R, KADI                | medication naive                  |                                                  |
| Carlisi et al. 2017b  | 49       | 20  | 29  | ≥70            | 15.29 ± 1.8 | 14.72 ± 1.8 | 11–17                                     | ICD-10                 | ADOS, ADI-R, SCQ                | medication naive                  |                                                  |
| Cascio et al. 2012a   | 27       | 14  | 13  | ≥70            | 30.8 ± 12.0 | 28.3 ± 10.7 | no range (but adults)                     | NA                     | ADOS, ADI-R                      | NA                                                                                |                                                  |
| Choi et al. 2015      | 20       | 5   | 15  | ≥80            | 9.5 ± 2.2   | 9.5 ± 2.2   | no range (but adults)                     | DSM-IV, ADOS           | no psychotropic medications on the day of scanning unmedicated | no psychotropic medications on the day of scanning unmedicated |                                                  |
| Deeley et al. 2007    | 18       | 9   | 9   | ≥70            | 17.00 ± 3.37| 16.64 ± 3.45| 14–26                                     | DSM-IV, ICD-10         | ADOS, ADI-R                      | unmedicated 4 ASD comorbid for ADD or ADHD                                      |                                                  |
| Delmonte et al. 2012  | 42       | 21  | 21  | ≥70            | 17.00 ± 3.37| 16.64 ± 3.45| 14–26                                     | DSM-IV, ICD-10         | ADOS, ADI-R                      | medicated (6 no drugs, 3 citalopram, 1 fluoxetine, one risperidone, 4 multiple psychotropic medications i.e. fluoxetine, lorazepam, clonidine, olanzapine, sertraline, aripiprazole) 12 no medications, 4 aripiprazole, 1 amphetamine/dextroamphetamine, 1 citalopram, 1 fluoxetine, 1 risperidone, 1 amphetamine/dextroamphetamine and fluoxetine |                                                  |
| Dichter et al. 2012a  | 36       | 20  | 16  | ≥80            | 25.4 ± 7.0  | 26.0 ± 9.1  | no range (but adults)                     | NA                     | ADOS                            | 7 no medications, 4 aripiprazole, 1 amphetamine/dextroamphetamine, 1 citalopram, 1 fluoxetine, 1 risperidone, 1 amphetamine/dextroamphetamine and fluoxetine |                                                  |
| Dichter et al. 2012b  | 31       | 16  | 15  | ≥80            | 27.5 ± 7.5  | 31.1 ± 11.6 | 17–45                                     | NA                     | ADOS                            | 8 methylphenidate, 1 atomoxetine, 1 methylphenidate and valproic acid no psychotropic medication |                                                  |
| Hsu et al. 2018       | 56       | 30  | 26  | NA             | 30.73 ± 2.09| 35.08 ± 2.24| 18–60                                     | DSM-IV                 | ADOS                            | NA                                                                                |                                                  |
| Kim et al. 2015       | 41       | 24  | 17  | >80            | 10.18 ± 2.04| 10.89 ± 2.06| NA                                        | DSM-IV                 | ADOS, ADI-R, ASSQ                | 8 methylphenidate, 1 atomoxetine, 1 methylphenidate and valproic acid no psychotropic medication |                                                  |
| Kohls et al. 2013     | 32       | 17  | 15  | ≥80            | 13.9 ± 3    | 14.6 ± 3.3 | 9–18 years (included participants, also includes TDC) | DSM-IV                 | ADOS, ADI-R, SCQ                | no psychotropic medication                                              |                                                  |
| Lassalle et al. 2017  | 48       | 21  | 27  | all >80        | 19.70 ± 7.74| 23.63 ± 9.86| 9–43                                      | DSM-IV                 | ADOS, ADI-R                      | NA                                                                                |                                                  |
| Mikita et al. 2016    | 1472     | 1402| 70  | ≥70            | 14.4 ± 0.4  | 14.4 ± 0.4  | no range - around 14 and around 16 years | NA                    | ASD section of DAWBA             | NA                                                                                | Generalized anxiety (19), social anxiety (13), depression (10), separation anxiety (10), specific phobia (5), agoraphobia (5), PTSD (4), OCD (3), panic disorder (2) |
|                       | 24       | 12  | 12  | ≥85            | 27 ± 6      | 26 ± 6      | DSM-IV                                    |                        |                                 |                                                                                   |                                                  | (continued on next page)
changes in ASD (Nickl-Jockschat et al., 2012), we compared the clusters resulting from both meta-analyses via calculation of the Dice’s coefficient.

