Atypical Tuning of Prediction Certainty in Autism: An EEG study on Anticipatory Processing During a Probabilistic Target Detection Task

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Research Article

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Atypical Tuning of Prediction Certainty in Autism: An EEG study on Anticipatory Processing During a Probabilistic Target Detection Task

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ABSTRACT

The brain generates predictions to prepare for upcoming events. As life is not always 100% predictable, it also estimates a level of certainty for these predictions based on their likelihood. Given that autistic individuals resist even small changes in everyday life, we hypothesized impaired tuning of prediction certainty in autism. To study this, EEG was recorded from adolescents and young adults with autism, and age- and IQ-matched controls while they performed a probabilistic cued target detection task in which cue validity was parametrically manipulated. A fully predictable condition (100% cue validity) was contrasted with less predictable conditions (84%, 67%, and 33% cue validity). The contingent negative variation (CNV), a brain response associated with the anticipation of a predictable target, was examined to test the influence of cue validity on target predictions. Whereas the CNV systematically modulated by cue validity in the control group, this was not the case for the autism group. In contrast, intact modulation of the target P3 response by cue validity indicated that stimulus statistics are registered in a typical manner in autism. This suggests that in autism target statistics were registered but were not effectively applied to modulate expectations (e.g., certainty) of upcoming predictable stimuli. This adds to our understanding of differences in predictive processing in autism and suggests that the tuning of prediction certainty is particularly vulnerable in this population.

SIGNIFICANCE STATEMENT

The ability to make predictions is integral to everyday life. Yet, as life is not always 100% predictable, it is also essential to adjust the certainty of these predictions based on the current context. This study reveals that individuals with autism are less efficient in adjusting the certainty of their predictions to the level of predictability of events, although they can process the stimulus statistics. Our findings reveal novel insights into the processes underlying impaired predictive processing in autism, which may open the door to developing targeted behavioral interventions to help autistic individuals make more flexible predictions to ease social- and rigidity-based symptoms.

Keywords: Predictive Processing, ASD, ERPs, P300, CNV, Decision Making, Predictions, Probabilistic Inference, Predictive Coding, Precision

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INTRODUCTION

Predicting what comes next is highly advantageous for adaptive behavior and leads to facilitated processing of information (Bar, 2007; Gregory, 1980; Hohwy, 2017). Many current theories of perception propose that the brain maintains a model of the environment that produces top-down predictions of upcoming stimuli at various hierarchical stages of processing, rather than simply acting on sensory inputs (Bar et al., 2006). These predictions are associated with high certainty for predictable environments and low certainty for volatile environments (Friston & Kiebel, 2009). For adaptive behavior, predictions and the associated level of certainty (e.g., *precision*) must be flexibly updated based on new information.

Over the last decade, predictive processing accounts of autism have gained popularity (Cannon et al., 2021) as they not only provide a model within which to generate falsifiable hypotheses (Friston & Kiebel, 2009), but also explanation for a diverse range of autism symptomology including cognitive-, sensory-, and motor-related characteristics (Gomot & Wicker, 2012; Van de Cruys et al., 2014). For example, problems in social communication have been attributed to a reduced ability to form generative models that can be used to predict and interpret social cues (Chambon et al., 2017; Palmer et al., 2015), and resistance to change to an overly rigid predictive model (Gomot & Wicker, 2012) such that unexpected changes cause discomfort. There is mounting support for suboptimal updating of the predictive model in autism (Coll et al., 2020; Palmer et al., 2017), including evidence of slower model updating (Sapey-Triomphe et al., 2021; Soulières et al., 2011; Vishne et al., 2021), and oversensitivity to prediction errors that leads to bigger model updates in response to errors ((Karvelis et al., 2018; Van de Cruys et al., 2014), but see (Knight et al., 2020)).

In a recent study, a smaller difference in response times between conditions where cues were more versus less predictive of a target (84% vs. 16%) was observed in autism compared to controls, which was interpreted as reduced surprise in autism upon prediction violation (Lawson et al., 2017). This and similar findings in individuals with

autism (Arthur et al., 2021) as well as in individuals in general population with high autistic traits (Perrykkad et al., 2021) appear counter-intuitive with clinical observations and introspective reports that autistic individuals overreact to violations of expected outcomes. In these studies, however, conclusions are based on comparison between conditions for which the cue is never fully predictive. Arguably, if resistance to change and rigid adherence to routines results from intolerance to any violation of predictions, a 100% predictable condition provides an important baseline against which to assess the magnitude of the surprise response. However, no study that we are aware of has juxtaposed a fully predictive condition with less predictive conditions.

To better understand prediction certainty in autism, we designed a probabilistic task where an initially fully stable environment was achieved with 100% cue validity, while three further levels of cue validity (i.e., 84%, 67%, and 33%) were presented later. Using this task accompanied by EEG recordings, we tested the representation of prediction certainty in individuals with autism. We measured well-characterized Event Related Potentials (ERPs) to gain insight into different aspects of predictive processing in response to changing environments: The contingent negative variation (CNV), a slow negative-going ERP that typically systematically varies in amplitude with the certainty of target expectation (Thillay et al., 2016) and represents anticipatory brain activity involved in expectation of a temporally predictable target (Brunia, 2003), and the P3 (aka P300), a positive-going ERP associated with target detection and evaluation that occurs in response to a target, and varies in amplitude with respect to target probability (Bidet-Caulet et al., 2012; Polich, 2007, 2012). While the P3 allowed us to assess the evaluation of the cue-target statistics, the CNV provided information about how individuals used these statistics to modulate the certainty of their expectations in preparation for upcoming targets.

In the control group, we expected a more-or-less linear relationship between the primary dependent measures and cue validity, indicating that certainty of predictions (CNV) is represented in a graded manner and that cue-target probabilities impact target-related processes (P3 and reaction time). In contrast, given that autistic individuals over-react

to deviations from expectations (Frith, 2003; Lord et al., 2012), we expected the autism group to show bigger differences between a fully predictable condition (i.e., 100% cue validity) and a slightly less predictable condition (i.e., 84% cue validity) compared to controls. On the other hand, we expected less clear differentiation among the less predictable conditions (e.g., across 84%, 67%, and 33% cue validities), consistent with findings in the literature of reduced differential responses to changes in less versus more predictable environments in autism (Arthur et al., 2021; Lawson et al., 2017).

METHODS

Participants

Nineteen individuals with autism (8 left-handed, mean age: 19.6 ±2.7 years old) and 21 Intelligence Quotient (IQ)- and age-matched control subjects (all right-handed; mean age: 20.7 ±2.32 years old) participated in the study, all aged between 16 and 28 years (Table 1). Autism diagnoses were made using the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al., 2012), the Autism Diagnostic Interview-R (Lord et al., 1994), and expert clinical judgment by a licensed psychologist at the Human Clinical Phenotyping Core of the Rose F Kennedy Intellectual and Developmental Disability Research Center (RFK IDDRC) at the Albert Einstein College of Medicine.

Participants were recruited without regard to sex, race, or ethnicity. Exclusionary criteria for both groups included a performance IQ below 80; a history of head trauma; premature birth; a current psychiatric diagnosis; or a known genetic syndrome associated with a neurodevelopmental or neuropsychiatric condition. Attention deficit/hyperactivity disorder (ADD/ADHD) was not used as an exclusion criterion for the autism group, given its high comorbidity with autism. Exclusion criteria for the control group additionally included a history of developmental, psychiatric, or learning difficulties, and having a biological first-degree relative with an autism diagnosis. Participants who were on stimulant medications were asked to not take them at least 24 hours prior to the experiment.

TABLE 1: Participant Demographics. Mean and standard deviation values are reported for age, full-scale IQ, and Social Responsiveness Scale (SRS). The Full-Scale IQ was based on Wechsler Abbreviated Scale of Intelligence (WASI).

