

1 **Neural gain control measured through cortical gamma oscillations is**
2 **associated with individual variations in sensory sensitivity.**

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4 Orekhova EV^{1,2,3}, Stroganova TA^{2,3}, Schneiderman JF⁴, Lundström S¹, Riaz B⁴, Sarovic
5 D¹, Sysoeva OV^{2,3}, Gillberg C¹, Hadjikhani N^{1,5}

6 1. University of Gothenburg, Gillberg Neuropsychiatry Centre (GNC), Gothenburg, Sweden

7 2. Moscow State University of Psychology and Education, Center for Neurocognitive
8 Research (MEG Center), Moscow, Russia.

9 3. Moscow State University of Psychology and Education, Autism Research Laboratory,
10 Moscow, Russia

11 4. University of Gothenburg, Institute of Neuroscience & Physiology, Department of Clinical
12 Neurophysiology and MedTech West, Gothenburg, Sweden

13 5. Harvard Medical School, MGH/MIT/HST Martinos Center for Biomedical Imaging,
14 Charlestown, MA USA

15

16

17 **Corresponding author:**

18

19 Elena V Orekhova

20 MEG Centre,

21 Moscow State University

22 of Psychology and Education,

23 Shelepihinskaja embankment 2a

24 123290 Moscow, Russia

25 orekhova.elena.v@gmail.com

26 tel: +46 73 591 23 92

27 tel: +7 499 256 45 13

28

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30 **Keywords:**

31 *Gamma oscillations, response gain control, sensory sensitivity, visual motion, magneto-*
32 *encephalography (MEG), autism spectrum disorders (ASD)*

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1

2 **Abstract**

3 Gamma oscillations facilitate information processing by shaping the excitatory input/output
4 of neuronal populations, and their suppression by strong excitatory drive may stem from
5 inhibitory-based gain control of network excitation. Individual variations in the gamma
6 suppression may therefore reflect efficiency of gain control and subjective sensitivity to
7 everyday sensory events. To test this prediction, we assessed the link between self-reported
8 sensory sensitivity and changes in magneto-encephalographic gamma oscillations as a
9 function of motion velocity of high-contrast visual gratings. The induced gamma oscillations
10 increased in frequency and decreased in power with increasing stimulation intensity. As
11 expected, weaker suppression of the gamma response correlated with sensory
12 hypersensitivity. Robustness of this result was confirmed by its replication in the two
13 samples: neurotypical subjects and people with autism, who had generally higher sensory
14 sensitivity. We conclude that intensity-related suppression of gamma response is a
15 promising biomarker of homeostatic control of the excitation–inhibition balance in the visual
16 cortex.

17

1 Introduction

2 The balance between excitation and inhibition (E/I balance) in neural networks orchestrates
3 neural activity in space and time, and is important for cortical functioning (Dornn et al., 2010;
4 Isaacson and Scanziani, 2011; Xue et al., 2014). Activity of the excitatory (E) and inhibitory (I)
5 neurons is fine-balanced in the normal brain and this balance is disrupted in epilepsy
6 (Dehghani et al., 2016) and neurodevelopmental disorders, such as e.g. autism and
7 schizophrenia (LeBlanc and Fagiolini, 2011; Lee et al., 2017; Nelson and Valakh, 2015;
8 Rubenstein and Merzenich, 2003).

9 Animal findings promote the discoveries of new drugs aimed to restore the neural
10 E/I balance in the patients with brain and mental health disorders (Lee et al., 2017; Tu et al.,
11 2017), however there are still considerable challenges in testing them in clinical trials. A lack
12 of quantifiable non-invasive measures of the E/I balance in the human brain precludes
13 stratification of heterogeneous patient populations according to the distinct E/I balance
14 subtypes, and hinders assessment of the treatment efficacy (Ecker et al., 2013; Levin and
15 Nelson, 2015).

16 The stimulus-induced high-frequency MEG/EEG gamma oscillations (30-100 Hz) have
17 attracted considerable attention as a putative noninvasive indicator of an altered E/I balance
18 in human cortex (Levin and Nelson, 2015; Nelson and Valakh, 2015). Gamma oscillations are
19 generated by populations of interconnected excitatory and inhibitory neurons and are
20 intimately related to the balance between inhibitory and excitatory neurotransmission
21 (Buzsaki and Wang, 2012; Vinck et al., 2013). However, the current attempts to define a
22 single parameter of human gamma response that would accurately capture the E/I balance
23 have led to ambiguous results (Cousijn et al., 2014; Edden et al., 2009; Perry et al., 2014).

24 In a previous study we put forward the idea that it is possible to estimate efficiency
25 of the E/I balance regulation in the visual cortex through probing input–output gain in the
26 strength of the visual gamma oscillations recorded by MEG (Orekhova et al., 2018).
27 Response gain control is a basic property of neural networks that works to both amplify the
28 neuronal responses to weak sensory signals and to saturate/suppress these responses under
29 conditions of excessive input (e.g. (Peirce, 2007)). The strength of visually induced gamma
30 oscillations is controlled in accord with this mechanism, in both animals (Jia et al., 2011; Jia
31 et al., 2013; Roberts et al., 2013; Salelkar et al., 2018) and humans (Orekhova et al., 2018),
32 wherein a gradual increase in excitatory drive elicits an increase in gamma power up to a
33 certain ‘transition’ point, and a stimulation intensity past that point leads to suppression of
34 the gamma response.