### 2.3. Additional analyses: functional connectivity analysis

In order to further characterize the functional properties of the identified brain regions, we used the clusters resulting from our ALE meta-analyses as seed regions for two different kinds of functional connectivity analysis, task-independent (resting-state) and task-based functional connectivity (based on meta-analytic connectivity modeling, MACM).

#### 2.3.1. Task-independent functional connectivity: resting state

Resting-state fMRI images from 192 healthy subjects included in the enhanced NKI-Rockland sample (age range 20 – 75 years, mean age 40.36 ± 16.68 years, 67 males, 125 females) (http://fcon_1000.projects.nitrc.org/indi/enhanced/) were downloaded. During image acquisition the subjects were instructed to look at a fixation cross, think about nothing and not to fall asleep (which was confirmed by a post-scan debriefing).

Images were acquired on a Siemens TimTrio 3T scanner using BOLD contrast [gradient-echo EPI pulse sequence, TR = 1.4 s, TE = 30 ms, flip angle = 65°, voxel size = 2.0 mm × 2.0 mm × 2.0 mm, 64 slices]. Physiological and movement artifacts were removed from the RS data by
using FIX (FMRIB’s ICA-based Xnoiseifier, version 1.061 as implemented in FSL 5.0.9 (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014), which decomposes the data into independent components (ICs) and identifies noise components using a large number of distinct spatial and temporal features via pattern classification. Unique variance related to the identified artefactual ICs is then regressed from the data together with 24 movement parameters (including derivatives and 2nd order effects as previously described and evaluated (Satterthwaite et al., 2013). The first four scans were excluded from analysis with SPM8 to allow magnet saturation. The remaining images were corrected for movement artifacts via two-pass (alignment to the initial volume followed by alignment to the mean after the first pass) affine registration. The mean EPI image for each subject was normalized to the ICBM-152 reference space using the “unified segmentation approach” (Ashburner and Friston, 2005). The ensuing deformation was applied to the individual EPI volumes. These were smoothed with a 5-mm FWHM Gaussian kernel. By computing the first eigenvariate of the time-series of all voxels, the time-course of each seed was extracted per subject. In order to reduce false correlations, variances based on the mean white matter or cerebrospinal fluid signal were removed from these time series. The remaining time-series was band-pass filtered between 0.01 and 0.08 Hz. The processed time-course of each seed was subsequently correlated with the (identically processed) time-series of all other grey matter voxels via linear (Pearson) correlation. The ensuing correlation coefficients were transformed into Fischer’s z-scores, which were entered in a second level ANOVA for group analysis. Subsequently a non-parametric permutation-based inference was performed using threshold-free cluster enhancement, (TFCE), and FWE-correction at p < 0.05.

2.3.2. Task-based functional connectivity: MACM

Each voxel resulting from the ALE meta-analysis was used as a seed region for meta-analytic connectivity modeling (MACM) (Eickhoff et al., 2011; Langner et al., 2014). This approach is based on the assumption that functionally connected regions should co-activate above chance. All experiments in the BrainMap database (http://www.brainmap.org) (Laird et al., 2011, 2009) which showed co-activation with at least one cluster from our ALE analysis were selected. Our aim was to identify functional neurobiological networks, which include the voxels derived from our meta-analysis. Therefore, we only included experiments with healthy subjects in the MACM. Studies examining medication effects or disease were excluded. We subsequently performed a separate ALE across all included experiments, which showed co-activations with a single cluster from our ALE meta-analysis. Results were thresholded at p < 0.05 and FWE-corrected for multiple comparisons.

