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1 **Neuromodulation in developing visual cortex after long-term monocular deprivation**

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1 *Abstract*

2 Neural dynamics are altered in the primary visual cortex (V1) during critical period
3 monocular deprivation (MD). Synchronization of neural oscillations is pertinent to
4 physiological functioning of the brain. Previous studies have reported chronic disruption of
5 V1 functional properties such as ocular dominance, spatial acuity, and binocular matching
6 after long-term monocular deprivation (LTMD). However, the possible neuromodulation and
7 neural synchrony has been less explored. Here, we investigated the difference between
8 juvenile and adult experience-dependent plasticity in mice from intracellular calcium signals
9 with fluorescent indicators. We also studied alterations in local field potentials power bands
10 and phase-amplitude coupling (PAC) of specific brain oscillations. Our results showed that
11 LTMD in juveniles causes higher neuromodulatory changes as seen by high-intensity
12 fluorescent signals from the non-deprived eye (NDE). Meanwhile, adult mice showed a
13 greater response from the deprived eye (DE). LTMD in juvenile mice triggered alterations in
14 the power of delta, theta, and gamma oscillations, followed by enhancement of delta-gamma
15 PAC in the NDE. However, LTMD in adult mice caused alterations in the power of delta
16 oscillations and enhancement of delta-gamma PAC in the DE. These markers are intrinsic to
17 cortical neuronal processing during LTMD and apply to a wide range of nested oscillatory
18 markers.

19

20

21 *Keywords*— Ocular dominance plasticity (ODP), long-term monocular deprivation (LTMD),
22 fiber photometry, local field potential (LFP)

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1 # I. INTRODUCTION

2 Amblyopia is a visual condition characterized by abnormal binocular vision and accompanied
3 by diminished acuity in early childhood (Hess and Thompson 2015). Ocular dominance
4 plasticity (ODP) has been demonstrated in juvenile mice. Short-term (4-5 days) monocular
5 deprivation (STMD) during postnatal day (P) 23 to 28 (P23-P28) causes the visually-driven
6 responses of neurons in the binocular zone of the primary visual cortex (V1) to shift towards
7 the non-deprived eye (open eye) (Gordon and Stryker 1996; Tagawa et al. 2005; Sato and
8 Stryker 2008). It has also been well established that following long-term monocular
9 deprivation (LTMD) from P21-P42, several functional properties in V1 become chronically
10 disrupted, including OD, spatial acuity, and binocular tuning properties (Wiesel and Hubel
11 1963; Gordon and Stryker 1996). This normal loss in plasticity with maturity, whilst
12 necessary for neural circuit stabilization, operates as a barrier to recovery because it hinders
13 cortical reorganization and can lock-in neural circuits (Lehmann and Lowel 2008).
14 Synchronization and desynchronization of neuronal ensembles at various oscillatory
15 frequencies enables the efficient routing of information between regions of plasticity during
16 critical period (CP) of development and maintenance of neuronal representation (Bonnefond
17 and Jensen 2015; Bonnefond et al. 2017). In our previous study on juvenile STMD, we
18 reported that the strengthening of new synchronous neural connections in V1 of the ipsilateral
19 eye was triggered by the augmentation of phase-amplitude coupling (PAC) in V1 of the
20 contralateral eye (Malik et al. 2022). PAC is a type of cross frequency coupling (CFC)
21 whereby the phase of low frequency oscillations modulates the amplitude of high-frequency
22 oscillations (Esghaei et al. 2022). The relationship between low-frequency oscillations
23 (LFOs) and high-frequency oscillations (HFOs) has been well established in wild-type (WT)
24 adult mice after STMD (Malik et al. 2022). However, more research is required to

1 comprehensively investigate the synchrony of neural oscillations after LTMD in both
2 juvenile and adult animals.
3 Currently, intracellular calcium signals with fluorescent indicators are used as biomarkers for
4 increased calcium activity from specific neuronal population (Cui et al. 2013; Cui et al. 2014;
5 Zhong et al. 2017; Li et al. 2019). Physiologically, changes in action potential leads to Ca^{2+}
6 influx into active neurons and this raises the cellular Ca^{2+} concentration. Fiber photometry is
7 sensitive to detect these changes in cellular Ca^{2+} concentration. Ca^{2+} CaM-binding peptide
8 (Ca^{2+} CaMP) is a widely used genetically encoded Ca^{2+} indicator (GECI/ GCaMP) composed
9 of circularly permuted green fluorescent protein (cpGFP) (Lutcke et al. 2010; Guo et al.
10 2015; Li et al. 2019; Qian et al. 2020). This GCaMP indicator can be expressed in excitatory
11 types of neurons using specific promoters. For example, previous studies injected an adeno-
12 associated virus (AAV) containing the GCaMP gene into V1 region. Subsequently, visual
13 stimulation was applied to alter the action potential of V1 neurons, resulting in the binding of
14 GCaMP to Ca^{2+}, and the increase in fluorescence intensity as detected by fiber photometry
15 (Denk et al. 1990; Korzhova et al. 2021). Despite the results obtained from previous studies,
16 there is still a need to have deepened understanding of the cortical neurodynamic and
17 neuromodulatory changes that occur after MD in both juvenile and adulthood.
18 In the present study, we investigated the change in neuronal functions in the V1 region of
19 head-fixed awake mice by comparing the calcium fluorescence of both eyes to the same
20 visual stimuli. In this regard, we monitored the neural responses to the visual stimulation in
21 form of alteration in calcium dynamics of V1 neurons. After STMD and LTMD in both
22 juvenile and adult animals, the difference in the calcium fluorescence was measured between
23 the deprived eye (DE) and non-deprived eye (NDE). We further explored the connection
24 between distinct frequency bands in the V1 of anesthetized mice by comparing the local field
25 potential (LFP) responses in the DE and NDE after LTMD of juvenile and adult mice in

response to the same visual stimuli. Subsequently, the changes in LFP power of V1 oscillations (delta, theta, alpha, beta and gamma) were measured. CFC allows different scales of neural populations to interact and enables high-level visual functions in V1. Thus, in the present study, CFC between the low (delta) frequency and high (low gamma to ultra-high gamma) frequency oscillations was also analyzed.

