A STUDY OF OCULAR DOMINANCE PLASTICITY: PROBING THE MOLECULAR MECHANISMS AND EXPLORING ITS EFFECT ON FUNCTIONAL CONNECTVITY

by

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ABSTRACT

Ocular dominance plasticity (ODP) is a well-characterized example of experience-dependent plasticity. Multiple molecular mechanisms have been implicated in the studying of ODP. We have previously demonstrated a temporal correlation between long-term depression (LTD) and ocular dominance plasticity. It has also been shown that blockade of LTD abolishes ocular dominance shift during the critical period, suggesting that LTD is necessary for ocular dominance plasticity. Here I go on to explore if LTD is sufficient for ocular dominance plasticity by augmenting it in adulthood. By administering D-serine, an NMDAR co-agonist that selectively enhances LTD in adult visual cortex, I am able to enhance ocular dominance plasticity in adulthood, as evidenced by data collected from single-unit recordings. D-serine operates via an LTD-like mechanism as its effect could be abolished by $GluR2_{3Y}$ peptide, a selective LTD blocker. I therefore argue that LTD plays a key regulatory role in both juvenile and adult ocular dominance plasticity. In addition, D-serine helps facilitate recovery of visual input in long-term monocularly deprived adult mice, suggestive of therapeutic potentials.

In addition, I have examined the functional consequences of monocular deprivation on the rest of primary visual cortex (V1) and cerebral cortex. This is achieved with help of *in vivo* imaging of intrinsic optic signals and calcium imaging. Within the visual cortex, monocular deprivation decreases the correlation between the contralateral monocular zone with the rest of V1. I have also observed transient changes in global functional connectivity correlating with the duration of lid suture during the critical period, in keeping with cross-modal plasticity. However,

this change in functional connectivity is not observed in adulthood, suggesting a sensory period for cross-modal connectivity.

PREFACE

All experiments in this thesis were conducted with the supervision and approval of the University of British Columbia Animal Care Committee. Certificates of approval are A11-0151, A11-0165, and A08-0445.

A portion of this thesis has been published.

Chapter 2 is published in:

Yang K, Xiong W, Yang G, Kojic L, Taghibiglou C, Wang YT, Cynader M (2011) The regulatory role of long-term depression in juvenile and adult mouse ocular dominance plasticity. Sci Rep 1:203.

I conducted experiments reported in Chapter 2 result sections. Dr. Wei Xiong contributed partly to Fig 2.7. The writing, analysis and figure preparation were done by myself, with the advice and assistance from the co-authors.

Chapter 3 is unpublished.

I conducted all experiments in Chapter 3. Jeffrey LeDue helped build the imaging apparatus and helped with data analysis by preparing custom-written scripts. Dr. Matthieu Vanni contributed to data analysis presented in Fig 3.12, 13 &16. Data collection, writing and figure preparation were done by myself, with the advice and assistance from Jeffrey LeDue, Drs. Murphy, Swindale, Vanni, and Cynader.

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LIST OF ABBREVIATIONS

ACSF	artificial cerebrospinal fluid
AMBC	Allen Mouse Brain Connectivity
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AP2	activating protein 2
BC	barrel cortex
BDNF	brain-derived neurotrophic factor
BOLD	blood oxygen level dependent
BZ	binocular zone
CBI	contralateral bias index
CMN	contrast modulated noise
dLGN	dorsal lateral geniculate nucleus
E/I	excitatory/inhibitory
ECM	extracellular matrix
EEG	electroencephalography
EPSC	excitatory postsynaptic current
EPSP	excitatory postsynaptic potential
FLS1	forelimb somatosensory cortex
fMRI	functional magnetic resonance imaging
GABA	*gamma*-aminobutyric acid
GAD65	glutamic acid decarboxylase 65
GECIs	genetically encoded calcium indicators
GluR	glutamate receptor
GSR	global signal regression
HLS1	hindlimb somatosensory cortex

ICA	independent component analysis
IOS	intrinsic optical signal
IP	intraperitoneal
LFS	low frequency stimulation
LGN	lateral geniculate nucleus
LTD	long-term depression
LTMD	long-term monocular deprivation
LTP	long-term potentiation
MD	monocular deprivation
mGluR	metabotropic glutamate receptors
MRI	magnetic resonance imaging
MZ	monocular zone
NMDA	*N*-methyl-D-aspartate
NSF	*N*-ethylmaleimide-sensitive factor
OD	ocular dominance
ODI	ocular dominance index
ODP	ocular dominance plasticity
PET	positron emission tomography
PP1	protein phosphatase 1
PV	parvalbumin
RGC	retinal ganglion cell
ROI	region of interest
SC	subcutaneous
SST	somatostatin
SWA	slow wave activity
TTX	tetradotoxin

VIP	vasoactive intestinal peptide
VSD	voltage-sensitive dye

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DEDICATION

To my family,

near and far,

here and gone.