



Research Report

Qualitative differences in the spatiotemporal brain states supporting configural face processing emerge in adolescence in autism



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ARTICLE INFO

Article history:

Received 28 May 2021

Reviewed 26 October 2021

Revised 17 December 2021

Accepted 29 June 2022

Action editor Holger Wiese

Published online 14 July 2022

Keywords:

Face processing

Autism

EEG

Face inversion effect

Development

ABSTRACT

Background: Studying the neural processing of faces can illuminate the mechanisms of compromised social expertise in autism. To resolve a longstanding debate, we examined whether differences in configural face processing in autism are underpinned by quantitative differences in the activation of typical face processing pathways, or the recruitment of non-typical neural systems.

Methods: We investigated spatial and temporal characteristics of event-related EEG responses to upright and inverted faces in a large sample of children, adolescents, and adults with and without autism. We examined topographic analyses of variance and global field power to identify group differences in the spatial and temporal response to face inversion. We then examined how quasi-stable spatiotemporal profiles – microstates – are modulated by face orientation and diagnostic group.

Results: Upright and inverted faces produced distinct profiles of topography and strength in the topographical analyses. These topographical profiles differed between diagnostic groups in adolescents, but not in children or adults. In the microstate analysis, the autistic group showed differences in the activation strength of normative microstates during early-

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<https://doi.org/10.1016/j.cortex.2022.06.010>

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stage processing at all ages, suggesting consistent quantitative differences in the operation of typical processing pathways; qualitative differences in microstate topographies during late-stage processing became prominent in adults, suggesting the increasing involvement of non-typical neural systems with processing time and over development.

Conclusions: These findings suggest that early difficulties with configural face processing may trigger later compensatory processes in autism that emerge in later development.

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1. Introduction

Autism is a developmental condition characterised by social communication difficulties, restricted interests and repetitive behaviours, and sensory issues (American Psychological Association, 2013). Animal and human studies have identified genetic, epigenetic and environmental factors involved in autism aetiology (De La Torre-Ubieta et al., 2016; Fernández et al., 2018; Gao et al., 2019; Mandy & Lai, 2016; Nomi & Uddin, 2015). However, the specific mechanisms through which these factors have cascading effects on brain functioning and produce difficulties in social communication remain unclear. A central debate is whether autism is best understood in terms of delays or ‘deficits’ in neurotypical brain development, or whether it is better characterized as a qualitatively different developmental endstate with a significant influence of compensatory and adaptive processes (Astle & Fletcher-Watson, 2020; Johnson et al., 2015). One way to provide insight into this question is to focus on specific neurocognitive domains in which brain responses can be precisely quantified. In particular, rapid and efficient face processing provides non-verbal information critical during social interactions (Frith & Frith, 2007) and can be dissected to provide insight into social development (Dawson et al., 2005a). Face processing typically develops with expertise, whereby cortical areas specialize towards rapidly coding relevant information from faces (Itier and Taylor, 2004a, 2004b; Johnson, 2011; Kuefner et al., 2010; Mares et al., 2020; Pascalis et al., 2011; Röder et al., 2013). Alterations in this skill during early life may have cascading effects on later social and language development (Chevallier et al., 2012; Dawson et al., 2005b; Mundy, 2018). Studying neural responses to faces can thus provide insight into the mechanisms that influence social brain development in autism.

One key element of face processing is configural processing, where the spatial relationship between face parts is encoded, allowing for rapid face detection, discrimination, and identification (Piepers & Robbins, 2012). Faces presented in upright orientation are recognized faster and more accurately compared to faces presented in inverted orientation where configural information is altered (Yin, 1969). This inversion effect is stronger for faces than non-face stimuli and relates to visual experience (Geldart et al., 2002; Röder et al., 2013) and expertise with the stimulus categories presented (Diamond & Carey, 1986; Piepers & Robbins, 2012; Yin, 1969). Compared to neurotypical individuals, some autistic individuals show reduced inversion effects with similar performance for upright and inverted faces (Teunisse & De Gelder, 2003); recognition of upright faces is more difficult in

the autistic group compared to the neurotypical group (Bookheimer et al., 2008; Dimitriou et al., 2015). Autistic individuals may obtain larger gains by focusing more on the isolated local face features compared to processing strategies depending on configural information (Dawson et al., 2005b; Elgar & Campbell, 2001), resulting in more accurate recognition of inverted faces (Deruelle et al., 2004; Ghuman et al., 2016; Joseph & Tanaka, 2003; Lahaie et al., 2006; Nishimura et al., 2008; Teunisse & De Gelder, 2003). Two neural mechanisms have been proposed to account for these differences in configural face processing in autism (Nomi & Uddin, 2015). One hypothesized mechanism is that differences in face processing in autism are connected to a reduction in the activation of brain systems specialized for configural processing relative to their activation during face processing in the neurotypical brain (Yovel, 2016; Yovel et al., 2014). This would predict that neural differences during face processing in autistic people involve a reduction in the magnitude of activation in neurotypically-activated regions. An alternative theory is that brain networks specialised for featural processing (e.g., those typically involved in object processing) are recruited for face processing in autistic but not neurotypical individuals (Haxby et al., 1999; Yovel, 2016; Yovel et al., 2014). This would predict that there will be additional regions that activate in response to faces in autistic versus neurotypical people. A third option is that both mechanisms are active but to a different extent in autistic compared to neurotypical individuals; variability in their balance could contribute to broader phenotypic variability in autism. Finally, the mechanisms involved in configural face processing in autism may change with development and reliance on them may vary between childhood and adolescence.

Based largely on functional neuroimaging data, evidence converges to suggest that both alterations in neurotypical brain systems and a qualitatively different response profile influence face processing in autism (Nomi & Uddin, 2015). First, some fMRI evidence is consistent with reduced engagement in neural systems that subservise face processing in the typical brain (Yovel, 2016; Yovel et al., 2014); for example, autistic individuals show reduced activation when viewing faces in face-sensitive brain regions (i.e., the fusiform gyrus (Hubl et al., 2003; Humphreys et al., 2008; Nickl-Jockschat et al., 2015; Scherf et al., 2010; Schultz et al., 2000), superior temporal sulcus (Humphreys et al., 2008; Pierce et al., 2001; Scherf et al., 2010, 2015), the amygdala (Pierce et al., 2001), and occipital areas (Pierce et al., 2001; Scherf et al., 2010, 2015)). Autistic people may also recruit alternative brain networks less suited to face processing (e.g., the inferior temporal gyrus (Schultz et al., 2000), lateral occipital cortex (Hubl et al., 2003;

Picci & Scherf, 2015; Scherf et al., 2010), superior parietal lobule and the frontal eye field (Hubl et al., 2003)), possibly to compensate for the inefficient operation of other pathways (Haxby et al., 1999; Yovel, 2016; Yovel et al., 2014). However, the poor temporal resolution of fMRI makes it difficult to determine how these mechanisms interact to shape face processing; for example, does recruitment of additional networks emerge later in the processing window to compensate for earlier reductions in neurotypical network engagement? Further, few studies have examined whether engagement of additional networks resembles patterns seen in younger typically developing children (consistent with continued employment of an immature processing style) or whether they emerge later in development (consistent with a compensatory or consequential function). Addressing these questions is important to moving towards a more mechanistic account of autism.

Examining both spatial and temporal characteristics of neural responses to faces over time may provide a tractable way to dissect key mechanisms underpinning social symptoms of ASD. Electroencephalography (EEG) is a highly temporally sensitive measure that also provides some spatial fidelity (Lopes da Silva, 2013). Traditional analysis of event-related potentials (ERPs) at pre-defined time windows and electrodes (Luck, 2014) indicate a temporally-precise processing cascade that becomes face sensitive around ~170 msec after stimulus onset at electrodes P7 and P8 (called the N170) (Bentin et al., 1996; Eimer, 2012). Autistic adults show slower N170 responses (Kang et al., 2018) and an attenuated N170 face inversion or orientation effect (slower N170 responses to inverted compared to upright faces (Bentin et al., 1996; Itier and Taylor, 2004c; Jacques et al., 2007; Rossion et al., 2000)) compared to neurotypical adults (Kang et al., 2018; Key & Corbett, 2020; McPartland et al., 2011; Vettori et al., 2019; Webb et al., 2012). Critically, this attenuated orientation effect confirms behavioral evidence of alterations in processing configural aspects of faces in autism (because configurations are harder to process when a face is upside down) (Dawson et al., 2005a; Elgar & Campbell, 2001; Teunisse & De Gelder, 2003; Yin, 1969); configural processing is a key indication of experience-driven face processing expertise (Diamond & Carey, 1986; Faja et al., 2012; Piepers & Robbins, 2012). However, whether altered configural processing reflects reduced neurotypical face processing or the recruitment of additional brain areas is unclear.