II. MATERIALS AND METHODS

A. Animals

In this study, WT (C57BL/6) mice were used. The animals were bred in the Laboratory Animal Research Unit (LARU) at the City University of Hong Kong. The mice were kept in individually ventilated cages on a 12-hour light/12-hour dark cycle. Five mice were housed in each cage with free access to food and water. All experimental protocols were approved by Animal Research Ethic Sub-committee, City University of Hong Kong and Department of Health, Hong Kong Special Administrative Region.

B. Experimental Design

We conducted two studies to evaluate the effect of MD during juvenile and adulthood (Fig. 1). In study 1, the effect of STMD and LTMD was examined in V1 via fiber photometry in a mouse model of amblyopia. Firstly, short-term MD in juvenile mice (n=5) and adult mice (n=5) was performed at P23 and P60 respectively (Fig. 1B, *purple shade*). Secondly, long-term MD in juvenile mice (n=7) and adult mice (n=5) was performed at P21 and P60 respectively (Fig. 1B, *green shade*). Effect of MD was evaluated by examining the response of the DE and NDE towards the visual stimuli (sinusoidal drifting gratings). The calcium fluorescence recording was performed in V1. In study 2, the effect of MD was examined in V1 via local field potentials (LFPs) in a mouse model of amblyopia. Long-term MD in juvenile mice (n=5) and adult mice (n=5) was performed at postnatal age P21 and P60

1 respectively (Fig. 1B, *blue shade*). Effect of MD was evaluated by examining the response of
2 the DE and NDE towards the visual stimuli (sinusoidal drifting gratings).

3 *C. Short-term and Long-term Monocular Deprivation*

4 For STMD, one eye was closed at P23 and P60 in juveniles and in adults, respectively, for 4
5 days. For LTMD, one eye was closed at P21 and P60 in the juveniles and in adults,
6 respectively, for 21 days. We followed a similar suturing method as detailed in our previous
7 study (Malik et al. 2022). The animals' eyes were inspected, and mice with scared corneas
8 were removed from the study.

9 *D. Visual Stimuli*

10 The visual stimuli were generated using a MATLAB (R2020b, MathWorks, USA) script
11 based on Psychtoolbox-3 (PTB-3) software on a liquid crystal display (LCD) panel with a
12 light-emitting diode backlight (Dell, P2311Hb, USA). In order to plot the receptive fields of
13 isolated single units, a monitor was placed 25 cm in front of the animal's eyes, at a 53° angle
14 to a line traced from the animals' midline. Lightbars were modified in size and orientation in
15 relevant cases to create a maximal response. Cells within the central 30-40° of the upper
16 portion of each hemifield could receive input from both the eyes (Gordon and Stryker 1996).
17 The binocular zone was defined as the central 25° of each visual hemifield. The vertical
18 meridian was defined as the intersection of the animal's midline with the tangent screen.
19 Visual stimuli of sinusoidal drifting gratings with increasing orientation angles (0-330°) and
20 0.4 cpd were presented in random order at a temporal frequency of 2 Hz. The movie lasted
21 1.5 seconds with a 1-second pause. The relative strength of the response was measured by
22 alternately presenting optimal stimuli to each eye. Same visual stimuli (sinusoidal drifting
23 gratings) were used for both calcium fluorescence and LFPs experiments.
24

1 *E. Fiber Photometry*

2 *i) Surgery and virus injection*

3 All surgical tools were autoclaved before starting the surgery. During preparation for the
4 virus injection in V1, the mice were anesthetized with pentobarbital sodium (80 mg/kg, i.p.,
5 Alfasan International B.V, Woerden, Netherlands). Lidocaine (2%, Tokyo Chemical
6 Industry, TCI, #L0156, Tokyo, Japan) was liberally applied to the incision site for local
7 analgesia. Dexamethasone (2 mg/kg, i.p., Sigma-Aldrich, Darmstadt, Germany) and
8 Carprofen (5 mg/kg, i.p., Sigma-Aldrich, Darmstadt, Germany) were injected for at least 1.5
9 hours before anesthesia to prevent brain swelling and inflammation (Li et al. 2017). To
10 maintain anesthesia during surgery, pentobarbital sodium was periodically supplemented
11 (Chen et al. 2019). The animal was mounted on a stereotaxic instrument (RWD Life Science,
12 Shenzhen, China), and the scalp was sterilized with 70% alcohol before the midline incision.
13 A section of the scalp over V1 was removed to reveal the cortex. The exposed cortical
14 surface was subsequently covered with extracellular saline to prevent drying. Throughout the
15 surgery, body temperature was maintained at 37–38°C with a heating blanket (homeothermic
16 blanket system, Harvard Apparatus, Holliston, MA, USA). The stereotaxic instrument was
17 adjusted to position the bregma and lambda at specific coordinates; anterior-posterior (AP): -
18 2.8 mm, mediolateral (ML): 3.2 mm, relative to bregma and dorsoventral (DV): 0.85 mm on
19 a leveled skull surface. About 250 nL of a 4-fold pAAV9-Syn-GCaMP6s-WPRE-SV40
20 ($2.70E^{+13}$ vg/mL) (Addgene, Watertown, MA, USA) was injected into V1 as a virus.
21 Nanoliter2000 system (World Precision Instruments, Sarasota County, FL, USA) was used
22 for all infusions. A fine-tip glass pipette filled with silicone oil was used to slowly inject viral
23 infusions into brain tissue at a rate of no more than 50 nL/min. The pipette was maintained in
24 the injection site for a further 5–10 minutes after infusion before the slow withdrawal. The
25 scalp was sutured, and a local anesthetic was administered when the pipette was removed.

1 After surgery, animals were monitored until they fully regained consciousness, after which
2 they were returned to the LARU for regular holding. After two weeks of viral expression, we
3 perfused the mice for intracellular calcium labelling.