1 According to modeling studies, suppression of the oscillatory gamma response at
2 high intensities of excitatory drive is caused by over-excitation of the I-neurons resulting in
3 the loss of neural synchrony (Borgers and Kopell, 2005; Borgers and Walker, 2013; Cannon
4 et al., 2014). Computational models further suggest that the gamma suppression is
5 substantially reduced when the excitation of the E-neurons is disproportionately higher than
6 that of the I-neurons (i.e. in the case of a high E/I ratio) (Borgers and Kopell, 2005). Indeed,
7 opto-genetic research in animals demonstrated that gamma oscillations are particularly
8 powerful when the high excitation of excitatory neurons is not properly balanced by
9 inhibition (Yizhar et al., 2011). In regard to humans, these considerations imply that the
10 brain of individuals exhibiting weaker suppression of the visual MEG gamma response is
11 characterized by less efficient inhibitory-based capacity to down-regulate the rising
12 excitation, i.e. by an E/I ratio shifted towards excitation (see (Orekhova et al., 2018) for
13 discussion).

14 If suppression of the visual gamma response does reflect the capacity to regulate
15 the E/I balance in the visual cortex, this phenomenon should have behavioral
16 manifestations. On the behavioral level, the enhanced neural excitability of sensory cortices
17 is associated with heightened or aversive reactions to intensive sensory input. Indeed,
18 subjective discomfort associated with intensive visual stimulation correlates positively with
19 hemodynamic responses in the visual cortex (Bargary et al., 2015; Haigh et al., 2013).
20 Moreover, people with neurological or neuropsychiatric disorders characterized by overt
21 clinical symptoms of elevated neuronal excitability, such as migraine with visual aura
22 (Bouloche et al., 2010; Maniyar et al., 2014; O'Hare and Hibbard, 2016) or epilepsy (van
23 Campen et al., 2015) often suffer from sensory hypersensitivity. It seems plausible that the
24 atypically strong cortical responses observed in people reporting sensory hypersensitivity
25 are caused by deficiency of the gain control mechanisms that balance excitation and
26 inhibition in the sensory cortices. Therefore, we predicted that reduced gamma suppression
27 at high intensities of visual input would be associated with enhanced sensory sensitivity in
28 everyday life.

29 Here, we sought to test this prediction in two independent samples of subjects:
30 neurotypical individuals (NT) and high-functioning individuals with autism spectrum disorder
31 (ASD). A large proportion of people with ASD are hypersensitive to environmental stimuli of
32 different modalities. Considerable variations in sensitivity to sensory events are also present
33 in the general population (Horder et al., 2014; Little et al., 2017), correlate with autistic
34 features (Horder et al., 2014; Robertson and Simmons, 2013), and share with them a

1 common genetic basis (Taylor et al., 2018). Therefore, we expected that the similar neuro-
2 behavioral association should characterize both groups. To test this prediction, we assessed
3 behavioral sensory sensitivity using the Adolescent/Adult Sensory Profile (A/ASP)
4 questionnaire (Brown and Dunn, 2002) and measured velocity-related suppression the visual
5 MEG gamma response in adults with and without ASD. Since we used moving visual stimuli,
6 we expected to find the most prominent neurobehavioral correlations for the visual
7 modality, and particularly for sensitivity to visual motion.

8

9 Results

10

11 Adolescent/Adult Sensory Profile (A/ASP)

12 To measure subjective sensory sensitivity we used the ‘Sensory Sensitivity’ scale of the
13 A/ASP questionnaire that characterizes noticing behaviors, distractibility, and discomfort
14 with sensory stimuli of different modalities. Since we measured the gamma response to
15 moving visual stimuli, we also assessed discomfort associated specifically with intensive
16 visual motion by combining two items of the A/ASP into the ‘Visual Motion Sensitivity’ scale
17 (see Materials and methods for details). Additionally, we calculated the ‘Visual Low
18 Thresholds’ – the A/ASP scale that measures a person’s notice of, or annoyance with
19 different types of visual stimuli.

20 The general Sensory Sensitivity was marginally higher in the ASD than in NT
21 participants ($T_{(37)}=2.25$, $p=0.03$), while no group differences were found for the visual scales
22 (Table 1). In *Supplementary Table 1*, we present the results of group comparisons for all
23 standard A/ASP scales.

24

25 *Table 1*

26 **Table 1.** Group differences in the A/ASP measures of sensory sensitivity.

A/ASP item	NT (19)	ASD (20)	T-statistic
Sensory Sensitivity	31.2	37.7	-2.3*
<i>A/ASP-derived measures of visual sensitivity</i>			
Visual Low Threshold	12.9	14.9	-1.5
Visual Motion Sensitivity	4	4.7	-1.0

27 * $p<0.05$

28

29 *MEG gamma responses in NT and ASD*

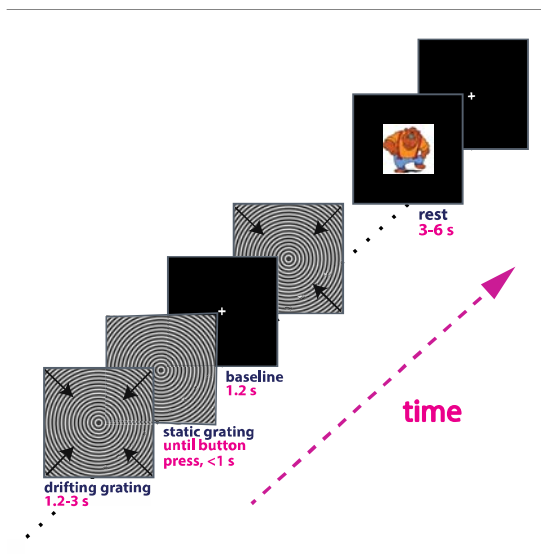
30 The experiment was designed to modulate the intensity of visual input by varying motion
31 velocity of high-contrast annular gratings (1.2, 3.6 or 6.0°/s) (Fig. 1). We localized the MEG

1 signal in the brain and found the ‘maximally induced voxel’ (Tan et al., 2016) – the source in
2 the visual cortex that displayed the greatest gamma response to the stimulation (see
3 Materials and methods for details).