Here, we use spatiotemporally sensitive multi-channel techniques (Habermann et al., 2018; Koenig et al., 2011, 2014; Pascual-Marqui et al., 1995) to examine configural face processing in a large group of autistic and neurotypical individuals between 6 and 31 years of age. First, we compared strength (global field power) and spatial profile (topographic analysis of variance) between groups on a millisecond-by-millisecond basis across the averaged neural response to upright and inverted faces. However, this may mask group differences if there are individual differences in the pace at which individuals move through a series of processing ‘stages’. Thus, we then extracted individual spatiotemporal profiles – microstates – to compare differences in the duration and strength of the mechanism that are engaged during a brief period of face processing. Microstates are quasi-stable

scalp potentials that are continually activated for several tens of milliseconds before transitioning to another scalp potential (Michel et al., 2009; Michel & Koenig, 2018; Pascual-Marqui et al., 1995). Across these techniques, we evaluate the evidence for quantitative and qualitative differences in configural processing in autism, and how this varies with development.

2. Materials and methods

2.1. Participants

Participants were part of the Longitudinal European Autism Project (LEAP) (Charman et al., 2017; Loth et al., 2017), a multi-site study collecting deeply phenotyped data at a large scale (Charman et al., 2017) (and see [Supplementary Material \(SM section 1\)](#)). Here, we included participants with and without a clinical diagnosis of autism with IQ in the typical range ($IQ \geq 75$) in 3 age groups: children (age 6–11 years), adolescents (12–17 years), and adults (18–31 years). The LEAP study design included recruitment of participants into these particular age groups aligning with transitions between formal education (i.e., from primary to secondary school at 12 years of age and ending formal education at 18 years of age). We furthermore decided to analyze the data into these age groups for comparison with previous studies that took a similar approach (Crawley et al., 2020). Autism Diagnostic Interview – Revised (ADI-R (Rutter et al., 2003)) subscales, the Autism Diagnostic Observation Scales (ADOS (Lord et al., 2000; Lord et al., 2012)) subscales, and the Social Responsiveness Scale, Second Edition (SRS-2 (Constantino & Gruber, 2012), parent report) subdomain raw scores were collected from all autistic participants to clinically characterize the sample (SM 2). Independent site-specific ethics committees approved the study (Loth et al., 2017). All participants (and their caregiver where appropriate) provided written informed consent.

In total, 174 children, 224 adolescents, and 255 adults were recruited to participate in the study. The final sample with sufficient clean EEG data included 53 autistic and 40 neurotypical children; 79 autistic and 67 neurotypical adolescents; and 87 autistic and 73 neurotypical adults (see [Table 1](#), and attrition rates in [SM 3](#)). Ages between diagnostic groups were similar in children, adolescents, and adults (p 's $\geq .108$). In both children and adolescents, autistic participants exhibited lower full scale IQ scores than neurotypical peers (for children: $m_{AUT} = 105$, $sd = 15$, and $m_{NT} = 112$, $sd = 14$, $t(88) = 2.35$, $p = .021$; for adolescents: $m_{AUT} = 98$, $sd = 14$, and $m_{NT} = 105$, $sd = 13$, $t(143) = 3.15$, $p = .002$). Full scale IQ did not differ between diagnostic groups in adults ($m_{AUT} = 104$, $sd = 15$, and $m_{NT} = 108$, $sd = 12$, $t(158) = 1.64$, $P = .103$).

Clinical characteristics of the autistic groups differed across age groups. For the ADI-R, scores on the Social Total were elevated for the adolescents compared to the children and adults who did not differ from each other ($F(2,205) = 5.38$, $p = .005$, $\eta_p^2 = .050$). Adolescents also displayed higher scores on the Communication Total compared to adults, whereas children did not differ from the other age groups ($F(2,205) = 4.78$, $p = .009$, $\eta_p^2 = .045$). Age groups did not differ on RRB Total scores ($p > .05$). For the calibrated severity scores

Table 1 – Demographic and clinical characterization of the current sample.

	Children		Adolescents		Adults	
	NT	AUT	NT	AUT	NT	AUT
N (female)	40 (18)	53 (15)	66 (25)	79 (17)	73 (20)	87 (23)
Age (years)	10.0 (1.4), 6.9–12.0	9.7 (1.4), 6.6–11.9	15.2 (1.7), 12.2–18.0	15.0 (1.8), 12.1–17.9	23.5 (3.3), 18.3–31.0	22.6 (3.4), 18.0–30.3
Full-scale IQ	112.3 (14.3), 76.0–142.0	105.1 (14.7), 74.0–139.0	105.4 (13.0), 76.8–133.0	98.3 (13.9), 75.0–130.0	107.7 (12.2), 75.6–142.0	104.1 (14.8), 75.9–148.0
ADI-R						
Social Total	NA	13.9 (7.5), 0–29	NA	17.3 (6.5), 2–29	NA	14.2 (7.1), 0–28
Communication Total	NA	12.0 (5.5), 3–23	NA	13.9 (5.8), 1–26	NA	11.2 (5.6), 0–24
RRB Total	NA	4.5 (3.1), 0–12	NA	4.2 (2.7), 0–10	NA	4.0 (2.5), 0–12
ADOS						
SA-CSS	NA	5.3 (2.5), 1–9	NA	6.6 (2.7), 1–10	NA	5.6 (2.7), 1–10
RRB-CSS	NA	5.0 (3.0), 1–10	NA	4.7 (2.7), 1–10	NA	4.9 (2.7), 1–10
CSS Total	NA	4.7 (2.5), 1–10	NA	5.9 (2.9), 1–10	NA	4.9 (2.6), 1–10
SRS-2 raw score	NA	92.4 (32.2), 32–163	NA	91.4 (27.3), 22–149	NA	78.4 (30.2), 20–136
Number of ERP trials						
Upright faces	44 (16), 20–76	42 (11), 23–74	50 (13), 22–77	48 (11), 24–73	49 (13), 21–75	46 (13), 20–76
Inverted faces	47 (17), 21–79	45 (12), 25–77	53 (14), 24–82	51 (13), 22–77	52 (13), 25–79	51 (14), 21–77

Values represent mean (standard deviation), minimum – maximum.

Data were missing for full-scale IQ in 3 AUT children; ADI-R in 3 AUT children, 1 AUT adolescent, and 7 AUT adults; ADOS in 6 AUT children, 13 AUT adolescents, and 18 AUT adults; and SRS-2 in 5 AUT children, 12 AUT adolescents, and 25 AUT adults.

(CSS) on the ADOS, adolescents showed elevated scores on the Social Affect (SA) subdomain compared to children and a tendency towards higher scores than adults, while children and adults displayed similar scores ($F(2,179) = 4.09, p = .018, \eta_p^2 = .044$). Adolescents furthermore had a tendency towards higher CSS Total scores than adults and children, whereas children and adults showed similar CSS Total scores ($F(2,179) = 3.50, p = .032, \eta_p^2 = .038$). CSS scores for the RRB domain were similar across age groups ($p > .05$). Finally, SRS-2 raw scores varied with age group ($F(2,174) = 4.15, p = .017, \eta_p^2 = .046$). Further comparisons showed lower scores in adults compared to children and adolescents, whereas there was no difference in scores between children and adolescents.