4 *ii) Fiber optic cannula implantation*

5 The surgical techniques and craniotomy were conducted in V1 using the above-mentioned
6 coordinates. Optic fibers (Outer diameter: 400 m, numerical aperture: 0.67; Newton Inc.,
7 Hangzhou, China) were implanted in V1 to transfer signals for fiber photometry (50–100 μm
8 above virus expression). Dental cement (mega PRESS NV + JET X, megadental GmbH,
9 Büdingen, Germany) was used to secure the optic fiber. Subsequently, a long screw was
10 fastened to the skull using dental cement at a 45° angle from the vertical axis for head
11 fixation.

12 *iii) Fiber photometry instrumentation*

13 The recording of Ca^{2+} signals was performed *in vivo* in head-fixed awake mice. Fiber
14 photometry recording of V1 neurons after two weeks of pAAV9-Syn-GCaMP6s-WPRE-
15 SV40 expression, was performed as previously described (Sun et al. 2022). Briefly, the
16 implanted optic fiber was connected to a commercial 1-site fiber photometry system (Doric
17 Lenses Inc, Quebec, Canada) and the RZ5D processor (TDT, Alachua, FL, USA). Two fiber-
18 coupled LEDs (M470F3 and M405FP1, Thorlabs, NJ, USA) emitted excitation light at 470
19 nm and 405 nm that was sinusoidally modulated at 210 Hz and 330 Hz. A LED driver
20 (LEDD1B, Thorlabs, NJ, USA) connected with the RZ5D processor via synapse software,
21 controlled the intensity of the excitation light. Excitation light was delivered to the animal via
22 a fiber-optic patch cord (400 m, 0.57 NA, Inper, Hangzhou, China) embedded in a dichroic
23 mirror fixed in a single fluorescence MiniCube (Doric Lenses, Quebec, QC, Canada). The
24 intensity of the excitation light at the tip of the patch cord was adjusted to less than 30 μW to
25 avoid photobleaching (Feng et al. 2021). The emission fluorescence was collected and

transmitted through a bandpass filtered by the MiniCube. Subsequently, the fluorescent signal was detected, amplified, and converted to an analogue signal by the photoreceiver (Doric Lenses). Finally, the analog signal was digitalized by the RZ5D processor and analyzed using the Synapse software at 1 kHz with a 5 Hz low-pass filter. The recording process lasted for 1800 seconds and consisted of 300 seconds of pre-visual stimulation and 50 seconds of post-visual stimulation periods. After capturing GCaMP6s activity, Ca^{2+} signals were analyzed by custom-made scripts in MATLAB (R2020b, MathWorks, USA). The normalized values of GCaMP6s signals (1F/F, expressed as percentages) were calculated as $(F - F_0)/F_0$, where F_0 is the 5 seconds average signal during the baseline period of each trial. The mean response was calculated as average ΔF/F over 0–20 seconds to visual stimuli. Brain tissue was harvested after the recordings for validation of viral expression and optic fiber locations (Fig. 1A).

iv) Histology

Animals were anesthetized with an overdose of pentobarbital sodium and perfused with 30 mL (per animal) of 0.01 M ice-cold phosphate-buffered saline (PBS) (Sigma-Aldrich, Darmstadt, Germany) followed by 4% paraformaldehyde (PFA) in 0.01 M PBS (~30 mL/each animal) (Santa Cruz Biotechnology, Dallas, TX, USA). The brain was gently removed and immersion-fixed in 4% PFA for 24 hours. Brains sections (40 μm thick) were made on a vibratome (Leica VT1000 S, Wetzlar, Germany). A Nikon Eclipse Ni-E upright fluorescence microscope (Tokyo, Japan) was used to acquire fluorescent images.

F. Electrophysiological Signals Recording

i) Surgical procedure

The mice were anesthetized via intraperitoneal injection of ketamine–xylazine mixture (ketamine: 100 mg/kg, xylazine: 10 mg/kg). Following the induction of anesthesia, each mouse was mounted on the stereotaxic instrument (RWD Life Science, Shenzhen, China) and

1 an incision was made along the midline of the mouse head. The stereotaxic instrument was
2 adjusted to place the bregma and lambda points of the skull on a flat skull surface at
3 coordinates of AP: −3.2 mm to −4.0 mm; ML: 3.0–3.8 mm, relative to bregma. The electrode
4 was lowered into the brain to an appropriate depth of V1 (< 1 mm) and was allowed to settle
5 for 30 minutes before recording began.

6 *ii) Local field potential recording*

7 Visual stimuli of sinusoidal drifting gratings with increasing orientation angles (0-330°) and
8 0.4 cpd were presented in random order to alternate eyes. The LFP recordings were
9 performed with the use of a polyimide-coated platinum/iridium (70:30) ribbon microelectrode
10 array (Clunbury Scientific LLC, USA), as shown in Fig. 1A. The tip resistances were 30–50
11 kΩ. The A-M Systems 3600 (A-M Systems, USA) and CED Micro 1401-3 (Cambridge
12 Electronic Design, UK) instruments were used as the amplifier and data acquisition system,
13 respectively. The signals were sampled at 25 kHz and bandpass-filtered at 0.3 Hz –300 Hz
14 for LFP, amplified, and fed to spike2 software (Cambridge Electronic Design, UK). Offline
15 analysis was performed using MATLAB (R2020b, MathWorks, USA). The raw data were
16 first converted to a MATLAB-compatible format. A notch filter was applied off-line to the
17 LFP signals in order to remove the 50 Hz noise of the power line. Thus, in one recording
18 session, we sampled neuronal signals from 16 recording sites in V1 of anesthetized mice.

19 *iii) Power spectrum analysis*

20 The power spectrum of the spontaneous LFP was computed using the multi-taper estimation
21 method in MATLAB with the Chronux package. After line noise (50 Hz) had been removed
22 to reduce the variation without destroying the features, next the spectrum was smoothed by
23 using the *LOCFIT* function (provided by the Chronux toolbox) (Chen, Rasch, et al. 2015).
24 Finally, the power was normalized to the mean power across all frequency bands (0.5 Hz –

1 300 Hz). Subsequently, the mean spectral power (dB) was computed between DE and NDE
2 across juvenile and adult mice after LTMD.