	Sex (M/F)	Age	Full-scale IQ	SRS
Control	12/8	20.7 ± 2.32	100.8 ± 11.7	49.9 ± 7.2
Autism	14/5	19.6 ± 2.7	105.3 ± 13.9	67.4 ± 10.2

Neuropsychological and clinical testing

IQ was measured via the Wechsler Abbreviated Scale of Intelligence (Simard et al., 2015). To quantify autism-related characteristics, both groups of participants completed the Social Responsiveness Scale-2 (SRS-2) (Constantino & Gruber, 2012) which has five subscales (i.e., Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior (RRB)). We used the self-report SRS-2 total t-scores to assess correlations with participant EEG and Reaction Time (RT) measures. For the SRS-2, lower scores indicate higher levels of social responsivity. Scores below 59 are considered to be in normal range, whereas scores of 76 and above indicate severe social impairment (Constantino & Gruber, 2012). Intermediate scores, between 60 and 75, are associated with mild to moderate social impairment.

Independent paired t-tests showed no significant group differences for age [$t(44) = 0.95$, $p=0.34$] or full-scale IQ [$t(40) = -0.40$, $p=0.69$]. Among various sub-domains of the Wechsler Intelligence test, only one domain, the processing speed index (PSI), showed a significant group difference [$t(30) = 7.59$, $p<0.01$] revealing that autism group was slower in processing information. As expected, the autism group had higher SRS-2 scores than the comparison group [$t(33) = -8.48$, $p<0.01$], as well as on each of the SRS-2 sub-domains.

Sequential Probabilistic Task

We designed a task to probe the ability to adjust prediction certainty based on changing probabilities in the environment.

Stimuli: Visual stimuli were presented to the participant, one at a time, on a computer screen at a viewing distance of 65 cm in a dimly lit room. Stimuli consisted of basic shapes presented in gray on a black background for 100 ms, with an 850 ms inter-stimulus interval (ISI). Participants performed a target detection task in which they responded as quickly as possible to the final item of a *target-sequence*. A target-sequence was either three arrows, the first upward-facing, the second rightward-facing, and the final downward-facing, or three parallelograms, the first left-tilted, the second straight, and the final right-tilted. The stimuli in these sequences are referred to as *cue1*, *cue2*, and *target* (Fig. 1A). When patterns were not completed, a circle, diamond, or triangle shape was presented instead, which we refer to as an *invalid item*. These shapes were also used as *fillers*, represented once or twice after invalid items or targets. To ensure that participants were responding to the shape sequence and not just the final shape in the sequence, *catch* trials in which the final shape was presented after filler shapes were also included.

Cue validity conditions: Throughout the experiment, the probability that a target-sequence was completed varied across four levels, in ~10-minute blocks (Fig. 1C). Pattern initiations, always represented by *cue1* of the pattern followed by cue2, were completed with the target stimulus 100%, 84%, 67% or 33% of the time, comprising four cue validity conditions (Fig. 1A). Participants were not informed of the cue validity condition they were in or when it changed. The two target-sequences were presented with equal probability within a given cue validity condition.

Blocks: Stimuli were presented in mini-blocks of ~1.5 minutes, separated by pauses during which time participants could rest. Each mini-block was composed of 24 pattern initiations (cue1 followed by cue2) (see Table S1 for more). Pattern initiations were completed with the target 24, 20, 16, or 8 times depending on the cue validity condition. Participants pressed the mouse key to initiate the next mini-block. Blocks of a given cue validity condition were composed of between 4 and 6 mini-blocks.

Instructions Part 1: The following instructions were printed on the screen in four parts, both for remote familiarization and the first experimental session:

> *"You will see a shape in the middle of the screen. The shape will change about every second. Sometimes 3 consecutive shapes appear in the orders below, which we call a pattern. There are two target patterns: (pattern shapes were shown to the participant below this sentence). Your job is to touch the screen (or press the mouse button) after Pattern 1 or Pattern 2 is completed. Try to be both quick and accurate. Remember, you should respond after the pattern is completed. You can ignore any other shape. Let's practice!"*

Remote Familiarization: To briefly familiarize participants with the stimuli and task prior to the experiment, we remotely presented the task (100% cue validity condition only) for six minutes using the Neurobehavioral Systems mobile app on their smart phone or tablet, one day before the experiment.

Experiment sessions: The experiment was composed of four sessions performed on a single day, separated by 15-30 minute breaks (Fig. 1C). In Sessions 1 and 2, the cue validity conditions were presented in the same order to all participants, whereas in Sessions 3 and 4, cue validity condition order was pseudo-randomized. Session 1 consisted of 7 mini-blocks of 100% cue validity condition. In Session 2, conditions were presented in the order of 84%, 67%, 33%, and 100%. Participants usually took a lunch break after Session 2, while taking a ~15-minute break between Session 3 and Session 4. In Sessions 3 and 4, cue validity conditions were presented in a pseudo-randomized order (sample order is shown in Fig. 1B). The initial 100% condition, presented during remote familiarization and Session 1, was designed to establish strong cue-outcome associations. This might correspond to never-broken rules that individuals with autism seek in adhering to strict routines in their everyday life.

Instructions Part 2: At the end of the first session, participants were informed that going forward, the cues would not always be followed by the target, and that in these cases they should withhold their response.