2.2. Upright-inverted faces task

EEG was continuously recorded whilst participants watched a series of trials consisting of a fixation stimulus (500–700 msec), followed by a face stimulus (of Asian-American, European-American, or African-American ethnicity (Tottenham et al., 2009; Webb et al., 2020), SM 4) in upright or inverted (rotated 180°) orientation (28 trials/condition, total 168) for 500 msec (randomized order), and a blank screen (350 msec). Participants were instructed to passively watch the stimuli.

Briefly, EEG data were harmonized across recording systems into a common EEGLab format (62-channel layout, horizontal electrooculogram, quality metrics and deriving impedance values, re-referencing to FCz, re-sampling to 1000 Hz) (Mason et al.). Data for the face task were segmented from –200 to

800 msec post-stimulus onset using FieldTrip open source Matlab toolbox (Oostenveld et al., 2011). Data were filtered with a .1–40 Hz bandpass filter, and an FFT-based DFT notch filter at 50 Hz (both with 2000 msec of padding). Whole-scalp and ocular artefacts were automatically detected and interpolated on a trial by channel basis and/or rejected using custom written scripts (see SM 5). Data were average re-referenced. Participants were excluded from further analysis if they had fewer than 20 clean trials per condition. All available clean trials were included in the individual averaged ERP. A higher number of clean trials was included for the inverted faces compared to the upright faces (in children: $F(1,91) = 14.76, p < .0001, \eta_p^2 = .140$; in adolescents: $F(1,143) = 31.30, p < .0001, \eta_p^2 = .180$; and in adults: $F(1,158) = 36.31, p < .0001, \eta_p^2 = .187$). This pattern of clean trials between conditions was consistent across diagnostic groups, and the overall number of clean trials did not differ between diagnostic groups (p 's $> .05$ for the Group effect, and Interaction effect in each age group, also see Table 1).

2.3. Multichannel analysis using RAGU

Planned multichannel analyses of the clean ERPs were performed using the Randomization Graphical User Interface (RAGU, vJune 2019 (Koenig et al., 2011), also see SM 6). Analyses with a 2×2 ANOVA with Orientation (upright, inverted) as within-subject factor, and Group (neurotypical, autistic) as between-subject factor were applied after L2 normalization, with 1000 randomization runs, and .05 as threshold for p -values (Habermann et al., 2018). Analyses were performed for

each age group (children, adolescents, and adults) separately, as large variability in scalp maps and strength across the large age range would decrease the fit and explained variance of the statistical analyses. We confirmed consistent scalp activations across individuals within conditions and groups using a Topographic Consistency Test (SM 7).

We first conducted analyses across the whole epoch (–200 – 800 msec). The Topographic Analysis of Variance (TANOVA) tests for significant differences between scalp maps at each data point. The Global Field Power (GFP) analysis tests for differences in the scalp map strength. A duration threshold was applied to the TANOVA and GFP results reflecting the minimum duration of subsequent significant p -values that could not have occurred by chance (threshold calculated from each randomization) (Habermann et al., 2018; Koenig et al., 2011, 2014).

Next, we compared the strength and duration of spatiotemporally-defined scalp potential configurations – microstates – between groups and orientations (Habermann et al., 2018; Koenig et al., 2011, 2014). We tested which number of microstates between 1 and 10 would best fit the data using the *atomize and agglomerate hierarchical clustering* (AAHC) algorithm (Murray et al., 2008) (smoothing with window size of 40 and non-smoothness penalty of .3 to suppress very short microstates) during 250 split-half cross-validation runs on 0–800 msec. The number of microstates providing the best fit was then fitted onto the data and effects for orientation, group, and interaction were tested for duration and mean GFP for each of the microstates (Habermann et al., 2018). We applied a Benjamini and Hochberg FDR correction across all the p -values for each effect within age groups (alpha levels at .05).

2.4. Associations between deviance in microstate features and autism symptom severity

In further planned analyses, we took a normative modelling approach (Marquand et al., 2016; Zabihi et al., 2019) in order to examine whether individual variability in microstate features was related to the variability in severity of autism symptomatology in the individuals with autism (SM 8). We first calculated the deviation in each microstate feature measured by z -scores (duration and mean GFP) from the neurotypical group for each autistic individual (using corresponding age group) while correcting for age. We then averaged the absolute deviation scores across all microstate features resulting in one overall deviance score per autistic individual. We finally calculated Spearman's rho between the overall deviance scores and age, the ADI-R (Rutter et al., 2003) subscales, the ADOS (Lord et al., 2000, 2012) subscales, and the SRS-2 (Constantino & Gruber, 2012) subdomain raw scores across all autistic individuals (and partial correlations while controlling for age). We applied a Benjamini and Hochberg FDR correction across all correlations (alpha levels at .05).

2.5. Transparency and openness on the study procedure, data, and analyses

Here, we report how we determined our sample size, all data exclusions (if any), all inclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. The current

study was based on data collected in the EU-AIMS LEAP study (Loth et al., 2017). The LEAP sample size was based on power calculations that revealed small effect sizes could be reached for a sample with 390 autistic and 255 neurotypical individuals or and moderate effect sizes if samples were split into 2, 3, or 4 subgroups (see Additional file 3 in (Loth et al., 2017)). All study procedures were pre-registered on the Open Science Framework and time-stamped: <https://osf.io/yvd2s/>. These procedures detail the inclusion and exclusion criteria for participants of the LEAP study, the experimental manipulations for the Upright-inverted Faces ERP task, and all demographic, clinical and EEG measures used in the current analyses. Matlab scripts for stimulus presentation are available in a GitHub repository via https://github.com/RianneHaartsen/LEAPspatiotemporal_states.git. Images of the stimuli can be found in the EEG SOP on the LEAP website (<https://www.eu-aims.eu/index.php?id=11160>) but are not further shared here due to lack of legal permissions. We refer researchers interested in using the NimStim Face Stimuli Set to the website of the creators of the images (<https://danlab.psychology.columbia.edu/content/nimstim-set-facial-expressions>).

Prior to the start of our analyses, our analysis plan entitled ‘Spatiotemporal neural responses to faces in individuals with and without autism’ was submitted to the AIMS-2-TRIALS internal registry for pre-registration and approval from the Core Analysis Group Leaders (see AIMS2_Proposal_Pre-registration_LEAP_microstates.pdf in the Supplementary Materials). Cleaned ERP and clinical data were shared with the first author who then performed the analyses once the proposed analyses had been approved. The dataset shared with the first author was the dataset from the LEAP Face ERP task in wave 1, version 20181214. All changes to the analysis plan are clearly identified in the text and the outcomes of the pre-registered and post hoc analyses are distinguished. Matlab scripts used to prepare the data for RAGU analyses and further follow-up analyses are also in the GitHub repository via https://github.com/RianneHaartsen/LEAPspatiotemporal_states.git.

Data presented in this article were derived from a dataset obtained from OWEY (app.owey.io), the datalake designed, developed and hosted at the Institut Pasteur, Paris, France (<https://www.pasteur.fr/en>). Due to the sensitive nature of the LEAP data, data are available through the policies and procedures of the EU-AIMS LEAP study (also see the website <https://www.eu-aims.eu/the-leap-study/>). Data will be shared in accordance with consent given by the participants. Researchers interested in the dataset are required to submit a research proposal that will be reviewed by a committee to ensure it follows the data protection and ethical standards laid out in the original consent forms. Once the proposal has been approved, researchers will be asked to sign a data agreement transfer before being given access to the dataset via OWEY. Further details can be obtained by emailing e.jones@bmk.ac.uk.

