Neuroplasticity and MRI : a perfect match

Neuroplasticity and MRI: a perfect match

Author names

Julie Hamaide [a], Geert De Groof [a], Annemie Van der Linden [a]

Affiliations

[a] Bio-Imaging Lab, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Corresponding author

annemie.vanderlinden@uantwerpen.be

Present & permanent address

Annemie Van der Linden

Bio-Imaging Lab

Campus Drie Eiken, UC 109

University of Antwerp

Universiteitsplein 1

2610 Wilrijk

Belgium

Abstract

Numerous studies have illustrated the benefits of physical workout and cognitive exercise on brain function and structure and, more importantly, on decelerating cognitive decline in old age and promoting functional rehabilitation following injury. Despite these behavioral observations, the exact mechanisms underlying these neuroplastic phenomena remain obscure. This gap illustrates the need for carefully designed in depth studies using valid models and translational tools which allow to uncover the observed events up to the molecular level. We promote the use of *in vivo* Magnetic Resonance Imaging (MRI) because it is a powerful translational imaging technique able to extract functional, structural and biochemical information from the entire brain. Advanced processing techniques allow performing voxel-based analyses which are capable of detecting novel loci implicated in specific neuroplastic events beyond traditional Regions-of-Interest analyses. In addition, its non-invasive character sets it as currently the best global imaging tool for performing dynamic longitudinal studies on the same living subject, allowing thus exploring the effects of experience, training, treatment etc. in parallel to additional measures such as age, cognitive performance scores, hormone levels and many others. The aim of this review is (i) to introduce how different animal

models contributed to extend the knowledge on neuroplasticity in both health and disease, over different life stages and upon various experiences and (ii) to illustrate how specific MRI techniques can be applied successfully to inform on the fundamental mechanisms underlying experience-dependent or activity-induced neuroplasticity including cognitive processes.

Keywords

MRI; neuroplasticity; animal; experience; cognition; training

Abbreviations

AChEI	Acetyl Choline Esterase Inhibitor
AD	Axial Diffusivity
ADC	Apparent Diffusion Coefficient
ASL	Arterial Spin Labeling
BBB	Blood-Brain-Barrier
BDNF	Brain-Derived Neurotrophic Factor
BrdU	Bromodeoxyuridine
BOLD	Blood-Oxygenation Level-Dependent
Ca^{2+}	Calcium
CA1	Cornu Ammonis 1
CA3	Cornu Ammonis 3
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
ChABC	Chondroitinase ABC
CD11b	cluster of differentiation molecule 11b
CD68	cluster of differentiation molecule 68
$CMRO_2$	Cerebral Metabolic Rate of Oxygen
CNS	Central Nervous System
Cho	Choline
CT	Computed Tomography
DBM	Deformation-based Morphometry
DCX	Doublecortin
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
fMRI	functional Magnetic Resonance Imaging
GABA	gamma-amino butyric acid
GAP43	Growth-Associated Protein 43
GFAP	Glial Fibrillary Acidic Protein
Glu	Glutamate
HDACI	Histon-Deacetylase Inhibitor
IGF-1	Insuline-Growth Factor 1
ISH	*In situ* Hybridization
LINGO-1	Leucine-rich repeat and Ig domain containing, Nogo receptor-interaction protein
LTP	Long-Term Potentiation
MD	Mean Diffusion
MEMRI	Manganese-enhanced Magnetic Resonance Imaging
Mn^{2+}	Manganese
$MnCl_2$	Manganese dichloride
MRI	Magnetic Resonance Imaging

mRNA	messenger RNA
MRS	Magnetic Resonance Spectroscopy
MWM	Morris Water Maze
NAA	N-Acetyl Aspartate
NgR	Nogo Receptor
NMDA	N-methyl-D-aspartate
Otx2	Orthodenticle Homeobox 2 homeoprotein
PD	Proton Density
PET	Positron Emission Tomography
PFF	Paradoxical Functional Facilitation
phMRI	pharmacological MRI
PirB	Paired-immuglobuline-like receptor B
PNN	Perineuronal Nets
rCBV	relative Cerebral Blood Volume
RD	Radial Diffusivity
rsfMRI	resting state functional Magnetic Resonance Imaging
RNA	Ribonucleic Acid
SPECT	Single-Photon Emission Computed Tomography
SSRI	Selective Serotonin Reuptake Inhibitors
Tau	Taurine
TBM	Tensor-based Morphometry
TE	Echo Time
TMS	Transcranial Magnetic Stimulation
TR	Repetition Time
VBM	Voxel-based Morphometry

