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Research paper

Short-term homeostatic visual neuroplasticity in adolescents after two hours of monocular deprivation

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ABSTRACT

In healthy adults with normal vision, temporary deprivation of one eye's visual experience produces transient yet robust homeostatic plasticity effects, where the deprived eye becomes more dominant. This shift in ocular dominance is short-lived and compensatory. Previous work shows that monocular deprivation decreases resting state gamma aminobutyric acid (GABA; inhibitory neurotransmitter) levels in visual cortex, and that those with the greatest reduction in GABA have stronger shifts due to monocular deprivation. Components of the GABAergic system in visual cortex vary with age (early childhood, early teen years, ageing); hence if GABA is critical to homeostatic plasticity within the visual system, adolescence may be a key developmental period where differences in plasticity manifest. Here we measured short-term visual deprivation effects on binocular rivalry in 24 adolescents (aged 10–15 years) and 23 young adults (aged 20–25 years). Despite differences in baseline features of binocular rivalry (adolescents showed more mixed percept $p < 0.001$ and a tendency for faster switching $p = 0.06$ compared to adults), deprived eye dominance increased ($p = 0.01$) similarly for adolescents and adults after two hours of patching. Other aspects of binocular rivalry – time to first switch (heralding the onset of rivalry) and mixed percept – were unaltered by patching. These findings suggest that binocular rivalry after patching can be used as a behavioral proxy for experience-dependent visual cortical plasticity in adolescents in the same way as adults, and that homeostatic plasticity to compensate for temporarily reduced visual input is established and effective by adolescence.

1. Introduction

To interact efficiently with the world, our brain must continuously adjust to changes in experience and environment through neuroplasticity. A particular form of neuroplasticity – homeostatic plasticity – works to maintain neural stability despite changes in the environment (Turrigiano, 2012) including in the sensory cortices (Gainey and Feldman, 2017). Homeostatic plasticity can boost neural activity (e.g., in rodent visual cortex) to compensate for reduced sensory input (e.g., monocular deprivation) (Hengen et al., 2013; Keck et al., 2013). Similar homeostatic mechanisms exist in the human visual system. Temporary deprivation of one eye's visual experience produces transient yet robust neuroplasticity effects on ocular dominance (Lunghi et al., 2011). In healthy adults with normal vision, both eyes provide approximately equal visual input to the brain. However, after patching for 15 minutes (Min et al., 2018) to 5 hours (Ramamurthy and Blaser, 2021), the deprived eye becomes temporarily more dominant (see recent reviews by Baroncelli and Lunghi, 2020; Castaldi et al., 2020).

This short-lived compensatory boost in vision has potential therapeutic effect. Traditionally, patching or penalization therapy for amblyopia – a neurodevelopmental condition caused by disrupted visual experience to one eye – has not been applied in adolescence, as such treatment was not considered effective past approximately 12 years of age (Repka, 2020). However, two hours of patching of either eye (the amblyopic or better eye) produces similar homeostatic plasticity effects on ocular dominance (Lunghi et al., 2016; Tao et al., 2020). Furthermore, amblyopic vision has been successfully remediated with repeated temporary patching over months (Lunghi et al., 2019; Zhou et al., 2019), suggesting that homeostatic plasticity might accumulate and lead to longer-term changes in ocular dominance (Bao et al., 2018; Basgoze et al., 2018). In this study, we were motivated to determine whether the mechanisms of visual cortical regulation that are likely to be critical for

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improving vision in amblyopia are active in adolescence, and whether they differ from early adulthood.

To quantify the shift in ocular dominance, many studies of homeostatic plasticity have used a binocular rivalry paradigm (Bai et al., 2017; Binda et al., 2018; Binda and Lunghi, 2017; Finn et al., 2019; Lunghi et al., 2011, 2013, 2015a, 2015b, 2019; Lunghi and Sale, 2015; Nguyen et al., 2021; Ramamurthy and Blaser, 2018; Sheynin et al., 2019a, 2019b; Virathone et al., 2021). Binocular rivalry occurs when the inputs to corresponding locations in the two eyes are markedly different, resulting in the visual system fluctuating between the two perceptual states representing the separate inputs. Rivalry involves periods of alternating physiological and perceptual dominance and suppression, driven by reciprocal inhibition from the two inputs prior to excitatory combination of binocular signals (Ding and Sperling, 2006; Meese et al., 2006).

Following short-term deprivation, altered periods of dominance in rivalry have been observed that reflect the putative change in brain excitatory-inhibitory (E-I) balance, i.e. increased signal/response from the deprived eye (and often a concomitant signal/response decrement from the fellow eye) measured using electrophysiology (Lunghi et al., 2015a; Zhou et al., 2015), neuroimaging (Binda et al., 2018; Chadnova et al., 2017) and perceptual contrast matching (Zhou et al., 2013). Monocular deprivation also decreases the resting state levels of the major inhibitory neurochemical gamma aminobutyric acid (GABA) in visual cortex (Lunghi et al., 2015b). Thus, interocular contrast gain control mechanisms – possibly mediated by GABA – may be altered by short-term monocular deprivation prior to binocular combination of signals (also supported by macaque studies, see Begum and Tso, 2015), which are then leveraged to restore the temporary disruption to ocular dominance induced by patching (Lunghi et al., 2011; Ramamurthy and Blaser, 2021; Spiegel et al., 2017).