3. Results

3.1. TANOVA and GFP

Fig. 1 displays the timings for the TANOVA and GFP results, and Fig. 2 displays the topographies of the TANOVA results

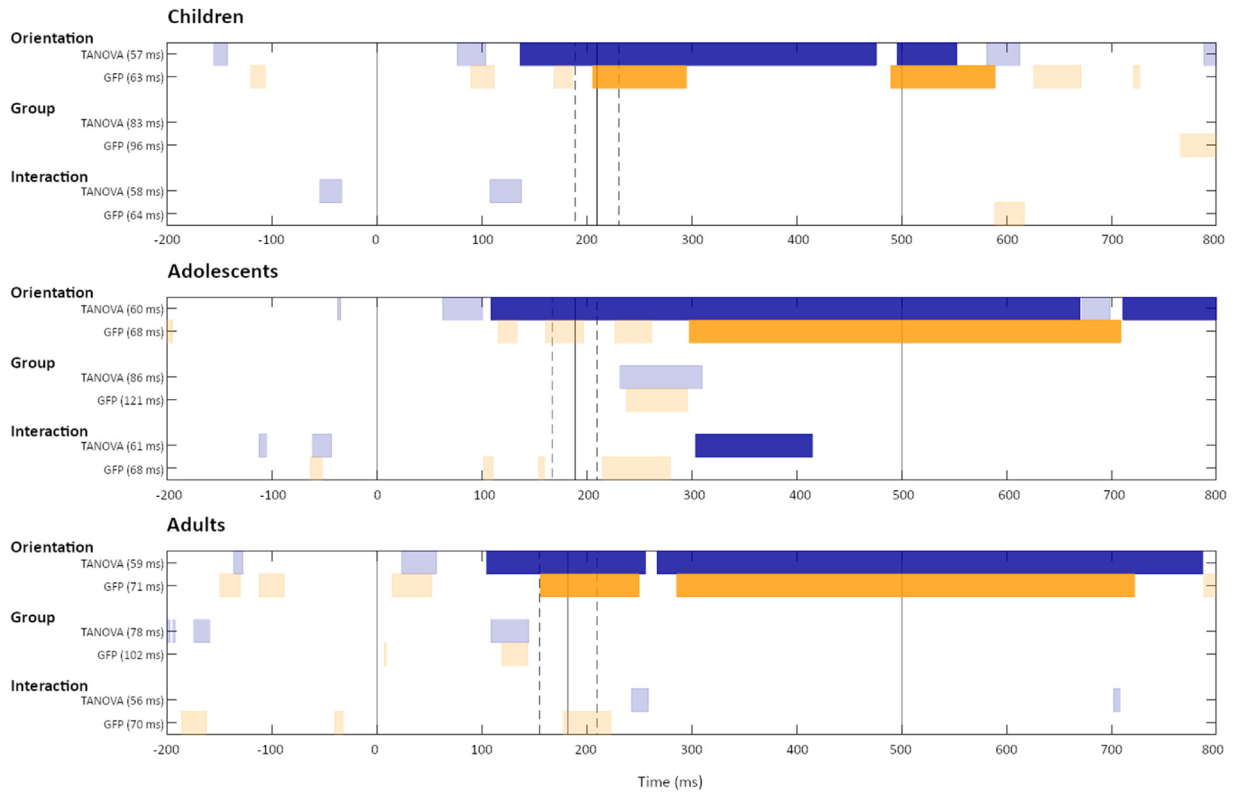


Fig. 1 – TANOVA and GFP results. Dark colored areas reflect time windows reaching significance for the main effects of Orientation, and Group, and interaction effect after duration thresholds have been applied (TANOVA in blue, and GFP in orange, threshold in msec). Light colored areas reflect time windows that did not survive the duration threshold (TANOVA in blue, and GFP in orange). Vertical solid lines represent the mean latency of the N170 at P7 and P8, and vertical dashed lines represent 1 standard deviation for this latency in each age group (for children, mean = 210 msec, std = 21 msec; for adolescents, mean = 189 msec, std = 21 ms; and for adults, mean = 183 msec, std = 27 msec).

from our pre-registered analyses. In children, patterns did not significantly differ by diagnostic group. Confirming the expected condition effects, topographic differences between face orientations occurred from 137 msec after stimulus onset (TANOVA: mean explained variance - $EV_{137-476 \text{ msec}} = 4.50\%$; with a peak for $EV_{272 \text{ msec}} = 7.69\%$, $P = .001$), and briefly around stimulus offset (TANOVA: $EV_{496-554 \text{ msec}} = 2.26\%$; $EV_{511 \text{ msec}} = 2.51\%$, $P = .008$). Orientation differences in map strength emerged during early face processing (GFP upright > inverted: $EV_{206-295 \text{ msec}} = 17.27\%$; $EV_{268 \text{ msec}} = 29.01\%$, $P = .001$), and post stimulus processing (GFP upright < inverted, $EV_{490-589 \text{ msec}} = 8.24\%$; $EV_{535 \text{ msec}} = 10.67\%$, $P = .002$).

Adolescents displayed topographic differences between orientations from 110 msec until the end of the trial (TANOVA: $EV_{109-669 \text{ msec}} = 4.15\%$, with peak $EV_{341 \text{ msec}} = 9.40\%$, $P = .001$, and $EV_{711-800 \text{ msec}} = 1.63\%$, $EV_{767 \text{ msec}} = 1.97\%$, $p = .002$). During later stage face processing, there was an orientation*group interaction within topographies. The autistic group showed a similar response to the neurotypical group to the inverted face but a frontal activation on the topography of the upright face response that resembles the response earlier in the waveform and is not present in the neurotypical group (TANOVA: $EV_{304-415 \text{ msec}} = 1.96\%$, $EV_{322 \text{ msec}} = 3.32\%$, $p = .011$). Simultaneously, there was a prolonged GFP increase to the inverted versus upright faces in both groups (GFP: $EV_{298-709 \text{ msec}} = 8.07\%$, $EV_{554 \text{ msec}} = 14.67\%$, $p = .001$).

In adults, patterns again confirmed expected condition differences but did not significantly differ by diagnostic group. Overall, there were topographic and map strength differences between orientations from about 100 msec after stimulus onset until the end of the trial: during early face processing, upright faces elicited prominent frontal activation and inverted faces posterior activation (TANOVA: $EV_{108-256 \text{ msec}} = 5.43\%$, $EV_{133 \text{ msec}} = 9.96\%$, $p = .001$), and this activation was increased for inverted versus upright faces (GFP: $EV_{156-250 \text{ msec}} = 11.36\%$, $EV_{179 \text{ msec}} = 25.64\%$, $p = .001$). During later processing, topographies between orientations continued to differ with more prominent frontal activation for inverted than upright faces (TANOVA: $EV_{267-787 \text{ msec}} = 5.65\%$, $EV_{431 \text{ msec}} = 10.80\%$, $p = .001$), and increased GFP for inverted versus upright faces (GFP: $EV_{286-722 \text{ msec}} = 18.50\%$, $EV_{445 \text{ msec}} = 27.96\%$, $p = .001$).

3.2. Microstates

Our pre-registered analyses revealed the optimal number of microstates (MS) was 7 in children, 5 in adolescents, and 6 in adults (see SM 9). The results for the microstate analyses in each age group are displayed in Fig. 3 and Table 2.

In children, MS1 occurred very early and late in the waveform (Fig. 3a and b) and varied in duration by group ($p = .001$), representing a return to 'baseline' after stimulus offset for the