1. Introduction

The most remarkable revolution in the field of neurosciences in the 20th century was the notion that instead of being fixed or immutable, the brain is constantly adapting its function and structure in response to experience or injury. Today, this phenomenon is defined as experience-dependent or activity-induced neuroplasticity and is the result from a delicate interplay between innate genotype and environmental stimuli to ensure adjusted functioning of neural networks and to maintain homeostasis upon changing surroundings (Butz, Wörgötter et al. 2009, Nagy and Turecki 2012). Indeed, numerous studies have illustrated the benefits of physical workout and cognitive exercise on brain function and structure (May 2011) and, more importantly, convincing experimental and clinical evidence points toward the active role of experience and physical activity to partially unlock neuroplasticity in adult life and promote functional rehabilitation upon trauma (Särkämö, Ripollés et al. 2014). An excellent review by Draganski and May (2008) compiles the state-of-the-art insights into the effect of motor training on brain morphometry and also highlights several 'flaws' in current understanding of training-induced brain adaptations: (i) the time-course of neuroplastic events is still relatively vague, (ii) the underlying biological mechanisms are far from clear and (iii) the relation between functional and structural neuroplastic adaptations is not yet understood (Draganski and May 2008). In order to resolve these key questions, animal experiments are needed which can divulge the observed neuroplastic events up to the molecular level.

Besides focusing on the effects of physical and cognitive exercising on brain structure and function, we aim to extend this review with exemplary high-impact studies which have led to major insights into mechanisms affecting or even directing neuroplasticity. We will start by exploring the effects of age and 'timing' on neuroplasticity after which we will discuss the effects of hormones on brain function and structure. Doing so, we intend to focus attention on how different MRI-based techniques have successfully captured neuroplastic events in different contexts but also on how MRI –besides conventional tools such as histology– might be of use in future experiments to study the effects of experience and activity on the brain.

2. *In vivo* MRI: the ultimate tool

Probably the most significant advantage of *in vivo* MRI is the possibility to sensitize the MR signal to functional, structural –both macro- and micro-level anatomy–, metabolic and vascular events in the living brain (Table 1). In addition, the non-invasive character along with its dependence on magnetism instead of ionizing radiation (CT) or radioactive substances (PET, SPECT), allows performing dynamic longitudinal studies where functional, structural and metabolic brain changes can be followed up *in vivo* upon experience, aging, maturation, training or treatment. Importantly, this experimental strategy allows for each animal to

serve as its own reference. However, the experimental design should be carefully considered and clearly reported especially for studies investigating the effect of e.g. training or experience on the brain (Thomas and Baker 2013).

Combining different MR modalities makes that each voxel can contain an abundance of biological information where the temporal evolution of functional, structural and biochemical modifications related to a specific disorder or event can be traced repetitively and in high precision. This might help in interpreting MRI findings, which is today one of the biggest challenges of MRI since a specific parameter readout does not relate one-on-one to a particular biological phenomenon (Zatorre, Fields et al. 2012). Artefacts related to acquisition e.g. measurement error due to for example physiological noise or head movements, or processing-induced inaccuracies might obscure the actual findings e.g. imperfect spatial normalization (Bookstein 2001, Davatzikos 2004) or abundant smoothing (Jones, Symms et al. 2005) prior to voxel-based processing. For a more elaborate study on several 'caveats' directly related to *in vivo* MRI used to study (training- or experience-induced) brain plasticity we refer to (Poldrack 2000, Ridgway, Henley et al. 2008, Thomas and Baker 2013). Likewise, both drawbacks also highlight the importance of validation studies using alternative methods to unravel the plausible cellular and molecular substrates of the observed *in vivo* findings. In addition, mapping the temporal profile of changes might help elucidate the underlying biology since not all events take place at the same speed e.g. dendritic sprouting takes place more rapidly than neurogenesis and neuronal migration. Moreover, repeated measures lead to a more direct understanding of the relative timing between and absolute time scale of different neuroplastic events. In addition, each MR examination can be accompanied by additional measures on the same individual such as cognitive scores or plasma hormone levels, which can be related to the neuroplastic events observed by *in vivo* MRI. This way, cause-consequence interrelationships can be established between specific behaviors –how they evolve– and the underlying biological substrate. Furthermore, since information from the entire field-of-view can be tested statistically in a voxel-wise manner, novel loci can be uncovered using an 'entire brain approach' as compared to traditional hypothesis-driven delineation of brain regions-of-interest.