In binocular rivalry, a mixture of percepts is also possible, but is less common than the truly rivalrous experience. The prominence of mixed percept has been causally linked to GABAergic inhibition through direct and specific pharmacological manipulation (Mentch et al., 2019). In adults, homeostatic plasticity effects can be predicted by the baseline proportion of mixed percept and duration of dominance phases (Steinwurzel et al., 2020) – two binocular rivalry features that depend on inhibition and are likely, but not necessarily exclusively, mediated by GABA. Hence, any conditions of brain E-I imbalance would predict altered homeostatic plasticity strength. Post-mortem tissue analysis of human visual cortex shows that components of excitatory and inhibitory neurotransmitter systems vary with age (Pinto et al., 2010; Siu et al., 2017). Adolescence, or the early teen years, is a key developmental period, after the approximate closure of the critical period and experience-dependent plasticity. To date, all reports investigating homeostatic plasticity effects on ocular dominance and binocular rivalry have tested adults with normal vision. In this study, we sought to determine whether adolescents show the same homeostatic plasticity effects on ocular dominance relative to younger and older adults, reflecting possible changes in cortical neurotransmitter that influence E-I balance across a lifetime.

2. Material and methods

2.1. General methods

The study was approved by the University of Melbourne Human Research Ethics Committee (#22990) and all procedures adhered to the Declaration of Helsinki. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study below. No part of the study procedures nor study analysis were pre-registered prior to the research being conducted.

2.2. Participants

Previous work (Lunghi et al., 2019) measured ocular dominance after two hours of patching and found a difference in visual homeostatic plasticity between two independent groups of large effect size (d=1.50). Based on this data, a power analysis in G*Power (Faul et al., 2007) determined that $n = 22$ in each group would be sufficiently powered (95 %) to detect a two-tailed difference in short-term visual plasticity of smaller effect size (d=1.125) between two independent group means at $\alpha = 0.05$.

We recruited adolescents (aged 10–15 years) and young adults (aged 20–25 years) via advertisements placed at The University of Melbourne and relevant community noticeboards, word-of-mouth, and from a database of previous participants willing to be contacted for research volunteer opportunities. Adult participants provided written informed consent, while written consent was obtained from both the parent/legal guardian and the adolescent participant. All participants received a $40 gift voucher to contribute to travel expenses incurred in attending the test session.

Participants underwent a brief vision and ocular health screening at the beginning of the test visit. The following inclusion criteria were established prior to data analysis: best-corrected distance monocular visual acuity of at least 6/7.5 (logMAR) in each eye (i.e., no amblyopia), spectacle correction no more than ± 5 D sphere and − 2 D astigmatism, normal ocular health findings on slit lamp biomicroscopy and ophthalmoscopy, no ocular disease, no history of patching or ocular surgery (including laser refractive correction), no systemic conditions known to affect vision (e.g., diabetes), no psychoactive medications (e.g., for epilepsy, attention deficit hyperactivity disorder, depression). Given the binocular rivalry task required participants to maintain binocular fusion of two disparate images, we also screened for significant ocular misalignment. One participant with a large exophoria was unable to consistently fuse the binocular rivalry target, leaving 24 adolescents (mean ± standard deviation: 13 ± 1 years) and 23 young adults (22 ± 2 years).

2.3. Experimental procedure

To ensure consistency of training, all participants were given the same set of instructions and examples of visual stimuli before completing at least one practice run. For baseline measures, participants completed up to three binocular rivalry runs (2.5 minutes each). Only two baseline runs were required if sensory ocular dominance was consistent for the first two runs, otherwise a third run was conducted to confirm the dominant eye to be patched. Two post-patching binocular rivalry runs were completed immediately after patch removal.

2.4. Binocular rivalry

The experimental setup was duplicated in two rooms to enable simultaneous testing for multiple participants. Software was written in PsychoPy Version 3.0 (Peirce et al., 2019) to present the visual stimuli on a gamma-corrected Zowie XL2430-B liquid-crystal display monitor (BenQ, Taipei, Taiwan; 100 Hz frame rate, 1920 × 1080 pixel resolution) or an iMac computer (Apple, Cupertino, USA; 60 Hz frame rate, 2560 × 1440 pixel resolution) set to the same mean luminance (52 cd/m^2 gray background). Participants viewed the stimuli dichoptically and with their appropriate refractive correction for the 60 cm working distance through a mirror stereoscope (ScreenScope, Stereo Aids, Albany, Australia).

The binocular rivalry stimuli were two equiluminant circularly windowed sinusoidal grating patterns (2° diameter, 2 cyc/deg spatial frequency) presented at the center of two annular fusion rings (12° diameter, 0.3° width of annulus). The fusion rings, consisting of random black and white dots with zero disparity, remained on screen throughout testing. At the start of each test run, participants confirmed fusion by

reporting alignment of a vertical line (0.5° length) and horizontal line (0.5° width), creating a binocularly fused central fixation cross that disappeared when the test run began. The red and green patterns were presented to the left and right eyes, respectively, and the stimuli presented to each eye remained consistent in color and orientation throughout the experiment. Colored gratings were used as these induce stronger effects on ocular dominance plasticity than achromatic stimuli (Lunghi et al., 2013).

Responses were collected via mouse button press. Participants were instructed not to press a button until the first change in percept (onset rivalry, measured by the time to first switch). Thereafter, participants pressed one of three buttons to indicate each change in percept during sustained rivalry (switching): right mouse button for an exclusive "red" or "right-tilted" (45° orientation) percept, left mouse button for an exclusive "green" or "left-tilted" (135° orientation) percept, and the middle mouse button for mixed percept (piecemeal or superimposed, when neither percept clearly dominated). The duration of each percept (time between switches) was recorded. For data analysis, time to first switch and time after final switch were deducted from the total test duration of 2.5 minutes to give the total sustained rivalry time. Four key binocular rivalry features depicted in the schematic of Fig. 1 were quantified: (a) ocular dominance index (Lunghi et al., 2019; Nguyen et al., 2021), taken as the ratio between total time spent seeing the dominant eye percept and the sum of time spent in exclusive percepts (dominant + non-dominant) during sustained rivalry; (b) percentage of time spent seeing mixed percept during sustained rivalry; (c) onset rivalry (time to first switch); and (d) switch rate (switches per minute) during sustained rivalry.