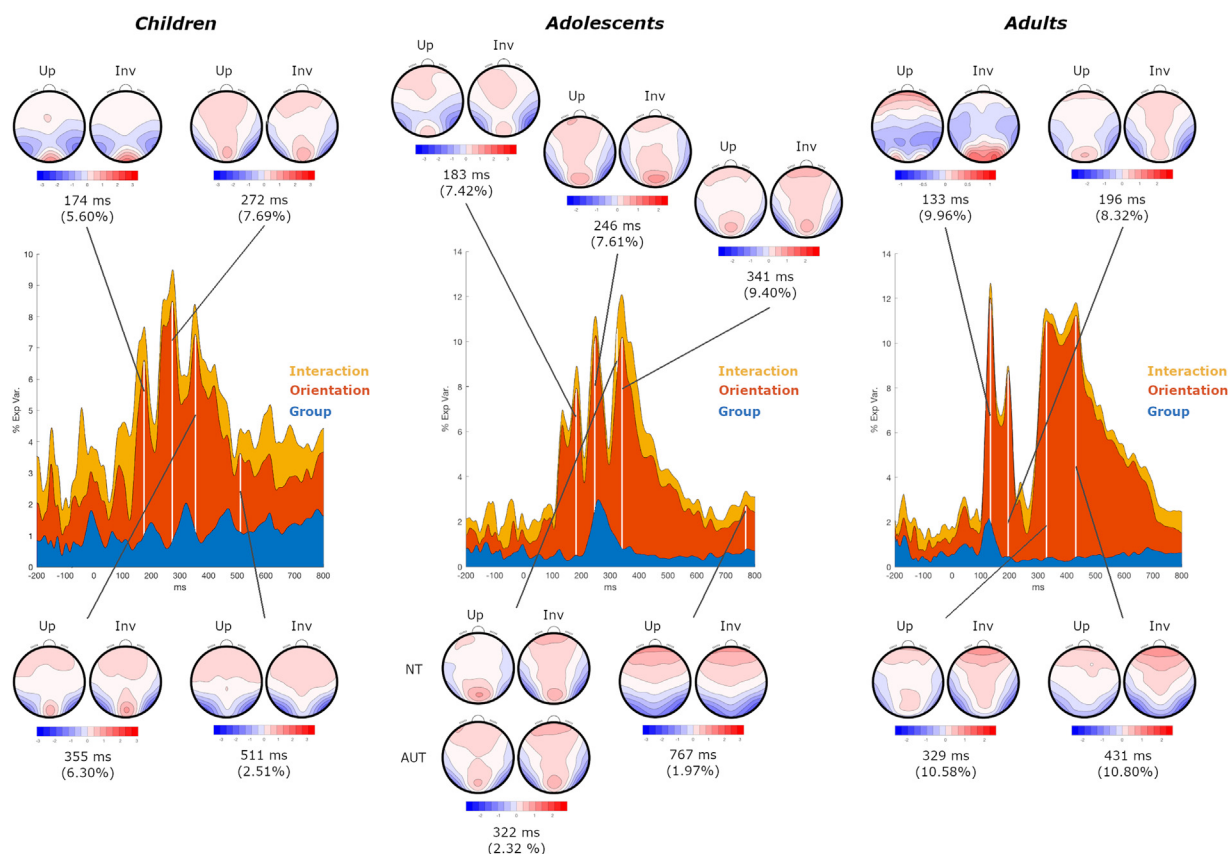


Fig. 2 – Explained variance and ERP mean maps for TANOVA results. Graphs represent the cumulative percentage of explained variance for each group at each time point and percentage explained variance for each effect (blue – Group effect; red – Orientation effect; and yellow – Orientation * Group interaction effect for children (left column), adolescents (middle column), and adults (right column). Topoplots reflect ERP mean maps at peaks in the explained variance within the significant TANOVA time windows in Fig. 1. Note the different scales for explained variance in GFP in the mean ERP maps. NT – neurotypical group; AUT – autism group; Up – upright faces; and Inv – inverted faces.

neurotypical but not autistic group (see SM 10 for post-hoc analyses on the baseline period). MS4 was an occipital positivity that occurred around 100–200 msec after stimulus onset and likely reflects early-stage visual processing. MS4 GFP varied by condition and group ($p = .033$), with higher power for MS4 to inverted than upright faces in the neurotypical group, and the opposite pattern in the autistic group. MS3 then reflected a bilateral negativity that occurs around 200–350 ms (the time-window of the N170 component in children). Mean GFP was greater and of longer duration for inverted faces than upright faces (p 's = .0005) in both diagnostic groups. MS2 and then MS5 occurred towards the end of the stimulus presentation period (c. 350–650 msec) and reflected bilateral negativities, with stronger frontal involvement compared to MS3. MS5 was shorter ($p = .007$) with greater mGFP for inverted versus upright faces ($p = .0005$). There were significant interactions between orientation and group such that there was a shorter duration of MS2 ($p = .048$), and a longer duration of MS5 ($p = .033$) for upright versus inverted faces in the neurotypical group only. After stimulus offset, MS6 was a frontal positivity and occipital negativity that did not significantly vary by group; in the autistic group only, this was followed by MS7, which had strong frontal involvement. Thus, autistic children showed weaker

modulation of several typically occurring microstates across the processing window (MS4, MS2, MS5) by face inversion.

In adolescents, MS1 occurred very early and late in the waveform and did not vary by orientation or group (Fig. 3c and d). MS2 occurred between 100 and 350 msec after stimulus onset and represented a pronounced bilateral posterior negativity. Mean GFP was increased for inverted faces compared to upright faces in MS2 ($p = .010$); this effect was strongest in the neurotypical group (interaction with group $p = .010$). MS4 was a lateral negativity with frontal positivity that started around 350 msec; mGFP ($p = .005$) was increased for inverted versus upright faces. MS3 represented a more pronounced posterior negativity that occurred at around 450–650 msec after stimulus onset; mGFP was larger ($p = .005$) and duration was shorter ($P = .020$) for inverted compared to upright faces. Finally, at the end of the post-stimulus processing period MS5 was a pronounced frontal positivity that did not vary by orientation or group. Thus, autistic adolescents showed weaker modulation of an early-stage typically occurring microstate (MS2) by face inversion than the neurotypical adolescents.

In adults, MS1 occurred very early and late in the waveform and did not vary by orientation or group (Fig. 3e and f). MS2 occurred between 100 and 350 msec after stimulus onset