3 *iv) The modulation index and the phase-amplitude comodulogram*

4 To assess the effect of LTMD on neural oscillatory synchrony in juveniles and adults, CFC
5 between LFOs and HFOs was analyzed using the PAC method. The modulation index (MI)
6 was computed based on the Kullback-Leibler MI estimation (Tort et al. 2009). The four
7 different types of CFC were investigated between the phase of the LFO [delta (0.5-5 Hz)] and
8 amplitude of HFOs [low gamma (30-55 Hz), medium gamma (60-115 Hz), high gamma
9 (125-175 Hz), and ultra-gamma (185-300 Hz)] respectively. To test the statistical
10 significance of the MI values, a distribution of 50 surrogate MI values was created. This was
11 achieved by random shuffling of the composite time series of high-frequency amplitude
12 envelopes and phases of a low-frequency signal after segmentation into 20 equal blocks.
13 Assuming the surrogate MI values were normally distributed, the MI value of the original
14 signal was considered significant if it reached the top 5% of this distribution of surrogate
15 data; otherwise, it was ignored and replaced with zero. In other words, in the comodulogram
16 plots, any MI value that was greater than zero was statistically significant. The MI values
17 were then computed between DE and NDE across juvenile and adult mice after LTMD.

18 *G. Statistical Analysis*

19 All statistical analyses were performed by the GraphPad Prism software package (version 8.0,
20 GraphPad Software Inc., CA, USA). All data were subject to tests for normality. Data for
21 which a normal distribution could not be assumed were analyzed with a Mann-Whitney U
22 tests. Data were presented as mean ± standard error of the mean (SEM).

23

24 III. RESULTS

A. Short-term Monocular Deprivation During the Critical Period Alters Calcium Fluorescence in V1

Ca^{2+} signals of V1 neurons were recorded *in vivo*, and the fluorescence intensity of GCaMP6s was used as an indicator. GCaMP6s were selectively expressed in V1 neurons. The activity of V1 neurons in juvenile and adult animals after STMD was examined using the calcium indicator GCaMP6s (Resendez and Stuber 2015) in head-fixed awake mice (Fig. 2). After STMD in juvenile mice, the neural Ca^{2+} signals in response to the visual stimuli in the DE and NDE were examined. The onset of the visual stimuli was defined as 0 seconds. Our results showed that the NDE neurons in V1 exhibited significantly higher fluorescence intensity as compared to the fluorescence intensity of DE neurons in V1 (DE vs. NDE, mean ± SEM, 0.387±0.043 vs. 0.589±0.031, $P<0.01$). In this regard, during the critical period STMD altered the neuronal activity of NDE (Fig. 2A, B, and E). As a comparison of the aforementioned results, the neural Ca^{2+} signals in DE and NDE in response to the visual stimuli in adult mice after STMD were examined. Again, the onset of the visual stimuli was defined as 0 seconds. We observed that the DE neurons in V1 exhibited significantly higher fluorescence intensity as compared to the fluorescence intensity of the NDE neurons in V1 (DE vs. NDE, mean ± SEM, 0.468±0.054 vs. 0.095±0.002, $P<0.001$) (Fig. 2C, D, and E).

B. Long-term Monocular Deprivation During the Critical Period Alters Calcium Fluorescence in V1

As stated above, Ca^{2+} signals of V1 neurons were recorded *in vivo*, and the fluorescence intensity of GCaMP6s was used as an indicator. Similarly, the activity of V1 neurons in juvenile and adult mice after LTMD was examined in head-fixed (awake) mice (Fig. 3).

After LTMD in juvenile mice, the neural Ca^{2+} signals in response to the visual stimuli in the DE and NDE were examined. The onset of the visual stimuli was defined as 0 seconds. From

1 our results, it was revealed that the NDE neurons in V1 exhibited significantly higher
2 fluorescence intensity compared to the fluorescence intensity of the DE neurons in V1 (DE
3 vs. NDE, mean ± SEM, 0.209±0.056 vs. 0.696±0.045, P<0.001). Thus, the neuronal activity
4 of NDE was altered by the LTMD (Fig. 3A, B and E). Again, we compared the neural Ca^{2+}
5 signals in V1 of DE and NDE respectively, in response to the visual stimuli in adult mice
6 after LTMD. As stated above, the onset of the visual stimuli was defined as 0 seconds. We
7 observed that the DE neurons in V1 exhibited significantly higher fluorescence intensity
8 compared with the corresponding fluorescent intensity of NDE neurons in V1 (DE vs. NDE,
9 mean ± SEM, 0.440±0.032 vs. 0.091±0.008, P<0.001) (Fig. 3C, D, and E).
10 The effect of MD on calcium fluorescence in juvenile mice was compared after STMD and
11 LTMD respectively. The percentage reduction in the calcium fluorescence was calculated for
12 DE compared to NDE neurons in V1. After LTMD in juvenile mice, a greater percentage
13 reduction in the calcium fluorescence was observed in DE in comparison to STMD (LTMD
14 vs. STMD, 69.90 % vs. 34.21%) (Fig. 3E & 2E).
15
16 *C. Distinct Frequency Bands Exhibit Different Power Variations During Juvenile LTMD*
17 The LFP power spectrum is a measure of the variance in the signal as a function of
18 frequency and is related to the time domain signals through the Fourier transform of the
19 autocorrelation function (Henrie and Shapley 2005). The changes were considered in the
20 LFP power spectrum across different frequency bands of V1 oscillations, namely delta (0.5–
21 5 Hz), theta (5–10 Hz), alpha (10.5–15 Hz), beta (15–30 Hz), and gamma (30–300 Hz) after
22 LTMD in juvenile and adult animals (Fig. 4). The mean power (MP) was calculated
23 (MP±SEM) and compared between the DE and the NDE.
24 After LTMD in juvenile mice, the MP±SEM in V1 of the DE was compared with that in V1
25 of the NDE. Significant increases in MP in V1 of the NDE compared to V1 of the DE were

