Attenuated Anticipation of Social and Monetary Rewards in Autism Spectrum Disorders

Sarah Baumeister², Carolin Moessnang², Nico Bast¹,², Sarah Hohmann¹, Julian Tillmann⁴,⁵, David Goyard⁶, Tony Charman⁴, Sara Ambrosino⁷, Simon Baron-Cohen⁶, Christian Beckmann⁶,²⁰, Sven Bölte¹¹,¹², Thomas Bourgeron¹³, Annika Rausch¹,²⁰, Daisy Crawley¹⁴, Flavio Dell’Acqua¹⁴,¹⁵, Guillaume Dumas¹³, Sarah Durston¹⁷, Christine Eckert¹, Dorothée L. Floris⁹,¹⁰, Vincent Frouin⁶, Hannah Hayward¹⁹, Rosemary Holt⁶, Mark H. Johnson⁷,³⁶, Emily J.H. Jones¹⁶, Meng-Chuan Lan³⁷,³⁸, Michael V. Lombardo³⁹,⁴¹, Luke Mason⁶⁶, Marianne Oldehinkel⁷⁸, Tony Persico²⁰,²¹, Antonia San José Cáceres⁴²,⁴³, Thomas Wolfers¹⁰, Will Sporens¹⁸, Eva Loth¹⁴,¹⁵, Declan G. M. Murphy¹⁴,¹⁵, Jan K. Buitelaar³⁷,³⁸,³⁹, Heike Tost², Andreas Meyer-Lindenberg³, Tobias Banaschewski¹, Daniel Brandeis¹,²⁵,²⁶,²⁷ and the AIMS-2-TRIALS group

¹Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany
²Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany
³Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Frankfurt am Main, Goethe University, Frankfurt, Germany
⁴Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, United Kingdom
⁵Department of Applied Psychology: Health, Development, Enhancement, and Intervention, University of Vienna, Vienna, Austria
⁶Neurospin Centre CEA, Saclay, Gif sur Yvette, France
⁷Department of Psychiatry, University Medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands
⁸Autism Research Centre, Department of Psychiatry, University of Cambridge, United Kingdom
⁹Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands
¹⁰Department of Cognitive Neuroscience, Radboud University Medical Centre, Nijmegen, The Netherlands
¹¹Center of Neurodevelopmental Disorders (KIND), Centre for Psychiatry Research; Department of Women’s and Children’s Health, Karolinska Institutet and Child and Adolescent Psychiatry, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden.
¹²Curtin Autism Research Group, School of Occupational Therapy, Social Work and Speech Pathology, Curtin University, Perth, Western Australia.
¹³Institut Pasteur, Human Genetics and Cognitive Functions Unit, Paris, France
¹⁴Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, United Kingdom
¹⁵Sackler Institute for Translational Neurodevelopment, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, United Kingdom
¹⁶Centre for Brain and Cognitive Development, Birkbeck, University of London
¹⁷Centre for Addiction and Mental Health and The Hospital for Sick Children, Department of Psychiatry, University of Toronto, Toronto, Canada
¹⁸Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
¹⁹Laboratory for Autism and Neurodevelopmental Disorders, Center for Neuroscience and Cognitive Systems @UniTn, Istituto Italiano di Tecnologia, Rovereto, Italy
Child and Adolescent Neuropsychiatry Unit, "Gaetano Martino" University Hospital, University of Messina, Messina, Italy
Mafalda Luce Center for Pervasive Developmental Disorders, University Campus Bio-Medico, Milan, Italy
Instituto de Investigación Sanitaria Gregorio Marañón, Hospital General Universitario Gregorio Marañón, Madrid, Spain
Roche Pharmaceutical Research and Early Development, NORD Discovery and Translational Area, Roche Innovation Center Basel, Basel, Switzerland
Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands
Department of Child and Adolescent Psychiatry and Psychotherapy, Psychiatric Hospital, University of Zurich, Zurich Switzerland
Neuroscience Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland
Center for Integrative Human Physiology Zurich, University of Zurich, Zurich, Switzerland

* Corresponding author: Sarah Baumeister, Ph.D.
Department of Child and Adolescent Psychiatry and Psychotherapy
Central Institute of Mental Health
Medical Faculty Mannheim / Heidelberg University
J5, 68159 Mannheim, Germany
Phone: +49 (0) 621 1703 4934
Email: sarah.baumeister@zi-mannheim.de

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Abstract

**Background:** Reward processing has been proposed to underpin atypical social behavior, a core feature of autism spectrum disorder (ASD). However, previous neuroimaging studies have yielded inconsistent results regarding the specificity of atypicalities for social rewards in ASD. Utilizing a large sample, we aimed to assess altered reward processing in response to reward type (social, monetary) and reward phase (anticipation, delivery) in ASD.

**Methods:** Functional magnetic resonance imaging during social and monetary reward anticipation and delivery was performed in 212 individuals with ASD (7.6-30.5 years) and 181 typically developing (TD) participants (7.6-30.8 years).