4 In both groups, the average location of the maximally induced voxel corresponded
5 to the left calcarine sulcus and did not significantly differ between groups for either x, y or z
6 coordinates (NT: $x=-0.18$, $y=-9.34$, $z=-0.15$; ASD: $x=0.23$, $y=-9.49$, $z=0.13$ cm). Figure 2 shows
7 the average source localization of the motion-related gamma response measured as the
8 weighted peak power (see Materials and methods for details) in the ASD and NT
9 participants. These results indicate that in both groups, and in all experimental conditions,
10 the gamma response predominantly reflects activity in the primary visual cortex.

11 For further analysis we averaged the response spectra across the maximally induced
12 voxel and the 25 closest voxels.

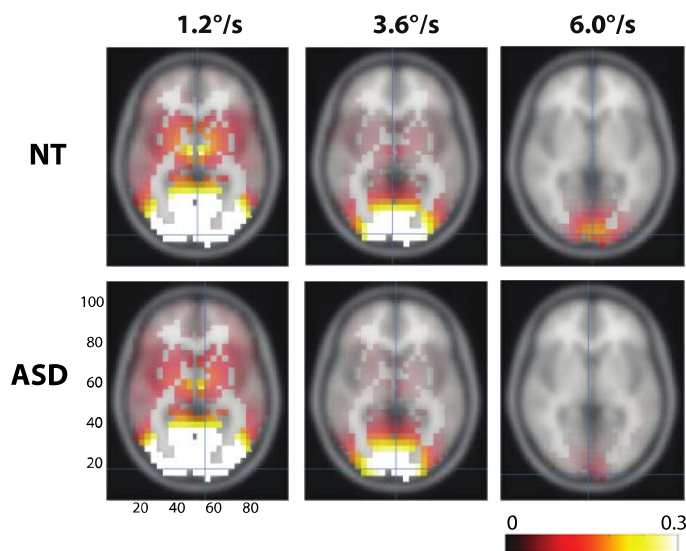
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16 Figure 1. Experimental design. Each trial began with presentation of a fixation cross that was
17 followed by an annular grating drifting inward for 1.2-3 seconds at one of the three
18 velocities: 1.2, 3.6, 6.0°/s. Hereafter, we referred to these velocities as ‘slow’, ‘medium’, and
19 ‘fast’. Arrows indicate direction of the motion. Participants responded to the termination of
20 motion with a button press. Short (3-6 s) animated cartoon characters were presented
21 randomly between every 2-5 stimuli to sustain vigilance and reduce visual fatigue. (See
22 Materials and methods for details).

23
24

Figure 2



1

2 **Figure 2.** Grand average source localization of the visual gamma responses in ASD and NT
3 individuals. Here and hereafter the magnitude of the gamma response was calculated as the
4 ratio: (stimulus-baseline)/baseline. In both groups and under all three velocity conditions the
5 gamma power ratio was maximal in the calcarine sulcus (marked with a blue crosshair).
6

6

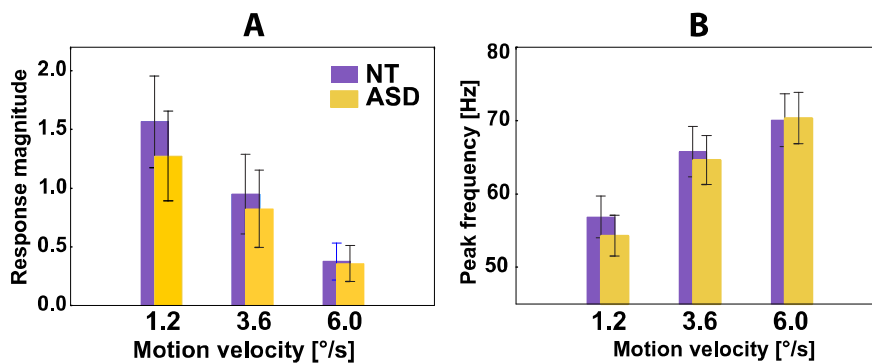
7 Previous studies suggest that visually induced gamma oscillations might be altered in people
8 with ASD (Dickinson et al., 2015; Stroganova et al., 2012). To test for the group differences
9 in gamma parameters, as well as for effect of condition and its interaction with the
10 experimental group, we used repeated measures ANOVA (rmANOVA) with the factors
11 GROUP and VELOCITY. The power of the gamma response strongly decreased with
12 increasing velocity ($F_{(2,74)}=74.2$, $p<0.00001$), but neither effect of GROUP nor GROUP x
13 VELOCITY interaction were significant for the gamma power ($p's>0.2$) (Fig. 3 A). To analyze
14 the frequency of the gamma response, we measured weighted gamma frequency in those
15 subjects and conditions where the stimulus-related increases in gamma power were reliable
16 at $p<0.0001$ level (see Materials and Methods for details). The rmANOVA was performed in
17 15 NT and 11 ASD subjects in whom the frequency was possible to assess in each of the
18 three velocity conditions. For the gamma frequency the rmANOVA revealed highly reliable
19 increase in frequency with increasing motion velocity ($F_{(2,48)}=152.6$, $p<0.00001$), but no effect
20 of GROUP or GROUP x VELOCITY interaction ($p's>0.5$) (Fig. 3 B). To sum up, suppression of
21 gamma response power and increase of gamma response frequency with increasing motion
22 velocity were observed in both NT and ASD individuals and did not differ between the
23 groups.