2.5. Short-term monocular deprivation

The dominant eye at baseline (i.e., sensory ocular dominance determined from binocular rivalry as per Ooi and He, 2020) was patched for two hours using two layers of translucent Leukofix adhesive tape (BSN Medical, Mulgrave, Victoria, Australia) that resulted in 28 % light attenuation and completely degraded form perception. Participants performed normal seated activities in standard room lighting for the duration of patching, such as working on a computer, watching a tablet or mobile device, drawing, or playing video games with their habitual refractive correction in place where appropriate.

2.6. Statistical analysis

Statistical analysis was conducted using SPSS version 27.0 (IBM, Armonk, NY, USA). First, baseline binocular rivalry measures were compared between groups. Next, to determine whether there was an effect of monocular deprivation (patching), we compared performance between baseline and 0 mins post-patch removal. For normally distributed data (Kolmogorov-Smirnov test $p > 0.05$), a repeated measures analysis of variance (RM-ANOVA) was conducted. When the assumption of normality was violated (Kolmogorov-Smirnov test $p < 0.05$), within-group paired Wilcoxon signed rank tests were used to compare baseline and post-patching performance. A significance level of $p < 0.05$ was set as our criterion for statistical significance, except where multiple comparisons were corrected by a Holm-Bonferroni sequentially rejective procedure. Effect sizes (η^2 or partial η^2 for parametric tests, Cliff's delta δ for non-parametric tests) are provided for all statistically significant comparisons. All raw data appear in the Supplementary material A.

3. Results

3.1. Experiment 1A: Baseline binocular rivalry in adolescents vs young adults

At baseline, ocular dominance was similar in the two groups ($t(45) = -0.84$, $p = 0.41$). Mean (± standard deviation) ocular dominance index in adolescents and adults was 0.54 (± 0.04) and 0.55 (± 0.04), respectively (Fig. 2A). Adolescents showed more mixed percept compared to adults (Fig. 2B; Mann-Whitney $U = 77.5$, $p < 0.001$, Cliff's delta $\delta = 0.72$). Median (interquartile range) percentage of mixed percept at baseline was 7.31 % (2.52–11.4 %) for adolescents compared to 0 % (0–0.90 %) for adults. Baseline onset rivalry, as measured by the time to first switch, was similar in adolescents and adults (Fig. 2C; Mann-Whitney $U = 216$, $p = 0.20$). Median (interquartile range) time to first switch for the adolescents and adults was 2.69 (2.25–3.55) seconds and 2.55 (2.07–3.06) seconds, respectively. Fig. 2D shows a trend ($t(45) = 1.90$, $p = 0.06$) for higher baseline switch rate in the adolescent group (mean ± standard deviation: 34.0 ± 8.84 switches per minute) compared to the adult group (29.5 ± 7.28 switches per minute).

3.2. Experiment 1A: Effect of deprivation in adolescents vs young adults

Ocular dominance was similar between groups at baseline and after patching (RM-ANOVA main effect of group: $F(1,45) = 1.80$, $p = 0.19$). The ocular dominance index after two hours of monocular deprivation for adolescents and young adults was 0.56 ± 0.07 (mean ± standard deviation) and 0.59 ± 0.07 respectively. Thus, immediately after patch removal, ocular dominance shifted by a similar magnitude in favor of the deprived eye in both adolescent and adult groups (Fig. 3A; RM-

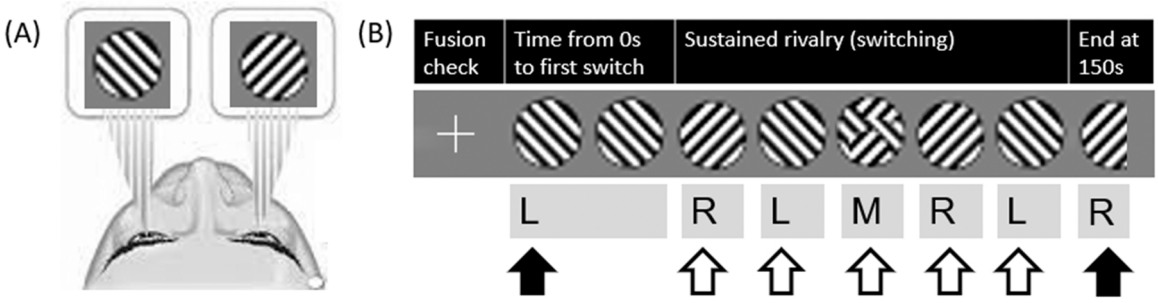

Fig. 1. Schematic of the binocular rivalry task. (A) Binocular rivalry occurs when perception (when the two eyes are open) alternates between two irreconcilable images that are shown to each eye separately. (B) Each binocular rivalry test run began after the participant confirmed a binocularly fused central fixation cross. The first percept (first filled arrow) was not counted as a switch; its duration was discarded from the total sustained rivalry time. Onset rivalry (time to first switch) was measured from time = 0 to the first button press (first unfilled arrow) to indicate the first perceptual switch. During sustained rivalry, the frequency of switching (switch rate) was measured by each button press (unfilled arrows). Participants could press one of three buttons (L, R, M) to indicate each new perceptual switch, where L and R are the exclusive dominance percepts and M indicates mixed percept, where neither percept dominated. Because the final percept was always truncated (final filled arrow) by the test run ending at 150 seconds, the time between final button press and end of test run was discarded. The durations of each percept (L, R, M) were summed to calculate the percentage of total sustained rivalry time spent in the dominant, non-dominant and mixed percepts.