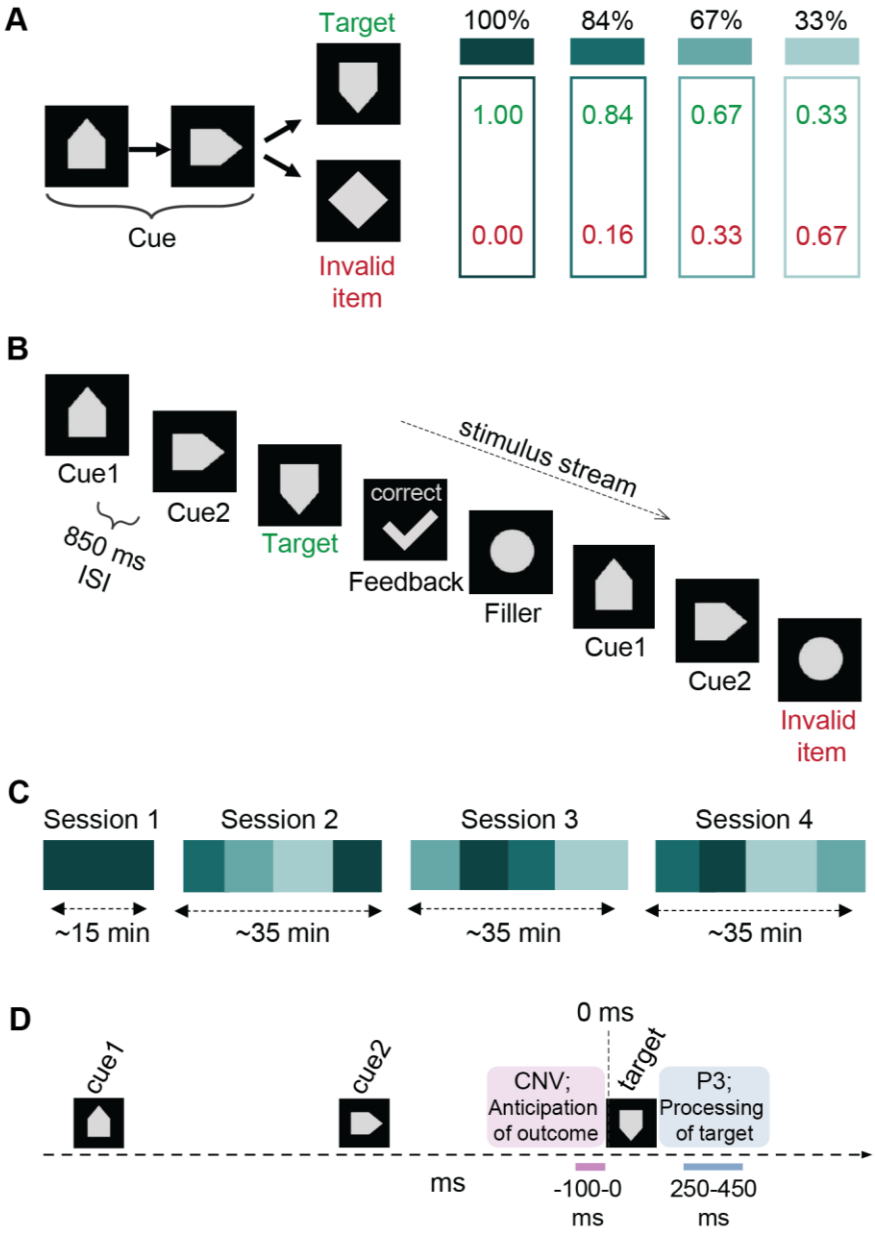

FIGURE 1: The Sequential Probabilistic Task (A) Participants respond to target sequences of stimuli while the probability of sequence completion is manipulated at four levels. Stimuli consist of basic shapes presented sequentially to the participant. The two possible target sequences: A sequence of 3 different arrows or 3 different parallelogram shapes are presented in specific orders. The participant's task is to respond after sequence completion with a mouse click while withholding the response when the sequence is completed with an invalid item. (B) A sample stimulus stream. The subject responds with a mouse click after completion of a three item target pattern, followed by a feedback message appearing on the screen. (C) The order of cue validity conditions throughout the experiment is shown for a sample participant. (D) Conceptual illustration of the temporal dynamics of evoked responses of interest: CNV and P3.

Feedback: To keep the participant on-task, visual feedback was provided: “correct” for responses to targets that fell within the response window of 100 to 950 ms; “miss” if they did not respond within 950 ms of the target; “too early” for responses occurring within 100 ms of target presentation (assumed to be anticipatory); and “wrong” for responses to a non-target. Feedback text was accompanied by an icon (a “✓” for correct, “x” for wrong, “!” for miss or too early). The feedback stimulus was presented for 200 ms.

EEG data collection and pre-processing

Continuous EEG was recorded from 160 scalp electrodes at a rate of 512 Hz using the BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, Netherlands). Biosemi replaces the ground electrodes that are used in conventional EEG systems with two separate electrodes: Common Mode Sense (CMS) and Driven Right Leg (DRL) passive electrodes. These two electrodes create a feedback loop, thus rendering them as references. Data were down-sampled to 128 Hz for subsequent analyses, to reduce computing demands. EEG data were pre-processed using Matlab and eeglab (Delorme & Makeig, 2004) on local computers or remote cluster computing via Neuroscience Gateway (Sivagnanam et al., 2013). Data were high-pass filtered at 0.75 Hz. The 60 Hz line noise was removed using the CleanLine function of eeglab, run twice with a window and step size of four. Channels that were two standard deviations away from the average power spectrum in the 0.1-50 frequency band were rejected.

Infomax Independent Component Analysis (ICA) was used to remove potential non-brain related activity, mainly eye-movement-related muscle artifacts. For each Independent Component (IC), the iclabel program (Pion-Tonachini et al., 2019) was used to calculate the probabilities for that IC belonging to the seven different IC categories including Brain, Muscle Noise, Eye Noise, Heart Noise, Line Noise, Channel Noise, and Other. A total noise metric was created via summation of muscle-, eye-, heart-, line-, and channel-related noise probabilities. An IC was excluded only if it met both of the following criteria: 1) had more than a 50% chance for the noise category, 2) had less than a 5% chance of the brain category. This led to an average of 5 ICs being

rejected among the top 20 ICs (i.e., the ICs that accounted for the majority of the signal). Three of these on average had more than a 50% chance of being a component related to eye blinks or movements. The channels that were rejected prior to ICA were interpolated using the linear interpolation method. After referencing data to the average of two scalp channels that are near the right and left mastoids (i.e., E17 and B18 on BioSemi 160 System). For P3 analyses data were epoched between -100 and 950 ms with respect to stimulus onset, with the first 100 ms of the epoch serving as baseline. For the CNV analyses data were epoched between -100 and 950 ms with respect to the second cue, with the first 100 ms serving as baseline. Noisy trials were rejected based on a custom script that rejects trials with amplitudes that are more than three standard deviations away from the mean of maximum global field power amplitudes for each trial type. After that, trials were averaged for each stimulus type.

Data analyses

EEG, reaction time, accuracy, and clinical data were analyzed in Matlab and Python using custom libraries and scripts. We assessed the effect of cue validity on two ERPs relevant to predictive processing: the CNV to index anticipation of upcoming targets and the P3 to index target evaluation. Selection of the temporal windows and scalp regions used for the analysis of each of these components was informed by the literature and modified if needed based on inspection of the specific timing and topography of the response of interest, without regard for experimental condition or group. The CNV was measured as the average amplitude over the 100 ms window preceding the onset of the imperative stimulus (the target or the invalid item), from a centrally placed electrode (one anterior to the classic Cz location) (Thillay et al., 2016). The P3 was measured as the average amplitude between 250-450 ms (+/-100 ms from the 350 ms peak) at Pz (Polich, 2007). For behavioral analyses, RT, percent hits, and false alarms were calculated for each participant for each cue validity condition, and subsequently averaged per participant group. In our tasks, in line with prior work, RT was expected to be faster with increasing cue validity across conditions (Lawson et al., 2014; Thillay et al., 2016).

To test the influence of cue validity on the ERP components of interest, we applied single trial linear mixed-effects models using the *statsmodel* package in Python (Seabold & Perktold, 2010). Models were fit using a maximum likelihood criterion defining subjects as a random factor. ERP amplitudes were numeric dependent variables. Group was a dummy-coded fixed factor. To test for the presence of significant linear relationships between cue validity and ERP amplitude, two sided linear least-squares regression analyses between cue validity and ERP amplitude was performed for both the P3 and the CNV for each group. For the linear regression analysis, data from the 84%, 67% and 33% conditions were normalized to the 100% condition. The same analysis on the unnormalized data are also presented, as supplementary data.

To test the hypothesis that flexibility in certainty of predictions relates to social responsiveness, we conducted correlation analyses between clinical scores and our primary EEG measures. We took the difference between 84% and 33% conditions as an index of a participants' ability to differentiate between different cue validity conditions (e.g., prediction flexibility index). We then performed Pearson's correlation between this index and social responsiveness (as measured by SRS-2). This analysis was performed on the full dataset across the two groups of participants to increase statistical power (Bonett & Wright, 2000; David, 1938). Acknowledging that group differences can drive a correlation, however, for significant regressions we also plotted regression fits for each group separately in the corresponding figure, to aid in interpretation of the regression results.

RESULTS

We designed a sequential probabilistic task where participants responded to the completion of three sequentially presented shapes (e.g., three arrows, the first upward-facing, the second right-facing, and the final downward-facing; aka cue1, cue2 and target) while parametrically manipulating sequence completion at four levels: 100%, 84%, 67%, and 33%. The effects of cue validity condition and autism diagnosis on brain responses and behavior were examined to understand how well different levels of

prediction certainty and stimulus probability are represented in the brains of individuals with autism, and the consequences for behavior.