24

25

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Figure 3

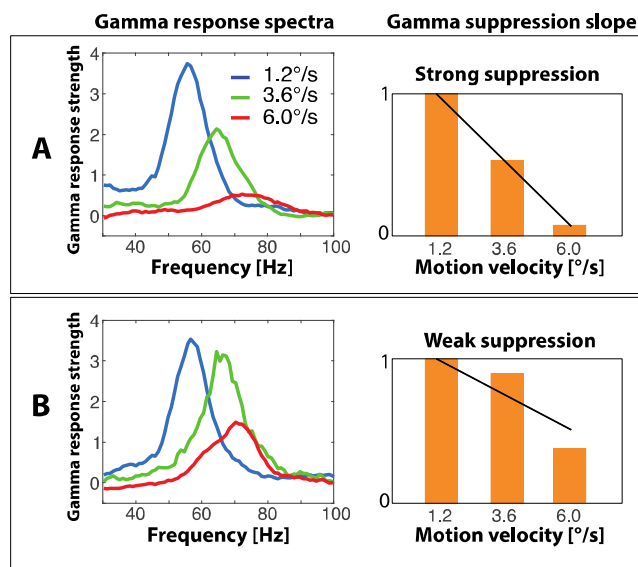


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3 **Figure 3.** Magnitude (A) and peak frequency (B) of gamma responses to moving gratings in
4 NT and ASD individuals. Parameters of the gamma response were measured in its focus in
5 the visual cortex (see Materials and methods for details). Vertical bars denote 0.95
6 confidence intervals.

7
8 *Gamma suppression and sensory sensitivity*

9 To quantify the velocity-related suppression of gamma response power, we introduced the
10 ‘gamma suppression slope’ (GSS) parameter (Figure 4, see Materials and methods for
11 details), where a more negative GSS value corresponds to stronger suppression.

12
13 *Figure 4*



14
15 **Fig. 4.** Gamma suppression slope (GSS) reflects strength of the gamma response suppression
16 caused by increasing velocity of visual motion. Subject **A** shows a strong suppression of
17 gamma response power with increasing motion velocity reflected in strongly negative slope
18 of the regression line. Subject **B** has a less prominent gamma suppression corresponding to
19 less negative GSS value.

1 Because the ASD and NT groups differed in neither visual sensitivity nor gamma
 2 parameters, we combined them for the correlation analysis. Table 2 and figure 5 show
 3 Spearman correlations between the sensitivity measures and the gamma suppression slope.
 4 As expected, less negative GSS (i.e. less prominent gamma suppression) correlated with
 5 higher scores on Sensory Sensitivity, visual Low Threshold, and Visual Motion Sensitivity
 6 scales. The correlation between Sensory Sensitivity and GSS remained significant when
 7 tested separately in the NT and the ASD groups. For the visual sensitivity measures the
 8 correlations with the GSS were in the same direction in the NT and the ASD groups, but did
 9 not reach significance level in the NT subjects. Correlations between the GSS and other
 10 A/ASP scales are presented in the *Supplementary Table 2* for comparison.

11
 12

Table 2

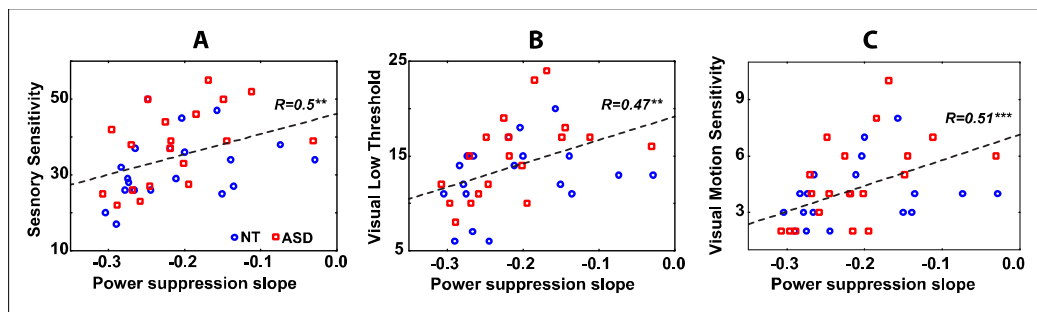
13 **Table 2.** Spearman correlations between gamma suppression slope and A/ASP sensitivity
 14 measures.