**Results:** Across social and monetary reward anticipation, whole-brain analyses (p<0.05, family-wise error-corrected) showed hypoactivation of the right ventral striatum (VS) in ASD. Further, region of interest (ROI) analysis across both reward types yielded hypoactivation in ASD in both the left and right VS. Across delivery of social and monetary reward, hyperactivation of the VS in individuals with ASD did not survive correction for multiple comparisons. Reward type by diagnostic group interactions, and a dimensional analysis of autism trait scores were not significant during anticipation or delivery. Levels of attention-deficit/hyperactivity disorder (ADHD) symptoms did not affect reward processing in ASD.

**Conclusions:** Our results do not support current theories linking atypical social interaction in ASD to specific alterations in processing of social rewards. Instead, they point towards a generalized hypoactivity of VS in ASD during anticipation of both social and monetary rewards. We suggest that this indicates attenuated subjective reward value in ASD independent of social content and ADHD symptoms.
Introduction

Altered reward processing has been proposed to underlie the challenges that individuals with autism spectrum disorder (ASD) face in social interactions. The social motivation hypothesis postulates that individuals with ASD from early in development do not perceive social stimuli as rewarding as typically developing (TD) individuals, which may impact the development of social learning and social skills (1).

Neurobiological evidence in favor of the social motivation hypothesis is however mixed. To assess atypical motivation, reward processing is commonly investigated during the anticipation of a potential reward (“wanting”), the delivery of the reward (“liking”) or during both phases. Further, different types of rewards can be assessed, with non-social (usually monetary) rewards being most commonly investigated across psychiatric conditions, while social rewards have been postulated to be specifically impacted in ASD as detailed in the social motivation hypothesis. Supporting the concept of atypical social reward processing in ASD, one study showed reduced activation in the ventral striatum (VS) (2), a key region for reward processing comprising the nucleus accumbens and caudate head (3), compared to control participants when receiving social rewards. A similar effect was observed in another study in more dorsal parts of the striatum (4). However, other studies did not find functional striatal differences between ASD and TD individuals for social rewards during delivery (5, 6) or anticipation (4, 5). Similarly mixed results exist for non-social rewards: while some previous studies report VS hypoactivation in individuals with ASD when receiving monetary rewards (7-9), this has not been found (5) or only at uncorrected thresholds (10) elsewhere. Results for the anticipation of monetary rewards are also inconsistent with some studies suggesting VS hypoactivation in ASD participants (5, 9, 11), while another showed no difference between ASD and TD (4). Some of the inconsistency of previous findings is likely due to the heterogeneity of ASD itself (12), but also to the relatively small sample sizes examined (ranging between 13 and 39 individuals per group). A recent meta-analysis has partly addressed the latter issue by summarizing the current literature (13). Comparing individuals with ASD to TD, the authors reported striatal hypoactivation
during social as well as non-social rewards in ASD. However, results differed between anticipation and delivery phases. They report hypoactivation of the left caudate during anticipation of social rewards, and hyperactivation during the anticipation of non-social rewards. In contrast, during reward delivery, striatal (left nucleus accumbens and caudate) hyperactivation to social rewards and right caudate hypoactivation to non-social rewards were observed in ASD. These findings suggest opposing atypicality patterns for social and monetary reward types between reward phases and do not imply typical non-social reward processing in ASD. Across the seven studies assessing social reward processing, caudate hypoactivation was linked (albeit only at trend-level) to severity of autistic traits as measured with the Social Responsiveness Scale (SRS). This meta-analysis was an important first step to provide a more comprehensive insight into atypical reward processing in ASD. However, the number of included studies is still small (e.g. only three studies allowed for the differentiation between reward phases for social reward) and should thus be regarded as exploratory. Further, task designs were heterogenous, which might have increased variability in brain responses and distorted task-specific effects. Finally, while some studies included in the meta-analysis administered social and non-social reward conditions in the same sample, some only assessed one type of reward, limiting direct comparability.

Another challenge is the fact that ASD and attention-deficit/hyperactivity disorder (ADHD) frequently co-occur (14) and atypical reward processing for monetary rewards is often reported in individuals with ADHD (15). However, ADHD comorbidity or symptoms have not been examined in the majority of studies exploring reward processing deficits in ASD (for exceptions, see 6, 16).

Hence, the brain functional mechanisms underpinning reward processing alterations in ASD remain unclear. We therefore investigated reward-related brain responses in a large, well-powered sample of individuals with ASD. The Longitudinal European Autism Project (LEAP; (17)) provides a deeply phenotyped dataset of children, adolescents and adults with and without ASD who performed a social and a monetary reward task. The task was chosen based on its ability to reliably elicit VS
reward signaling (18) and allows for the analysis of both reward anticipation and reward delivery phases. We comprehensively assessed differences in reward signaling based on clinical diagnosis as well as dimensional autistic traits. Based on the recent meta-analysis (13), compared to TD, we hypothesized that neurofunctional responses in the VS would show a pattern of increased activity in ASD during monetary, and reduced activity during social reward anticipation - and the opposing pattern during reward delivery. We expected to observe this pattern in categorical case-control comparisons as well as in dimensional analyses based on autism traits. Further, based on previous findings (16), we hypothesized an additive effect of ADHD comorbidity, with reward processing being most severely altered in autistic individuals with elevated ADHD symptoms.
Methods and Materials