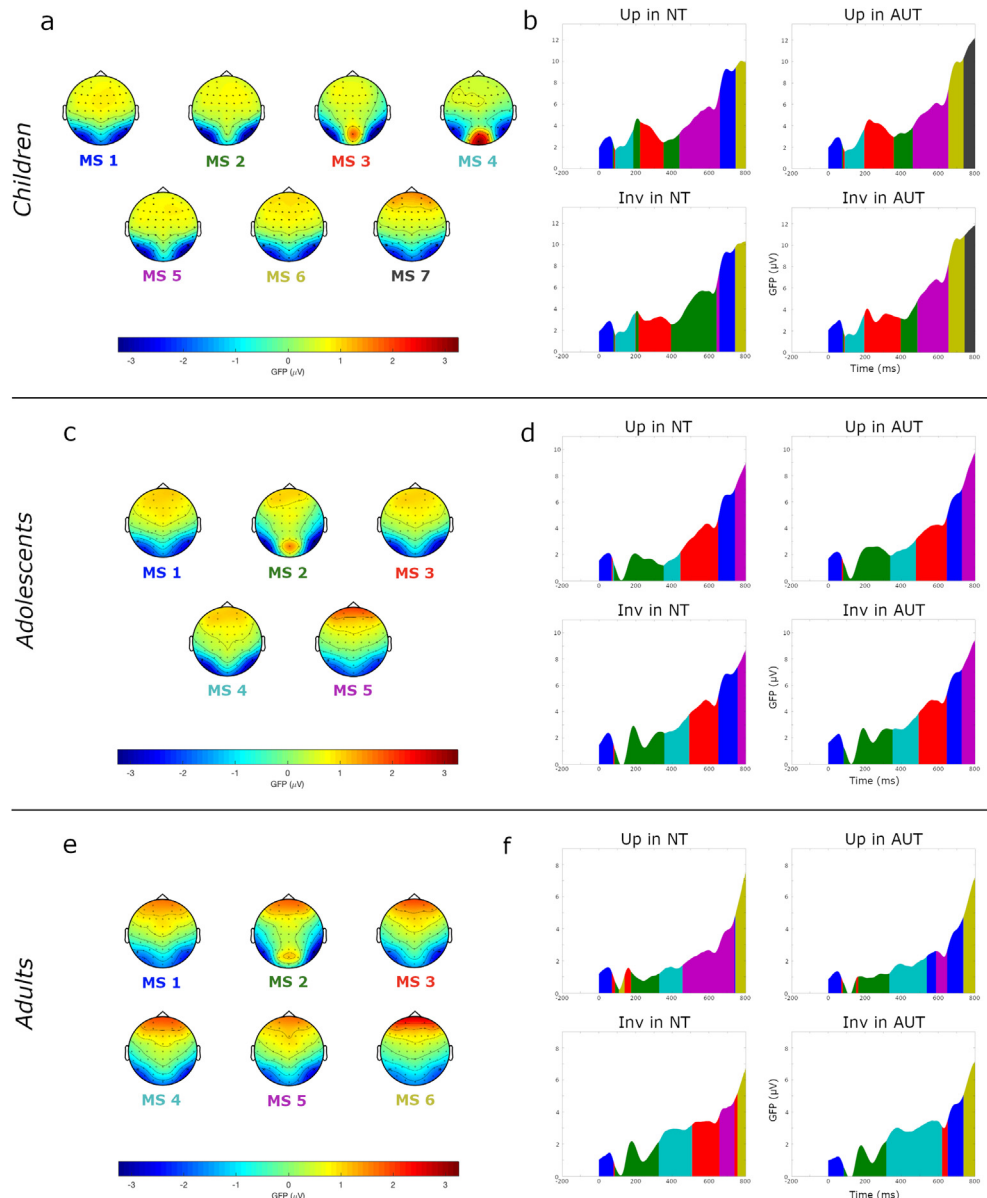


Fig. 3 – Microstates. Results for the microstate analyses displaying the microstate plots (left column) and time during which they are active in different conditions and groups (right column) in children (top row), adolescents (middle row), and adults (bottom row). MS – microstate; NT – neurotypical group; AUT – autism group; Up – upright faces; and Inv – inverted faces.

and shows a pronounced lateral negativity. Mean GFP was increased for inverted versus upright faces ($p = .003$). Duration varied by orientation and group ($p = .026$) with longer duration for inverted than upright faces and a stronger difference between orientations in the neurotypical group than in the autistic group. MS4 was a posterior negativity that started around 320 msec; mGFP was increased ($p = .003$) and showed a longer duration ($p = .003$) for inverted versus upright faces but this did not vary by group. MS3 and MS5 represented more pronounced posterior negativities that occurred most clearly in the autistic and neurotypical groups respectively around 500–750 msec after stimulus onset; MS3 showed increased mGFP for inverted versus upright faces ($p = .003$). MS5 displayed longer duration ($p = .038$) for upright

versus inverted faces. Of note, MS5 (which features a less pronounced fronto-central positivity than MS3) was not present in the autistic group in response to inverted faces, while mGFP was increased for inverted versus upright faces in the neurotypical group. At the end of the epoch, MS6 reflected a pronounced frontal positivity that was longer for upright faces ($p = .031$) but showed greater mGFP for inverted faces ($p = .007$). This varied by group (p 's = .026) such that differences in duration and mGFP were more pronounced for the neurotypical than the autistic group. Thus, autistic adults showed weaker modulation of an early-stage typically-occurring microstate (MS2) by face inversion, and did not show additional recruitment of a later microstates as seen during inverted faces in the neurotypical group (MS5).

Table 2 – FDR-corrected *p*-values for microstate duration and mean Global Field power.

Schedule	MS	Feature	Main effect of Orientation	Main effect of Group	Interaction effect of Orientation* Group
Children	1	Duration	.770	.001** NT = 161 msec AUT = 77 msec	1
		mGFP	1	.104	1
	2	Duration	1	.478	.048* NT up = 131 msec NT inv = 270 msec AUT up = 110 msec AUT inv = 98 msec
		mGFP	.129	.957	.173
	3	Duration	.0005*** Up = 146 msec Inv = 201 msec	.848	1
		mGFP	.0005*** Up = 3.78 μ V Inv = 3.36 μ V	.686	1
	4	Duration	.676	.957	.096
		mGFP	.578	.957	.033* NT up = 3.33 μ V NT inv = 3.53 μ V AUT up = 3.50 μ V AUT inv = 3.22 μ V
	5	Duration	.007** Up = 203 msec Inv = 140 msec	.842	.033* NT up = 220 msec NT inv = 15 msec AUT up = 194 msec AUT inv = 169 msec
		mGFP	.0005*** Up = 5.37 μ V Inv = 6.29 μ V	.842	.096
	6	Duration	1	.842	1
		mGFP	.184	.957	.713
	7	Duration	1	.078	1
		mGFP	1	NaN ^a NT = NA AUT = 11.46 μ V	NaN ^a NT up = NA NT inv = NA AUT up = 11.45 μ V AUT inv = 11.45 μ V
Adolescents	1	Duration	.058	.563	.630
		mGFP	.105	.563	.313
	2	Duration	.500	.590	.639
		mGFP	.010* Up = 1.84 μ V Inv = 2.06 μ V	.270	.010* NT up = 1.55 μ V NT inv = 1.99 μ V AUT up = 2.12 μ V AUT inv = 2.14 μ V
	3	Duration	.020* Up = 190 msec Inv = 162 msec	.563	.630
		mGFP	.005** Up = 3.80 μ V Inv = 4.49 μ V	.563	.795
	4	Duration	.190	.563	.468
		mGFP	.005** Up = 2.11 μ V Inv = 2.30 μ V	.293	.120
	5	Duration	.348	.270	.253
		mGFP	.500	.563	.644
Adults	1	Duration	.204	.492	.633
		mGFP	.461	.491	.633

(continued on next page)

Table 2 – (continued)

Schedule	MS	Feature	Main effect of Orientation	Main effect of Group	Interaction effect of Orientation* Group
	2	Duration	.065	.869	.026* NT up = 175 msec NT inv = 241 msec AUT up = 232 msec AUT inv = 243 msec
		mGFP	.003** Up = .97 μ V Inv = 1.39 μ V	.869	.633
	3	Duration	.714	.965	.495
		mGFP	.003** Up = 1.14 μ V Inv = 3.37 μ V	.869	.994
	4	Duration	.003** Up = 170 msec Inv = 233 msec	.491	.495
		mGFP	.003** Up = 1.70 μ V Inv = 2.96 μ V	.869	.901
	5	Duration	.038* Up = 176 msec Inv = 0 msec	.491	.495
		mGFP	NaN ^a Up = 2.64 μ V Inv = NaN μ V	NaN ^a NT = 3.44 μ V AUT = NaN μ V	NaN ^a NT up = 2.83 μ V NT inv = 4.31 μ V AUT up = 2.48 μ V AUT inv = NaN μ V
	6	Duration	.031* Up = 66 msec Inv = 56 msec	.598	.026* NT up = 88 msec NT inv = 45 msec AUT up = 64 msec AUT inv = 63 msec
		mGFP	.007** Up = 5.71 μ V Inv = 6.12 μ V	.965	.026* NT up = 4.29 μ V NT inv = 5.99 μ V AUT up = 6.07 μ V AUT inv = 6.26 μ V

*P < .05, **P < .01, ***P < .001 MS; microstate.

P-values are Benjamini and Hochberg FDR corrected across the effects within age group (e.g., correcting p-values for the effect of orientation in the children includes all the p-values for duration and mGFP for the 7 microstates: 2 * 7 = 14 p-values).

^a Test for differences in mGFP could not be performed as the microstate is not occurring in one of the conditions or groups.

3.3. Associations between deviance in microstate features and autism symptom severity

Overall, 17% of autistic individuals (37 out of 219) had an overall deviance score higher than 1 standard deviation above the mean of the neurotypical group (none displayed values above 2). None of the correlations between overall deviance scores and symptom severity reached significance after FDR correction (Table 3; p 's \geq .210).

4. Discussion

This study used an integrative spatio-temporal analysis to investigate whether social configural perception in autistic people is associated with the recruitment of alternative brain networks, or differences in strength in the engagement of neurotypical processes. We examined responses to upright and inverted faces; this manipulation is known to disrupt the configural processes that develop with expertise

and may be a particular area of difficulty in autism (Dawson et al., 2005a; Elgar & Campbell, 2001; Teunisse & De Gelder, 2003). Analysis of averaged waveforms on a millisecond-by-millisecond basis showed that modulation of scalp topography by face inversion varied most prominently between diagnostic groups in adolescence. Individual-level dissection of brief temporal brain states further revealed that the autistic group showed a weaker magnitude of activation in the typical neural correlates of early-stage configural processing; this appeared consistent across age. Conversely, qualitatively different scalp profiles between conditions and diagnostic groups occurred during later face processing stages in adults. Taken together, these results suggest that atypical configural processing in autism may begin with weaker early-stage perceptual processing and subsequently involve the development of compensatory mechanisms by use of alternative processing networks in adolescents and adults (Livingston & Happé, 2017). Since variability in overall deviance in microstate features from the neurotypical group did not relate to autistic symptom

Table 3 – Correlations between overall deviance scores and autism symptom severity in the group of autistic individuals (N = 219).

