Tug-of-peace: Visual Rivalry and Atypical Visual Motion Processing in MECP2 Duplication Syndrome of Autism

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ABBREVIATIONS

ASD: autism spectrum disorder

CA: cross angle

EMs: eye movements

LM: littermate

MECP2: methyl CpG binding protein 2

MECP2-ds: MECP2 duplication syndrome

OKN: optokinetic nystagmus

V1: primary visual cortex (mouse)

WSR: Wilcoxon signed rank two-sided test

ABSTRACT

Extracting common patterns of neural circuit computations in autism spectrum and pinning them as a cause of specific core traits of autism is the first step towards identifying cell- and circuit-level targets for effective clinical intervention. Studies in human subjects with autism have identified functional links and common anatomical substrates between core restricted behavioral repertoire, cognitive rigidity, and over-stability of visual percepts during visual rivalry. To be able to study these processes with single-cell precision and exhaustive neuronal population coverage, we developed the visual bi-stable perception task for mice. Our task is based on plaid patterns consisting of two transparent gratings drifting at an angle of 120° relative to each other. This results in spontaneous reversals of the perception between local component motion (motion of the plaid perceived as two separate moving grating components) and integrated global pattern motion (motion of the plaid perceived as a fused moving texture). This robust paradigm does not depend on the explicit report of the mouse, as the direction of the optokinetic nystagmus (OKN, rapid eye movements driven by either pattern or component motion) is used to infer the dominant percept. Using this paradigm, we found that the rate of perceptual reversals between global and local motion interpretations of the stimulus is reduced in MECP2 duplication mouse model of autism. Moreover, the stability of local motion percepts is greatly increased in MECP2 duplication mice at the expense of global motion percepts. Thus, our model reproduces a subclass of core features in human autism (reduced rate of visual rivalry and atypical perception of visual motion). This further offers a well-controlled approach for dissecting neuronal circuits underlying these core features if combined with mesoscale 2-photon imaging and optogenetic manipulation of neuronal circuits.

INTRODUCTION

Autism is a group of neurodevelopmental disorders that have been traditionally conceptualized as impairments of high-level cognitive functions leading to deficient social communication and repetitive restricted behavioral repertoire. These high-level features of the condition are accompanied by a distinct perceptual style and sensory picture of the world, focusing on the fine details of the environment rather than global integrated scenes (Robertson and Baron-Cohen, 2017; Van der Hallen et al., 2019). Altered sensation and atypical sensory perception are experienced by over 90% of individuals with autism, appear before social deficits become evident and affect every sensory modality (Simmons et al., 2009; Grzadzinski et al., 2013; Roberstson and Simmons, 2015; Robertson and Baron-Cohen, 2017; Van der Hallen et al., 2019). A recent version of DSM (2013) now lists atypical sensory perception as a core diagnostic feature of autism, together with social communication deficits and restricted repetitive behaviors (American Psychiatric Association, 2013). Another relevant feature of autism is the heterogeneity of expression of core traits and remarkable behavioral diversity across individuals, affecting all aspects of interaction with physical and social environments (Baron-Cohen et al., 2009; Bolton et al., 2020; Lawson et al., 2015; Shafritz et al., 2008; Robertson & Baron-Cohen, 2017, Van der Hallen et al, 2019, Uddin, 2021). Thus, to explain the autistic brain, one must consider what it is in the brain that provides common ground for apparently disparate phenomena such as social communication, cognitive rigidity and atypical visual perception. What can account for the phenotypical diversity of the condition and at the same time ensure the presence of its core features in most affected individuals? Importantly, it becomes critical to develop behavioral paradigms and approaches that can reliably measure these putative common ground processes and be applied in mouse models of autism with the long-term goal of studying the circuit basis of the condition and providing the pipeline for fast drug candidate screening.

Here we apply a bi-stable visual perception paradigm to study the mouse model of *MECP2* duplication syndrome (Collins et al., 2004; Ramocki et al., 2010), a syndromic ASD caused by genomic duplication of methyl-CpG-binding protein 2 (Ramocki et al., 2010) that exhibits 100% penetrance in males. In humans MECP2 duplication syndrome shows all core features of idiopathic autism (Ta et al., 2022; Peters et al., 2013). MECP2 duplication mice carry a number of core autism features including repetitive stereotyped behaviors, altered vocalizations, increased anxiety, motor savant phenotype and over-reliable visual responses (Collins et al., 2004; Samaco et al., 2012; Jiang et al., 2013; Sztainberg et al., 2015; Zhang et al., 2017; Zhou et al., 2019; Ash et al., 2017, 2021, 2022).

Bistable visual perception (visual rivalry) paradigms are a logical choice for the study of autistic brains. First, the dynamics of visual rivalry is altered in idiopathic human autism, with subjects showing

decreased rate of perceptual reversals (Robertson et al., 2013, Spiegel et al., 2019). Second, visual rivalry is a distributed computation involving both low-level sensory cortical areas and high-level association areas, such as secondary motor cortex and prefrontal cortex (Kleinschmidt et al, 1999; Leopolod & Logothetis, 1996, 1999; Knapen et al., 2011; Lumer et al., 1998, 1999). Thus, its dynamics is based on both stimulus representation subnetworks in early visual cortex and visuomotor areas, and on high-level cognition-related non-sensory subnetworks of higher order cortical areas. As a result, it can be a good candidate method to evaluate both 1) low-level sensory processing dysfunction that involves the primary sensory cortex, and 2) high-level dysfunction like cognitive rigidity and restricted social communication, which rely on distributed computations in non-sensory association frontal and prefrontal cortical areas. Indeed, in human autism slower rate of bistable alternations was shown to share an anatomical substrate with general cognitive rigidity, and binocular rivalry phenotype predicts the severity of social phenotype and the diagnosis of ASD (Watanabe et al., 2019; Spiegel et al., 2019). Importantly, it was suggested that the dynamics of the visual rivalry is dependent on brain-wide excitatory-inhibitory balance - a process that is also proposed to be altered in autism, leading to the expression of core traits of ASD (reviewed in Zhao et al., 2022). Finally, our visual rivalry paradigm utilizes a bistable moving plaid, in which the subject's perception switches between the local motion-based, 'transparent' interpretation of the stimulus versus the global motion-based, 'coherent' interpretation. Thus, our paradigm also offers the additional advantage of exploring another core trait of autistic brains: atypical processing of visual motion and detail-oriented sensory processing style (reviewed in van der Hallen, 2019, Robertson & Baron-Cohen, 2017).

Using our paradigm, we found that MECP2-duplication mice recapitulate the phenotype found in a subset of subjects with idiopathic autism. Specifically, compared to unaffected littermates, MECP2-duplication mice display reduced rate of perceptual reversals during visual rivalry and strongly prefer to focus on local moving cues rather than the integrated percept of coherent global motion.