observed in delta (DE vs. NDE, 19.298±0.110 vs. 23.670±1.330, P<0.001), theta (DE vs. NDE, 4.201±0.040 vs. 5.220±0.3750, P<0.05), and gamma (DE vs. NDE, 3.012±0.431 vs. 5.467±0.455, P<0.01), as shown in Fig. 4. No significant differences in the V1 MP were found between the DE and the NDE in alpha (DE vs. NDE, 0.516±0.040 vs. 0.432±0.037, P>0.05) and beta (DE vs. NDE, 1.301±0.136 vs. 1.338±0.131, P>0.05) oscillations. Similarly, after LTMD in adult mice, the MP±SEM in V1 of the DE was compared with that in V1 of the NDE. Significant increase in V1 MP of the DE was observed compared with V1 MP of NDE in delta (DE vs. NDE, 35.021±2.235 vs. 28.926±1.941, P<0.05). No significant differences in the V1 MP were found between the DE and NDE in theta (DE vs. NDE, 1.443±0.123 vs. 1.171±0.091, P>0.05), alpha (DE vs. NDE, 0.467±0.019 vs.0.419±0.020, P>0.05), beta (DE vs. NDE, 0.520±0.010 vs. 0.501±0.012, P>0.05), and gamma (DE vs. ND, 1.431±0.072 vs. 1.321±0.083, P>0.05) oscillations.

D. Phase-to-amplitude Modulations and Possible Cross-Frequency Interactions of Low-Frequency Band with Different Gamma Bands May Correlate with Juvenile LTMD Changes in V1 but not in Adult LTMD

To determine the frequency bands that were involved in PAC, comodulogram plots were constructed depicting the MI value between LFOs and HFOs on a heat map (Fig. 5A & B). After LTMD in juvenile (Fig. 5A) and adult animals (Fig. 5B), the amplitudes of the gamma HFOs were similarly modulated by the phase of the delta LFOs in both the DE and the NDE (Fig. 5A-B, dotted white box). From the comodulogram plots it was observed that after LTMD juvenile mice displayed enhanced neural oscillatory synchrony (DE vs. NDE) compared with adult mice.

In addition to comodulogram plots, the effect of MD on neuronal oscillatory synchrony was quantified by computing the MI values. Subsequently, the MI values were compared between

1 V1 of the NDE and V1 of the DE. After LTMD in juvenile mice, a significant increase in
2 MI±SEM was observed in the NDE compared with the DE (delta-gamma, DE vs. NDE,
3 0.131±0.049 vs. 5.136±0.0292×10^{-3}, $P<0.001$) (Fig. 5C). We further studied the possible
4 cross-frequency interactions of delta oscillations with different gamma bands after LTMD.
5 The MI was calculated across four different frequency combinations in V1: low-frequency
6 delta (0.5–5 Hz) and high-frequency gamma1 (30–55 Hz), gamma2 (60–115 Hz), gamma3
7 (125–175 Hz), and gamma4 (185–300 Hz) were compared between the DE and the NDE
8 (Fig. 5C). After LTMD in juvenile mice, the MI±SEM in V1 of the DE was compared with
9 that in V1 of the NDE between delta and gamma1 (DE vs. NDE, 1.934±0.130 vs.
10 8.081±0.128×10^{-3}, $P<0.001$), gamma2 (DE vs. NDE, 0.897±0.000 vs. 5.788±0.007×10^{-3},
11 $P<0.001$), gamma3 (DE vs. NDE, 1.961±0.011 vs. 3.842±0.045×10^{-3}, $P<0.001$), and gamma4
12 (DE vs. NDE, 0.482±0.000 vs. 2.831±0.057×10^{-3}, $P<0.001$). Significant differences in V1
13 MI were observed between the DE and the NDE in the coupling of the delta with different
14 gamma bands.
15 Similarly, after LTMD in adult mice, PAC between delta and gamma was measured. The
16 effect of MD on neuronal oscillatory synchrony was investigated in V1 of the NDE and the
17 DE respectively. The MI was compared between both eyes. No significant difference in V1
18 MI±SEM was observed between the DE and the NDE (delta–gamma, DE vs. NDE,
19 3.481±0.215 vs. 3.261±0.236×10^{-3}, $P>0.05$). We further explored the possibility of cross-
20 frequency interactions between delta oscillation and different gamma bands in V1, after
21 LTMD. The MI was calculated across four different frequency combinations: low-frequency
22 delta (0.5–5 Hz) and high-frequency gamma1 (30–55 Hz), gamma2 (60–115 Hz), gamma3
23 (125–175 Hz), and gamma4 (185–300 Hz) were compared between the DE and the NDE
24 (Fig. 5C). After LTMD in adult, the V1 MI±SEM of the DE was compared with that of the
25 NDE between delta and gamma1 (DE vs. NDE, 5.57±0.392 vs. 5.22±0.413×10^{-3}, $P>0.05$),

1 gamma2 (DE vs. NDE, 4.132±0.189 vs. 3.74±0.264×10^{-3}, P>0.05), gamma3 (DE vs. NDE,
2 2.631±0.214 vs. 2.551±0.180×10^{-3}, P>0.05), and gamma4 (DE vs. NDE, 1.572±0.070 vs.
3 1.152±0.050×10^{-3}, P>0.05) respectively. No significant differences in the V1 MI were
4 observed between the DE and the NDE with regards to the coupling of the delta with
5 different gamma bands.
6
7 IV. DISCUSSION
8 In the mouse model of amblyopia, visual function impairment that affects one eye can be
9 efficiently treated in juveniles but becomes irreversible in adults. This is because V1
10 plasticity declines dramatically at the end of the CP (Sale and Berardi 2015). Several studies
11 have explored the transient, persistent, and physiological effects of CP neuroplasticity. MD
12 during CP is sufficient to induce maximal loss of responsiveness of cortical neurons to the
13 DE, leading to a shift in OD (Gordon and Stryker 1996). Here, we used the calcium
14 fluorescence approach to monitor cell-type specific population activity in the OD plasticity
15 animal model. Using fiber photometry several groups have observed neural activation
16 patterns during effective reward and punishment-related behaviours (Li et al. 2016; Wang et
17 al. 2017; Zhong et al. 2017), feeding behaviours (Chen, Lin, et al. 2015), social behaviours
18 (Wang et al. 2015; Li et al. 2016; Wang et al. 2017), and long-term learning (Wang et al.
19 2017; Zhong et al. 2017). The effect of MD on the Ca^{2+} signals in the V1 of juvenile and
20 adult mice respectively remains unaddressed. Therefore, the current study used calcium
21 fluorescence to investigate the impact of short-term MD and long-term MD in head-fixed
22 awake animals on neuronal activity in V1. The alteration in the Ca^{2+} signals in V1 were
23 recorded.
24 The results showed that STMD in juvenile mice enhanced the Ca^{2+} fluorescence of neurons in
25 V1. Significant enhancement in Ca^{2+} fluorescence (P<0.01) was observed in V1 of the NDE