2.3.3. Functional connectivity conjunction analysis: consensus connectivity network

In order to detect FC patterns irrespective of task or rest, we performed a conjunction analysis across the thresholded maps resulting from the MACM and resting state connectivity analyses for each cluster from our ALE meta-analysis by using the image calculator (imcalc) in SPM12 and minimum statistics (Nichols et al., 2005). This resulted in a consensus connectivity network (CCN) for each cluster from our ALE meta-analysis, which contained regions that were only present in both – the maps resulting from the MACM and resting state connectivity analysis. We applied the same method to generate an overlap CCN, which only contained regions which were present in all CCNs.

2.4. Additional analyses: functional decoding

To functionally characterize the regions identified in our ALE meta-analysis and their CCNs, we analyzed the associated BrainMap metadata (http://www.brainmap.org) (Laird et al., 2011, 2009) for significant associations with behavioral domains or paradigm classes. Behavioral domains comprise action, cognition, emotion, interoception and perception as main categories (http://www.brainmap.org/taxonomy/behaviors.html). Experimental tasks are categorized in paradigm classes, which use well-known experimental paradigms, like, e.g., Go/No-Go, n-Back, passive viewing, etc. (http://www.brainmap.org/taxonomy/paradigms.html).

For our analyses, we used forward and reverse inference approaches. While forward inference tests the probability of a special behavioral process relating to activation in a brain region, reverse inference tests, if a given behavioral domain is active, when a particular region is activated (Wensing et al., 2017). To assess significance in the forward inference approach we used a binomial test (p < 0.05, FDR corrected). For significance testing in the reverse inference approach a chi-square test (p < 0.05, FDR corrected) was used. This data-driven assignment of functions to brain regions avoids the problems that come with functional assignments to brain regions that are based on subjective hypothesis.

3. Results

3.1. Striatal hypoactivation during reward processing in ASD

Our analysis pooling over hypoactivations in ASD subjects resulted in 2 clusters. The larger of these clusters comprised mainly the right putamen and the right accumbens, with its fringes extending into the fronto-orbital cortex, the subcallosal cortex as well as into the right caudate nucleus (Table 3, Fig. 2a). In order to investigate the influence of potentially confounding variables, like specific reward type (monetary, non-monetary, social, non-social), age (adults only or also including minors) or medication status (mediated, non-medicated), we determined their contribution to each ALE cluster. The first cluster, which is mainly located in the right putamen and right accumbens, received 39% of its contributions from experiments with social paradigms and 43% from experiments with non-social paradigms. The former only included experiments with faces as social rewards, while the latter only included experiments with monetary rewards as non-social rewards. The majority of contributions to this cluster included minors (62%) and ASD patients taking psychotropic medications (68%). The cluster was associated with positive emotion (reward/gain), cognition (attention, reasoning), perception (gustation) and interoception (sexuality).

The second cluster extended from the left caudate, the left accumbens and the pre-genual area to the basal forebrain (Table 3, Fig. 2b). Contributions to this cluster came exclusively from experiments using non-social paradigms (only monetary rewards) and including minors. The majority of contributions to this cluster experiments included ASD-patients taking psychotropic medications (72%). With the exception of perception, which was missing in this cluster, the behavioral domains were the same for the two clusters. However, contributions to the second cluster came from as few as two independent patient samples (Dichter et al., 2012b, 2012c; Kohls et al., 2013), indicating a less robust convergence across studies.

Pooling over contrasts with hyperactivations only did not yield any significant results. An analysis pooling over all activations irrespective of their directionality (i.e., hyper- and hypoactivations) also yielded a cluster in the right putamen and nucleus accumbens (Table 3, Fig. 2c).

3.2. Functional and structural findings in the striatum in ASD do not overlap

The comparison of the clusters resulting from this ALE meta-analysis with the ones of a previous ALE meta-analysis on structural changes in ASD (Nickl-Jockschat et al., 2012) via Dice’s coefficient did not show an overlap between clusters indicating functional and those indicating structural alterations in ASD. However, a cluster in the right caudate nucleus from the structural ALE meta-analysis was directly adjacent to a cluster from our functional ALE meta-analysis (Fig. 3).
### Table 3