EXPERIMENTAL PROCEDURES

Animals. All experiments and animal procedures were performed in accordance with guidelines of the National Institutes of Health for the care and use of laboratory animals and were approved by the Brigham and Women's Hospital (BWH) Institution Animal Care and Use Committee. We used mice of two different backgrounds: mixed background (C57*FVB)-MECP2 duplication mice and 129-MECP2 duplication mice (Ash et al., 2022). Mixed background mice were produced by crossing C57Bl6J mice to FVB MECP2-duplication line (Tg1, Collins et al., 2004) mice to generate F1 C57;FVB MECP2-duplication mice and non-transgenic littermate controls. Experiments were performed in 4-6-month-old animals. Cohorts were balanced in terms of animal sex (129 background: 3 male +3 female pairs; C57*FVB background: 4 male + 4 female pairs)). The experimenters were blind to animal genotype during experiments and analysis.

Surgery. All procedures were performed according to animal welfare guidelines authorized by the Brigham and Women's Hospital IACUC committee. Mice were anesthetized with 1.5% isoflurane. The mouse head was fixed in a stereotactic stage (Kopf Instruments), and eyes were protected with a thin layer of artificial tears ointment (GenTeal). The scalp was shaved and disinfected by applying consecutive swabs of povidone-iodine solution and 70% ethanol, and then the scalp was resected. A custom-made titanium headplate was attached to the skull with dental acrylic (Lang Dental), making sure to prevent occlusion of mouse's visual field.

Visual stimulation. Visual stimuli were generated in MATLAB and displayed using Psychtoolbox (Brainard, 1997). The stimuli were presented on two LCD monitors with a 60 Hz frame rate, positioned ~10 cm in front of the right eye and covering 180 degrees of right visual field of the mouse. The screens were gamma-corrected, and the mean luminance level was photopic at 80 cd/m^2. Visual stimuli consisted of drifting square-wave gratings and plaids of 120 degrees cross angle composed of the grating stimuli components. The gratings had the following parameters: temporal frequency – 1.7 Hz, spatial frequency 0.06 cycles/°, spatial duty cycle 0.8 (white bar = 60%, black bar = 40%). These parameters were selected to accommodate average spatial frequency and velocity preferences in visually-responsive neurons across mouse visual cortical hierarchy (Ohki et al., 2005; Niell and Stryker, 2008; Gao et al., 2010; de Vries et al., 2019). Additive plaid patterns were constructed by summing up component gratings of 50% contrast (Smith et al., 2005). Each instance of plaid or grating movie was preceded by a gray isoluminant screen for 5 minutes. We kept mean luminance constant throughout both the background and the stimulation periods.

Optokinetic nystagmus. We recorded optokinetic eye movements elicited during observation of drifting gratings and plaids in 13 head-posted mouse MEPC2-duplication – littermate pairs. 7 pairs were

C57*FVB mixed background mice and 6 pairs were 129 background mice. The stimulus was presented on two screens covering ~ 180 degrees of visual field of the mouse. The center of each screen was located at 10 cm from the mouse (Fig.1). We used an infrared camera (model MAKO U-29, Allied Vision Technologies) and a hot mirror to record the movements of the right eye at 300 Hz. We analyzed 5 to 15-min-long movies off-line with Deep Lab Cut toolbox (Mathis et al., 2018) to detect the pupil and extract its diameter and position. Optokinetic eye movement (EM) is composed of smooth pursuit following the motion of salient features in the stimulus, followed by a rapid saccade in the direction opposite to the direction of the global stimulus drift to stabilize the image on the retina (Cahill & Nathans, 2008). This pattern of movements - slow pursuit phase plus rapid saccade phase - repeats as long as the stimulus (drifting grating or plaid) is present and is attended by the animal. We analyzed both vertical and horizontal EM components to classify plaid-induced OKN as aligned with local motion percept vs aligned with global motion percept. Periods containing eye-blink artifacts and mouse grooming that were identified by the Deep Lab Cut algorithm as having a probability of being a pupil below 0.95 were removed from the analysis. We applied a linear fit to the slow pursuit phase of each EM and calculated the eye movement amplitude from each fit (Fig.1C). The direction of each EM was determined by comparing the amplitude of horizontal and vertical saccade projections of EM components. We then histogrammed the directions of EMs around 0°, which corresponds to the horizontal direction (the direction of the drift of the global stimulus; see Fig.1). For the plaid-induced OKN, we classified each EM as component or pattern aligned. For this, we first determined the horizontal direction and the average width of the distribution of EM angles evoked by horizontally drifting gratings. We used 1 standard deviation (SD) from the mean as the threshold for pattern-aligned EM angles. Thus, any EM whose angle exceeded this threshold was classified as component aligned, while EMs with angles inside the [-SD, +SD] interval are classed as pattern motion-aligned (Fig.1E & G).

To study the dynamics of OKN alternations between following the global pattern motion or following component motion we analyzed 2-6 15 minute movies of OKN induced by the plaid stimulus moving in the temporonasal (T->N) direction. We extracted the periods of the stable OKN (at least two saccade–pursuit pairs, occurring without break between the pairs; e.g., saccadic movement is followed by the pursuit phase of the next pair). To identify periods without the OKN (breaks), we first examined the distribution of lengths of pursuits of individual nystagmoid eye movements. Periods of eye drift without return saccades exceeding the 95th percentile of this distribution of lengths were considered as breaks in the OKN. During breaks mouse either was not attending to the stimulus, and thus experienced no OKN, closed eyes or experienced eye blinks and grooming bouts. Periods of OKN between breaks (OKN epochs) had to contain at least two consecutive saccade-pursuit pairs to be accepted for the

analysis of perceptual reversals. Each movie had to contain at least 3 minutes of OKN to be accepted for the analysis.

We determined the following parameters:

1. Perceptual reversal rate in each individual OKN epoch. The rates were averaged over epochs and over movies to obtain a median value per animal.

2. The probability to experience a switch within 1 minute of the beginning of bistable OKN.

3. The durations of “coherent” and “transparent” OKN periods in each animal. Durations were averaged over movies and over animals to obtain one median value per animal.

4. Fraction of eye movements aligned with pattern and component motion across all movies of a specific animal.

5. Fraction of OKN epochs with no observed perceptual reversals (non-reversal OKN epochs).

Statistical tests. Comparison of the per animal reversal rates, dominance period durations and component/pattern motion ratio we used paired Wilcoxon signed rank test comparing MECP-duplication mouse to his littermate. Statistics was computed across animals. The distributions of switch rates per OKN epoch, and durations of dominance periods were fitted with gamma distribution function. To accept or reject the fit for the gamma distribution fitting of dominance duration periods and of switch rates, we used a χ^2 test.