1 as compared with that in V1 of the DE. In contrast, our results showed that STMD in adult
2 mice significantly enhanced the Ca^{2+} fluorescence of neurons in V1 of the DE as compared
3 with that in V1 of the NDE (Fig. 2). Similarly, the results showed that LTMD in juvenile
4 mice enhanced the Ca^{2+} fluorescence of neurons in V1. Significant enhancement in Ca^{2+}
5 fluorescence was observed in V1 of the NDE as compared with that in the V1 of DE.
6 Interestingly, LTMD in juvenile produced a more significant change in Ca^{2+} fluorescence
7 between V1 of the DE and V1 of the NDE ($P<0.001$) compared to STMD in juvenile
8 ($P<0.01$). In contrast, after LTMD in adult mice significant enhancement was observed in V1
9 of the DE as compared with V1 of the NDE (Fig. 3). Interestingly, after LTMD in juvenile
10 mice, a greater percentage reduction in the calcium fluorescence was observed in DE in
11 comparison to STMD (LTMD vs. STMD, 69.90 % vs. 34.21%) (Fig. 3E & 2E). Our results
12 suggest that the Ca^{2+} fluorescence of neurons in V1 exhibits different neuronal processing
13 paradigms in juvenile MD and adulthood MD. The results also indicate that Ca^{2+}
14 fluorescence may represent a potential neuronal dynamic marker for CP plasticity. The
15 experience-dependent plasticity that juvenile MD induced was characterized by the increased
16 Ca^{2+} fluorescence in V1 of the NDE neurons. Thus, in the present study, the use of Ca^{2+}
17 fluorescence signals to detect changes in the dynamics of V1 population neurons reassured us
18 that MD during the CP of development alters the circuit plasticity in V1. Thus, these changes
19 are induced by experience-dependent plasticity in the V1.
20 In our present study, the relationship between neural activity and LTMD in juvenile and adult
21 animals respectively was examined with a focus on different oscillatory bands (delta, theta,
22 alpha, beta, and gamma). The results showed that LTMD in juvenile significantly enhances
23 the delta, theta, and gamma bands in V1 of the NDE compared with V1 of the DE ($P<0.001$,
24 $P<0.05$, and $P<0.01$). In contrast, LTMD in adult mice showed significant ($P<0.05$)
25 enhancement in delta band only in V1 of the DE compared with that in the V1 of the NDE

1 (Fig. 4). These altered oscillations are assumed to be caused solely by neural activity changes
2 that were induced by experience-dependent plasticity in the V1. The study of coupling
3 functions (LFOs and HFOs) adds a new dimension and perspective to how local neural circuit
4 interactions happen and manifest themselves in a biological system. Decomposition of
5 changes in coupling functions can be employed as biomarkers for changes in neural circuit
6 intrinsic features (Bragin et al. 1995; Roopun et al. 2008). The experience-dependent
7 plasticity is characterized by the change in the coupling between low- and high-frequency
8 synchrony. Our results suggest that PAC exhibits different neuronal processing paradigms in
9 juvenile period in comparison to adulthood after LTMD (Fig. 5). In juvenile mice, after
10 LTMD significant enhancement of PAC of the delta oscillations with all gamma bands was
11 observed in V1 of the NDE compared with that in the V1 of the DE ($P<0.001$). In contrast,
12 LTMD in adult mice did not show any significance ($P>0.05$) enhancement of PAC between
13 delta-gamma oscillations. These results indicate that PAC serves as a potential neuronal
14 dynamic marker of experience-dependent plasticity. Our results demonstrate that there may
15 be a broad range of nested oscillatory markers that are inherent to neuronal processing during
16 critical period monocular deprivation (CPMD). This is consistent with the hypothesized
17 increase in an intrinsic coupling arising from the neural oscillatory phase alignment. Thus,
18 the use of LFP signals in the present study to detect changes in the strength of PAC across
19 different states reassured us that oscillatory activity plays an active role in enabling circuit
20 plasticity in V1.

21 One common feature from LFP-based experiments that accompanies the use of anesthesia is
22 the emergence of high amplitude, coherent, low-frequency (< 12 Hz) oscillations (Sellers et
23 al. 2013; Lee et al. 2021) in V1 region, that correlate with loss of consciousness (Purdon et al.
24 2013; Lee et al. 2017). Our power spectral analysis reports similar results. In this regard, the
25 use of ketamine in rodents has been reported to increase spontaneous gamma oscillations in

both cortical and subcortical structures (Slovik et al. 2017). Furthermore, it has been reported that ketamine-xylazine mixed anesthesia have effects on CFC analysis such as increase in theta-gamma coupling/theta-HFO in hippocampus (Cardin et al. 2009) and delta-HFO CFC in the cortex (Cordon et al. 2015). In a clinical study, ketamine was not associated with increase in the power of frontal alpha rhythms, characteristic CFC patterns of frontal alpha power and slow-oscillation phase (Lee et al. 2013). Thus, it is likely that the use of ketamine-xylazine mixed anesthesia may contribute to visually induced neuronal oscillations during LTMD in juvenile and adult. Therefore, further investigations on the actual mechanism of ketamine or other anesthesia influence on our CFC results are warranted.