Besides the biological versatility of MRI, technological advancements in imaging hardware and processing techniques (Van Reeth, Tham et al. 2012) allow to obtain sufficient spatial and temporal precision enabling the detection of acute functional adaptations such as LTP (s-min) (Álvarez-Salvado, Pallarés et al. 2014), microstructural remodeling of the hippocampus after only 2 hours of spatial learning (Sagi, Tavor et al. 2012) or long-term re-mapping of cortical regions after several weeks of coordinated motor training (Boyke, Driemeyer et al. 2008, Draganski and May 2008, Sampaio-Baptista, Scholz et al. 2014).

--TABLE 1--

3. Neuroplasticity and cognition, what can we learn from animals?

With the advent of neuroimaging tools designed to extract functional, structural and metabolic information of the brain in a non-invasive manner, the field of neuroscience has expanded widely. Numerous studies have described volume or shape changes of cortical brain areas upon specific motor or cognitive training programs (Draganski and May 2008), microstructural deficits related to cognitive decline in neurodegenerative disorders (Niccolini and Politis 2014, McConathy and Sheline 2015), functional reallocation of specific brain areas after trauma (Frasnelli, Collignon et al. 2011) etc. Also the effects of stress (O'Doherty, Chitty et al. , Dedovic, Renwick et al. 2005), hormones (Brabant, Cain et al. 2011), (drug) addiction (Fowler, Volkow et al. 2007, Parvaz, Alia-Klein et al. 2011, Salo and Fassbender 2012, Moulton, Elman et al. 2014, Viswanath, Velasquez et al. 2015) and aging (Lockhart and DeCarli 2014) on the brain have been evaluated thoroughly.

Most clinical studies describe effects observed with *in vivo* imaging tools often related to a specific behavioral phenotype, but fail to target the underlying biological mechanisms. Biomedical research, on the other hand, applies well-established translational models that mimic specific parts of disease or response upon experience. In addition, a laboratory setting allows to strictly control environmental input including diet, social interaction, rearing conditions, age, hormonal status etc., all of which are crucial determinants in experience-dependent or activity-induced neuroplasticity. Importantly, over the last decades genetically engineered animals –especially rodents– have become available and greatly help in elucidating mechanism underlying specific biological effects by knocking *in* or *down* specific genes translating molecular elements suspected to be involved. Moreover, animals with identical genetic backgrounds strongly reduce variance associated to differences in plasticity-related gene expression profiles, leaving the experimental intervention as single variable. Furthermore, the lifespan of most animals is markedly shorter and is characterized by an accelerated succession of developmental stages making it possible to study e.g. disease ontogenesis up to more advanced stages or the age-dependency of neuroplastic processes within the same animal on relatively short timescales. Interestingly, several animal studies have already illustrated human-like plasticity in response to physical exercise e.g. voluntary wheel running in mice (Biedermann, Fuss et al. 2012) and rats (Sumiyoshi, Taki et al. 2014), and cognitive training (Quallo, Price et al. 2009, Sagi, Tavor et al. 2012) etc., indicating that most plasticity-related mechanisms are conserved among species.

Besides these advantages, several drawbacks should be mentioned as well. Despite the high conservation of biological processes amongst mammals and most vertebrates, important differences still exist which question the translational character of animal findings. Furthermore, studying genetically engineered animals sheds light onto very specific parts of disease or response upon a given experience, but still does not provide a clear understanding of the complete biological basis and how different systems interact to

result in a specific behavior. Although it broadens the variety of techniques and tests that can be applied, animal research narrows the range of biological questions that can be addressed. For example, information regarding higher cognitive skills such as reasoning and complex emotions, mathematics and planning etc., is in most cases impossible to extract from the animal brain. Notwithstanding, several training procedures have been developed to assess human-like higher cognitive functionality in the animal brain e.g. maze training for spatial learning and memory (Vorhees and Williams 2014), conditioning paradigms (Aguado 2003, Delgado, Olsson et al. 2006), etc.