RESULTS

Report-free bi-stable perception paradigm. A reliable way to infer the perceptual state when a bistable visual motion-based stimulus is presented is to measure the direction of the optokinetic nystagmus elicited by the different directions of drift generated by the rivaling stimuli (Enoksson, 1963; Fox et al., 1975; Logothetis and Schall, 1990; Wei and Sun, 1998; Watanabe, 1999; Naber et al., 2011; Leopold et al., 1995). Unambiguous fully coherent full-field moving visual stimuli, such as dot fields, coherently moving natural scenes and high-contrast drifting gratings induce optokinetic nystagmus (OKN) reflex in vertebrate animals such as mammals, birds and fish (Cahill & Nathans, 2008). The OKN is required for the stabilization of retinal input under the conditions of a drifting visual environment. OKN eye movements consist of a slow pursuit in the direction of the stimulus followed by a fast saccade returning the eye to its initial position. OKN has been extensively validated as a reliable indicator of the dominant percept in experimental designs involving ambiguous stimuli, such as binocular rivalry (Fox et al., 1975; Logothetis and Schall, 1990; Wei and Sun, 1998; Watanabe, 1999; Naber et al., 2011). Under ambiguous visual conditions, the direction of pursuit during slow phases of OKN is aligned with the direction of motion of the dominant percept (Palagina et al., 2017).

We have previously shown that mice can exhibit visual bistable perception when exposed to a moving transparent additive plaid stimulus covering ~270 degrees of the visual field (Palagina et al., 2017). The symmetric transparent additive plaid we used is composed of two transparent gratings of equal contrast and velocity moving at an angle to each other. Under the range of bi-stability promoting stimulus properties, the subjective perception of this stimulus alternates between the “transparent” interpretation, where two full-field component gratings slide on top of each other, and the “coherent” interpretation, where a fused pattern drifting in a direction half-way between the directions of component gratings is seen (Adelson and Movshon, 1982; Moreno-Bote et al., 2010). Large cross-angle between the grating components of the plaid, “transparency-promoting” intersection luminance values of the dark bars (equal to the sum of the luminances of the components), high component grating velocity, asymmetric intersections (occurring when the cross angle between component gratings is above or below 90 degrees) promote a transparent interpretation (Movshon et al., 1985; Moreno-Bote et al., 2010). Symmetry in component gratings’ contrast, spatial frequency and velocity favor the coherent percept (Adelson and Movshon, 1982; Yo and Demer, 1992). In the previous work, using stimuli fulfilling these criteria (60 or 120 degrees cross-angle between components, contrast normalization, drift velocity 2 cycles/degree of visual field, spatial frequency 0.05 cycles/degree and symmetry in the properties of component gratings) we were able to elicit bistable OKN in C57 wild-type mice. These properties were tailored to be optimal for mouse area V1 (Ohki et al., 2005; Niell and Stryker, 2008; Gao et al., 2010). In the present study we modified the stimulus keeping in mind the necessity to drive as large a

proportion of neurons as possible in different visual areas, which have varying preferences for the drift velocity and spatial frequency of the stimuli. To do this, we changed the duty cycle of the stimuli to 0.8 and drift velocity to 1.7 cycles/degree, while keeping the components symmetric (spatial frequency 0.06 cycles/degree) and contrast normalized to achieve transparency-promoting luminance of the intersections. We used 120° CA (cross-angle) plaids as this was shown to induce an equidominant state (where the observer spends nearly equal time on transparent and coherent percepts) in both human observers (Moreno-Bote et al., 2010) and mice (Palagina et al., 2017). We also reduced the coverage of the visual field to 180 degrees of the right eye's visual field, as this was shown to induce reliable OKN in mice (Cahill & Nathans, 2008) while allowing us to combine the behavioral task with 2-photon imaging or electrophysiological recordings in future experimental work.

Under the updated conditions we show that both 129-background and C57*FVB mixed background mice show bi-stable optokinetic nystagmus, aligned either with the direction of component gratings or the direction of coherent pattern motion [Fig.1], similarly to what we observed in C57 mice previously (Palagina et al., 2017). We observed no difference in the rate of generation of OKN between littermates and MECP2 duplication mice or in the magnitude of eye movements (eye movement amplitude (arbitrary units): littermates, 7.43±0.5, MECP2-ds, 6.33±0.51; $p = 0.308$, WSR; OKN rate (Hz): littermates, 9.7±1.7, MECP2-ds, 7±0.75, $p = 0.216$, WSR). There was no difference between 129 background animals and C57*FVB background animals in terms of OKN properties and dynamics of visual rivalry, thus these two groups were pooled together. Experimental setup is shown in Figure 1. Stimuli were presented on two contiguous screens covering 180° of the mouse contralateral visual field, and pupil position was recorded with the help of hot mirror and an infrared camera. Figure 1D shows an example of OKN elicited by a vertically oriented grating moving from the temporal to nasal direction. In this case the eye movements elicited by the stimulus are aligned with the horizontal direction (0°, taken along the temporal->nasal direction). In contrast to the unambiguous horizontally drifting gratings, OKN eye movements elicited by a 120° CA plaid show a tri-modal distribution of eye movement directions: a considerable fraction of eye movements is aligned with one of the two component grating directions in addition to the horizontally aligned OKN that corresponds to the fused pattern motion percept [Fig.1D]. This strongly suggests that the perception of the mouse alternates between pattern and component motion for our stimuli in the recorded cohort of mice.

MECP2 duplication mice show reduced rate and probability of perceptual reversals. We next examined the dynamics of bi-stable reversals between 'coherent' interpretation OKN (mouse tracking global pattern; OKN eye movements aligned with the global pattern direction) and 'transparent' interpretation OKN (mouse tracking the component gratings; OKN eye movements aligned with the direction of drift of either component grating) in MECP2- duplication animals versus unaffected

littermates. Both MECP2-duplication animals and littermates displayed bi-stable reversals. However, in MECP2-duplication syndrome mice the rate of reversals was reduced compared to their normal littermate pairs [Fig.2, A-C], and MECP2 duplication animals displayed more frequent OKN epochs where only a single interpretation of the stimulus was consistently followed and no perceptual reversals occurred [Fig.2D; non-reversal OKN fraction: littermates, mean±sem: 0.33±0.055, median: 0.374; MECP2-ds, mean±sem: 0.555±0.04, median: 0.54; p = 0.0027, WRS]. Consequently, the fraction of OKN epochs showing bi-stable reversals was reduced in MECP2 duplication animals. Littermates showed on average 2.8 reversals per one minute of OKN movie (mean±sem: 2.8±0.58, median: 2.05), while MECP2-ds mice showed 1.9 reversals per minute (mean±sem: 1.895±0.325, median: 1.485), a significant reduction in bi-stable reversal rate (p = 0.0134, WSR, n=13 pairs) [Fig.2A, B]. The probability to observe a switch after 1 minute of uninterrupted plaid-driven OKN was consequently reduced in MECP2- duplication mice (littermates, mean±sem: 0.4425±0.054, median: 0.407; MECP2-duplication mean±sem: 0.284±0.028, median: 0.308; p = 0.0142, WSR) [Fig.2C]. In sum, the properties of bi-stable reversal dynamics are altered in MECP2-duplication mice, with duplication animals showing increased proportion of reversal-free OKN epochs and reduced reversal rate and probability.