Experimental procedure

Sample

In the LEAP study, 437 individuals with ASD and 300 typically developing individuals, aged between 6 and 30 years, underwent comprehensive clinical, cognitive, and MRI assessment at one of six study sites: Institute of Psychiatry, Psychology and Neuroscience, King’s College London, United Kingdom (KCL); Autism Research Centre, University of Cambridge, United Kingdom (UCAM); Radboud University Nijmegen Medical Centre, the Netherlands (RUNMC); University Medical Centre Utrecht, the Netherlands (UMCU); Central Institute of Mental Health, Mannheim, Germany (CIMH); University Campus Bio-Medico of Rome, Italy (UCBM) (17). The study was approved by the local ethical committees of participating centers and written informed consent was obtained from all participants or their legal guardians (for participants <18 years). For further details about the study design we refer to Loth et al. (17), and for a comprehensive clinical characterization of the LEAP cohort we refer to Charman et al. (19). For this study, the final sample consisted of n=213 ASD and n=181 TD participants (see table 1). Standard operating and quality control procedures leading to the final sample are detailed in the supplemental material.

Clinical measures

Participants in the ASD group had an existing clinical diagnosis of ASD according to the DSM-IV/ICD-10 or DSM-5 criteria. ASD symptoms were comprehensively assessed using the Autism Diagnostic Interview-Revised (ADI-R; (20)) and Autism Diagnostic Observation Schedule 2 (ADOS-2; (21)) within the ASD group. We used the total raw score on the Social Responsiveness Scale Second Edition (SRS-2; (22)) to assess continuous autism traits, which was available across the study sample. Parent-rated scores were collected for ASD and TD individuals except for TD adults where only the self-report was assessed. We used self-rated scores wherever parent-rated scores were not available. Parent- or self-report of a psychiatric disorder was an exclusion criterion for the TD group. Information on the
presence of a confirmed diagnosis of ADHD was not available in our sample. As a proxy, we estimated diagnostic status by applying DSM-5 criteria based on symptom scores collected with the parent- and self-rated ADHD DSM-5 rating scales (23).

**Experimental paradigm**

We adapted a social and a monetary incentive delay task (SID, MID) (4) as part of a reliable task battery (18, 24, 25). For details see figure 1 and supplementary material. SID and MID were collected as separate paradigms and combined during data analysis. SID was always presented first, followed by MID. The fMRI scanning session was preceded by a training session outside the MRI to ensure that all participants understood the task.

**fMRI data acquisition**

Functional MRI data were acquired on 3T scanners from different manufacturers (General Electric, Philips, Siemens) and harmonized as much as possible across sites (for details see supplementary material). Functional images were acquired using a BOLD-sensitive T2*-weighted echo-planar imaging (EPI) sequence (repetition time (TR) = 2 s, echo time (TE) = 30 ms, flip angle = 80°, matrix: 64 × 64, FOV: 192 × 192 mm, in-plane resolution: 3 x 3 mm, slice thickness: 4 mm, gap: 1 mm, 28 axial slices). A total of 151 volumes were obtained for each task, oriented approximately 20° steeper than the AC-PC-plane.

**Data analysis**

**fMRI data preprocessing**

Image preprocessing followed standard processing routines in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/), including a two-pass realignment procedure, slice time correction, registration of the functional mean image to the Montreal Neurological Institute (MNI) template and spatial normalization into standard stereotactic space, application of resulting
normalization parameters to the functional time series, resampling to 3 mm isotropic voxels, and smoothing with an 8 mm full-width at half-maximum Gaussian Kernel.

**Whole-brain level fMRI data analysis**

SID and MID tasks were combined as two sessions in a general linear model (GLM) on the single subject level (see supplementary material for details). Within-subject effects were addressed at the subject-level by quantifying within subject effects of condition as differential response to win cues as compared to neutral cues for reward anticipation and differential response to successful win compared to neutral trials for reward delivery. Additionally, to quantify differential reward-specific responses between tasks, a contrast image for the interaction between condition (win, neutral) and task (SID, MID) was calculated.

Based on within-subject contrasts we assessed reward-specific brain activation (within subject effect of condition) and differential reward-specific responses between tasks (within-subject interaction condition x task) across the entire sample and tested for between-group differences. Contrast images were subjected to second-level GLMs with between-subject factor group (ASD vs. TD) and covariates age, sex, and site. The impact of ADHD comorbidity was explored in a separate model, where the ASD group was split into subgroups with (n=69) and without (n=118) comorbid ADHD based on estimated diagnostic status (ASD<sub>ADHD</sub> and ASD<sub>-ADHD</sub>, respectively) and compared to TD. TD individuals with elevated ADHD scores were excluded from this analysis. To assess the effect of autism traits, SRS-2 raw scores were added as additional covariate of interest in a separate model. Note that diagnostic group was accounted for in this model, ensuring that effects were not driven by differences in group means. To explore group differences on a whole-brain level, significance was defined as p<sub>FWE</sub> < .05 with a cluster threshold of k≥5, peak-level corrected across the whole brain.
Region of interest analysis