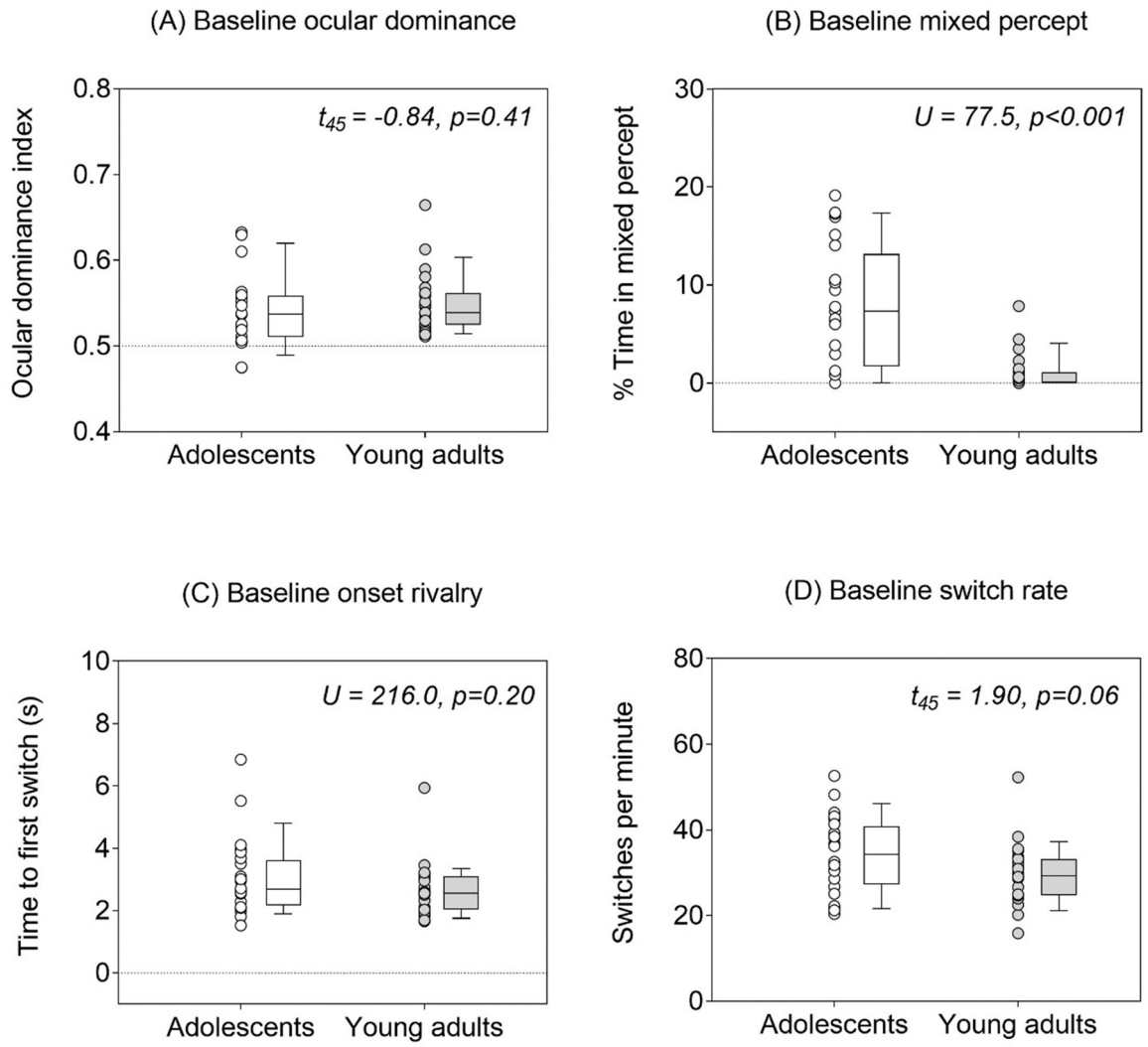

Fig. 2.. Baseline binocular rivalry features in the adolescent (n = 24, unfilled symbols) and young adult (n = 23, filled symbols) groups. (A) Ocular dominance index, where an index of 0.5 (horizontal dotted line) indicates equal dominance of the two eyes and an index > 0.5 shows that one eye is more dominant than the other. (B) Percentage of total time spent seeing mixed percept. (C) Onset rivalry, measured by the time to first switch (seconds). (D) Switch rate, measured by the number of switches per minute. For all panels, individual data are shown in addition to summary boxplots. Boxes depict the median and 25th and 75th percentiles, and the whiskers depict the 10th and 90th percentiles. P-values are shown for the between group comparisons.

ANOVA main effect of patching: $F(1, 45) = 8.41$, $p = 0.01$, partial $\eta^2 = 0.16$; group × patching interaction: $F(1, 45) = 0.75$, $p = 0.39$).

Patching did not affect the percentage of time spent in mixed percept for either adolescents (Fig. 3B; Wilcoxon signed rank test: $p = 0.19$) or adults (Fig. 3B; Wilcoxon signed rank test: $p = 0.30$). Median (interquartile range) percentage of mixed percept after patching was 8.9 % (2.08–16.9 %) for adolescents, compared to 0 % (0–2.04 %) for adults.

Onset rivalry, measured by time to first switch, did not change after patching for the adolescent group (Fig. 3C; Wilcoxon signed rank test: $p = 0.12$; median [interquartile range]: 3.15 [2.93–4.66] seconds) but did increase in the adult group (Fig. 3C; Wilcoxon signed rank test: $p = 0.01$, Cliff's delta $\delta = 0.82$) to 2.95 (2.63–3.47) seconds after two hours of monocular deprivation.