	Correlation	Partial correlation controlling for age
Age (years)	$r = -.17, [-.29, -.04], P = .210$	NA
ADI-R ^a		
Social Total	$r = .03, [-.10, .17], P = .972$	$r = .05, [-.10, .19], P = .972$
Communication Total	$r = .07, [-.07, .21], P = .972$	$r = .04, [-.12, .18], P = .972$
RRB Total	$r = .05, [-.10, .19], P = .972$	$r = .03, [-.11, .15], P = .972$
ADOS ^b		
SA-CSS	$r = 0, [-.15, .15], P = .985$	$r = -.03, [-.19, .13], P = .972$
RRB-CSS	$r = .02, [-.14, .18], P = .985$	$r = -.05, [-.21, .12], P = .972$
CSS Total	$r = 0, [-.14, .17], P = .985$	$r = -.03, [-.20, .13], P = .972$
SRS-2 raw score ^c	$r = .06, [-.07, .20], P = .972$	$r = 0, [-.16, .15], P = .985$

Spearman's rho values and 95% BCa confidence intervals for full and partial correlations controlling for age, with FDR-corrected p-values. Correlations reaching significance are printed in bold.

^a Data were missing for 11 individuals.
^b Data were missing for 37 individuals.
^c Data were missing for 42 individuals.

severity, we propose that this may be a feature of categorical rather than dimensional autism.

4.1. Time-locked neural responses across the scalp

Analyses of the evolving spatial extent and strength of neural responses to faces over the stimulus epoch showed developmental changes in face inversion effects in both diagnostic groups. Inversion effects on topography and GFP occurred at earlier onsets and longer sustained periods with increasing age, consistent with shorter P1 and N170 latencies (Itier and Taylor, 2004a, 2004b; Kuefner et al., 2010) and encoding accuracy in multivariate pattern analyses (Mares et al., 2020). Faster face processing may result from increased expertise and efficiency (Diamond & Carey, 1986; Piepers & Robbins, 2012; Yin, 1969), and changes in brain structure and functioning with increasing age (Cohen Kadosh et al., 2013a; Scherf et al., 2014). Inversion effects for GFP during the N170 time window were consistent with previous N170 amplitude findings with opposite patterns in children (Itier and Taylor, 2004a) and adults (Eimer, 2012). Continued inversion effects in frontal areas during later face processing stages in adolescents and adults may relate to late frontal ERPs associated with increased difficulty of inverted face processing (Itier and Taylor, 2004a). These developmental changes between childhood and adulthood may relate to a shift from featural to configural face processing (Cohen Kadosh et al., 2013b; Passarotti et al., 2007) or refinements of the face processing network with more flexible engagement of different brain regions with increasing age (Cohen Kadosh et al., 2011; Grayson & Fair, 2017).

Face inversion effects furthermore varied with diagnostic group and age. In an analysis comparing strength and topography of neural responses across the whole waveform, adolescents showed the most pronounced diagnostic group differences for scalp topographies. Combined with the microstate analysis in which qualitative changes were most pronounced in adulthood, these results are consistent with a model of adolescence as a time of transition in social brain function. Adolescence is marked by emerging biological

changes, such as re-organization of brain networks (Scherf et al., 2012), and changes in the social environment (Blakemore, 2012; Blakemore & Mills, 2014; Kilford et al., 2016; Scherf et al., 2012). Possibly, autistic adolescents are displaying an emerging altered re-organization of brain networks than their neurotypical peers (Picci & Scherf, 2015) which becomes more prominent during adulthood (as seen in the microstate analysis); alternatively, the social demands of adolescence may be experienced differently by autistic people and they may need to adopt more compensatory strategies in daily life during adolescence than childhood (when social interactions are more scaffolded). Of note, findings from previous studies in the LEAP cohort focusing on brain anatomy (Zabihi et al., 2019), brain functioning during resting state (Garcés et al., 2022; Holiga, et al., 2018) and social cognition (reward processing (Baumeister et al., 2020), and animated shapes task (Moessnang et al., 2020)), and eye-tracking during social processing (Del Bianco et al., 2020) commonly show interactions between age and diagnostic group, with some domains showing atypicality in autism increasing with age (Del Bianco et al., 2020; Garcés et al., 2022; Holiga, et al., 2018), some stable (Baumeister et al., 2020; Crawley et al., 2020; Holiga, et al., 2018; Zabihi et al., 2019), and others decreasing (Moessnang et al., 2020). In showing the emergence of brain state differences in adolescence, our findings are most consistent with previous analysis of resting state (Garcés et al., 2022; Holiga, et al., 2018) and visual social attention (Del Bianco et al., 2020) which may reflect a coherent picture of general age-related increases in temporal fluctuations in co-activated brain networks underpinning social attention. Future cross-modality analysis could address this question.

4.2. Coherent spatio-temporal states

Microstate analysis (where the waveform is chunked into periods with a common topography that likely reflect the activation of particular brain networks) revealed more nuanced diagnostic group differences that were present in each developmental stage. During early-stage perceptual processing, autistic children exhibited stronger responses to

upright than inverted faces, whereas neurotypical children displayed the opposite pattern. These early responses may reflect atypical visual sensory processing in autistic children. One theory of autism suggests perceptual sensory atypicalities during early development underlie the early emergence of behavioural symptoms (Hamilton & Pelphrey, 2018; Jones et al., 2018; Thye et al., 2018). Possibly, early perceptual hypersensitivity leads to stronger neural responses to upright faces (as reflected in P1 amplitude (Jones et al., 2018)) and correspondingly increased GFP for a microstate map with a central-occipital topography. However, prior studies have revealed mixed findings for the P1 ERP component during early-stage perceptual processing. One study reported increased P1 amplitude for inverted compared to upright faces in neurotypical 9- to 17-year-olds as in the current study. In contrast to the current findings, that study reported no difference between orientations in the autistic peers (Hileman et al., 2011). Another study found an inversion effect with larger P1 amplitude for inverted than upright faces in both diagnostic groups (8-14-year-olds (McPartland et al., 2011)), while others found no inversion nor diagnostic effects for P1 amplitude (in 8–13-year-olds (Tye et al., 2013) and 14-year-olds (Naumann et al., 2018)). These discrepancies between findings may arise from the relatively limited age range, sample size, variability in experimental design (e.g., frequency, randomisation, and intervals between the presentation of stimuli) and focus on posterior areas rather than whole scalp spatio-temporal states as in the current study. It has been suggested the P1 component may be more sensitive to face inversion effects during childhood, whereas the N170 component may be more sensitive to face inversion during adolescence and adulthood (Hileman et al., 2011). This would be consistent with our findings of effects during early-stage perceptual processing in the younger age group only.

Consistent with previous work on the N170 (McPartland et al., 2004, 2011), both autistic adolescents and adults displayed attenuated inversion effects in the time-window associated with early-stage face processing. This is consistent with previous findings of attenuated inversion effects on N170 latency and amplitude in 8 to 14-year-old autistic adolescents and adults compared to neurotypical peers (McPartland et al., 2004, 2011). Reduced inversion effects in autism may result from atypical specialization towards faces. Children exhibit overall increased fMRI-assessed activation towards faces than adolescents and adults, but face inversion effects become more refined and stronger with increasing age and expertise (Passarotti et al., 2007). Atypical specialization towards faces during adolescence may result in attenuated face inversion effects and quantitative differences between diagnostic groups as observed here.