Clusters resulting from our ALE meta-analysis on reward processing in ASD and their Consensus Connectivity networks (CCNs)

| Analysis | Cluster name (MNI X, Y, Z), voxel size | Maximum Probability Map | Contributing studies |
|----------|----------------------------------------|--------------------------|----------------------|
| ALE hypoactivations | Cluster 1 (12, 10, −10) 161 voxel | 34.2% Right Putamen | Assaf et al. 2013 (14%) |
| | | 19.1% Right Accumbens | Kohls et al. 2013 (14%) |
| | Cluster 2 (−6, 6, −4) 98 voxel | 2.6% Right Area Fo2 | Lassalle et al., 2017 (18%) |
| | | 24% Left Accumbens | Richey et al. 2015 (20%) |
| | | 5.1% Left Caudate18.8% | Schwarz et al., 2020 (18%) |
| | | Left Area 33 | Dichter et al., 2012b+ c studies collapsed (16%) |
| | | 13.8% BF (CH1-3) | Dichter et al., 2012b+ c studies collapsed (72%) Kohls et al.2013 (29%) |
| | Cluster 3 (8, 18, 2) 208 voxel | 81.4% Cingulate Gyrus anterior division | Kohls et al. 2013 (13%) Lassalle et al., 2017 (20%) Richey et al. 2015 (19%) Rabko et al., 2012 (9%) |
| | Cluster 4 (−6,32,28) 198 voxel | 38.1% Area p24ab | Schwarz et al., 2020 (16%) Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 5 (4, 36, −12) 131 voxel | 50.3% Area p32 | Dichter et al., 2012b+ c studies collapsed (72%) Kohls et al.2013 (29%) |
| | Cluster 6 (6,28,16) 96 voxel | 56.9% Paracingulate Gyrus | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 7 (4,20,50) 16 voxel | 18.0% Cingulate Gyrus, anterior division | Assaf et al. 2013 (14%) Kohls et al. 2013 (13%) Lassalle et al., 2017 (20%) Richey et al. 2015 (19%) Rabko et al., 2012 (9%) |
| | Cluster 8 (0,4, −4) 6483 voxel | 8.7% Right Thalamus | Assaf et al. 2013 (14%) Kohls et al. 2013 (13%) Lassalle et al., 2017 (20%) Richey et al. 2015 (19%) Rabko et al., 2012 (9%) |
| | Cluster 9 (4,36, −2) 224 voxel | 7.6% Left Thalamus | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 10 (8,18,30) 208 voxel | 81.4% Cingulate Gyrus anterior division | Assaf et al. 2013 (14%) Kohls et al. 2013 (13%) Lassalle et al., 2017 (20%) Richey et al. 2015 (19%) Rabko et al., 2012 (9%) |
| | Cluster 11 (−6,32,28) 198 voxel | 38.1% Area p24ab | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 12 (4, −36, 36) 131 voxel | 50.3% Area p32 | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 13 (4, −24, 18) 16 voxel | 38.1% Area p24ab | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 14 (8, −36, 36) 131 voxel | 50.3% Area p32 | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 15 (4, −24, 18) 16 voxel | 38.1% Area p24ab | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 16 (8, −36, 36) 131 voxel | 50.3% Area p32 | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 17 (4, −24, 18) 16 voxel | 38.1% Area p24ab | Dichter et al., 2012b+ c studies collapsed (15%) |
| | Cluster 18 (8, −36, 36) 131 voxel | 50.3% Area p32 | Dichter et al., 2012b+ c studies collapsed (15%) |

### Table 3 (continued)

Characterization of the clusters derived from the ALE meta-analyses which included all contrasts and from the TDC > ASD analysis with peak coordinates, voxel size, Maximum Probability Map assignment as well as the individual publications contributing to the respective cluster. Additionally, this table shows the peak coordinates, voxel sizes and Maximum Probability Map assignments of the consensus connectivity networks (CCNs) for which the ALE clusters served as seed regions.

#### 3.3. Consensus connectivity networks (CCNs) of the clusters derived from our ALE meta-analysis and their functional characterization

We, then, wanted to investigate, in which networks the clusters derived from our ALE analyses were enrolled in healthy subjects. To this end, we modeled task-dependent (MACM) and task-independent
functional connectivity of these clusters (see inline supplementary figures 1 and 2 for detailed results of these analyses). In the following section, we will depict the results for the conjunction of both task-dependent and task-independent networks, so-called consensus connectivity networks (CCNs).