Electrophysiological data

To assess if brain potentials reliably modulate as a function of cue validity and whether this significantly differs by group, we performed two separate linear mixed effect models for CNV and P3. ERP amplitudes were best fit by a linear mixed effect model by including an interaction term between group (control and autism) and cue validity (100%, 84%, 67%, 33%). Post-hoc mixed models were conducted for each potential pairwise comparison (100-84%, 100-67%, 100-33%, 84-67%, 84-33%, 67-33%) to unpackage significant main effects and group-by-condition interactions. Results are reported below and summarized in Table 1 (and see supplementary Table 2).

CNV: In both the autism and control groups, a CNV was observed just prior to onset of the imperative stimulus (target or invalid item). The CNV, which had a central negativity, was most prominent in the 100 ms prior to target onset (Fig. 2A, S2). In the control group, CNV amplitude was bigger (more negative going) as cue validity decreased. This amplitude/cue validity relationship is in line with prior work in healthy adults on anticipation of implicitly learned probabilistic regularities (Kóbor et al., 2021). In contrast, in the autism group, while CNV amplitude clearly segregated the three less predictable conditions (i.e., 84%, 67%, 33%) from the 100% condition, differences among these three conditions were greatly reduced compared to the control group (Fig. 2). Statistical testing of the data revealed a significant effect of condition (ß=1.54, SE=0.18, $p<0.01$) and a group-by-condition interaction (ß=-0.64, SE=0.26, $p=0.01$) (Table 2). Follow-up tests revealed that this interaction was driven by a smaller difference between the 33% condition and each of the other conditions in the autism group, in addition to revealing a significant main effect of group for the 100%-84% comparison due to a larger difference in autism (Table S2). Linear least-squares regression between cue validity and ERP amplitude showed that CNV amplitude was significantly more negative as cue validity

decreased for the control group, (ß(60)=2.26 ± 0.74, p=0.003) but not for the autism group (ß(57)=0.75 ± 0.88, p=0.40) (Fig. 2B, also see Fig. S1).

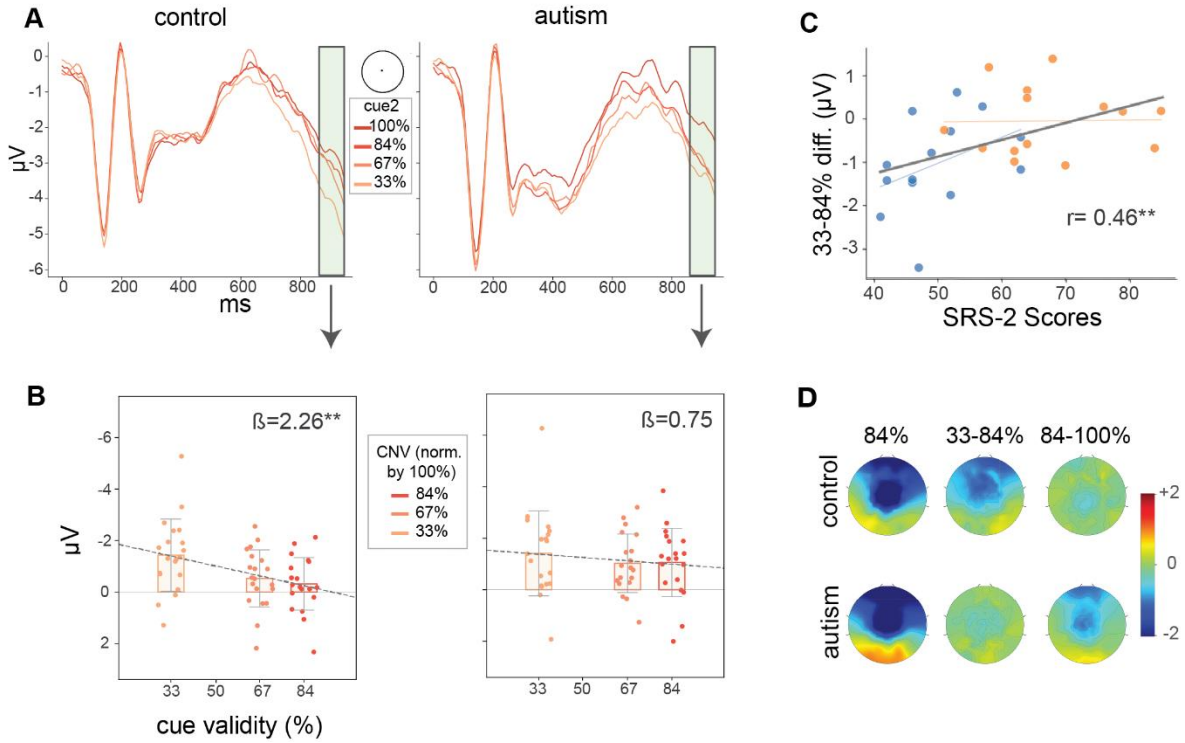

FIGURE 2: CNV (A) ERP waveforms showing responses timelocked to cue2 at Cz for each of the cue validity conditions. The CNV time window is highlighted in green (100 ms prior to target onset). **(B)** CNV amplitudes across 84%, 67%, 33% conditions normalized for the 100% condition, dotted line showing linear regression between cue validity and CNV amplitude based on individual subject data points. While the x axis shows evenly spaced tick labels from 33% to 84%, there was no 50% cue validity condition in the design. Error bars show 95% confidence intervals. Slopes of the linear regression lines are shown on top of plots. **(C)** Pearson's correlation between SRS-2 Scores and CNV difference between 33% and 84% conditions across all participants (gray). Regression lines are also shown for each group (orange: autism, blue: controls). **(D)** CNV topographies for 84% condition (left), difference between 33% and 84% conditions (middle), and difference between 84% and 100% conditions (right).
** denotes p <0.01.

P3: Both groups exhibited a typical P3 in response to target stimuli that was positive-going over posterior-central scalp and peaked at about 350 ms. In both groups, the amplitude of the P3 varied as a function of cue validity (Fig. 3A-B, S1, S2) such that higher cue-validity conditions yielded larger P3 amplitudes. The P3 statistical model revealed a significant effect of condition (ß=-3.19, SE=0.21, p<0.01), while showing no

main effect of group (ß=-0.43, SE=9.02, p=0.96) or group-by-condition interaction (ß=0.14, SE=0.30, p=0.65) (Table 1). Linear regression analyses between P3 and cue validity revealed that P3 amplitude was significantly more positive as cue validity decreased for both the control (ß(60)=-5.44 ± 0.98, p=0.00000072) and autism (ß(57)=-3.19 ± 1.18, p=0.009) groups (Fig. 3B, S1).