A/ASP item	NT+ASD (38)	ASD (19)	NT (19)
<i>A/ASP quadrants</i>			
Sensory Sensitivity	0.5**	0.57*	0.5*
<i>A/ASP-derived measures of visual sensitivity</i>			
Visual Low Threshold	0.47**	0.62**	0.32
Visual Motion Sensitivity	0.51***	0.63**	0.41 [#]

15 Significance values *p<0.05, **p<0.01, ***p<0.001, [#]p<0.1

16
 17

Figure 5



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Figure 5. The relationship between gamma suppression slope and Sensory Sensitivity (A),
 Visual Low Threshold (B), and Visual Motion Sensitivity (C) in the combined sample of ASD
 (read squares) and NT (blue circles) individuals.

23 The GSS is a relational measure and its correlations with the sensory sensitivity could
 24 be predominantly driven by gamma responses at particular velocities of the visual motion.
 25 In accord with the ‘gain control’ hypothesis the variability in gamma response strength to
 26 the most intensive stimulation (‘fast’ visual motion) should make major contribution to the

1 individual variation in sensory sensitivity. Indeed, as predicted, the generally elevated visual
2 sensitivity/avoidance and, in particular, sensitivity to visual motion were associated with
3 higher gamma responses to the fast motion (Tab. 3).

4 *Table 3*

5 **Table 3.** Spearman correlations between gamma response strength in the three velocity
6 conditions and the A/ASP measures in the combined sample (NT+ASD).

A/ASP item	Gamma response magnitude: (stimulus - baseline)/baseline		
	Slow	Medium	Fast
Sensory Sensitivity	-0,23	0.08	0.27#
Visual Low Threshold	0.05	0.26	0.44**
Visual Motion Sensitivity	0.03	0.31	0.46**

7 Significance values #p<0.1, **p<0.01

8

9 Unlike the gamma suppression slope, neither the peak frequencies of gamma
10 oscillations nor their velocity-related changes were related to the A/ASP measures of
11 sensitivity (all p's>0.05).

12

13 **Discussion.**

14

15 Our study shows that inter-individual variations in sensory sensitivity are strongly related to
16 the capacity to modulate MEG gamma oscillations according to intensity of the visual input.

17 We found that subjects who reported heightened sensory sensitivity were characterized by
18 weakened suppression of the gamma response with increasing velocity of visual motion. This
19 result indicates that the neural mechanisms underlying gamma suppression also modulate
20 subjective reactivity to sensory events in the everyday life. Moreover, the similar pattern of
21 findings in the NT and ASD individuals suggests that sensory hypersensitivity shares a
22 common neural ground in people with autism and in general population.

23 In both NT and ASD subjects, the increase in velocity of the visual motion from 1.2 to
24 6°/s elicited a strong and reliable suppression of the visual gamma response accompanied by
25 a substantial increase in gamma frequency for almost 15 Hz (Fig 3). These findings extend
26 our previous results on the velocity-related changes of visual gamma response in NT subjects

1 (Orekhova et al., 2015; Orekhova et al., 2018) and children with ASD (Stroganova et al.,
2 2015) by replicating these findings in a group of adult ASD individuals.

3 Increasing motion velocity of full-contrast visual gratings up to 6.0°/s likely promotes
4 excitation of interconnected excitatory and inhibitory neurons in the visual cortical areas
5 (see (Orekhova et al., 2018) for discussion). According to the computational modeling results
6 of Borgers and colleagues, increasing excitation of the I-neurons above some critical
7 threshold leads to neuronal de-synchronization and thus suppression of gamma oscillations
8 (Borgers and Kopell, 2005; Borgers and Walker, 2013; Cannon et al., 2014). This inhibitory-
9 based physiological mechanism offers a reasonable explanation for the relative suppression
10 of the induced gamma response at high stimulation intensities (visual motion at 3.6 and 6°/s,
11 Fig. 3) in our study. Since gamma synchrony increases the impact of synaptic input from a
12 neuronal group onto its postsynaptic targets (Fries, 2005, 2009, 2015; Ni et al., 2016; Vinck
13 et al., 2013), the reduction of gamma power at high stimulation intensities may limit signal
14 transmission between activated neural assemblies, thus protecting them from sensory-
15 driven hyper-excitation. Hence, gamma suppression may reflect a suppressive gain-control
16 mechanism, which affects sensory perception by reducing the impact of high-intensity
17 stimulation. In a similar vein, a weaker suppression of visual gamma oscillations at the high
18 motion velocities may be associated with a heightened behavioral sensitivity to the high-
19 intensity visual stimulation.

20 To pursue this hypothesis, we introduced a measure that quantified the suppression
21 of the gamma response with increasing stimulation intensity -- the 'gamma suppression
22 slope' (GSS). As expected, a weaker negative slope (i.e. lower gamma suppression and less
23 efficient homeostatic regulation of the E/I balance) correlated with a higher incidence of
24 sensory noticing/discomfort and avoidant behaviors in both the NT and the ASD individuals
25 (Table 2 and Fig.3). Presence of similar correlation patterns in the NT and ASD subjects
26 suggests that variations in response gain control contribute similarly to individual differences

1 in sensory sensitivity in the ASD group and the general population. The higher correlations in
2 the ASD individuals can be explained by somewhat greater variability of their sensory
3 sensitivity scores comparing to those in the NT subjects. The fact that the highly sensitive
4 individuals displayed elevated gamma responses to the high-intensity stimuli, rather than
5 reduced responses to those at lower intensities (Table 3), gives additional support for the
6 suggested link between sensory hypersensitivity and inefficient down-regulation of
7 excessive activation of the visual cortex. In general, these results confirm our hypothesis that
8 the mechanisms leading to gamma suppression in response to strong sensory input also
9 serve to protect the brain from hyper-excitation.