The CCN of the larger cluster from the HC > ASD analysis, located in the right putamen and accumbens, was involved in a large bilateral network, mainly comprising basal ganglia (putamen, pallidum, caudate nucleus, nucleus accumbens), thalamus, amygdala, hippocampus and insula, but also operculum, frontal orbital cortex and midbrain. Moreover, it included the cingulate and paracingulate gyrus and the subcallosal cortex (Table 3, Fig. 4a). Functional decoding of this network revealed an association with positive (reward/gain, happiness) as well as negative emotion (loss/punishment, fear, sadness, disgust), emotion intensity, cognition (reasoning), perception (somesthesis/pain, gustation, olfaction) as well as interoception (sexuality).

The CCN of the second, less robust, cluster in the left caudate, left accumbens and the pre-genual area, which emerged from the TDC > ASD ALE analysis, showed a very similar pattern. The network encompassed similar regions as the CCN of the former cluster (Table 3, Fig. 4b). Functional characterization of this network included positive (reward/gain), and negative emotions (punishment/loss, disgust, fear), emotion intensity, perception (olfaction, gustation, somesthesis/pain), cognition (reasoning) and interoception (sexuality, thermoregulation).

The CCN from the cluster of our ALE pooling over both hyper- and hypoactivations largely recapitulated the results from cluster 1 of our analysis on hypoactivations, as both clusters largely resemble each other regarding location, extent and shape (Fig. 4c).

4. Discussion

Dysfunctional processing of rewards is commonly regarded as a major pathomechanism of ASD (Dichter et al., 2012a). Our ALE meta-analysis on reward processing in ASD with a subsequent functional characterization of implicated brain regions highlighted three important neurobiological aspects of this mechanism. First, our ALE findings, which are based on the included studies on reward processing in ASD, pinpoint the striatum as an important hub within the extensive reward processing network mediating impaired reward processing in autism. Second, they indicate that general impairments in reward processing rather than exclusive deficits for social stimuli underlie autism pathophysiology. Additionally, modelling the functional connectivity of the clusters resulting from our meta-analysis in a separate dataset with healthy subjects suggests that these clusters are involved in the processing of both positive emotions associated with reward, and negative emotions associated with loss, punishment, fear, sadness and disgust. Therefore, we hypothesize that the ASD-related alterations in the processing of positive emotions associated with reward might also affect the pathophysiology of processing negative emotions.

4.1. The striatum is a dysfunctional central hub of the reward network in autism

The reward processing network involves multiple cortical and subcortical brain regions (Dichter et al., 2012a), but convergent evidence for altered activation patterns implicated the striatum, with only peripheral involvement of other regions. This view of striatal pathologies driving dysfunctional reward processing is supported by multiple lines of evidence. A previous neuroimaging meta-analysis, for example, pointed to altered striatal activations associated with reward in ASD patients (Clements et al., 2018). Our own results corroborate a major role for striatal dysfunction in the reward network, as a pathomechanism that is conserved across different ages.

Structural pathologies have also indicated a central role of the striatum in autism. A previous meta-analysis from our lab on structural MRI publications found convergent evidence for changes in the right caudate and the left putamen (Nickl-Jockschat et al., 2012). These structural changes were located in close proximity to, but did not overlap with, the functional alterations found in this meta-analysis. This lack of overlap might be in part attributable to the spatial uncertainty that is inherent in coordinate-based meta-analyses, as the coordinates from original publications are treated as centers of a Gaussian 3D probability distribution (Eickhoff et al., 2009; Turkeltaub et al., 2012). However, it should be noted that a spatial dissociation between structural and functional brain changes is frequently observed in psychiatric disorders. Structural alterations are oftentimes located in consensus connectivity networks of the regions with functional changes (Chase et al., 2018; Nickl-Jockschat et al., 2015). Future studies using high-resolution MRI will have to follow up on the question of how structural findings relate to altered brain function in the reward circuitry of ASD patients. Alternatively, the lack of overlap could originate in different functional properties of the subregions of the striatum (Tian et al., 2020). Hence, structural alterations found in our previous meta-analysis on structural alterations in ASD (Nickl-Jockschat et al., 2012)
and the reward-related alterations found in the meta-analysis presented here could affect different subregions of the striatum.