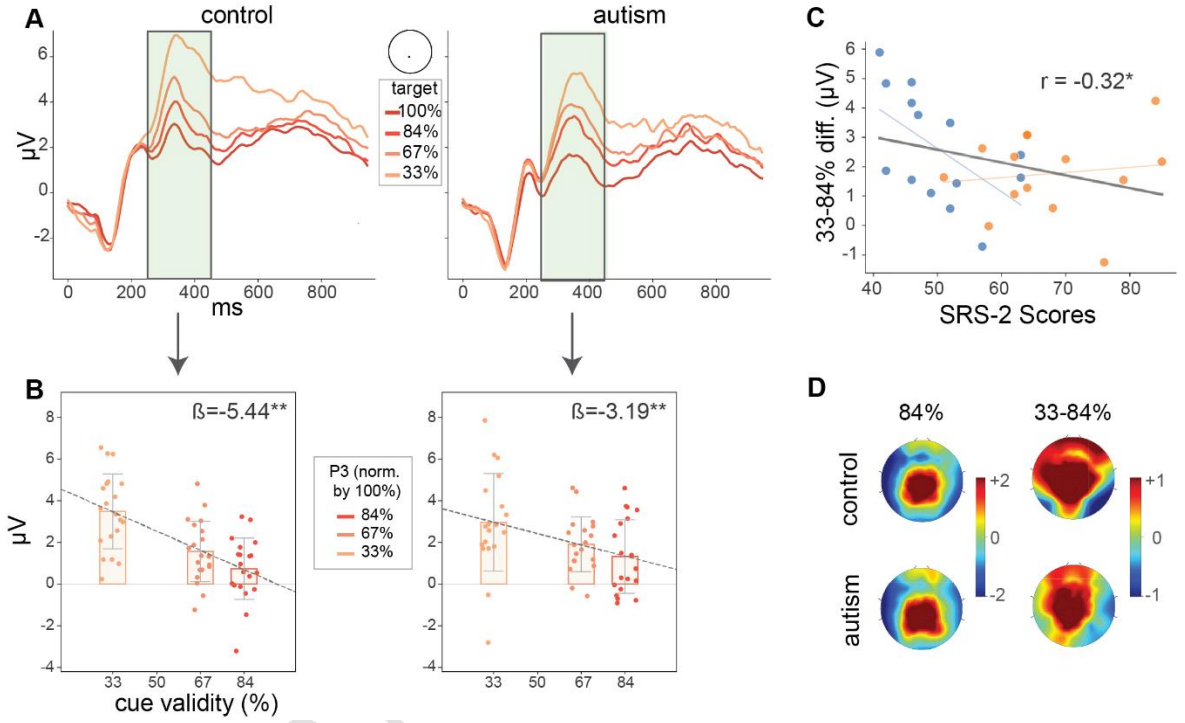

FIGURE 3: P3 (A) Target-locked ERPs at Pz. P3 time window highlighted by green panel. **(B)** P3 amplitudes across 84%, 67%, 33% conditions normalized for the 100% condition, error bars showing 95% confidence intervals. While the x axis shows evenly spaced tick labels from 33% to 84%, there was no 50% cue validity condition in the design. The dotted line shows the linear regression between cue validity and P3 amplitude. Slopes of the linear regression lines are shown on top of plots along with their statistical significance (* for p<0.05, ** for p <0.01). **(C)** Pearson's correlation between SRS-2 Scores and P3 difference between 33% and 84% conditions across all participants (gray). Regression lines are also shown for each group (orange: autism, blue: controls). **(D)** P3 topographies for the 84% condition (left) and P3 difference topographies between 84% and 33% conditions (right) are included for each group. * denotes p<0.05 and ** p <0.01.

Behavioral Results

Mean RT collapsed across the four cue validity conditions was 330 and 349 ms, respectively, for the control and autism groups. Considering the individual cue validity conditions for both groups, mean RTs were fastest for the highest cue validity condition

and slowest for the lowest. For the control group these RT differences scaled with cue validity, increasing by ~20 ms as cue validity decreased (309, 325, 351, and 373 ms for the highest to lowest cue validity conditions respectively). For the autism group however, although mean RT changed between the highest and lowest cue validity conditions, it did not differ between the 84% and 67% conditions (335, 354, 354, 385 ms for the highest to lowest cue validity conditions respectively) (Fig. 4A). A linear mixed effect model for RT with an interaction term between group and cue validity condition revealed both a significant effect of condition (ß=-96.37, SE=4.23, p<0.01) and a group-by-condition interaction (ß=-34.43, SE=6.10, p<0.01) while showing no main effect of group (ß=-6.43, SE=183.55, p=0.97) (Table 2). Follow-up mixed-model tests revealed that the condition effect was driven by all pairwise comparisons between cue validity conditions, and the group-by-condition interaction by significantly smaller differences in mean RTs in the autism group for the 100%-67%, 84%-67%, 84%-33% and 100%-33% condition pairs, (Table S3). Thus, cue validity effects on RT were significantly smaller in the autism compared to the control group.

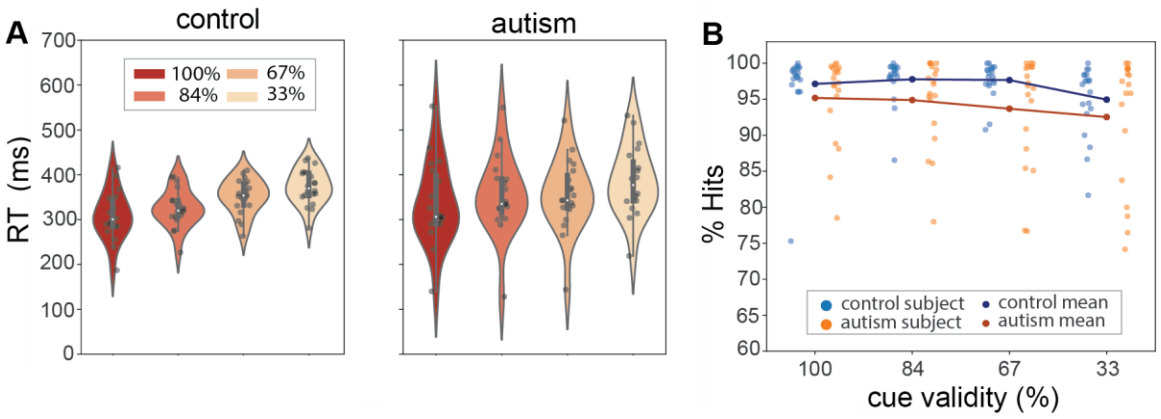

FIGURE 4: Reaction Time and Performance. (A) RTs in ms for the four cue validity conditions for control (left) and autism (bottom) groups. **(B)** Percent hit rate by cue validity condition. Dots that are connected by lines show averages. Each stand-alone dot represents an individual subject.

We examined the relationship between our neural and RT measures of flexibility in certainty of predictions (flexibility index: difference between 33% and 84% conditions) and SRS scores. These analyses were performed on a subset of the data due to missing SRS scores from 10 participants (5 each from the control and autism groups).

We found significant correlations for the CNV (r(28) = 0.46, p = 0.007) (Fig. 2C) and P3 (r(28) = -0.32, p = 0.049) (Fig. 3C), whereas no significant correlation was found for RT (r(28) = -0.14, p = 0.22). Regression lines for each of the groups, which given the small Ns should be considered purely descriptive, suggest that in both cases the significant correlations may have been driven by the control data. Both groups performed the task with high accuracy (96% and 93% respectively for control and autism groups; see Fig. 4B). Mean hit rate to targets for the control group was more than 97% in the three highest cue validity conditions, and 94% for the lowest cue validity condition. For the autism group, hit rates decreased as cue validity decreased, from 95% to 92%. Statistical analyses revealed a main effect of condition (ß=0.02, SE<0.01, p<0.01) and a group-by-condition interaction (ß=0.02, SE<0.01, p=0.03; see Table S4).

TABLE 2: Mixed Model Results for CNV, P3, and RT. Group (Grp) = autism and neurotypical; Condition (Con) = cue validity condition; 100%, 84%, 67%, 33%).