Previously, human studies have identified that short-term MD boosts the BOLD (blood-oxygen-level-dependent) signals to the DE recorded during fMRI and this is related to the visual response in V1(Binda et al. 2018). BOLD fMRI primarily reflects the changes in deoxyhemoglobin driven by localized changes in brain blood flow and blood oxygenation, that are coupled to underlying neuronal activity by a process termed "neurovascular coupling" (Hillman 2014). Despite extensive research, the quantitative understanding of the neural basis of BOLD signals is lacking, resulting in known limitations, such as its limited spatial and temporal resolution with regard to underlying neural activity (O'Herron et al. 2016). Our study reveals that calcium signals reflect proxy of the neural activity based on the assumption that increase in calcium fluorescence reflects increase in spiking of the underlying population in experience-dependent plasticity model (Legaria et al. 2021). The LFP signals reflects the direct activity from the population of the cells in V1.

V. LIMITATION

Neural oscillatory activities indicate the plastic state of the cortex and play an important role in enabling circuit plasticity. The goal of the current study was to understand experience-

1 dependent visual cortical plasticity in juvenile and adult animals. The neural activity in V1
2 was monitored using the fluorescent signals and LFPs from a specific neural population. The
3 limitation of fiber photometry is that it has a shorter wavelength of light and scatters more in
4 tissues compared to two-photon imaging. Subsequently, fiber photometry cannot penetrate
5 greater depths of V1. Lastly, owing to the size of the optic fiber, visualizing deeper V1 layers
6 may results in greater surgical damage in experimental animals.
7
8 ## VI. CONCLUSION

9 Our study showed that experience-dependent plasticity is modulated by neuronal population
10 activity using calcium signals and phase-amplitude coupling. The measurement described in
11 this study can be used as a biomarker of experience-dependent plasticity during both juvenile
12 and adulthood. Results from this study highlight that oscillatory activity plays an active role
13 in enabling circuit plasticity in V1. The present study opens the door to a deeper
14 understanding on how neuronal population activity is altered by monocular deprivation in the
15 developing visual cortex of mice.
16
17 ## FUNDING

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21
22 ## NOTES

23 *Conflict of interest statement.* None declared.
24
25

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Captions to figures

Fig.1. Experimental study design. (A) Schematic drawing showing the experimental setup of the same visual stimuli used for the fiber photometry (left) and electrophysiology (right) experiments. (B) The animal group classification and the timeline of the experiments. Abbreviations: *STMD*, short term monocular deprivation; *LTMD*, long term monocular deprivation; *EO*, eye opening; *EP*, eye patching; *EPR*, electrophysiology recording; *FPR*, fiber photometry recording; *VI*, viral injection; *aw*, head fixed awake animal; *an*, anesthetic animal.

Fig.2. Effects of short-term MD in juvenile and adult C57BL/6 mice with alteration in Ca^{2+} signals to visual stimuli. The percentage change in the Ca^{2+} signals were seen in V1 of the DE and NDE. (A-D) show the (%) change in the Ca^{2+} signals in response to the visual stimuli (130 trials) as indicated on the heat map and the signals. (A-B) A significant difference ($P<0.01$) was seen in the NDE and the DE in juvenile after STMD on Ca^{2+} signals across all trials. NDE calcium fluorescence was higher than DE. (C-D) Across all trials, a significant difference ($P<0.001$) was seen in V1 of the DE and the NDE in adult mice after STMD. Calcium fluorescence in V1 of the DE is higher than that of the corresponding NDE. (E) The percentage change in the Ca^{2+} signals across the groups. Juvenile mice after STMD showed significantly higher Ca^{2+} signals in V1 of NDE compared with that of the corresponding DE (**$P<0.01$). Conversely, adult mice after STMD showed significantly higher Ca^{2+} signals in V1 of DE compared with that of the corresponding NDE (**$P<0.001$). Error bars in this study indicate the standard error of the mean (SEM).

Fig.3. Effects of long-term MD in juvenile and adult C57BL/6 mice with alteration in Ca^{2+} signals to visual stimuli. The percentage change in the Ca^{2+} signals were seen in V1 of the DE and NDE. (A-D) show the

1 percentage change in the Ca^{2+} signals in response to the visual stimuli (130 trials) as indicated on the heat map
2 and the signals (A-B) Across all trials, a significant difference (P<0.001) in Ca^{2+} signals was seen in V1 of the
3 NDE and the DE in juvenile mice after LTMD. V1 of the NDE showed higher calcium fluorescence compared
4 with that in V1 of the DE. (C-D) Across all trials, a significant difference (P<0.001) in Ca^{2+} signals was seen in
5 V1 of the DE and the NDE respectively in an adult, after LTMD. Specifically, calcium fluorescence in V1 of the
6 DE was higher than that in V1 of the NDE. (E) The percentage change in the Ca^{2+} signals across the groups.
7 After LTMD, juvenile mice showed a significant difference between V1 of the DE and V1 of the NDE
8 (***P<0.001). Similarly, after LTMD, adult mice showed a significant difference between V1 of the DE and V1
9 of the NDE (***P<0.001). Error bars in this study indicate the standard error of the mean (SEM).
10

11 Fig.4. Effects of long-term MD on spontaneous LFP power in juvenile and adult C57BL/6 mice across different
12 oscillatory frequency bands. In juvenile mice, after LTMD, a significant difference was observed between V1 of
13 the DE and V1 of the NDE in only delta (***P<0.001), theta (*P<0.05) and gamma oscillations (**P<0.01). All
14 other oscillatory frequency bands showed no significant difference between V1 of the DE and V1 of the NDE
15 (alpha (P>0.05) and beta (P>0.05)). In adult mice, after LTMD, a significant difference was observed between
16 V1 of the DE and V1 of the NDE in only delta (*P<0.05). All other oscillatory frequency bands showed no
17 significant difference between V1 of the DE and V1 of the NDE (theta (P>0.05), alpha (P>0.05), beta (P>0.05)
18 and gamma (P>0.05)).
19