The causal factors that lead to the emergence of these structural and functional changes in the striatum are currently unknown, but animal models highlight the importance of genetic variation. Behavioral changes during reward processing and learning, pointing towards a disruption of cortico-striatal circuits, have been identified across different mouse models of genetic lesions associated with ASD (Grissom et al., 2018; Jaramillo et al., 2017; Wang et al., 2017). In one of these models, 16p11.2 deletion (Weiss et al., 2008), neuroimaging studies documented striatal volume increases (Portmann et al., 2014) and neuroanatomical changes of the peristriatal fiber tracts (Kumar et al., 2018). These gross morphological changes may reflect a disbalance between two major neuronal populations in the striatum: a relative excess of D2 receptor expressing medium spiny neurons (D2 MSNs) at the expense of D1 receptor expressing neurons (D1 and D2 MSNs) (Grissom et al., 2018; Portmann et al., 2014). D1 and D2 MSNs are antagonists, with D1 MSNs initiating, and D2 MSNs inhibiting reward-directed actions (Agnoli et al., 2013; Kravitz et al., 2012; Nishizawa et al., 2012). Increased D2 MSN signaling could explain impaired reward processing in these animals. Recent human studies with small sample sizes support this hypothesis, by showing increased D2 receptor mRNA expression in striatal medium spiny neurons (MSNs) in ASD relative to controls (Brandenburg et al., 2020), but no change in striatal DA D1 receptor occupancies in ASD (Kubota et al., 2020).

Our study certainly does not allow inference on a cellular level.
However, our finding of a striatal hypoactivation during reward would fit very well with these results from animal studies suggesting disproportionate inhibitory neurotransmission in the striatum. This renders the investigation of disbalances between D1 and D2 as a potential aim for future studies with larger patient populations.

4.2. Evidence for a general disruption of both social and non-social reward processing

Persistent deficits in social interaction are a core criterion for the diagnosis of autism (APA, 2013). Infants later diagnosed with autism show impaired social behaviors early on: they exhibit significantly decreased tendencies to gaze at their parents’ faces at an age as early as 12 months (Gangi et al., 2018). At later ages, children on the autism spectrum also prefer non-social over social stimuli (Gale et al., 2019). Researchers have interpreted these findings as indicative of particularly social stimuli being processed as non-rewarding (the so-called “social motivation deficit hypothesis of autism”) (Chevallier et al., 2012). If the main premise of the social motivation deficit hypothesis – particularly social stimuli being mis-processed in patients – held up, we could expect aberrant activations within the reward network for social stimuli, while non-social rewards would not (or only to a minor part) contribute to these changes.

The right putamen-accumbens cluster resulting from our analysis received equal contributions from experiments with social and non-social stimuli. Therefore, reward type does not seem to have a major impact on striatal hypoactivations during reward. However, coordinate-based meta-analyses are aimed at exploring the spatial coherence of neuroimaging results (Eickhoff et al., 2012) and do not allow a determination of effect sizes. Consequently, a direct quantitative comparison between the extents of the deactivation for both types of stimuli is not possible. Nevertheless, our findings suggest a shared functional architecture for social and non-social reward processing deficits.

As the contribution of studies with minors to this cluster largely reflects the percentage of experiments including minors, age doesn’t seem to have a major impact on reward-related striatal hypoactivations.

Given that the contribution of experiments with patients on psychotropic medications to both of our ALE clusters is higher than their total share, medication-effects might have influenced the outcome of our ALE meta-analysis.

Striatal pathologies might account not only for reward processing deficits, but also for other core symptoms of ASD. Recent data suggests that striatal activation is altered during the processing of circumscribed interests (Kohls et al., 2018). Analyzing a potential spatial overlap or dissociation between reward-related hypoactivations and hyperactivations due to circumscribed interests will be an important subject for future research.