Local versus global motion processing in MECP2 duplication mice and increased stability of local motion 'transparent' percepts. The slower rate of rivalry in MECP2 duplication mice was accompanied by pronounced changes in the processing of visual motion. Specifically, MECP2-duplication animals showed strong preference for the component motion compared to their normal littermates [Fig.3]. The latter either spent approximately equal time following component gratings vs coherent pattern direction, or showed preference for coherent pattern direction. This effect was seen both in the total fraction of OKN eye movements aligned with the component versus the pattern directions [Fig.3A], and in the duration of component- versus pattern-dominance periods [Fig.3 B - C]. Interestingly, for dominance periods, the strongest effect was observed in the duration of component percepts, which were on average twice as long in MECP2- duplication animals as in littermate controls [Fig.3C, littermates, mean±sem: 27.5±7.11, median: 20.2; MECP2-ds, mean±sem: 49.2±11.5, median: 31]. This effect was highly reproducible across pairs and highly significant (Fig.3C, p = 0.0081, WSR). In contrast to the component-aligned OKN periods, the durations of pattern motion-aligned OKN periods showed disparate effects: in some duplication-littermate pairs MECP2 duplication led to an increase in pattern percept durations, while in other a decrease was observed (Fig.3D). Pooled data, including both durations of component and pattern motion-aligned OKN showed a net increase in dominance period durations, consistent with a reduced rate of perceptual reversals (Fig.3B, littermates, mean±sem: 25.2±4.5, median: 21; MECP2-ds, mean±sem: 36.7±8, median: 25; p = 0.0342, WSR). In addition, MECP2 duplication animals showed a consistent shift of the ratio between component motion

percept duration and pattern motion percept duration in favor of component motion percepts (Fig.3E). These findings imply that the bulk of the effect that MECP2 duplication has on the perceptual reversals occurs due to increased stability of the component motion ‘transparent’ percepts and a resulting shift of the ratio between component / pattern motion percept duration in favor of the component (‘transparent’) interpretation. Ultra-stable component motion percepts then may contribute to lower probability to observe a reversal.

FIGURES and LEGENDS

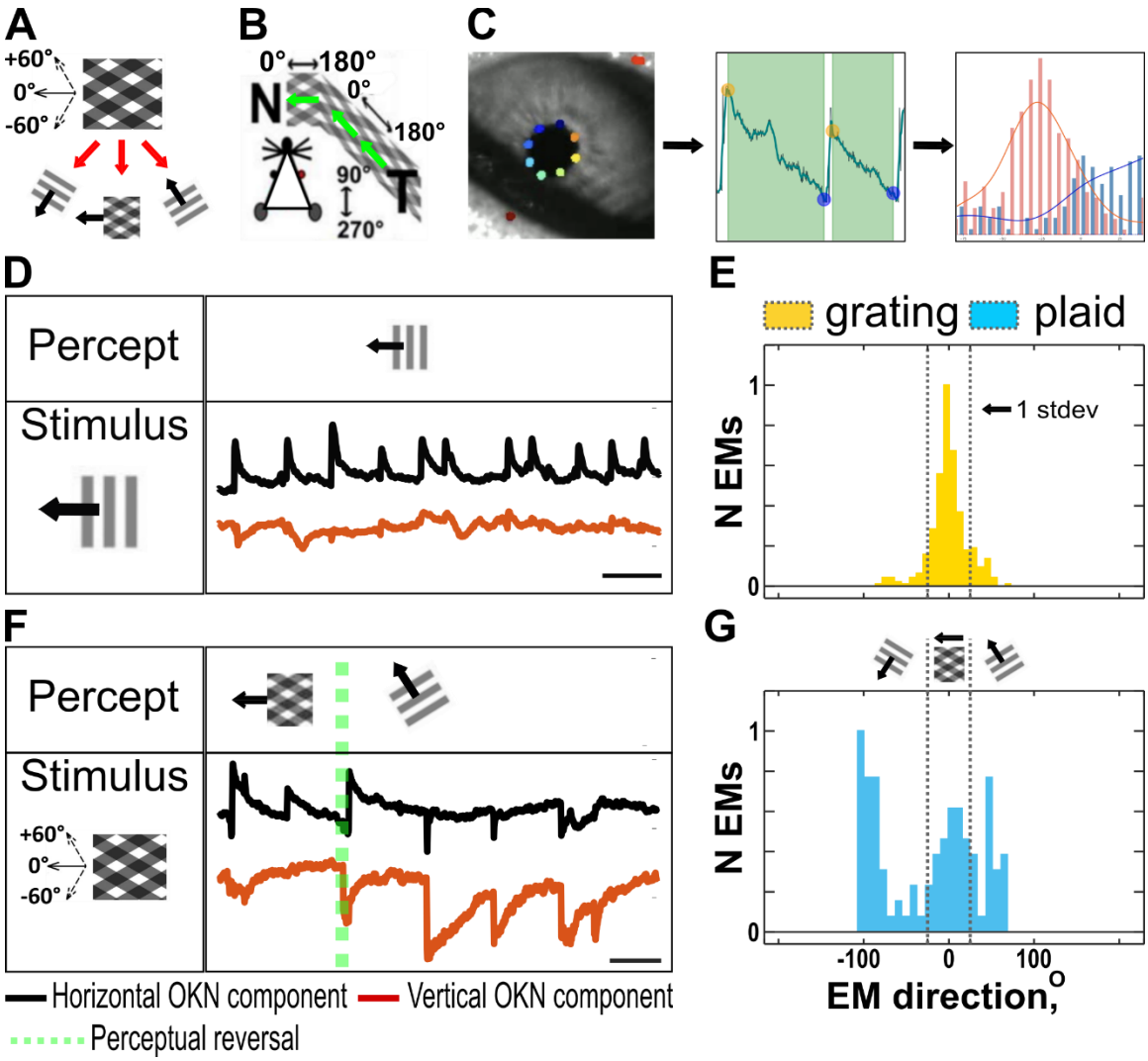

Figure 1. Bistable OKN responses under visual rivalry. A. Bistable moving plaid stimulus. Type I symmetric plaid is composed by summing two 50% contrast component gratings. The gratings move at an angle of 120 degrees relative to each other. This plaid can be seen as either two individual gratings moving at an angle, or a sum of gratings integrated percept of pattern motion. The direction of pattern motion lies in between the directions of motion of each grating. Thus, the observer can follow three directions of motion (lower panel): pattern motion (direction set at 0 degrees), and either of the component grating's drift, offset at +60 and -60 degrees from the vector of the plaid's motion (insets). **B. Experimental setup.** We presented the stimuli on two screens positioned at equal distances from the mouse head to cover 180° of the mouse ipsilateral visual field. We head posted the mouse to prevent the head movements and monitored eye movements with an infrared camera. The mouse could walk freely on the free-moving wheel. Green arrows, direction of the global drift of the stimulus. The stimulus was moving towards mouse's nose to induce robust optokinetic movements. **C. Data**