20 Fig.5. Effects of long-term MD in juvenile and adult C57BL/6 mice across low-frequency delta (0.5-5 Hz) and
21 high-frequency gamma (30-300 Hz) bands. (A-B) shows the comodulogram which indicates the modulation
22 index as a heat map. (A) In juvenile mice, after LTMD, a distinct difference was observed in delta-gamma PAC
23 between V1 of the DE and that in V1 of the NDE (dotted white box). (B) In adult mice, after LTMD, no obvious
24 difference was observed in delta-gamma PAC between V1 of the DE and that in V1 of the NDE. (C) Shows the
25 effects of LTMD across delta-gamma1-4 and four different frequency combinations between low-frequency
26 (delta (0.5-5 Hz) and high-frequency (gamma1 (30- 55 Hz), gamma2 (60- 115 Hz), gamma3 (125- 175 Hz) and
27 gamma4 (185- 300 Hz)) bands. In juvenile mice, after LTMD, a significant difference is observed between V1
28 of the DE and V1 of the NDE in delta–gamma1-4 (***P<0.001), delta–gamma1 (***P<0.001), delta–gamma2
29 (***P<0.001), delta–gamma3 (***P<0.001) and delta–gamma4 (***P<0.001). In adult mice, after LTMD, no

1 significant difference is observed between V1 of the DE and V1 of the NDE in delta–gamma1-4 ($P>0.05$),

2 delta–gamma1 ($P>0.05$), delta–gamma2 ($P>0.05$), delta–gamma3 ($P>0.05$), and delta–gamma4 ($P>0.05$).

3

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Experimental study design. (A) Schematic drawing showing the experimental setup of the same visual stimuli used for the fiber photometry (left) and electrophysiology (right) experiments. (B) The animal group classification and the timeline of the experiments. Abbreviations: STMD, short term monocular deprivation; LTMD, long term monocular deprivation; EO, eye opening; EP, eye patching; EPR, electrophysiology recording; FPR, fiber photometry recording; VI, viral injection; aw, head fixed awake animal; an, anesthetic animal.

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Effects of short-term MD in juvenile and adult C57BL/6 mice with alteration in Ca^{2+} signals to visual stimuli. The percentage change in the Ca^{2+} signals were seen in V1 of the DE and NDE. (A-D) show the (%) change in the Ca^{2+} signals in response to the visual stimuli (130 trials) as indicated on the heat map and the signals. (A-B) A significant difference ($P<0.01$) was seen in the NDE and the DE in juvenile after STMD on Ca^{2+} signals across all trials. NDE calcium fluorescence was higher than DE. (C-D) Across all trials, a significant difference ($P<0.001$) was seen in V1 of the DE and the NDE in adult mice after STMD. Calcium fluorescence in V1 of the DE is higher than that of the corresponding NDE. (E) The percentage change in the Ca^{2+} signals across the groups. Juvenile mice after STMD showed significantly higher Ca^{2+} signals in V1 of NDE compared with that of the corresponding DE (**$P<0.01$). Conversely, adult mice after STMD showed significantly higher Ca^{2+} signals in V1 of DE compared with that of the corresponding NDE (**$P<0.001$). Error bars in this study indicate the standard error of the mean (SEM).

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Effects of long-term MD in juvenile and adult C57BL/6 mice with alteration in $Ca2+$ signals to visual stimuli. The percentage change in the $Ca2+$ signals were seen in V1 of the DE and NDE. (A-D) show the percentage change in the $Ca2+$ signals in response to the visual stimuli (130 trials) as indicated on the heat map and the signals (A-B) Across all trials, a significant difference ($P<0.001$) in $Ca2+$ signals was seen in V1 of the NDE and the DE in juvenile mice after LTMD. V1 of the NDE showed higher calcium fluorescence compared with that in V1 of the DE. (C-D) Across all trials, a significant difference ($P<0.001$) in $Ca2+$ signals was seen in V1 of the DE and the NDE respectively in an adult, after LTMD. Specifically, calcium fluorescence in V1 of the DE was higher than that in V1 of the NDE. (E) The percentage change in the $Ca2+$ signals across the groups. After LTMD, juvenile mice showed a significant difference between V1 of the DE and V1 of the NDE (***$P<0.001$). Similarly, after LTMD, adult mice showed a significant difference between V1 of the DE and V1 of the NDE (***$P<0.001$). Error bars in this study indicate the standard error of the mean (SEM).

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Effects of long-term MD on spontaneous LFP power in juvenile and adult C57BL/6 mice across different oscillatory frequency bands. In juvenile mice, after LTMD, a significant difference was observed between V1 of the DE and V1 of the NDE in only delta (***P<0.001), theta (*P<0.05) and gamma oscillations (**P<0.01). All other oscillatory frequency bands showed no significant difference between V1 of the DE and V1 of the NDE (alpha (P>0.05) and beta (P>0.05)). In adult mice, after LTMD, a significant difference was observed between V1 of the DE and V1 of the NDE in only delta (*P<0.05). All other oscillatory frequency bands showed no significant difference between V1 of the DE and V1 of the NDE (theta (P>0.05), alpha (P>0.05), beta (P>0.05) and gamma (P>0.05)).

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Effects of long-term MD in juvenile and adult C57BL/6 mice across low-frequency delta (0.5-5 Hz) and high-frequency gamma (30-300 Hz) bands. (A-B) shows the comodulogram which indicates the modulation index as a heat map. (A) In juvenile mice, after LTMD, a distinct difference was observed in delta-gamma PAC between V1 of the DE and that in V1 of the NDE (dotted white box). (B) In adult mice, after LTMD, no obvious difference was observed in delta-gamma PAC between V1 of the DE and that in V1 of the NDE. (C) Shows the effects of LTMD across delta-gamma1-4 and four different frequency combinations between low-frequency (delta (0.5-5 Hz) and high-frequency (gamma1 (30- 55 Hz), gamma2 (60- 115 Hz), gamma3 (125- 175 Hz) and gamma4 (185- 300 Hz)) bands. In juvenile mice, after LTMD, a significant difference is observed between V1 of the DE and V1 of the NDE in delta–gamma1-4 (***$P<0.001$), delta–gamma1 (***$P<0.001$), delta–gamma2 (***$P<0.001$), delta–gamma3 (***$P<0.001$) and delta–gamma4 (***$P<0.001$). In adult mice, after LTMD, no significant difference is observed between V1 of the DE and V1 of the NDE in delta–gamma1-4 ($P>0.05$), delta–gamma1 ($P>0.05$), delta–gamma2 ($P>0.05$), delta–gamma3 ($P>0.05$), and delta–gamma4 ($P>0.05$).