10 Most probably, the suppression of the gamma response at the highest stimulus
11 velocity/temporal frequency used in our study ($6^\circ/s$ or 10Hz) is associated mainly with
12 decrease in the efficacy of transient interactions between neural populations rather than
13 with reduction of neuronal firing. Indeed, a recent study in monkeys showed that the 50-80
14 Hz power in local field potential (LFP) recordings reaches its maximum at lower temporal
15 frequencies of visual motion than the neuronal spiking does (Salelkar et al., 2018). In
16 particular, when the temporal frequency of visual motion increased from 2 to 8 Hz the LFP
17 gamma suppression in monkeys was paralleled by an increase or absence of change in
18 neuronal firing. Similarly, in humans, BOLD activation in visual cortical areas elicited by
19 drifting visual gratings drops only after increasing temporal frequency beyond 9 Hz (Singh et
20 al., 2000), suggesting high level of cortical activation at this temporal frequency. According
21 to the model of Borgers and Kopell (2005), the asynchronous activity of the over-excited I-
22 neurons, corresponding to the 'no gamma state', can suppress activity of the E-neurons. It is
23 therefore likely that motion velocities/temporal frequencies yet higher than those applied in
24 our study would result in a complete blockage of gamma oscillations paralleled by a
25 decrease in E-neurons firing in the visual cortex.

1 Given that the homeostatic control of neural excitability may differ between cortical
2 areas, we expected that the suppression of visual gamma response would be most closely
3 related to behavioral sensitivity in the visual domain. Indeed, in case of the ‘Low Threshold’
4 A/ASP measures, the correlation with the GSS was highest for the visual modality
5 (*Supplementary Table 2*). Correlations with the GSS in non-visual sensory or behavioral
6 domains can be explained by presence of common neural factors affecting response gain
7 control across sensory modalities, i.e. global variations in neural excitability, functional or
8 structural connectivity, etc.

9 It is noteworthy that the majority of the ASD and NT participants in our study
10 differed neither in regard to visual sensitivity (Table 1), nor gamma parameters (Fig. 2).
11 These results suggest that the capacity to down-regulate growing neural excitation with
12 increasing intensity of a sensory input was relatively preserved in the visual cortex in our
13 high-functioning adult participants with ASD. Although an altered E/I balance is thought to
14 be an important mechanism of ASD (Levin and Nelson, 2015; Rubenstein and Merzenich,
15 2003), it is possible that it is less affected (or better compensated for (Nelson and Valakh,
16 2015)) in the visual cortex than in other cortical areas. For example, Gaetz and colleagues
17 (Gaetz et al., 2014) reported that the concentration of the inhibitory transmitter gamma-
18 aminobutyric acid (GABA) was normal in the visual cortex of adolescents with ASD, whilst
19 being significantly reduced in their auditory and motor cortices. Yet another possibility is
20 that our participants with ASD represented a subgroup characterized by a relatively low
21 prevalence of atypical sensory sensitivity, including that in the visual domain, compared to a
22 more general ASD population. For example, in the study of Crane et al, the Sensory
23 Sensitivity scores in adults with ASD were higher than in our study (Crane et al: 45.0; this
24 study: 37.7), while the corresponding scores for the NT subjects were more similar (Crane et
25 al: 33.8; this study: 31.2).

1 Recent advances in genetics and neuroscience clearly demonstrate that behavioral
2 symptoms of ASD and other neurodevelopmental disorders may stem from cardinal
3 different genetic and molecular etiologies that cause either increases or decreases in the E/I
4 ratio (Lee et al., 2017; Nelson and Valakh, 2015). Given the heterogeneous nature of ASD
5 (Gillberg, 2010; Jeste and Geschwind, 2014; Tordjman et al., 2018), the abnormal capacity to
6 regulate the E/I balance in the visual cortex could characterize only a proportion of ASD
7 individuals, as well as, e.g., patients with fragile X syndrome who are often hypersensitive to
8 visual stimuli and are suggested to have elevated neural excitability of the visual cortex
9 (Rigoulot et al., 2017; Schneider et al., 2009; Sinclair et al., 2017; Van der Molen et al., 2012).
10 Considering the reliable correlation between sensory sensitivity and GSS (Fig. 5), one may
11 predict that these individuals would demonstrate strongly reduced gamma suppression. In
12 this respect, the GSS measure may provide a biomarker that can be used to select ASD
13 subgroups according to a distinct neural phenotype – E/I imbalance in the visual cortex.
14 Considering that many promising pharmacological agents tested or being testing in the ASD
15 in clinical trials target the E/I balance, stratification of this clinical population according to
16 the relevant neural deficits is important for selection of an individually appropriate
17 treatment and tracking the treatment outcome.

18 Our study has several limitations. *First*, our participants were nearly exclusively
19 males. An additional study is needed to generalize the results to females. *Second*, each of
20 the experimental groups had a relatively small sample size, which stress the need for an
21 independent replication study. Besides, as a group, our participants with ASD did not differ
22 in their sensory responsiveness from the NT individuals, and it would be important in the
23 future to investigate gamma suppression parameters in individuals characterized by
24 excessive visual hypersensitivity. *Fourth*, our experimental paradigm was specifically aimed
25 at testing the gain control in the visual cortex, and it's unclear whether a similar modulation

1 of cortical gamma responses by input intensity is present in other sensory modalities, e.g.
2 auditory or tactile.