preprocessing pipeline. *Left:* infrared image of the mouse eye. OKN images were collected at 300 Hz and 20 randomly selected mouse pupil movies were used to train Deep Lab Cut ResNET-150 model to extract position and size of the animal's pupil during the OKN. *Middle:* Next, the vertical and horizontal components of the OKN were sorted into saccade-pursuit eye movement pairs, and eye-blink and grooming-related artifacts were located using custom-written Python toolbox and excluded from analysis (Bogatova et al., in preparation). Next, the pursuit phases of the nystagmus were fitted with linear polynomial fit using Matlab curve fitting toolbox to determine the amplitudes of each eye movements. Using the ratio of the vertical and horizontal components's amplitudes, the directions of the eye movements were determined (see Methods section for details). *Right:* distributions of the directions of pursuit phases of OKN for two different OKN movies. **D, E. Grating-induced OKN.** To determine the location of zero direction (pattern motion direction) and classify eye movements as aligned with pattern motion or alternatively the motion of the components, we used OKN data obtained by presenting the 0 direction grating moving in temporonasal direction, similarly to plaid setup. As such a grating has only one unambiguous direction of drift, it is possible to use the mean of the eye movement direction distribution as a zero direction, and [-standard deviation +standard deviation] as a bracket in which most eye movements aligned with zero direction fall (Fig.1E). The grating-induced OKN is shown in D: as expected, OKN eye movements contain sole horizontal component (black trace), with no consistent vertical deflections (red trace), and this stimulus does not result in visual rivalry as only one interpretation of the stimulus is possible. In E, the distribution of grating-induced OKN is shown (yellow histogram, 13 zero-direction grating movies from 13 animals were used to determine zero position and the standard deviation bracket for eye movement classification). [-standard deviation, +standard deviation] interval around the zero direction is then applied to plaid OKN data: the eye movements with directions inside this interval are classed as pattern-motion aligned, while eye movements with directions outside of this interval are classed as component-motion aligned (Fig.1G, blue histogram). **F, G. Plaid-induced OKN shows bi-stable reversals of the eye movement directions.** In F, the mouse can follow either the plaid or the grating direction while observing the unchanging plaid stimulus. Green dotted line – location of perceptual switch, defined as the start of the saccade where animal starts following a different stimulus interpretation. Initially, the animal is following a pattern motion direction, as evident from OKN parameters – presence of robust horizontal component and no consistent vertical component (before the green dotted line). After the reversal, a strong vertical component appears (red trace), as animal stops following the pattern motion and starts following the -60 degrees component. **G**, blue histogram: the EM directions distribution of OKN induced by plaid stimulus. Gray dotted lines correspond to the pattern-component OKN classification bracket derived from grating OKN data (see yellow histogram in E). In contrast to grating data, plaid OKN, in addition to central peak corresponding to pattern-motion aligned eye movements, has two additional peaks

located at approximately +60 and -60 degrees off the central peak and corresponding to component motion-aligned OKN.

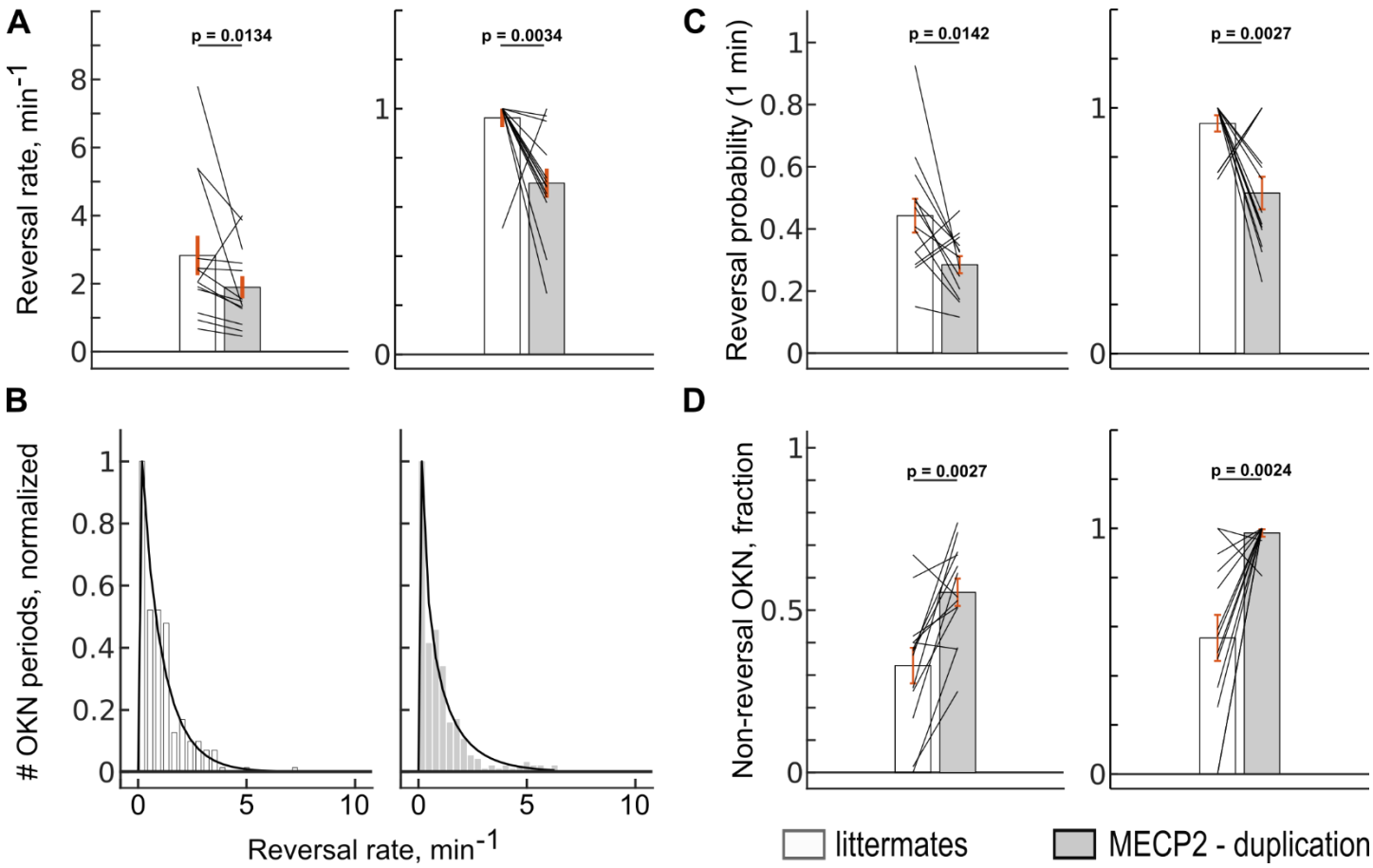

Figure 2. MECP2 duplication syndrome results in reduced perceptual reversal rate during visual rivalry. Clear bars – littermates; gray bars – MECP2 duplication syndrome. **A. Reversal rate (per minute of OKN) is consistently lower in MECP2-ds than in normal littermates.** Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair. Reversals per minute: littermates, mean±sem: 2.8±0.58, median: 2.05; MECP2-ds, mean±sem: 1.895±0.325, median: 1.485. **B. The distribution of perceptual reversal rates of individual OKN periods.** Left panel (clear bars) – littermates; right panel (gray bars) – MECP2 duplication. The distributions follow gamma distribution fit (littermates: $p< 0.0001$; MECP2-ds: $p<0.0001$, χ^2 test). Data was pooled data across OKN periods belonging to 13 littermates and 13 MECP2 duplication animals respectively. Before pooling each animal's dataset was normalized by its mean rate. **C. In accordance with the reduced reversal rate in MECP2 duplication, the probability to observe a switch after 1 minute of ongoing plaid induced OKN was also reduced in MECP2 duplication mice.** Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair. Reversal probability: littermates, mean±sem: 0.4425±0.054, median: 0.407; MECP2-ds, mean±sem: 0.284±0.028, median: 0.308. **D. MECP2 duplication mice consistently show a substantial fraction of OKN periods where no reversals occur, and the animal persistently tracks either pattern ('coherent' percept) or component direction ('transparent' percept).** Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair. Non-reversal

OKN fraction: littermates, mean±sem: 0.33±0.055, median: 0.374; MECP2-ds, mean±sem: 0.555±0.04, median: 0.54. All p-values are determined by two-sided Wilcoxon signed rank test (WSR), n = 13 pairs.