4.3. Differentially activated striatal regions are involved in networks mediating positive and negative affective responses related to reward in healthy subjects

Network connectivity is a major determinant of the functional properties of a region. Our network modeling of the right putamen and left caudate clusters from our analysis on contrasts reporting hypoactivation in patients revealed bilateral networks involving canonical regions of the reward processing network, including basal ganglia, thalamus, insula, cingulate, paracingulate and subcallosal cortex in separate datasets with healthy subjects. Most of these regions are associated with the processing of positive emotions related to reward. Remarkably, regions also associated with negative emotions, such as punishment, loss, disgust, fear and sadness, were part of these consensus connectivity networks. Behavioral data from healthy controls points to a close interplay between rewarding and punishing experiences as necessary for the acquisition of goal-directed behaviors (Kubanek et al., 2015). Congruent with that idea, animal data show a partial overlap of neuronal circuits mediating positive and negative valence (Toyote et al., 2015). Our ALE results strongly suggest an involvement of dysfunctionally activated striatal regions in networks related to positive reinforcement and motivation due to rewarding stimuli. Given that the
connectivity profile of a brain region mainly determines its functional properties, it is interesting that the clusters from our ALE analysis are associated with the processing of both, positive and negative emotions, like punishment, in healthy subjects. If this connectivity profile allows inference on neural changes in ASD, we regard it as proximate that the striatal deficits in the processing of positive emotions associated with reward in ASD may at the same time be associated with impairments in the processing of negative emotions. However, this hypothesis needs additional testing.

On a behavioral level, these neural alterations could translate into diminished pleasure, reduced motivation to acquire rewarding stimuli, and less avoidance of punishment. This finding could have several important implications. First, impaired motivation and reduced feelings of frustration due to a loss of reward could well explain why individuals on the autism spectrum fail to engage in social interactions early on. Second, the consistent hypoactivation across different ages renders the striatum a promising target for neuromodulation. However, its anatomical position will pose considerable challenges for clinicians in this regard.

Current treatments for ASD are oftentimes reward-based. While the current literature provides evidence for the efficacy of those treatments – children on the autism spectrum, e.g. respond better to therapies in a context that the child regards as rewarding (Koegel et al., 1987; Schreibman et al., 2015) - the therapeutic effects might be improved by the use of also non-emotional techniques. This hypothesis is based upon connectivity modeling of our ALE clusters in separate datasets with healthy subjects that revealed an involvement in networks that are also associated with the processing of negative emotions.

5. Methodological considerations

With 29 original publications (23 that actually provide coordinates), our meta-analysis can be expected to yield robust results (Eickhoff et al., 2016). However, the comparatively small number of publications meeting inclusion criteria did not allow us to conduct sub-analyses. Given the broad phenotypical range of individuals on the autism spectrum, different degrees of symptom severity might likely impact neural activation patterns.

In order to identify functional correlates of impaired reward-processing throughout the lifespan, we pooled across all ages. However, this approach is less sensitive to detect age-specific alterations of reward processing.

A considerable number of individuals in the studies included received antidopaminergic medications, antidepressants, and stimulants. All of these medications have been shown to alter reward processing (Abler et al., 2007; Stoy et al., 2012; Vollm et al., 2004). We cannot rule out that this has influenced our findings but would not regard it as likely that our results are entirely driven by medication effects, as these should not converge systematically across sites.

To delineate the task-dependent and task-independent networks of regions showing aberrant activation patterns during reward in individuals with ASD, we used two well-validated and widely used approaches (Laird et al., 2009, 2013), which allow robust inference on co-activation patterns in healthy subjects. Although these results do not allow direct inference on altered connectivity in ASD itself, we would like to point out that the use of these approaches was motivated by our main aim to better understand the functional properties of brain regions that are differentially activated in patients in reward processing. Given that the characterization of the functional properties of a brain region is a prerequisite to fully understand its role in disease-related processes, we used these methods to guide the generation of data-driven hypothesis for future studies on reward processing in ASD.

6. Conclusions

Our study provides robust evidence for aberrant activations particularly of the striatum as a neural correlate for impaired processing of both social and non-social rewards in ASD. These findings point toward a distinct hub within the reward processing network that might be a promising target for therapeutic interventions.

Funding

This research did not receive any specific grant from grant funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102700.

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