3

4 In conclusion, the modulation of gamma response power by intensity of visual input may
5 give important information about the neural mechanisms that mitigate rising excitation and
6 maintain E/I balance in the visual networks. Given the need for sensitive and objective
7 measures of region-specific cortical excitability in different patient populations, this input-
8 output relationship in gamma response strength offers a promising translational tool for
9 clinical research. We suggest that the slope of the stimulus-response function of visual
10 gamma oscillations may provide a tractable and accessible measure of the capacity to
11 regulate the E/I balance in visual circuitry according to intensity of the visual input. It could
12 be an especially appropriate measure in some groups of patients characterized by an
13 elevated cortical excitability and high sensitivity to visual stimuli, such as patients with
14 photo-sensitive epilepsy, migraine, and some forms of ASD. This non-invasive biomarker for
15 unbalanced cortical excitability could also be used to select distinct sub-groups of patients
16 within heterogeneous clinical populations (e.g., within ASD) and to track the impact of
17 tailored pharmacological interventions in clinical trials.

18

19 **Materials and methods**

20

21 *Participants.*

22 Twenty individuals (1 female) with ASD were included in the study, these were drawn from
23 two study groups that have been described elsewhere (Davidsson et al., 2017; Helles et al.,
24 2015). Briefly, 14 individuals had been assigned an ASD-diagnosis at three different
25 occasions by structured clinical interviews. The remaining 5 individuals had been assigned an
26 ASD-diagnosis at the Clinical Neuropsychiatry Centre in Gothenburg and then via a parental

1 interview. One individual with ASD was recruited via advertisement, whose health journals
2 were scrutinized and reviewed by a senior child and adolescent psychiatrist in order to verify
3 the diagnosis. Nineteen 'neuro-typical' (NT) participants were recruited via advertisement.
4 The NT participants underwent a brief screening focusing on neurological and psychiatric
5 disorders in order to rule out psychopathology. To assess cognitive ability the Wechsler
6 Adult Intelligence Scale, fourth edition (WAIS-IV) was used (for a few subjects in the ASD-
7 group WAIS-III data was used). Individuals with an IQ below 80 were excluded. The NT and
8 ASD group did not differ significantly in either age (ASD: 18.8-50.0 years, mean=31.1, SD=7.9;
9 NT: 19.2-40.1 years, mean=27.3, SD=6.4; $p>0.1$) or general IQ (ASD: 78-140, mean=108.8,
10 SD=15.7; NT: 96-135, mean=114.0, SD=11.5; $p>0.2$). The study has ethical approval from the
11 regional ethical review board in Gothenburg (DNR: 552-14). Participants followed the
12 informed consent procedure and were repeatedly given the option to discontinue their
13 participation in the study.

14

15 *Assessment of sensory function*

16 All the subjects filled in the Adolescent/Adult Sensory Profile questionnaire (A/ASP) (Brown
17 and Dunn, 2002). This instrument combines information about sensory processing into four
18 categories: 'Low Registration', 'Sensation Seeking', 'Sensory Sensitivity', and 'Sensation
19 Avoiding'. Here, we were interested in the Sensory Sensitivity scale that measures passive
20 behavioral responses that characterize an individual's sensitivity to environmental events,
21 such as noticing behaviors, distractibility, and discomfort with sensory stimuli.

22 The A/ASP also allows assessment of the 'Neurological Thresholds' by combining the
23 items across categories. Combined scores on the 'Sensory Sensitivity' and 'Sensation
24 Avoiding' categories constitute the 'Low Neurological Threshold' (called below 'Low
25 Threshold') that measures a person's notice of, or annoyance with, sensory stimuli. This 'Low
26 Threshold' category can be pooled for sensory modalities, as well as calculated separately

1 for sensory/behavioral domains. Here we were mainly interested in the ‘Low Threshold’ for
2 the visual modality.

3 Since we used moving visual stimuli in the present study, the velocity-related
4 suppression of gamma response might most closely reflect subject’s sensitivity to the
5 *moving* visual stimuli. Therefore, we also introduced the ‘Visual Motion Sensitivity’ scale by
6 combined two A/ASP items that measured subject’s discomfort associated with intensive
7 visual motion (i.e. Item 22: ‘*I am bothered by unsteady or fast moving visual images in*
8 *movies or TV*’; Item 25: ‘*I become bothered when I see lots of movement around me (for*
9 *example, at a busy mall, parade, carnival)*’).

10

11 *Experimental task*

12 To measure gamma, we applied an experimental paradigm that has been shown to induce
13 reliable MEG gamma responses in the visual cortex in our previous studies (Orekhova et al.,
14 2015; Orekhova et al., 2018; Stroganova et al., 2015). The stimuli were generated using
15 Presentation software (Neurobehavioral Systems Inc., USA) and presented using a FL35 LED
16 DPL gamma-corrected projector with 1920×1080 screen resolution and 120 Hz refresh rate.
17 They consisted of black and white sinusoidally modulated annular gratings with a spatial
18 frequency of 1.66 cycles per degree of visual angle and an outer diameter of 18 degrees of
19 visual angle. The gratings appeared in the center of a screen over a black background and
20 drifted to the central point at velocities of 1.2, 3.6, or 6.0°/s, (which approximately
21 corresponds to temporal frequencies of 2, 6, and 10 Hz, respectively); hereafter, we
22 respectively refer to these three velocities as ‘slow’, ‘medium’, and ‘fast’. Each trial began
23 with the presentation of a white fixation cross in the center of the display over a black
24 background for 1200 ms that was followed by the moving grating that persisted for 1200-
25 3000 ms and then stopped. The participants were instructed to respond to the termination
26 of motion with a button press. If no response occurred within 1 second, the grating was