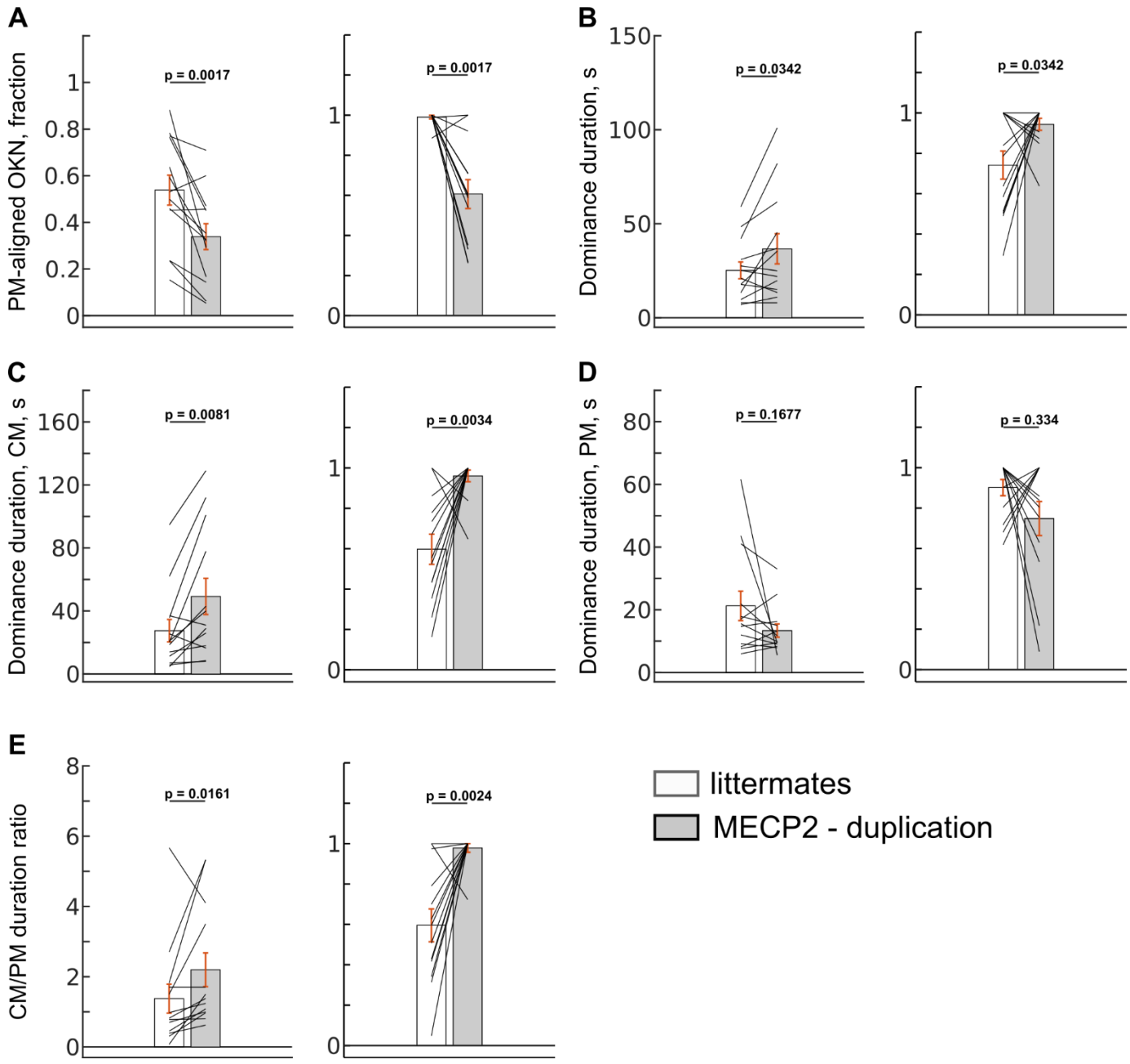

Figure 3. Atypical preference for local motion processing in MECP2 duplication syndrome. Reduced rate of perceptual reversals in MECP2 duplication mice is driven by the lengthening and over-stability of component motion ('transparent') percepts. **A. Total fraction of nystagmoid eye movements aligned with pattern motion direction ('coherent' percept).** Even though there is a considerable variance across data, in normal littermates (clear bar) nearly equal fraction of eye movements are aligned to either pattern motion direction ('coherent' percept, global motion) and component motion direction ('transparent' percept, local motion). In contrast, in MECP2 duplication mice greater portion of OKN eye movements is allocated to component local motion, and the fraction of pattern motion-aligned eye movements is reduced. Littermates, mean±sem: 0.538±0.064, median:

0.53; MECP2-ds, mean±sem: 0.339±0.055, median: 0.326. Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair. **B. Dominance duration is increased in MECP2-duplication mice, following the decrease in reversal rate and reversal probability** (Fig.2); littermates, mean±sem: 25.2±4.5, median: 21; MECP2-ds, mean±sem: 36.7±8, median: 25. Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair; p-values, WSR. **C, D. The increase in average dominance duration is carried mainly by the increased durations of 'transparent' percepts, when the mouse is following the local motion of component gratings** (C, littermates, mean±sem: 27.5±7.11, median: 20.2; MECP2-ds, mean±sem: 49.2±11.5, median: 31), while the global motion 'coherent' percepts show inconsistent changes with shortening in some animals and lengthening in other (D, littermates, mean±sem: 21.2±4.7; MECP2-ds, mean±sem: 13.36±2.2). As a result, even though there is a general trend of shorter pattern-motion percepts in MECP2 duplication mice, it is not significant (p = 0.1677). Left panels – raw data, right panels – data normalized by maximum inside each littermate – MECP2 duplication pair. **E. The ratio of dominance period durations is shifted in favor of transparent local motion percepts at the expense of global motion 'coherent' percepts.** Littermates, mean±sem: 1.376±0.41, median: 0.82; MECP2-ds, mean±sem: 2.2±0.48, median: 1.38. Left panel – raw data, right panel – data normalized by maximum inside each littermate – MECP2 duplication pair. Clear bars – littermates, gray bars – MECP2 duplication. All p-values are determined by two-sided Wilcoxon signed rank test (WSR), unless noted otherwise, n = 13 pairs.