Both groups showed a reduction in switch rate after patching (Fig. 3D; RM-ANOVA main effect of patching: $F(1, 45) = 7.87$, $p = 0.01$, partial $\eta^2 = 0.15$). Monocular deprivation produced less frequent switching in the adolescents of 33.3 ± 9.40 (mean ± standard deviation) switches per minute, and in adults, a rate of 26.0 ± 6.32 switches per minute. The tendency for higher baseline switch rate observed in the adolescents compared to adults was maintained after patching (Fig. 3D; RM-ANOVA main effect of group: $F(1,45) = 7.02$, $p = 0.01$, partial $\eta^2 = 0.14$); however, the difference in effect of patching on switch rate between groups did not reach statistical significance (RM-ANOVA group × patching interaction: $F(1,45) = 3.30$, $p = 0.08$). Overall, two hours of monocular deprivation produced similar outcomes in adolescents as in adults.

3.3. *Experiment 1B: Effect of deprivation – Comparison to older adult data*

Given there was no difference between adolescents and young adults in the effect of deprivation on ocular dominance shift (Fig. 3A) nor on switch rate (Fig. 3D), we pooled the two groups into a 'younger' group to compare against published 'older' group data collected using the same methods (Nguyen et al., 2021). Participants in the older group were aged 60–81 years (mean ± standard deviation: 68 ± 6 years). Although older adults showed more balanced (i.e., closer to 50 %) ocular dominance at baseline compared to the combined adolescents and young adult group (Mann Whitney U test: $p = 0.002$, Cliff's delta $\delta = 0.43$), ocular dominance index at baseline shifted towards the deprived eye by the same magnitude for both younger and older groups (Fig. 4A; RM-ANOVA main effect of patching: $F(1,75) = 13.89$, $p < 0.001$, partial $\eta^2 = 0.16$;

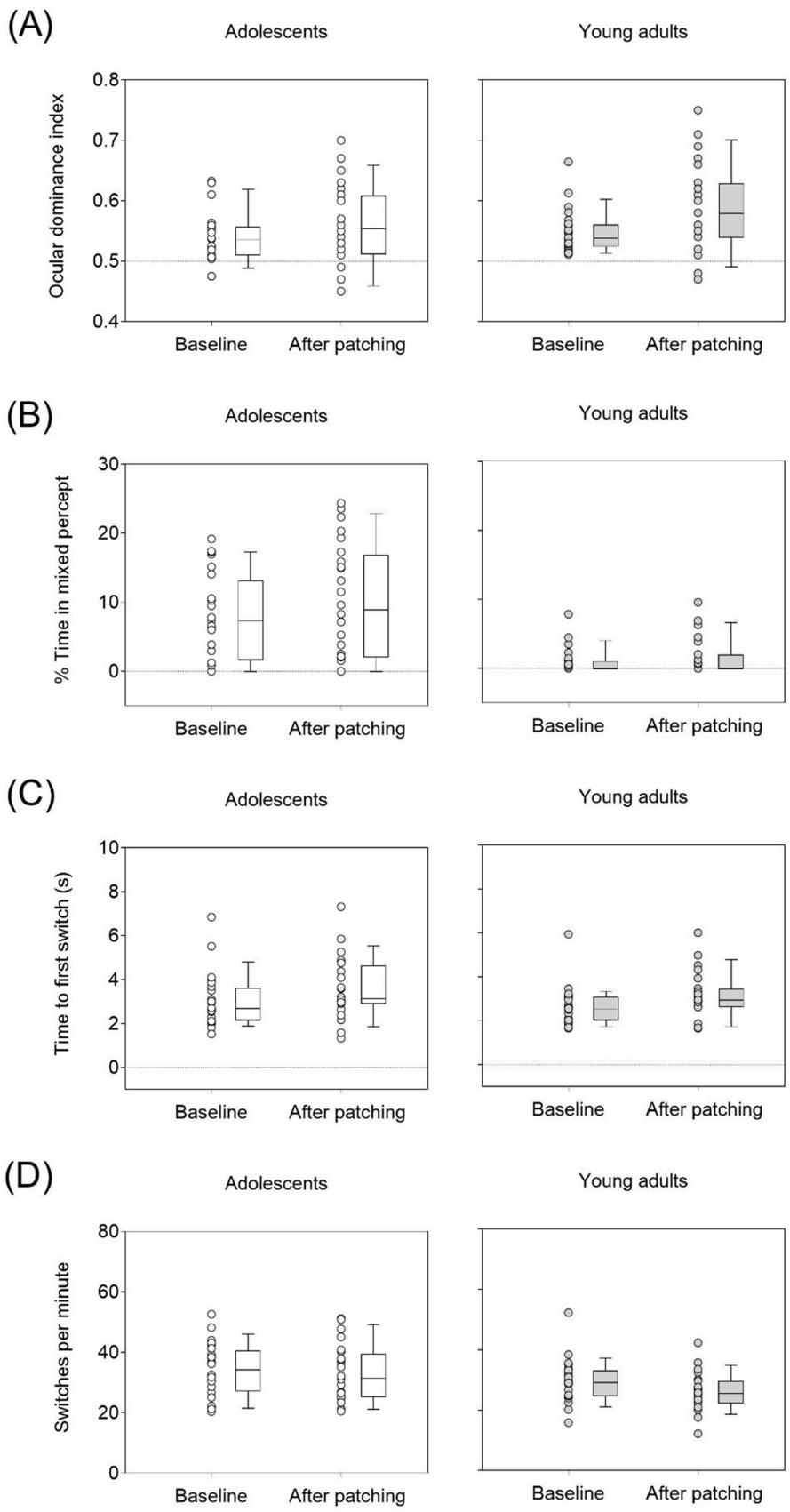

Fig. 3.. Binocular rivalry features at baseline and after patching in the adolescent (n = 24, unfilled symbols) and young adult (n = 23, filled symbols) groups. (A) Ocular dominance index, where an index of 0.5 (horizontal dotted line) indicates equal dominance of the two eyes and an increase in index > 0.5 indicates a shift in ocular dominance towards the deprived eye after patching. (B) Percentage of total time spent seeing mixed percept. (C) Onset rivalry, measured by the time to first switch (seconds). (D) Switch rate, measured by the number of switches per minute. For all panels, individual data are shown in addition to summary boxplots. Boxes depict the median and 25th and 75th percentiles, and the whiskers depict the 10th and 90th percentiles.