To increase sensitivity for putative case-control differences in the VS, we performed region of interest (ROI) analysis within a well-established a-priori defined bilateral mask of the VS (18). Mean contrast estimates (CE, contrasts cue win>cue neutral and successful win>neutral) for each participant and both tasks were extracted and analyzed using SPSS Software package (Version 25, IBM Corp., Armonk, NY, USA). Separate repeated measures ANOVAs with the within-subject factor task (MID, SID) and between-subject factor diagnosis (TD, ASD), and covariates age (mean-centered), sex, and study sites (dummy coded), were used to assess group differences for both reward processing phases (anticipation, delivery) in the left and right VS. To correct for investigating left and right VS activity separately, the critical alpha threshold was adjusted to p<.025 based on the Bonferroni procedure. Additionally, Bonferroni-correction was applied to all post-hoc pairwise comparisons. To assess the effect of autism traits, SRS-2 raw scores were added as additional covariate of interest in a separate model. Interaction terms between diagnosis and SRS-2 were added as well. The impact of ADHD comorbidity was explored in another separate model, where the between-subject factor diagnosis comprised three levels (TD, ASD\textsubscript{ADHD} and ASD\textsubscript{ADHD}).
Results

Functional activation analysis

Reward anticipation

Whole-brain level analysis

Reward-specific brain activation was observed in an extensive network with peak activations in the bilateral VS, ACC/SMA, Thalamus, bilateral precentral gyrus and bilateral anterior insula/IFG for the anticipation of win compared to neutral trials collapsed across both reward tasks.

Reward-specific brain activation differed between diagnostic groups at the whole-brain level in the right VS ($F_{(1,384)}=22.84$, $p_{FWE}=.017$, $k=8$) during reward anticipation. A post-hoc T-test showed that activation was reduced in ASD compared to TD individuals.

See figure 2 A and B and table 2 for details.

Differential reward-specific responses between tasks yielded activation in a network with peak activations in the bilateral VS, anterior cingulate cortex (ACC)/supplementary motor area (SMA), thalamus, bilateral precentral gyrus and bilateral anterior insula/inferior frontal gyrus (IFG) (see fig 3A and table 3). Post-hoc T-tests showed stronger differential activation in the MID compared to the SID across all these regions.

Differential reward-specific responses between tasks did not differ between individuals with and without ASD, however, we report differences between ASD and TD in the SID and MID separately in the supplementary material (figure S1 and tables S2 and S3) to allow for a comparison with previous studies.

ROI analysis

Individuals with ASD differed from TD individuals on average regarding reward-specific brain activation within the left ($F_{(1,384)}=14.163$, $p<.001$, partial $\eta^2=.036$) and right ($F_{(1,384)}=18.693$, $p<.001$, partial $\eta^2=.046$) VS ROI with reduced activation in ASD (left: $M=1.45$, $SD=1.53$, right: $M=1.54$, $SD=1.58$) compared to TD individuals (left: $M=2.03$, $SD=1.53$, $d=-0.39$, right: $M=2.25$, $SD=1.59$, $d=-$
0.44). See figure 3C. There was no significant interaction between diagnosis and task (left VS: \( F_{(1,384)}=2.754, p=.098, \text{partial } \eta^2=.007 \), right VS: \( F_{(1,384)}=2.999, p=.084, \text{partial } \eta^2=.008 \)).

**Reward delivery**

**Whole-brain level analysis**

During reward delivery, collapsed across both reward tasks, the feedback of successful win compared to neutral trials activated a network with peak activations in the visual cortex, ACC/SMA, thalamus, bilateral precentral gyrus and bilateral anterior insula/IFG, while reduced activation in comparison to neutral trials was observed in a network comprising occipital, frontal and temporal regions as well as the thalamus and the bilateral pallidum.

There was no significant effect of diagnostic group on reward-specific brain activation at the whole-brain level. See figure 4A and table 2 for details.

Differential reward-specific responses between tasks showed activation in a network with peak activations in the bilateral VS, ACC/SMA, thalamus, left precentral gyrus and bilateral anterior insula/IFG (see fig 3B and table 3). Subsequent T-tests indicated stronger differential activation in the MID compared to the SID in these peak regions (see figure 3C), while stronger differential activation in the SID compared to the MID was found in a network with peak activations in bilateral hippocampus, bilateral fusiform gyrus, bilateral lingual gyrus and ACC (see figure 3D).

The interaction effect of diagnosis was not significant for differential reward-specific responses between tasks. However, we report differences between ASD and TD in the SID and MID separately in the supplementary material (figure S2 and tables S2 and S3) to allow comparison with previous studies.