	Coefficient	SE	z	P
CNV				
Intercept	-2.7	7.77	-0.35	0.73
Condition effect	1.54	0.18	8.69	<0.01
Group effect	1.38	10.99	0.13	0.9
Con:Grp Interaction	-0.64	0.26	-2.5	0.01
P3				
Intercept	4.2	6.38	0.66	0.51
Condition effect	-3.19	0.21	-15.43	<0.01
Group effect	-0.43	9.02	-0.05	0.96
Con:Grp Interaction	0.14	0.3	0.46	0.65
RT				
Intercept	399.55	129.23	3.09	<0.01
Condition effect	-96.38	4.23	-22.76	<0.01
Group effect	-6.43	183.55	-0.03	0.97
Con:Grp Interaction	34.43	6.10	5.63	<0.01

DISCUSSION

We investigated how young adults with and without autism adjust prediction certainty, a central feature of predictive processing, upon parametric manipulation of cue validity ranging from 33% to 100%. Distinct brain responses served to index the anticipation of temporally predictable targets (CNV) and the evaluation and registration of target events (P3). Whereas the control group showed graded modulation of these brain responses and RT that was proportional to the level of cue validity (predictability), this pattern was not uniformly evident in the autism group. In particular, for the CNV, there was a pronounced difference between the fully predictable condition (100% cue validity) and the less predictable conditions, whereas differences among the three less predictable conditions were substantially reduced (Fig. 2). The relatively outsized responses to small deviations from what is expected (i.e., the response difference between 84%-100% conditions) arguably mirrors the insistence on sameness phenotype, in which even small deviations from expectation cause distress and rules and routines are perpetually sought. On the other hand, reduced differences between the three conditions in which predictions were violated (84%, 67% and 33%) points to the possibility that prediction certainty is more categorical (certain and uncertain) in autism whereas it is more graded in controls. These CNV data suggest that autistic individuals do not modulate certainty of their predictions based on changes in cue validity in the same highly flexible manner as do controls.

The behavioral data also supported altered cue validity effects in autism. Whereas mean RT followed the expected pattern in the control group such that responses were faster when cue validity was higher and slower when it was lower (Fig. 4), in the autism group mean RT differences between adjacent conditions were significantly smaller for all comparisons except for the 100% vs 84% comparison (Table S3), and the two intermediate conditions (84 and 67%) did not differ in mean RT value at all. In contrast, the target P3 systematically modulated by cue validity not only in the control group but also in the autism group (Fig. 3), aligning with studies showing that autistic individuals represent stimulus statistics in a typical manner (Cannon et al., 2021; Knight et al.,

2020; Manning et al., 2017). Taken all together, relatively intact P3 modulation combined with impaired CNV and RT modulation suggests that while stimulus statistics are calculated, the application of this information to modulate prediction certainty and influence downstream behavior is impaired.

These data appear to fit well with the theory of Highly Inflexible and Precise Prediction Errors in Autism (HIPPEA) proposed by Van de Cruys and colleagues (Van de Cruys et al., 2014). This theory posits that under volatile conditions a uniformly high level of precision is assigned to prediction errors in autism, by which even little variances in the environment will induce an update in the predictive model; this in turn leads to overfitted models, as even insignificant details/changes are considered important and reacted to, rather than being disregarded. Thus, with more precise prediction errors, even small changes evoke a large response, much as we see in the CNV for the autism group (i.e., 84% versus 100%). This uniformly applied high precision could also account for the impaired differentiation among the different levels of uncertainty that we observed in our CNV data where the differentiation between lowest three cue validity conditions (84%, 67%, 33%) was reduced in the autism group.

Bearing in mind that many processes lie between any given brain measure and the variables that make up a clinical or cognitive score, of interest is whether and how these electrophysiological and behavioral indices of flexibility of prediction certainty map onto the autism phenotype. To begin to address this question we focused on SRS scores, which provide a continuous measure of characteristics associated with the autism phenotype in the broader population as well as in autism (Constantino & Gruber, 2012). As one might expect, we found that greater flexibility of predictive processing (a larger CNV differential between 33 and 84% conditions) was associated with greater social responsiveness (lower SRS scores). However, looking at the regression lines for control and autism groups separately (Fig. 2C & 3C), it appears that this relationship may have been driven by trends in the control group. Clearly the participant numbers in the individual group regression analyses are inadequate and further investigation in larger

543 samples is needed to assess the reliability of this relationship in the general population
544 and the nature of this relationship in autism.
545
546 While our approach cannot identify the precise neural locus of disrupted processing,
547 prior studies suggest several cortical/subcortical regions that contribute to CNV
548 generation and the modulation of prediction certainty. For example, the anterior
549 cingulate cortex (ACC) monitors the likelihood of events (Brown & Braver, 2005), has
550 been highlighted in probabilistic tasks in human functional imaging studies (Agam et al.,
551 2010; O'Reilly et al., 2013) as well as animal studies (Kennerley et al., 2006; Kolling et
552 al., 2016; Stolyarova et al., 2019), and is thought to contribute to the CNV response
553 (Gómez et al., 2003; Mulert et al., 2004; Nagai et al., 2004). The thalamus has also
554 been implicated in the representation of precision in the context of predictive models
555 (Kanai et al., 2015), and has been shown to contribute to trial-by-trial modulation of
556 CNV amplitude (Nagai et al., 2004). Likewise, the prefrontal cortex is implicated in the
557 representation of basic and more abstract prediction errors (Alexander & Brown, 2018;
558 Zarr & Brown, 2016), and contributes to the CNV response (Gómez et al., 2007; Gómez
559 et al., 2003; Mulert et al., 2004; Scheibe et al., 2010). Compellingly, activity in all of
560 these brain regions has been shown to differ in autism (Balsters et al., 2016; Di Martino
561 et al., 2009; Solomon et al., 2015; Tomasi & Volkow, 2019).
562
563 The current results suggest that the CNV may be a powerful biomarker of altered
564 representation of prediction certainty in autism. This belies the question of its potential
565 as a diagnostic biomarker. To this end it will necessary to assess at-risk populations
566 (e.g., siblings of individuals diagnosed with autism) before the emergence of autism
567 symptomatology, during infancy/early childhood (<2 years of age; e.g., see (Constantino
568 et al., 2021)). For this, robust experimental assays of altered predictive processing for
569 administration to very young children are needed. Promisingly, recent work reported
570 anticipatory processes similar to the CNV in infants as young as 4 months of age, in
571 response to a voice cue to an upcoming face (Mento et al., 2022).
572

To conclude, the findings from the current study contribute to our understanding of altered predictive processing in autism by revealing that representation of prediction certainty in this population is overly circumscribed, such that situations are anticipated to be predictable or unpredictable, with very little in-between. As such, cognitive-behavioral therapies directed at teaching individuals to form and apply more nuanced representations of probabilistic relationships when navigating their everyday life may be useful for individuals with autism. The CNV data, furthermore, suggest a potential neuromarker of the representation of prediction certainty. Finally, our study suggests that inclusion of a 100% cue validity condition, which is usually absent in studies on the representation of uncertainty in autism, provides an essential baseline when assessing magnitude of uncertainty effects in clinical groups. Future work will be needed to determine if these findings are specific to environments where cue-target contingencies change over relatively short periods of time and must be learned implicitly, as in the present study, or if they represent a more generalized mode of operation whereby prediction certainty is represented in a more binary manner across a broad range of circumstances in autism.

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DECLARATIONS

Ethical Approval

All procedures were approved by the Institutional Review Board at Albert Einstein College of Medicine. Before beginning the study, informed written consent was obtained from participants who were aged 18 or older. From participants who were younger than 18, written assent was obtained, along with informed written consent from their parents or legal guardians.

Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

S.R. and S.M. conceptualized and designed the study; S.R. collected and analyzed data; S.M. and M.J.C. provided guidance and supervision on data analysis; S.R., M.J.C. and S.M. contributed to data interpretation; S.R. generated figures; S.R. wrote the first draft of the manuscript and received extensive editorial input from S.M.. All the authors reviewed the content of the paper and approved the final version.

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Availability of data and materials

Data from the findings of this study are available from the authors upon request. The codes that were generated for stimulus presentation, data analyses and visualization are available at https://github.com/seydareisli.

REFERENCES

Agam, Y., Joseph, R. M., Barton, J. J. S., & Manoach, D. S. (2010). Reduced cognitive control of response inhibition by the anterior cingulate cortex in autism spectrum disorders. *Neuroimage*, *52*(1), 336-347. https://doi.org/10.1016/j.neuroimage.2010.04.010

Alexander, W. H., & Brown, J. W. (2018). Frontal cortex function as derived from hierarchical predictive coding. *Scientific reports*, *8*(1), 1-11.