DISCUSSION

Slower dynamics of visual rivalry in MECP2 duplication syndrome. We view the world as generally stable even in the face of fast dynamic changes, such as fast-moving objects and emerging stimuli. This stability rests on an uncertain foundation: naturalistic scenes are inherently ambiguous and the stable percepts of them are a result of a probabilistic process reflecting the most likely interpretation of the inputs. As a result, neuronal populations are constantly engaged in such ongoing interpretation and adjust their decision variables accordingly (Leopold and Logothetis, 1999; Sterzer et al, 2009; Aggelopoulos, 2015). In bi-stable and multi-stable perception the competing interpretations of the sensory input cannot ultimately win against each other; as a result, the brain vacillates between the conflicting interpretations even though the stimulus stays the same. Visual rivalry is a distributed computation, relying on the interactions between low-level sensory processing of physical attributes of the visual stimulus and the high-level top-down cortical influences stemming from sensorimotor integration, attention, and decision-making. This involves a network of areas spanning V1, association visual areas, frontal lobe, supplementary motor cortex and prefrontal cortex (Kleinschmidt et al, 1999, Leopolod & Logothetis, 1996, Knapen et al., 2011, Lumer et al., 1998, 1999). Perception, decision-making and cognate sensory processing are pervasively impacted in neurological circuitopathies such as schizophrenia and autism (Robertson et al., 2013; Schmack et al.,2015; Heeger et al., 2017). Specifically, in idiopathic human autism atypical sensory perception co-exists with higher order deficits in social communication, cognitive flexibility and executive function (Simmons et al., 2009; Robertson & Baron-Cohen, 2017; Van der Hallen et al., 2019; DSM-5, American Psychiatric Association, 2013). As a distributed computation involving both the low-level sensation and perception processes and high-level processes pertaining to attention and decision-making, visual rivalry emerges as an attractive paradigm to study these processes and their interaction in autism spectrum. In our study, we applied a monocular rivalry paradigm to explore if the dynamics of bistable visual perception was affected in the mouse model of MECP2 duplication syndrome of autism (Collins et al., 2004). This model reproduces some features of human autistic syndromes, including enhanced motor learning, motor and visual stereotypies, and increased likelihood of seizure events (Collins et al., 2004; Samaco et al., 2012; Jiang et al., 2013; Sztainberg et al., 2015; Zhang et al., 2017; Zhou et al., 2019; Ash et al., 2017, 2021, 2022). We found that the rate of perceptual reversals is decreased [Fig.2] in MECP2 duplication syndrome, while the average duration of individual percept dominance periods is prolonged [Fig.2]. These effects occurred irrespective of genetic line background of the mice, as we used both 129-MECP2 duplication line and FVB*C57 mixed background duplication line (Ash et al., 2022). Reduced rate of perceptual reversals under visual rivalry conditions in MECP2 duplication mice recapitulates the phenotype occurring in human idiopathic autism. Specifically, the rate of binocular rivalry is reduced in human

autism (Robertson et al., 2013; Spiegel et al, 2019). The magnitude of this reduction correlates with expression of other autistic core traits, such as severity of social communication deficits and ADOS score (Spiegel et al, 2019). Furthermore, in autistic subjects, slower binocular rivalry shares common anatomical substrate with general cognitive rigidity – a part of the core repetitive restricted behaviors and interests (Watanabe et al., 2019).

Atypical perception of visual motion in MECP2 duplication syndrome. Enhanced attention to visual detail and superior processing of local visual information are core traits of autism. Specifically, in autism the visual perception is superior when the task is based on detecting local elements in the visual scene, and the performance suffers when the subjects must focus on global elements (Shah & Frith, 1983,1989; Jolliffe & Baron-Cohen, 1997, Plaisted et al., 1998,1999; Mottron et al., 1999, Jarold et al., 2005; Happe et al., 2001; Rhinehart et al., 2000; Robertson & Baron-Cohen 2017), a perceptual phenotype known as “not seeing the forest behind the trees” (Robertson et al., 2012, Frith, 1989). Of particular relevance to our study are autism-related changes in the processing of visual motion and integration of local moving cues into a global moving percept (van der Hallen et al., 2019; Robertson et al., 2012, 2014; Brieber et al., 2010; Bertone et al., 2003; Pellicano et al., 2005; Kaiser & Shiffrar, 2009; Koldewyn et al., 2010). The bi-stable-perception paradigm in our study makes use of two competing interpretations of a moving plaid: 1) the “transparent” interpretation where component gratings are seen as separate stimuli moving on top of each other, and 2) the “coherent” interpretation, where the stimulus is seen as a fusion of two moving component gratings resulting in a percept of moving pattern (Adelson & Movshon, 1982; Castelo-Branco et al, 2000; Smith et al, 2005). It is proposed that processing of complex stimuli like moving plaid rests on two distinct populations of neurons: orientation- and direction-selective component neurons, specializing in local motion information and responding to individual moving grating components, and direction-of-motion selective pattern cells, that ignore the orientation of the grating components, and instead respond to any stimulus moving in the preferred direction, including large-sized moving patterns like naturalistic moving visual scenes. Pattern motion selectivity of the latter cells is posited to arise by integration of the inputs from component-motion sensitive neurons. As one moves from primary visual areas to more specialized areas of visual dorsal stream, the fraction of pattern cells and neurons integrating various types of local sensory information and computing global motion and global scenes increases (Rust et al., 2006; Smith et al., 2005; Movshon and Newsome, 1996; Rodman & Albright, 1989; Scanell et al., 1996; Juavinett & Callaway, 2016, Palagina et al., 2017; Albright & Stoner, 1995; Khawaja et al., 2009; Gizzi et al., 1990). Pattern-motion processing in lower-order visual areas like V1 is strongly dependent on feedback from higher-order areas (Guo et al., 2004), while the integration of local motion cues into the global moving scenes by higher order areas depends on the feedforward inputs from the V1 (Movshon & Newsome, 1996).

Thus, in our paradigm the bi-stable perceptual reversals occur not between two competing static image interpretations, or between competing locations of a salient non-ambiguous stimulus (like in binocular rivalry paradigms and bi-stable image displays). Our competing interpretations are based on categorically different subtypes of visual motion – local motion (when two individual component gratings are seen) and global motion, occurring via integration of local motion cues and subsequent fusion of two gratings into a global moving pattern (as occurs in coherent moving plaid interpretation). Moreover these two processes (global vs local motion) are linked by feedforward and feedback connections occurring across the cortical hierarchy.