**ROI analysis**

The difference regarding reward-specific brain activation between ASD and TD individuals within the left (\( F_{(1,370)}=4.829, p=.029, \text{partial } \eta^2=.013 \)) and right VS (\( F_{(1,370)}=4.719, p=.030, \text{partial } \eta^2=.013 \)) yielded increased activation in ASD (left: \( M=.31, SD=1.46 \), right: \( M=.42, SD=1.47 \)) compared to TD (left: \( M=-.02, SD=1.46, d=0.23 \), right: \( M=.09, SD=1.47, d=0.23 \)) but did not survive correction for multiple
comparisons. See figure 4C. There was no significant interaction between diagnosis and task (left VS: 
\( F_{(1,370)}=1.057, p=.304, \text{ partial } \eta^2=.003, \) right VS: 
\( F_{(1,370)}=1.684, p=.195, \text{ partial } \eta^2=.005). \)

**Dimensional effects**

For both reward anticipation and delivery there was no significant main effect of autism trait scores and no interaction between diagnosis and autism trait scores in the VS or on the whole-brain level. Statistics are summarized in table 4. Autism trait scores also showed no significant effect when analyzing TD and ASD individuals separately.

**Effect of ADHD comorbidity**

During reward anticipation, ROI analysis yielded a significant effect of group in the left (\( F_{(1,307)}=5.172, p=.006, \text{ partial } \eta^2=.032) \) and right (\( F_{(1,307)}=6.761, p=.001, \text{ partial } \eta^2=.042) \) VS (see figure 5 A). Pairwise comparisons revealed that this effect was driven by significantly increased VS activity in TD compared to ASD\textsubscript{ADHD} (left: \( p=.006, d=0.40), \right: p=.001, d=0.46), while there was no significant difference between TD and ASD\textsubscript{ADHD} (left: \( p=.144, d=0.30, \right: p=.099,
\right: p=.32) \) or between the two ASD subgroups (left: \( p=1.000, d=0.09, \right: p=1.000, d=0.13). For reward delivery, a borderline significant effect of group emerged in the right VS (\( F_{(1,297)}=3.715, p=.026, \text{ partial } \eta^2=.024, \)) with significantly increased VS activity in ASD\textsubscript{ADHD} compared to TD (\( p=.020, d=0.35 \)) and no difference between TD and ASD\textsubscript{ADHD} (\( p=.741, d=0.18 \)) or between the two ASD subgroups (\( p=.810, \right: d=0.17)). Across both reward processing stages, there was no significant effect of group on the whole-brain level and no significant interaction with the type of reward (social, monetary).

**Control analyses**

Supplemental control analyses showed that results were not systematically explained by head motion, acquisition site, handedness, sex, intelligence quotient (IQ) or medication status. Effects of age (linear and quadratic) were observed during reward delivery in the right superior medial frontal
gyrus and the left amygdala, pallidum and (at trend-level) the VS, respectively. These effects did not differ between ASD and TD. For reward delivery, we were not able to replicate the effect of diagnosis when investigating only female participants, only right-handed participants, or when excluding participants from RUNMC or KCL. While this likely reflects decreased statistical power due to reduced subsample sizes, it also warrants further exploration of potential sources of heterogeneity in future studies. Details on the control analyses are provided in the supplementary material.
Discussion

In the present study, we assessed functional brain activation during monetary and social reward anticipation and delivery in a well-powered sample comprising ASD and TD individuals. This allowed us to examine effects of reward type during both reward processing phases. We found a reduction of VS activity during reward anticipation in individuals with ASD that did not differ between social and monetary rewards. In contrast, during reward delivery, we found that increased VS activity in ASD compared to TD across both social and monetary reward conditions did not survive correction for multiple comparisons. These results do not support opposing effect of social and monetary reward types, but rather point towards a general hypoactivity of VS in ASD during anticipation of rewards. This is in contrast to the hypothesis of a predominantly social motivation deficit (1) and previous findings in a recent meta-analysis (13). We conclude that, in ASD, general hypoactivation during the anticipation of rewards indicates attenuated subjective reward value independent of social content.

Our finding is in line with a previous study investigating negative social and monetary reinforcement (26) and extends beyond ASD to other conditions such as schizophrenia and bipolar disorder (27), pointing towards a potential shared motivational shift in these conditions that need further investigation.

Our results on reward delivery do not show substantial differences between ASD and TD individuals. While this is in contrast to meta-analytic findings (13) and previous studies showing striatal hypoactivity during monetary reward delivery (7-9), it is in line with studies showing no significant group differences during social reward (5, 6), monetary reward (5), or showing differences only at an uncorrected threshold (10). In summary, our results suggest that both monetary and social rewards are eliciting reward-related brain activity upon delivery that is not strikingly different in ASD and TD. Behaviorally, individuals with ASD did not differ from TD rewarding reaction times and accuracy (see supplementary material), which is in line with previous findings (6, 7, 10, 28-30).