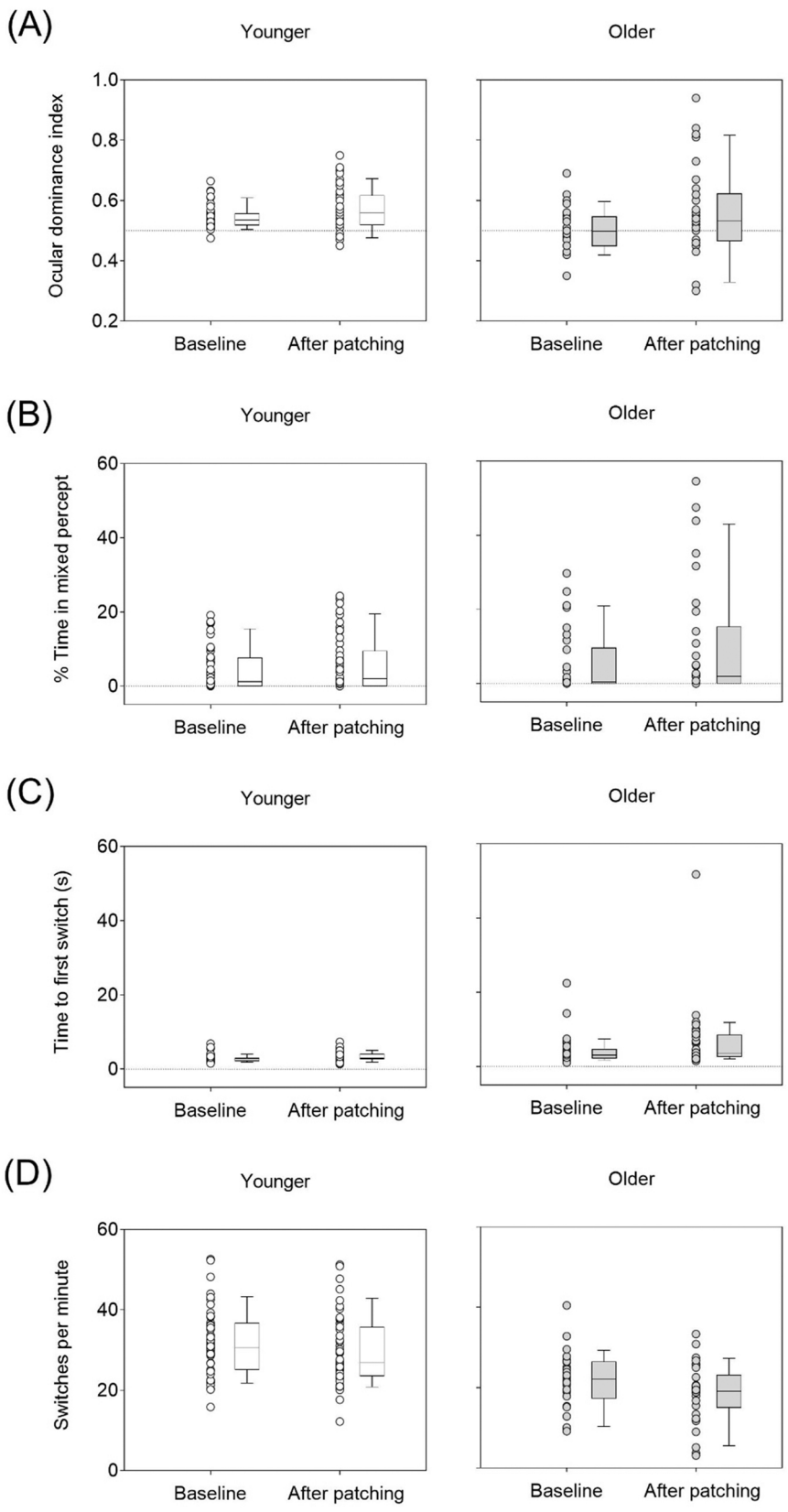

Fig. 4.. Binocular rivalry features at baseline and after patching in the combined adolescent and young adult group (n = 47, unfilled symbols) and older (n = 30, filled symbols) groups. Older adult data is a subset of data from Nguyen et al., 2021): replotted and reanalyzed. (A) Ocular dominance index, where an index of 0.5 (horizontal dotted line) indicates equal dominance of the two eyes and an increase in index > 0.5 indicates a shift in ocular dominance towards the deprived eye after patching. (B) Percentage of total time spent seeing mixed percept. (C) Onset rivalry, measured by the time to first switch (seconds). (D) Switch rate, measured by the number of switches per minute. For all panels, individual data are shown in addition to summary boxplots. Boxes depict the median and 25th and 75th percentiles, and the whiskers depict the 10th and 90th percentiles.

group × patching interaction: $F(1,75) = 1.43$, $p = 0.24$). Similarly, despite the younger group demonstrating faster switch rates at baseline ($t(75) = 5.44$, $p < 0.001$, $\eta^2 = 0.28$), both younger and older groups showed similar magnitudes of reduction in switch rate after two hours of monocular deprivation (Fig. 4B; RM-ANOVA main effect of patching: $F(1,75) = 19.70$, $p < 0.001$, partial $\eta^2 = 0.21$; group × patching interaction: $F(1,75) = 0.89$, $p = 0.35$). Thus, our results find consistent short-term homeostatic visual plasticity effects across adolescence,

younger adulthood and older adulthood, when the patching duration is 2 hours.