In MECP2 duplication mice we observed a pronounced preference for local motion percepts, both in terms of the fraction of eye movements aligned with component gratings and in terms of the duration of transparent versus coherent percepts [Fig.3]. This recapitulates the visual motion processing peculiarities found in a subset of human subjects with autism (van der Hallen et al., 2019, Robertson & Baron-Cohen, 2017). Namely, in studies using random dot kinematogram displays a subset of subjects with autism show increased motion coherence thresholds (e.g. larger fraction of dots have to move together in the specified direction for the subject to detect coherent motion); however, this difference diminishes and disappears when the decision time (during which the subject can view and report coherent motion) is extended, implying that integration of local moving cues into global moving percept is slowed down, but not fundamentally impaired or absent in autism spectrum (Robertson et al., 2014). Another group of studies found no differences in behavioral performance of subjects when viewing RDK displays; however, subjects with autism still showed differential activation of visual areas in the dorsal stream, such as V1 and hMT while observing and reporting coherent motion (Brieber et al., 2010; van der Hallen et al., 2019). In a similar vein, our MECP2 duplication mice still consistently display global moving pattern percepts; however, their durations show inconsistent changes (longer in one subgroup of MECP2-duplication animals and shorter in the others), while the duration of transparent percepts relying on local motion processing is consistently and dramatically increased compared to normal littermates [Fig.3].

Interaction between atypical perception of visual motion and reduced rate of perceptual reversals. In our paradigm, the MECP2 duplication mice show prolonged dominance periods of local motion, while the global motion percepts are generally shortened or unchanged, leading to shifted motion processing ratio in favor of local motion information over integrated motion information (Fig.3). Additionally, the total fraction of OKN eye movements aligned with component motion is greatly increased in MECP2 duplication, while OKN fraction aligned with pattern motion is reduced [Fig.3]. These observations imply that the capacity of neuronal populations reserved for the global motion percept formation and / or maintenance is reduced in MECP2 duplication syndrome, or the dynamics

of such integration is altered. This is in line with two theories of autism – dorsal stream deficit theory (Braddick et al., 2003; Greenway et al., 2013; Macintyre-Beon et al., 2010; Chieffi et al., 2019) and weak central coherence theory (Dakin and Frith, 2005; Happe et al., 2001; Happe & Frith, 2006). Dorsal stream deficit theory states that circuitry allocated to computing global motion from local moving cues is deficient in autism. In children with autism this is exemplified by difficulties in following multiple moving objects simultaneously, impaired imitation visual learning tasks and performing complex movements like climbing the ladder without somatosensory feedback, as visual guidance of the motor output is disrupted (Williams et al., 2004; Macintyre-Beon et al., 2010). Weak central coherence, on the other hand, proposes that global motion perception deficit may be due to general cognitive style that prioritizes fine local details over global features (Happe & Frith, 2006). In both types of explanation, preference of MECP2 duplication mice for local features at the expense of global coherent motion may be a major contributor to diminished rate of visual rivalry. Visual rivalry processing relies on the interaction of two processes – top-down influences related to attention and executive function, and competition of neuronal subnetworks supporting the rivaling percepts in low-level sensory areas like V1 (Leopold and Logothetis, 1999). The bias for one specific rivaling interpretation of the stimulus may impair the ability of the brain to select an alternative interpretation and thus affect the rate of visual rivalry. In MECP2 duplication the coherent motion percepts appear to either not amass enough neuronal population activity or synchrony to remain stable, while local-motion percepts gain in stability [Fig.3]. Interestingly, the physiological basis for these changes may occur as early as primary visual cortical area V1. First, pyramidal neurons in area V1 of MECP2 duplication mice show ultra-reliable firing in response to local motion information (for example, when moving gratings are used as a stimulus (Ash et al., 2022). In addition, area V1 harbors a significant portion of visual neurons dedicated to the processing of local motion and, in mice, contributes to the dynamics of bistable perception: removing V1 via lesion causes a decrease in the fraction of component motion-aligned OKN corresponding to local motion percepts (Palagina et al., 2017). In idiopathic human autism, hyperactivation of area V1 was found in a subset of subjects with autism during the processing of coherent motion (Brieber et al., 2010), while in another subset of subjects the areas of dorsal stream, including V1 and middle temporal area showed delayed activity during motion coherence processing (Robertson et al., 2014). Second, neuronal responses of MECP2 duplication mice in area V1 show reduced coupling to ongoing cortical activity (Ash et al., 2022). This may result in disruption of both feedforward inputs from V1 to higher order areas dedicated to integration of local moving cues into global motion percept and weakening of the feedback from these higher-order areas to V1, reducing the integration of local motion cues there (Ash et al., 2022). Taken together, these observations point to an interesting possibility that the over-representation of local component motion in area V1 and disrupted feedforward and feedback connections between V1 and the rest of the visual dorsal stream are major contributors to the reduced

rate of visual rivalry in autism, as they confer advantage to the local motion information in the moving stimuli, while the synthesis of local information into the global motion of the scenes becomes impaired.

Rate of visual rivalry, global motion synthesis and excitatory-inhibitory balance in cortical circuits. One of the prominent theories in autism states that core traits of the condition occur secondary to altered development of cortical interneurons and resulting shift in balance between excitation and inhibition in cortical circuits across sensory and higher-order cortical areas (Rubenstein & Merzenich, 2003; Casanova et al., 2003; Gogolla et al., 2009; Robertson et al., 2014, 2016). Dynamics of visual rivalry and the rate of perceptual reversals are similarly hypothesized to depend on excitation-inhibition dynamics and circuit wiring in the competing clusters of neurons coding for rivalrous percepts (Laing and Chow, 2002; Seely & Chow, 2011; Wilson, 2003; van Loon et al., 2013). Computational models of binocular rivalry show that shifting excitatory-inhibitory ratio either in favor of excitation or inhibition causes increase in dominance durations, as eye-specific inputs maintain stable activity for longer periods (Dayan et al., 1998; Klink et al., 2010). Altered local opponent inhibition in visuomotor areas was proposed to underlie the delayed integration of local moving features into global motion percepts in autism (Robertson, 2014). MECP2 dysfunction was shown to alter synchrony and net excitation-inhibition balance in neuronal circuits, with greater burden on the phenotype of GABAergic interneurons, and overexpression of MECP2 was shown to affect predominantly genes pertaining to GABAergic signaling (Chao 2010, Cai et al., 2020), with the result of disrupted synchronization within local and brain-wide networks (Shou et al., 2017). Thus, our findings that visual rivalry dynamics is slowed in MECP2-duplication mice and that they favor local potion percepts over global motion percepts is consistent with the altered excitation-inhibition dynamics hypotheses of the autistic brain.

In summary, our MECP2 duplication mice phenotype reproduces core features of autism spectrum – atypical perception of visual motion and slower dynamics of visual rivalry, and thus can serve as a valid model of autism. Going forward, our bi-stable perception paradigm combined with 2-photon imaging and optogenetic manipulations (Yizhar et al., 2011; Sofroniew et al., 2016; Nikolenko et al., 2013) in MECP2 duplication mouse model can be used to directly and causally test the following theories of autistic spectrum: excitatory-inhibitory imbalance, weak central coherence, dorsal stream deficiency and disrupted intracolumnar and cortex-wide connectivity.

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AUTHOR CONTRIBUTIONS

GP and SMS conceived of the project and designed the experiments, GP performed the experiments, DB wrote the analysis software, DB and GP analyzed the data and prepared the figures, GP wrote the manuscript, SMS reviewed the manuscript.

ACKNOWLEDGEMENTS

Authors thank Dr. George Keliris for valuable comments.