The failure to sufficiently activate the reward system during anticipation of these rewards might suggest a disrupted feedback loop between “liking” a reward and “wanting” a subsequent reward in
ASD compared to TD. This might suggest atypical reinforcement-dependent learning (31) and/or salience processing in ASD (32-35), irrespective of reward type, and does not support the idea of a reward processing deficit predominantly for social rewards, as proposed by the social motivation hypothesis (1). A hypothesis of generally atypical reinforcement-dependent learning in ASD is however challenged by studies reporting elevated reward system responsivity in ASD to stimuli of high interest for autistic individuals (6, 9). These findings indicate intact, possibly even hyperactive reinforcement-dependent learning when stimuli with high individual interest are involved. Future work is therefore needed, exploring potential changes in feedback loops underlying altered reinforcement-dependent learning in ASD using connectivity metrics (36-38) and different reward types, as well as exploring links to atypical salience processing in ASD (39-41).

While significant differences between diagnostic groups were found, we did not observe significant associations between autism trait scores (SRS-2) and functional brain activation across the whole sample or within ASD and TD separately. Clements et al. (13) found a large (r=-.72) but non-significant association between SRS scores and activity in the caudate, with decreased activity associated with increased symptom severity for social reward types only. In supplemental analyses (see supplementary table S2) we assessed effects of autism trait scores for MID and SID separately, but observed no significant effect in this separate analysis. Although others found associations between dimensional autism measures and reward-related brain activity (5, 10, 29), our results are in line with previous studies also finding no association with dimensional autism measures (7, 9). Previous studies argued that their null findings might be due to insufficient power and insufficient range of scores in the ASD group (7, 9), which can be ruled out by the present findings.

Elevated levels of ADHD symptoms did not have an additive effect on reward system dysfunction in ASD, in contrast to our hypothesis. During reward anticipation, VS activity was reduced only in those individuals with ASD that had subthreshold levels of ADHD (ASD_{ADHD}) compared to TD, while those individuals with ASD that had elevated ADHD levels (ASD_{+ADHD}) did not differ significantly from TD or ASD_{ADHD}. During reward delivery, differences between the three groups were not strong enough to
reach statistical significance when correcting for multiple comparisons. However, the direction of the effect also suggested the largest deviation for the ASD\textsubscript{ADHD} group. These results support an alternative hypothesis of ADHD symptoms partly balancing out ASD-related motivational deficits. This would be in line with previous findings, where individuals with ASD showed generally low VS reactivity, and individuals with ADHD showed high VS reactivity to both social and monetary reward types (10). However, this study did not differentiate between reward anticipation and delivery. While during monetary reward anticipation, VS hypoactivation is discussed as a fairly consistent finding in adults and adolescents with ADHD (15, but see 42), findings are more inconsistent in children (11, 43). For monetary reward delivery, increased VS activity in ADHD has been reported ((42, 44-46) but see (29)). Importantly, information on social reward processing in ADHD is scarce. Information on the presence of a confirmed diagnosis of ADHD was not available in our sample, and a questionnaire-derived proxy was used instead. This might have significantly impacted our findings, as ADHD-like behaviors might have been misclassified. As a consequence, our finding requires further investigation using clinically confirmed information on ASD-ADHD co-occurrence.

While the present study provides important insights into group-level, on-average reward processing alterations in autism, a number of limitations need to be addressed. First, while our findings of differences in reward processing between ASD and TD were significant for the anticipatory phase, effect sizes were small. This likely reflects substantial between-subject heterogeneity partly attributable to the multicenter design of the study and to the intention of collecting a representative dataset but most importantly reflecting the heterogeneity of ASD. We aim to further explore this heterogeneity within the LEAP sample using classification and stratification approaches (47) in future studies. Second, the task design did not allow for a neat separation between feedback presentation and motor response (short inter-stimulus interval, no jitter). Thus, we cannot rule out that findings in the delivery phase were influenced by motor activity.

In summary, the present study demonstrates significant reduction of VS activity during the anticipation of rewards in individuals with ASD irrespective of the type of reward, and subthreshold
hyperactivity of VS during the delivery of these rewards. In contrast to our hypothesis, altered reward processing was not exacerbated by elevated ADHD symptoms. This might suggest generally atypical reward processing in ASD that is partly balanced out by co-occurring ADHD. This provides important insights, specifically as the impact of co-occurring ADHD has not been consistently assessed in previous studies on reward processing alterations in ASD and might contribute towards the heterogeneity of findings. Although further exploration of the underlying mechanisms is needed, the present study advances our understanding of the neuronal underpinnings of ASD by suggesting attenuated subjective reward value independent of social content and ADHD symptoms.