3.4. Relationship between ocular dominance plasticity and baseline demographics

To investigate the inter-individual variability of short-term homeostatic ocular dominance plasticity, we combined the young adult and adolescent data in our study (given no difference between the groups in the effect of deprivation). Age did not predict the shift in ocular dominance after patching across the entire age range ($n = 77$, Pearson $r = 0.13$, $R^2 = 0.02$, $p = 0.25$). There was also no relationship between baseline mixed percept and post-deprivation ocular dominance (Spearman rho $= 0.09$, $p = 0.42$).

Duration of dominance phases is inversely related to switch rate; we found that baseline switch rate did not predict ocular dominance variability after short-term monocular deprivation (Pearson $r = -0.09$, $R^2 = 0.01$, $p = 0.44$). The lack of correlation is not surprising given that adolescents differed from adults in their proportion of mixed percept (Fig. 2B) and switch rate (Fig. 2D) at baseline, but showed similar ocular dominance plasticity effects (Fig. 3 A).

4. Discussion

Homeostatic plasticity is considered to be adaptive and compensatory, hence the growing interest in the capacity of sensory cortices to adapt, remodel or reverse the negative effects of abnormal experience, and respond effectively to new treatments such as artificial vision restoration devices (Baroncelli and Lunghi, 2020; Castaldi et al., 2020). Our study explored whether the homeostatic plasticity effects on binocular rivalry seen after two hours of monocular deprivation, which are well-established in adults (Bai et al., 2017; Binda et al., 2018; Binda and Lunghi, 2017; Finn et al., 2019; Lunghi et al., 2011, 2013, 2015a, 2015b, 2019; Lunghi and Sale, 2015; Nguyen et al., 2021; Ramamurthy and Blaser, 2018; Sheynin et al., 2019a, 2019b; Virathone et al., 2021), are also present in adolescents. We confirm a similar shift in ocular dominance in adults (both younger and older) and adolescents in favor of the deprived eye for patching durations of 2 hours. Our findings, consolidated across several of our studies using the same methods, are encouraging for future attempts to use homeostatic plasticity to rehabilitate or restore visual function in a wide age range of people, as the ability of the visual system to boost its response to environmental pressure (i.e., visual deprivation) is preserved from adolescence through adulthood, and even into the 7th or 8th decade of life (Nguyen et al., 2021).

Because patching influences interocular contrast gain control mechanisms, at least in adults (Zhou et al., 2013, 2015), we presume that the same mechanisms also underlie the plasticity effects on ocular dominance observed here in adolescents. Unlike infants (Candy et al., 2001; Garcia-Quispe et al., 2009) and younger children (Pei et al., 2017; Zemon and Gordon, 2006), typically developing adolescents show comparable contrast gain characteristics as adults, measured electrophysiologically (Pei et al., 2017; Zemon et al., 1995; Zemon and Gordon, 2006). This suggests that the neural mechanisms that flexibly adjust to changes in the environment (e.g., different levels of contrast) to enable efficient coding are still immature in early childhood but undergo the final stage of development during late childhood and adolescence.

Although the main focus of this study was to explore short-term homeostatic visual plasticity, our results also contribute to the literature on binocular rivalry in healthy children and adolescents. Spontaneous alternations between two rivalrous percepts can be demonstrated physiologically using dichoptic visual evoked potential recordings (non-invasive electrophysiology) in adults, but similar techniques in infants aged between 5 and 15 months have failed to detect physiological evidence of binocular rivalry (at least for orthogonal 1 cyc/deg gratings reversing at 5 and 7.5 Hz) despite normal development of binocularity i.e., existence of fully segregated ocular dominance columns and combination of monocular signals to form binocular vision (Brown et al., 1999). Binocular rivalry switch rates were found to be significantly higher in young children aged 5–6 years compared to adults (Kovacs and Eisenberg, 2005). Similarly, 9 and 12 year-olds (Hudak et al., 2011) and, in our study, adolescents aged between 10 and 15 years showed a tendency for faster switching than young adults, lending support for the general observation that alternation time (percept duration) gradually prolongs with age across a lifetime (Jalavisto, 1964; Pitchaimuthu et al., 2017; Ukai et al., 2003).

At baseline, we also found more binocular rivalry mixed percept in adolescents compared to young adults. While this finding was unexpected, we confirm that the use of a mirror stereoscope rules out the possibility of bleeding of the images between the eyes, and therefore the increased mixed percept in the adolescents cannot be attributable to a methodological limitation of our experimental apparatus. To explore this novel finding further, future studies could investigate binocular rivalry as a function of stimulus size and induce more mixed percept in adults using larger stimuli, as per previous work (Kovacs and Eisenberg, 2005). There is also complementary data in 5–14 year-olds showing immature long-range spatial integration compared to adults (Kovacs, 2000; Kovacs et al., 1999), which would predict a greater incidence of mixed binocular rivalry percept in children and adolescents as observed here. Overall the literature suggests a prolonged developmental trajectory of binocular vision, visual spatial integration and the interocular inhibitory neural machinery and/or neurotransmitter systems that are putatively involved in generating mixed percept.