Arthur, T., Harris, D., Buckingham, G., Brosnan, M., Wilson, M., Williams, G., & Vine, S. (2021). An examination of active inference in autistic adults using immersive virtual reality. *Scientific reports*, *11*(1), 1-14.

Balsters, J. H., Mantini, D., Apps, M. A. J., Eickhoff, S. B., & Wenderoth, N. (2016). Connectivity-based parcellation increases network detection sensitivity in resting state fMRI: An investigation into the cingulate cortex in autism. *Neuroimage Clin*, *11*, 494-507. https://doi.org/10.1016/j.nicl.2016.03.016

Bar, M. (2007). The proactive brain: using analogies and associations to generate predictions. *Trends Cogn. Sci.*, *11*(7), 280-289. https://doi.org/10.1016/j.tics.2007.05.005

Bar, M., Kassam, K. S., Ghuman, A. S., Boshyan, J., Schmid, A. M., Dale, A. M., Hämäläinen, M. S., Marinkovic, K., Schacter, D. L., Rosen, B. R., & Halgren, E. (2006). Top-down facilitation of visual recognition. *Proc. Natl. Acad. Sci. U. S. A.*, *103*(2), 449-454. https://doi.org/10.1073/pnas.0507062103

Bidet-Caulet, A., Barbe, P.-G., Roux, S., Viswanath, H., Barthélémy, C., Bruneau, N., Knight, R. T., & Bonnet-Brilhault, F. (2012). Dynamics of anticipatory mechanisms during predictive context processing. *Eur. J. Neurosci.*, *36*(7), 2996-3004. https://doi.org/10.1111/j.1460-9568.2012.08223.x

Bonett, D. G., & Wright, T. A. (2000). Sample size requirements for estimating Pearson, Kendall and Spearman correlations. *Psychometrika*, *65*(1), 23-28.

Brown, J. W., & Braver, T. S. (2005). Learned predictions of error likelihood in the anterior cingulate cortex. *Science*, *307*(5712), 1118-1121. https://doi.org/10.1126/science.1105783

Brunia, C. H. M. (2003). CNV and SPN: Indices of Anticipatory Behavior. In M. Jahanshahi & M. Hallett (Eds.), *The Bereitschaftspotential: Movement-Related Cortical Potentials* (pp. 207-227). Springer US. https://doi.org/10.1007/978-1-4615-0189-3_13

Cannon, J., O'Brien, A. M., Bungert, L., & Sinha, P. (2021). Prediction in Autism Spectrum Disorder: A Systematic Review of Empirical Evidence. *Autism Res.*, *14*(4), 604-630. https://doi.org/10.1002/aur.2482

Chambon, V., Farrer, C., Pacherie, E., Jacquet, P. O., Leboyer, M., & Zalla, T. (2017). Reduced sensitivity to social priors during action prediction in adults with autism spectrum disorders. *Cognition*, *160*, 17-26. https://doi.org/10.1016/j.cognition.2016.12.005

Coll, M.-P., Whelan, E., Catmur, C., & Bird, G. (2020). Autistic traits are associated with atypical precision-weighted integration of top-down and bottom-up neural signals. *Cognition*, *199*, 104236. https://doi.org/10.1016/j.cognition.2020.104236

Constantino, J. N., Charman, T., & Jones, E. J. (2021). Clinical and translational implications of an emerging developmental substructure for autism. *Annual review of clinical psychology*, *17*, 365-389.

Constantino, J. N., & Gruber, C. P. (2012). *Social responsiveness scale: SRS-2*. Western psychological services Torrance, CA.

David, F. N. (1938). *Tables of the ordinates and probability integral of the distribution of the correlation coefficient in small samples*. Cambridge University Press.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods*, *134*(1), 9-21. https://doi.org/10.1016/j.jneumeth.2003.10.009

10.1016/j.jneumeth.2003.10.009.

Di Martino, A., Shehzad, Z., Kelly, C., Roy, A. K., Gee, D. G., Uddin, L. Q., Gotimer, K., Klein, D. F., Castellanos, F. X., & Milham, M. P. (2009). Relationship between cingulo-insular functional connectivity and autistic traits in neurotypical adults. *Am. J. Psychiatry*, *166*(8), 891-899. https://doi.org/10.1176/appi.ajp.2009.08121894

Friston, K., & Kiebel, S. (2009). Predictive coding under the free-energy principle. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, *364*(1521), 1211-1221. https://doi.org/10.1098/rstb.2008.0300

Frith, U. (2003). Autism: Explaining the enigma. https://psycnet.apa.org/record/2003-00578-000

https://scholar.google.ca/scholar?cluster=15712096939503413415,18008765383514486030,16763683680195034002&hl=en&as_sdt=0,5&sciodt=0,5

Gómez, C. M., Flores, A., & Ledesma, A. (2007). Fronto-parietal networks activation during the contingent negative variation period. *Brain Res. Bull.*, *73*(1-3), 40-47. https://doi.org/10.1016/j.brainresbull.2007.01.015

Gómez, C. M., Marco, J., & Grau, C. (2003). Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density. *Neuroimage*, *20*(1), 216-224. https://doi.org/10.1016/s1053-8119(03)00295-7

Gomot, M., & Wicker, B. (2012). A challenging, unpredictable world for people with autism spectrum disorder. *Int. J. Psychophysiol.*, *83*(2), 240-247. https://doi.org/10.1016/j.ijpsycho.2011.09.017

Gregory, R. L. (1980). Perceptions as hypotheses. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, *290*(1038), 181-197. https://doi.org/10.1098/rstb.1980.0090

Hohwy, J. (2017). Priors in perception: Top-down modulation, Bayesian perceptual learning rate, and prediction error minimization. *Conscious. Cogn.*, *47*, 75-85. https://doi.org/10.1016/j.concog.2016.09.004

Kanai, R., Komura, Y., Shipp, S., & Friston, K. (2015). Cerebral hierarchies: predictive processing, precision and the pulvinar. *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, *370*(1668). https://doi.org/10.1098/rstb.2014.0169

Karvelis, P., Seitz, A. R., Lawrie, S. M., & Seriès, P. (2018). Autistic traits, but not schizotypy, predict increased weighting of sensory information in Bayesian visual integration. *Elife*, *7*. https://doi.org/10.7554/eLife.34115

10.7554/eLife.34115.

Kennerley, S. W., Walton, M. E., Behrens, T. E. J., Buckley, M. J., & Rushworth, M. F. S. (2006). Optimal decision making and the anterior cingulate cortex. *Nat. Neurosci.*, *9*(7), 940-947. https://doi.org/10.1038/nn1724

Knight, E. J., Oakes, L., Hyman, S. L., Freedman, E. G., & Foxe, J. J. (2020). Individuals With Autism Have No Detectable Deficit in Neural Markers of Prediction Error When Presented With Auditory Rhythms of Varied Temporal Complexity. *Autism Res.*, *13*(12), 2058-2072. https://doi.org/10.1002/aur.2362

Kóbor, A., Kardos, Z., Horváth, K., Janacsek, K., Takács, Á., Csépe, V., & Nemeth, D. (2021). Implicit anticipation of probabilistic regularities: Larger CNV emerges for unpredictable events. *Neuropsychologia*, *156*, 107826. https://doi.org/10.1016/j.neuropsychologia.2021.107826

Kolling, N., Behrens, T., Wittmann, M. K., & Rushworth, M. (2016). Multiple signals in anterior cingulate cortex. *Curr. Opin. Neurobiol.*, *37*, 36-43. https://doi.org/10.1016/j.conb.2015.12.007

Lawson, R. P., Mathys, C., & Rees, G. (2017). Adults with autism overestimate the volatility of the sensory environment. *Nat. Neurosci.*, *20*(9), 1293-1299. https://doi.org/10.1038/nn.4615

Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Front. Hum. Neurosci.*, *8*, 302. https://doi.org/10.3389/fnhum.2014.00302

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). Autism diagnostic observation schedule, (ADOS-2) modules 1-4. *Los Angeles, California: Western Psychological Services*.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J. Autism Dev. Disord.*, *24*(5), 659-685. https://www.ncbi.nlm.nih.gov/pubmed/7814313

https://link.springer.com/article/10.1007/bf02172145

https://link.springer.com/content/pdf/10.1007/BF02172145.pdf

Manning, C., Kilner, J., Neil, L., Karaminis, T., & Pellicano, E. (2017). Children on the autism spectrum update their behaviour in response to a volatile environment. *Dev. Sci.*, *20*(5). https://doi.org/10.1111/desc.12435

Mento, G., Duma, G. M., Valenza, E., & Farroni, T. (2022). Face specific neural anticipatory activity in infants 4 and 9 months old. *Scientific reports*, *12*(1), 12938.