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Analytics, and has received lectures fees including travel fees from Boehringer Ingelheim, Fama Public Relations, Institut d’investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Janssen-Cilag, Klinikum Christophsbad, Göppingen, Lilly Deutschland, Luzerner Psychiatrie, LVR Klinikum Düsseldorf, LWL Psychiatrie Verbund Westfalen-Lippe, Otsuka Pharmaceuticals, Reunions i Ciencia S. L., Spanish Society of Psychiatry, Südwestrundfunk Fernsehen, Stern TV, and Vitos Klinikum Kurhessen. DM has served on advisory boards for Roche and Servier, and has received research grants from Roche and J&J. W.M. has received lecture or travel fees from Pfizer, Grünenthal, University of Zürich, International Association for the Study on Pain (IASP) and European Federation of IASP Chapters (EFIC). S.B. discloses that he has in the last 5 years acted as an author, consultant or lecturer for Medice and Roche. He receives royalties for text-books and diagnostic tools from Huber/Hogrefe (German/Swedish versions of ADI-R, ADOS-2, SRS, SCQ), Kohlhammer and UTB. T. B. has served in an advisory or consultancy role for Actelion, Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, Otsuka, PCM Scientific, Shire and Viforpharma. He received conference support or speaker’s fee by Medice, Novartis and Shire. He is/has been involved in clinical trials conducted by Shire and Viforpharma. He received royalties from Hogrefe, Kohlhammer, CIP Medien, and Oxford University Press. D. B. serves as an unpaid scientific consultant for an EU-funded neurofeedback trial. ASJC receives consultant fees from Roche and Servier. JKB has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. All other authors report no potential conflict of interest. The present work is unrelated to the above grants and relationships.
References

Table 1: Sample characteristics.

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### Clinical Characteristics

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<td>Communication</td>
<td>12.47</td>
<td>± 5.69</td>
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<td>RRB</td>
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<td>± 2.67</td>
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<table>
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<tr>
<th>ADOS-2 (CSS)</th>
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<td>Social Affect</td>
<td>5.71</td>
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<td>RRB</td>
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<td>± 2.46</td>
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<tr>
<td>Total</td>
<td>4.85</td>
<td>± 2.60</td>
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<th>SRS-2</th>
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<tr>
<td>Raw score</td>
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<td>± 30.45</td>
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<td>T-score</td>
<td>68.62</td>
<td>± 12.20</td>
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<td>χ²(1)=36.905, p&lt;.001</td>
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<th>DAWBA comorbidities</th>
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<tr>
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<td>Anxiety symptoms</td>
<td>2.60</td>
<td>± 1.31</td>
<td>(0 - 5)</td>
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<tr>
<td>Depression symptoms</td>
<td>0.84</td>
<td>± 1.00</td>
<td>(0-5)</td>
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</tbody>
</table>

| Sample characteristics. KCL: Institute of Psychiatry, Psychology and Neuroscience, King’s College London, United Kingdom. UCAM: Autism Research Centre, University of Cambridge, United Kingdom. Nijmegen Medical Centre, the Netherlands. UMCU: University Medical Centre Utrecht, the Netherlands. CIMH: Central Institute of Mental Health, Mannheim, Germany. UCBM: University Campus Bio-Medico of Rome, Italy. ADI-R: Autism Diagnostic Interview-Revised. Scores were computed for reciprocal interaction (social interaction), communication, and restrictive, repetitive stereotyped behaviors and interests (RRB). ADOS-2 (CSS): Autism Diagnostic Observation Schedule 2. Calibrated severity scores were computed for social affect, restricted and repetitive behaviors (RRB) and the overall total score. SRS-2: Social Responsiveness Scale-2. Total raw and total T scores (sex-age normalized) are reported. The raw SRS-2 scores were used in our analyses. ADHD research diagnosis was based on applying DSM-V criteria to symptom scores in the parent- and self-rated ADHD rating scale. Self-rated scores were used when parent-rated scores were not available. Comorbid symptoms of ADHD, depression and anxiety were assessed with the Development and Well Being Assessment Inventory.
(DAWBA), generating six levels (ordinal scores 0 to 5) of prediction of the probability of a disorder (~0.1%, ~0.5%, ~3%, ~15%, ~50%, >70%). SID social incentive delay task, MID monetary incentive delay task.

Table 2: Whole-brain effects of brain activation during reward anticipation and delivery.

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<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
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Table provides test statistic of significant peak voxel(s) for whole-brain analysis. Voxel-level statistics were family-wise error (FWE) corrected for the number of voxels across the whole brain for each test. Significance was defined as pFWE< .05 with a cluster threshold of k≥5. Significant whole-brain results are localized in MNI space and labeled according to the automated anatomical labeling atlas 3 (aal3).

Table 3: Whole-brain effects of brain activation for interaction between cue (win, neutral) and task (SID, MID).

<table>
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<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>Direction</th>
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<th>x</th>
<th>y</th>
<th>z</th>
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<td></td>
</tr>
<tr>
<td><strong>INTERACTION TASK*CUE</strong></td>
<td></td>
<td></td>
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<td></td>
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<td>pallidum</td>
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<td>MID&gt;SID</td>
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<td>-1</td>
<td>56</td>
<td>862.060</td>
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Table provides test statistic of significant peak voxel(s) for whole-brain analysis. Voxel-level statistics were family-wise error (FWE) corrected for the number of voxels across the whole brain for each test. Significance was defined as pFWE<.05 with a cluster threshold of k≥5. Significant whole-brain results are localized in MNI space and labeled according to the automated anatomical labeling atlas 3 (aal3). Direction of the effect tested post-hoc via t-tests.

Table 4: Whole-brain and region of interest (ROI) effects of autism trait-related brain activation during reward anticipation and delivery.