1 substituted by a discouraging message “too late!” that remained on the screen for 2000 ms,
2 after which a new trial began. Error trials (misses or responses that occurred <150 ms after
3 the stop) were excluded from the MEG analysis. Stimuli were presented in three
4 experimental blocks in a random order resulting in 90 repetitions of each stimulus type. The
5 luminance of the screen measured at the position of the observer's eyes was 53 Lux during
6 the stimulation and 2.5 Lux during the inter-stimulus interval. Short (3-6 s) animated cartoon
7 characters were presented randomly between every 2-5 stimuli to increase vigilance and
8 minimize fatigue.

9

10 *MEG recording*

11 MEG was recorded at the NatMEG Centre (The Swedish National Facility for
12 Magnetoencephalography, KarolinskaInstitutet, Stockholm) using 306-channel system
13 (ElektaNeuromag TRIUX). The data was recorded with a band-pass filter of 0.1-330 Hz,
14 digitized at 1000 Hz, and stored for off-line analysis. The subjects' head position during MEG
15 recordings was continuously monitored.

16

17 *MRI recording*

18 Structural brain MRIs (1 mm³ T1-weighted) were obtained for all participants and used for
19 source reconstruction.

20

21 *MEG data preprocessing*

22 The data was first de-noised using the Temporal Signal-Space Separation (tSSS) method
23 (Taulu and Hari, 2009) and adjusted to a common head position. The de-noised data was
24 filtered between 1 and 145 Hz and resampled at 500 Hz. Independent component analysis
25 (ICA) was used for correction of biological artifacts. The data was then epoched (-1 to 1.2 s
26 relative to the stimulus onset) and checked for the presence of residual artifacts. After

1 rejection of the artifact-contaminated epochs and error trials, the average number of the
2 'good' epochs for the 'slow', 'medium' and 'fast' conditions was 79.5, 79.1, 77.1 in the NT,
3 and 75.4, 75.9, 76.9 in the ASD, groups. No group differences in the numbers of valid trials
4 were found (all p 's>0.3). Details for the preprocessing are given in the *Supplementary*
5 *Methods*.

6

7 *MEG source analysis*

8 Source localization was performed using linearly constructed minimum variance (LCMV)
9 beamformer implemented in the FieldTrip M/EEG toolbox (Oostenveld et al., 2011) (see
10 *Supplementary Methods* for details). For each subject and experimental condition, the
11 weighted peak gamma power and frequency were then calculated for the average spectrum
12 of the virtual sensors in 26 voxels closest to and including the 'maximally modulated voxel'
13 (the voxel in the visual cortex with highest increase of 45-90 Hz power during stimulation). A
14 frequency range of interest was defined as those frequencies where the (stimulus-
15 baseline)/baseline power ratio exceeded 2/3 of the maximum for the particular subject and
16 condition. The gamma peak frequency was calculated as the center of gravity, whereas the
17 peak power was the average power, over that range. For each subject/condition, we also
18 calculated probabilities of the post-stimulus increase in the 45-90 Hz gamma power in the
19 selection of the 26 voxels. The individual peak gamma frequencies were analyzed only if the
20 probability of the gamma power increase during stimulation relative to pre-stimulus period
21 was significant at $p < 0.0001$.

22 In order to quantify the suppression of the gamma response power with increasing
23 visual motion velocity, we introduced the 'gamma suppression slope' index. We calculated
24 the coefficient of regression of the weighted gamma power to velocity using the 'fitlm'
25 Matlab function: `fitlm(x,y,'y~x1-1')`; where $x=[1.2, 3.6, 6.0]$, $y=[0, POW_{medium}/POW_{slow}-1,$
26 $POW_{fast}/POW_{slow}-1]$ and 'y~x1-1' sets the intercept of the regression line to zero. The

1 resulting regression coefficient b is equal to zero in the case of a constant response power in
2 the three experimental conditions (i.e. 'no suppression') and is proportionally more negative
3 in case of stronger suppression of the gamma response with increasing motion velocity (Fig.
4 4).

5 The suppression of gamma response with increasing velocity can be reliably
6 estimated only if a reliable response is observed in the slow velocity condition (i.e. the
7 condition that induces a greater gamma response than the 'medium' and 'fast' conditions
8 (Orekhova et al., 2015)). Therefore, we estimated the power suppression slope only if the
9 probability of the post-stimulus gamma increase in the 'slow' condition relative to pre-
10 stimulus baseline was high ($p < 0.0001$); this lead to exclusion of one ASD participant from the
11 correlation analysis.

12

13 *Statistical analysis*

14 T-test was applied to analyze group differences in the A/ASP measures. Since the
15 distribution of some MEG parameters failed a normality test, we used Spearman coefficients
16 for correlation analyses. The repeated measures ANOVA was initially used to test for the
17 effects of Condition, Group, and Group \times Condition interaction on the gamma parameters,
18 and the post-hoc comparisons were performed using the nonparametric Mann-Whitney U-
19 test.

20

21

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4

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7

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