Some insight about which neurotransmitters might differ between adolescents and adults comes from direct manipulations of GABA using drugs that increase inhibition in the brain in healthy human adults (Mentch et al., 2019). Both $GABA_A$ and $GABA_B$ receptor subtypes are densely expressed in the input layer 4 of the human primary visual cortex (March and Shaw, 1993; Munoz et al., 2001). Time spent in mixed percept is significantly reduced with administration of clobazam, a $GABA_A$ agonist, and slightly reduced with arbaclofen, a $GABA_B$ agonist (Mentch et al., 2019). Faster switching and more mixed percept suggest earlier release of inhibition or less inhibition at baseline in adolescents. Developmental changes in the components of the GABAergic signaling system early in adolescence are complex and do not predict a single overall effect on visual cortical inhibition. However, the balance of evidence – albeit in a very small sample of post-mortem tissue – appears to be in favor of increased circulating GABA in the adolescent (pre-teen) visual cortex. Reduced cannabinoid CB1 receptor expression levels would predict increased GABA release, increased GAD65 enzyme would predict increased GABA synthesis and reduced VGAT (vesicular transporter) would predict reduced loading of GABA into synaptic vesicles (Pinto et al., 2010). Note that other GABAergic system components have not been identified to be different between adults and teenagers (e.g. gephyrin, GABAAα1 and GABAAα2 protein expression) (Pinto et al., 2010). We recognize the limitations in predicting how single molecular changes observed in post-mortem tissue relate to in vivo overall visual cortical processing and visual perception.

Despite having a different visual cortical E-I balance at baseline, the adolescents showed similar regulation of E-I processes to young adults as a consequence of patching. In adults, the shift in monocular deprivation is correlated with a reduction in resting state GABA levels visual cortex (Lunghi et al., 2015b); however, that study did not show that the baseline level of GABA is itself correlated with the magnitude of the patching effect. Consistent with faster switching and more mixed percept, we might therefore have predicted a smaller shift in ocular dominance in adolescents following temporary monocular deprivation. We did not find such an effect, providing further support that binocular rivalry inhibition is not exclusively modulated by GABA and other neurotransmitters (e.g., acetylcholine) are possibly involved in regulating gain control in human vision and neural responses (Kosovicheva et al., 2012; Nguyen et al., 2018; Schallmo et al., 2018; Sheynin et al.,

2019) that contribute to the homeostatic plasticity effect on ocular dominance. Alternately, our results could be interpreted as indicating that the baseline level of inhibition – or baseline resting GABA level – does not relate to the ability to regulate inhibition during short-term monocular deprivation. In other words, baseline resting GABA does not appear to predict both the magnitude of the ocular dominance shift due to patching and the magnitude of change in resting state GABA due to patching.

A recent study demonstrated that deprivation effects are biphasic, reflecting two opposing processes acting at two different timescales (Ramamurthy and Blaser, 2021). Monocularly occluding one eye for 10 hours in adults is associated with a rapid homeostatic shift in ocular dominance to favor the deprived eye (by upregulation) up until about 5 hours of deprivation. Thereafter, once homeostatic mechanisms have saturated, there is a shift in dominance back to the non-deprived eye that effectively suppresses monocular input of limited utility. It is this latter, prolonged deprivation and downregulation that is thought to lead to the extreme, permanent changes to vision and ocular dominance (e.g. amblyopia) during development (Sengpiel and Blakemore, 1996). Given that most studies of homeostatic visual plasticity have been conducted in adults with healthy balanced vision, it is unknown whether the consequences of short- to longer-term deprivation are more modest in the human adult system compared to during development, as recently suggested (Ramamurthy and Blaser, 2021). We can only comment on the effects of two hours of patching, but future studies might reveal different timescales of ocular dominance effects in adults and adolescents using more prolonged periods of patching, reflecting developmental differences in upregulatory and downregulatory processes that are yet to be explored.

There is some variance in the effect of deprivation noted across the homeostatic visual plasticity literature, likely owing to minor methodological differences between studies. All studies on homeostatic visual plasticity are relatively small samples (typically $n = 15–20$), which would need to be collated to achieve a broader understanding of the range of inter-individual differences in human observers. While there have been a variety of ways to summarize the effect of deprivation on ocular dominance, these are not directly comparable and produce numerically different results. Rather than taking a single estimate of central tendency (e.g., mean or median percept duration) to represent ocular dominance, we have chosen to sum all available data (i.e., % of total time spent in the dominant or non-dominant eye percepts) to compute the effect of monocular deprivation, before and after two hours of deprivation, for direct comparison to previously published data (Lunghi et al., 2019). Using this calculation, the effect of deprivation in our study is smaller (mean $\pm$ standard deviation: adolescents 0.02 ± 0.06, younger adults 0.04 ± 0.07, and older adults 0.03 ± 0.07) than some reports, although similar to that reported for a group with obesity (Lunghi et al., 2019) and with shorter periods of monocular deprivation (Kim et al., 2017; Lunghi et al., 2013). The magnitude of our deprivation effects, whilst small, are significant and in the general direction of previously published literature (i.e., consistent reports of a shift in dominance towards the deprived eye), observed in different cohorts of participants we have tested using similar methods previously (Nguyen et al., 2021; Virathone et al., 2021) and also by other groups.

5. Conclusions

In conclusion, we demonstrate that homeostatic plasticity mechanisms that impact on ocular dominance are as effective in adolescents as in young adults. We find no evidence for differences in the ability of the healthy adolescent brain to rapidly adjust (after two hours of monocular deprivation) to changes in visual experience, despite some differences between groups in the baseline features of binocular rivalry. This data adds to the growing literature demonstrating that such homeostatic, compensatory mechanisms remain consistent and active across a wide age range, from adolescence through to older adulthood.

Compliance with ethical standards

The study was approved by the Human Research Ethics Committee of The University of Melbourne. All procedures performed were in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants involved in the study.

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CRediT authorship contribution statement

Bao N Nguyen: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing – Original draft, Writing – Review and Editing. **Rekha Srinivasan:** Data Curation, Investigation, Writing – Review and Editing. **Allison M McKendrick:** Conceptualization, Funding Acquisition, Methodology, Resources, Software, Supervision, Validation, Writing – Review and Editing.

Declaration of Competing Interest

The authors declare that they have no declarations of interest.

Data availability

The authors confirm that the data supporting the findings of this study are available in the supplementary material (Supplementary Material A).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2023.04.003.

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