<table>
<thead>
<tr>
<th>Effect of SRS-2</th>
<th>Interaction SRS-2 *diagnosis</th>
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<tr>
<td><strong>ANTICIPATION</strong></td>
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<tr>
<td><strong>WHOLE BRAIN</strong></td>
<td>all F&lt;20.55, p_{FWE}&gt;.05</td>
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<tr>
<td>ROI</td>
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<tr>
<td><strong>DELIVERY</strong></td>
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<tr>
<td><strong>WHOLE BRAIN</strong></td>
<td>all F&lt;21.11, p_{FWE}&gt;.05</td>
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<tr>
<td>ROI</td>
<td></td>
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</tbody>
</table>

Table provides test statistic for whole-brain and region of interest (ROI) analysis. Voxel-level statistics were family-wise error (FWE) corrected for the number of voxels across the whole brain for each test. Significance was defined as pFWE<.05.
with a cluster threshold of k≥5. For ROI analysis in the left and right VS, the critical alpha level was adjusted to p<.025 to control for multiple comparisons. SRS-2 Social Responsiveness Scale Second Edition.
**Figure legends**

**Figure 1**: Task design of the monetary incentive delay task (MID) and social incentive delay task (SID). Participants were asked to give a speeded response (button press) to a visual target (screen flash). A cue arrow pointing upwards indicated the possibility to obtain a reward if responses were given within a predefined response time window (win trial). No reward option was given in trials preceded by a horizontal cue arrow (neutral trial). Sufficiently fast responses on win trials were followed by the presentation of a 2€/2£ coin in the MID and a smiling female face in the SID as feedback. Please note that due to BioRxiv policy, the actual face stimulus had to be replaced by a smiley in figure 1. Blurred control stimuli were presented in neutral trials and as feedback following slow responses in win trials. Cue presentation represents reward anticipation phase, while feedback presentation represents reward delivery phase. Note that the feedback presentation was temporally decoupled from the target presentation but not from the button press.

**Figure 2**: Brain activation to win compared to neutral cues. A) Whole-brain familywise error corrected activation across both ASD and TD individuals. B) Whole-brain familywise error corrected effect of diagnosis in the right ventral striatum C) Effect of diagnosis in the region of interest (ROI) analysis of the left and right ventral striatum with corresponding distribution plots. ***p<.001. Distributions of ROI activation in cases and controls were compared using the Kolmogorov-Smirnov test, which suggested unequal distributions (left VS: D[212,181] = 1.56, p = .017; right VS: D[212,181] = 1.93, p = .001).

**Figure 3**: A) Interaction effect of cue (win, neutral) and task (SID, MID) indicating higher differential activation in MID compared to SID. B) Interaction effect of feedback (win, neutral) and task (SID, MID) C) Differentially increased activity in MID compared to SID for successful win compared to neutral trials. D) Differentially increased activity in SID compared to MID for successful win compared to neutral trials.

**Figure 4**: Brain activation to reward delivery. A) Whole-brain familywise error corrected activation increase (warm colours) and decrease (cold colours) to successful win compared to neutral trials across both ASD and TD individuals. B) Effect of diagnosis in the region of interest (ROI) analysis of the left and right ventral striatum with corresponding distribution plots. *p<.05. Distributions of ROI activation in cases and controls were compared using the Kolmogorov-Smirnov test, which suggested no evidence for unequal distributions (left VS: D[205,174] = 1.20, p = .134; right VS: D[205,174] = 1.12, p = .190).

**Figure 5**: Contrast estimates for ventral striatal activation in individuals with ASD and elevated ADHD symptoms (ASD+ADHD), individuals with ASD without elevated ADHD symptoms (ASD-ADHD) and typically developing individuals without elevated ADHD symptoms (TD) during A) reward anticipation and B) delivery. **p<.01, *p<.05.
MID

- cue win
- flash target
- feedback win
- cue neutral

SID

- cue win
- flash target
- feedback win
- cue neutral

Duration cue: 250 ms
Duration flash: 100 ms
Duration feedback: 1500 ms
ISI between cue and target: 2750-3750 ms
ISI between target and feedback: 400-800 ms
ITI: 3500-4500 ms
reward anticipation

A) Cue win > cue neutral

B) TD > ASD

C) ROI analysis

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**Statistical Analysis**

- **Contrast Estimates**
  - Left VS
  - Right VS

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**Note:** The images and charts above illustrate the comparison of neural activity between different conditions. The analyses were performed using statistical software, and the results are presented with appropriate significance levels (***). The plots show the distribution of contrast estimates across different regions of interest (ROIs) identified as significant (p < 0.001, corrected for multiple comparisons).
A) reward anticipation – cue*task interaction

B) reward delivery – feedback*task interaction

C) reward delivery – MID_{(successful win>neutral)} > SID_{(successful win>neutral)}

D) reward delivery – SID_{(successful win>neutral)} > MID_{(successful win>neutral)}
reward delivery

A) successful win > neutral

B) ROI analysis

left VS

right VS