During later stage face processing, we found differences between autistic and neurotypical groups in active microstate maps that were most prominent in adults. In the adult group, scalp activity in frontal and right parietal-occipital areas was increased for inverted compared to upright faces in the neurotypical group, while this scalp activity did not occur during inverted faces in the autistic group. It is possible that this pattern of changes between different age groups reflects the development of compensatory processes with increased involvement of the prefrontal cortex and use of alternative

processing pathways to keep up with changing processing demands (Johnson, 2012; Johnson et al., 2015; Livingston & Happé, 2017) (also see SM 11 and 12 for post-hoc analyses examining similarities and dissimilarities between microstates).

Microstate maps during post stimulus processing differed between autistic and neurotypical individuals in childhood and adulthood, but not adolescence. Autistic children displayed a specific pattern including a frontal positivity (not modulated by inversion) that did not occur in neurotypical children. Possibly, the frontal positivity in autistic children reflects inefficient suppression of sensory processing after stimulus disappearance due to weaker neural inhibition (Millin et al., 2018; Schallmo et al., 2020). Autistic adults returned to the baseline whereas neurotypical adults did not.

Further normative modelling analyses revealed that overall deviation in microstate strength and duration from the neurotypical group did not relate to symptom severity (see also (Del Bianco et al., 2020)). The neural mechanisms that underpin autism emergence may actually be separable from the mechanisms that underpin variability in symptomatology within an autistic group (Constantino et al., 2021). Autistic monozygotic twins exhibited weaker twin–twin associations in individual symptomatology than non-autistic twins, suggesting that the inherited liabilities that underpin the categorical presence of an autism diagnosis do not underpin variation in symptomatology once the diagnostic threshold is reached (Castelbaum et al., 2020). Non-shared environmental factors may play a significant role once canalization is impacted by an altered developmental trajectory (Constantino et al., 2021).

Limitations to this study include: a) the lack of nonsocial stimuli, making interpretations on the specificity to social processing limited. b) A slightly higher number of clean trials was included for inverted compared to upright faces (mean difference around 3). However, control analyses suggested this pattern was consistent across individuals and numbers of clean trials were not related to condition or group differences in microstate features or overall deviance scores (SM 13). c) Developmental trends in configural processing from childhood to adulthood may not have been detected by our analysis approach using separate recruited age groups. Supplemental post-hoc analyses suggest higher similarity across spatio-temporal states in adolescents and adults compared to children which could indicate greater developmental changes during childhood and adolescence than thereafter. Further, we observed only a weak correlation in the adolescents with increasing face inversion effects for GFP in MS 2 with increasing age. We found no associations between age and overall deviance scores in MS features (linear, quadratic, or cubic, see SM 14). d) Associated conditions such as depression and anxiety could impact face processing and confound results. However, depression and anxiety measures were consistent across age groups (SM 15), and these and other clinical measures were not significantly associated with overall deviance in microstate features, suggesting differences in clinical measures between age groups were unlikely to explain diagnostic and age differences in the observed microstate patterns. e) Although we implemented rigorous artifact-detection procedures, it remains possible

that subthreshold artefacts could contribute to the patterns observed in the microstate analyses; further, different artifact patterns could relate to variation in emotional states that could also be reflected in analyzed microstates. Current findings will benefit from replication in independent cohorts with additional measures of psychophysiological variables (such as heart rate or muscle tension) for external validation and extension.

5. Conclusions

In this study, autistic people showed differences in the processing strength of neurotypical networks during early-stage processing across the lifespan, and use of alternative networks during later-stage configural processing during adolescence and adulthood. Future longitudinal research from infancy to adulthood could reveal whether there are causal relationships between the observed early sensory atypicalities and later-emerging recruitment of additional brain networks, and whether the latter may serve a compensatory function or rather compound earlier difficulties. Active paradigms to tax the face processing system to a greater extent (Livingston & Happé, 2017; Picci & Scherf, 2015; Scherf et al., 2012) and source localization methods could further elucidate our understanding of primary atypicalities and compensatory processes in autism. Finally, the developmental changes observed in the present study are important to consider when generating biomarkers, whose relevance may vary with developmental stage.

Credit author statement

Author statements are as follows: *Rianne Haartsen*: Conceptualization, Methodology, Formal analysis, Writing – Original Draft/ Review & Editing, Visualization, Project administration. *Luke Mason*: Conceptualization, Software, Formal analysis, Data curation, Writing – Review & Editing. *Pilar Garcés*: Software, Formal analysis, Data curation, Writing – Review & Editing. *Anna Gui*: Software, Writing – Review & Editing. *Tony Charman*: Conceptualization, Data curation, Writing – Review & Editing. *Julian Tillmann*: Investigation, Data curation. *Mark H. Johnson*: Conceptualization, Methodology, Writing – Review & Editing, Funding acquisition. *Jan Buitelaar*: Conceptualization, Methodology, Funding acquisition. *Eva Loth*: Conceptualization, Methodology, Funding acquisition. *Declan Murphy*: Conceptualization, Methodology, Funding acquisition. *Emily J.H. Jones*: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project administration, Funding acquisition.

Open practices

The study in this article earned a Preregistered badge for transparent practices. Materials and data for the study are available at https://github.com/RianneHaartsen/LEAPspatio-temporal_states.git.

Declaration of competing interest

PG is an employee at F. Hoffmann-La Roche Ltd TC has served as a paid consultant to F. Hoffmann-La Roche Ltd and Servier; and has received royalties from Sage Publications and Guilford Publications. JT is an employee at F. Hoffmann-La Roche Ltd JB has been in the past 3 years a consultant to/member of advisory board of/and/or speaker for Janssen Cilag BV, Eli Lilly, Takeda/Shire, Roche, Novartis, Medice, Angelini, 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, and royalties.

For the individuals in the EU-AIMS LEAP group: Tobias Banaschewski served in an advisory or consultancy role for ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker's fee by Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships. Sven Bölte receives royalties from Hogrefe Publishers. He has in the last 3 years acted as a consultant or lecturer for Medice and Roche. Daniel Brandeis served as an unpaid scientific advisor for an EU-funded neurofeedback trial unrelated to the present work. Daisy Crawley has served as a paid consultant to F. Hoffmann-La Roche Ltd Joerg Hipp is an employee at F. Hoffmann-La Roche LTD. Andreas Meyer-Lindenberg has received consultant fees and travel expenses from Alexza Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Defined Health, Decision Resources, Desitin Arzneimittel, Elsevier, F. Hoffmann-La Roche, Gerson Lehrman Group, Grupo Ferrer, Les Laboratoires Servier, Lilly Deutschland, Lundbeck Foundation, Outcome Sciences, Outcome Europe, PriceSpective, and Roche Pharma; and has received speaker's fees from Abbott, Astra-Zeneca, BASF, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Pfizer Pharma, and Servier Deutschland. Antonio M. Persico has published textbooks with the S.E.U. editing company, and is participating in a pharmaceutical trial with Servier. Antonia San Jose Caceres currently works as a consultant for Servier and has, in the past, worked also for Roche as a consultant. The current work is unrelated to the grants and relations mentioned above.

All other authors and other members of the EU-AIMS LEAP group report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

We would like to thank the EU-AIMS (European Autism Interventions) Longitudinal European Autism Project (LEAP) group for the data collection, the quality control, and the preprocessing of the data, and all the participants and their families to participate in the study. The primary contact of the EU-AIMS LEAP group is Bethany Oakley.

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This work was supported by EU-AIMS (European Autism Interventions), which received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no. 115300, the resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (grant FP7/2007–2013), from the European Federation of Pharmaceutical Industries and Associations companies' in-kind contributions, and from Autism Speaks as well as AIMS-2-TRIALS which received support from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777394. This joint undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and AUTISM SPEAKS, Autistica, SFARI. Disclaimer: The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. Any views expressed are those of the author(s) and not necessarily those of the funders.

This work has further been supported by the UK Medical Research Council [grant number G0701484 & MR/K021389/1](M/J/E), and Economic and Social Research Council [grant number ES/R009368/1](E), and the Horizon 2020 programme of the European Union [CANDY project, grant number 847818](J/B).

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2022.06.010>.

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