Mulert, C., Pogarell, O., Juckel, G., Rujescu, D., Giegling, I., Rupp, D., Mavrogiorgou, P., Bussfeld, P., Gallinat, J., Möller, H. J., & Hegerl, U. (2004). The neural basis of the P300 potential. *Eur. Arch. Psychiatry Clin. Neurosci.*, *254*(3), 190-198. https://doi.org/10.1007/s00406-004-0469-2

Nagai, Y., Critchley, H. D., Featherstone, E., Fenwick, P. B. C., Trimble, M. R., & Dolan, R. J. (2004). Brain activity relating to the contingent negative variation: an fMRI investigation. *Neuroimage*, *21*(4), 1232-1241. https://doi.org/10.1016/j.neuroimage.2003.10.036

O'Reilly, J. X., Schüffelgen, U., Cuell, S. F., Behrens, T. E. J., Mars, R. B., & Rushworth, M. F. S. (2013). Dissociable effects of surprise and model update in parietal and anterior cingulate cortex. *Proc. Natl. Acad. Sci. U. S. A.*, *110*(38), E3660-3669. https://doi.org/10.1073/pnas.1305373110

Palmer, C. J., Lawson, R. P., & Hohwy, J. (2017). Bayesian approaches to autism: Towards volatility, action, and behavior. *Psychol. Bull.*, *143*(5), 521-542. https://doi.org/10.1037/bul0000097

Palmer, C. J., Seth, A. K., & Hohwy, J. (2015). The felt presence of other minds: Predictive processing, counterfactual predictions, and mentalising in autism. *Conscious. Cogn.*, *36*, 376-389. https://doi.org/10.1016/j.concog.2015.04.007

Perrykkad, K., Lawson, R. P., Jamadar, S., & Hohwy, J. (2021). The effect of uncertainty on prediction error in the action perception loop. *Cognition*, *210*, 104598. https://doi.org/10.1016/j.cognition.2021.104598

Pion-Tonachini, L., Kreutz-Delgado, K., & Makeig, S. (2019). ICLabel: An automated electroencephalographic independent component classifier, dataset, and website. *Neuroimage*, *198*, 181-197. https://doi.org/10.1016/j.neuroimage.2019.05.026

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clin. Neurophysiol.*, *118*(10), 2128-2148. https://doi.org/10.1016/j.clinph.2007.04.019

Polich, J. (2012). Neuropsychology of P300. *The Oxford handbook of event-related potential components.*, *641*, 159-188. https://psycnet.apa.org/fulltext/2013-01016-007.pdf https://psycnet.apa.org/record/2013-01016-007

Sapey-Triomphe, L.-A., Weilnhammer, V. A., & Wagemans, J. (2021). Associative learning under uncertainty in adults with autism: Intact learning of the cue-outcome contingency, but slower updating of priors. *Autism*, 13623613211045026. https://doi.org/10.1177/13623613211045026

Scheibe, C., Ullsperger, M., Sommer, W., & Heekeren, H. R. (2010). Effects of parametrical and trial-to-trial variation in prior probability processing revealed by simultaneous electroencephalogram/functional magnetic resonance imaging. *J. Neurosci.*, *30*(49), 16709-16717. https://doi.org/10.1523/JNEUROSCI.3949-09.2010

Seabold, S., & Perktold, J. (2010). Statsmodels: Econometric and statistical modeling with python. Proceedings of the 9th Python in Science Conference,

Simard, I., Luck, D., Mottron, L., Zeffiro, T. A., & Soulières, I. (2015). Autistic fluid intelligence: Increased reliance on visual functional connectivity with diminished

792 modulation of coupling by task difficulty. *Neuroimage Clin*, *9*, 467-478.
793 https://doi.org/10.1016/j.nicl.2015.09.007
794 Sivagnanam, S., Majumdar, A., Yoshimoto, K., Astakhov, V., Bandrowski, A. E., Martone, M.
795 E., Carnevale, N. T., & Others. (2013). Introducing the neuroscience gateway. *IWSG*,
796 *993*.
797 http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.415.7150&rep=rep1&type=pdf
798 Solomon, M., Frank, M. J., Ragland, J. D., Smith, A. C., Niendam, T. A., Lesh, T. A., Grayson,
799 D. S., Beck, J. S., Matter, J. C., & Carter, C. S. (2015). Feedback-driven trial-by-trial
800 learning in autism spectrum disorders. *Am. J. Psychiatry*, *172*(2), 173-181.
801 https://doi.org/10.1176/appi.ajp.2014.14010036
802 Soulières, I., Mottron, L., Giguère, G., & Larochelle, S. (2011). Category induction in autism:
803 Slower, perhaps different, but certainly possible. *Quarterly journal of experimental*
804 *psychology*, *64*(2), 311-327.
805 Stolyarova, A., Rakhshan, M., Hart, E. E., O'Dell, T. J., Peters, M. A. K., Lau, H., Soltani, A., &
806 Izquierdo, A. (2019). Contributions of anterior cingulate cortex and basolateral amygdala
807 to decision confidence and learning under uncertainty. *Nat. Commun.*, *10*(1), 4704.
808 https://doi.org/10.1038/s41467-019-12725-1
809 Thillay, A., Lemaire, M., Roux, S., Houy-Durand, E., Barthélémy, C., Knight, R. T., Bidet-
810 Caulet, A., & Bonnet-Brilhault, F. (2016). Atypical Brain Mechanisms of Prediction
811 According to Uncertainty in Autism. *Front. Neurosci.*, *10*, 317.
812 https://doi.org/10.3389/fnins.2016.00317
813 Tomasi, D., & Volkow, N. D. (2019). Reduced Local and Increased Long-Range Functional
814 Connectivity of the Thalamus in Autism Spectrum Disorder. *Cereb. Cortex*, *29*(2), 573-
815 585. https://doi.org/10.1093/cercor/bhx340
816 Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., &
817 Wagemans, J. (2014). Precise minds in uncertain worlds: predictive coding in autism.
818 *Psychol. Rev.*, *121*(4), 649-675. https://doi.org/10.1037/a0037665
819 Vishne, G., Jacoby, N., Malinovitch, T., Epstein, T., Frenkel, O., & Ahissar, M. (2021). Slow
820 update of internal representations impedes synchronization in autism. *Nat. Commun.*,
821 *12*(1), 5439. https://doi.org/10.1038/s41467-021-25740-y
822 Zarr, N., & Brown, J. W. (2016). Hierarchical error representation in medial prefrontal cortex.
823 *Neuroimage*, *124*(Pt A), 238-247. https://doi.org/10.1016/j.neuroimage.2015.08.063
824