Besides the above mentioned advantages of non-invasive *in vivo* imaging, MRI is a highly translational tool. Consequently, given its wide range of biological sensitivity, MRI has been used intensively in neuroplasticity research over the last decade to uncover brain loci affected by experience, activated upon stimulation etc. in various species (Van der Linden, Van Camp et al. 2007, Van der Linden, Van Meir et al. 2009, Pelled 2011). This way several important determinants in setting boundaries on neuroplasticity have been uncovered. Age is the most well-known and strongest factor, but also hormones, physical workout, cognitive training programs etc. affect the brain at various levels. In the following sections, the above mentioned mechanisms along with appropriate models to assess the behavioral outcome will be introduced briefly and the involvement of MRI in tracing the resulting neuroplastic changes will be discussed. These findings have led to a deeper understanding of neuroplasticity in general, also related to the brains' response to physical and cognitive exercise in adulthood.

3.1. The impact of age on neuroplasticity

The susceptibility of the brain to undergo neuroplastic changes is strongly dependent on age. For example, children born blind due to e.g. congenital cataract, or deaf should receive adequate medical treatment before respectively 6 weeks or 2 years of age to prevent impaired visual acuity (Fledelius, Goldschmidt et al. 2014) or altered auditory perception and language accuracy in adult life (Svirsky, Teoh et al. 2004, Kral 2013). This age-dependent variation in prognosis can be ascribed to the existence of critical periods or precisely delineated time windows in early life during which environmental stimuli most potently shape cortical brain circuitries responsible for the acquisition of various skills and abilities required in later life (Jon 2012). When reaching adulthood, previously established neural networks encoding acquired skills are consolidated, imposing strict boundaries on the brains' ability to adapt. Fortunately, neuroplasticity is never entirely down-regulated, allowing the adult organism to learn and retain memory at later life stages or for the adult brain to 'reshape' upon cognitive and physical training.

A very interesting study illustrating this age-dependent, differential sensitivity of the brain to motor learning was performed by Bengtsson and colleagues. They investigated the effects of piano practice on the brain plasticity during distinct developmental periods i.e. childhood, adolescence and adulthood. During childhood the largest number of brain areas displayed changes, whereas in older ages only a limited number of brain regions showed training-induced adaptations (Bengtsson, Nagy et al. 2005). Also in preclinical research the age-dependency of neuroplastic events has been observed. Blumenfeld-Katzir and colleagues (2011) found that 1, 4 and 12 month old rats showed a similar pattern of brain areas actively undergoing changes after 5 days of Morris Water Maze (MWM) training, however, the extent of the changes was different between the ages (Blumenfeld-Katzir, Pasternak et al. 2011). In addition, Van Praag et al. (2005) investigated the effects of voluntary wheel running in young versus old mice (3 versus 19 months of age), and found that spatial learning and hippocampal neurogenesis did not improve equally indicating that physical activity in mice exerts different effects on brain plasticity in early compared to older life stages (van Praag, Shubert et al. 2005). Understanding age-dependent mechanisms posing 'temporal' boundaries on plasticity might help in finding possible targets implicated in enabling neuroplasticity following training in adulthood or old age.

Behavior is affected by age as well. Indeed, Albani and colleagues (2015) detected dissimilar performances in the elevated plus maze –experimental setup to assess anxiety-related behavior in rodents (Walf and Frye 2007)– when testing rats at two successive maturational stages in early postnatal life i.e. p17-19 versus p22-24, or when varying the illumination level of the environment i.e. dim versus bright. Interestingly, they also zoomed in on neuronal activation by investigating the expression of the immediate early gene Arc and found differential expression in the amygdala and visual cortex stipulated by age and surroundings (illumination). This study underlines important methodological considerations given that little differences in age (<1 week) or environment can have a major impact on the functional activation of neural substrate encoding specific behaviors (Albani, Andrawis et al. 2015).

3.1.1.Childhood

3.1.1.1. Critical periods of development

Current insights into critical period plasticity have been extracted mainly from research devoted to the acquisition of sensorimotor modalities such as the visual (ocular dominance theory (Hensch 2004, Levelt and Hübener 2012)), auditory (tonotopic mapping, pitch learning (Kral 2013)) and somatosensory or tactile (whisker-barrel pathway (Erzurumlu and Gaspar 2012)) systems in mammals. Using invasive methods, several factors have been put forward as major critical period delineators including (i) structural factors e.g.

myelin, perineuronal nets (PNNs) etc., (ii) functional mediators e.g. excitation-inhibition balance through GABA and glutamate etc., and (iii) molecular elements e.g. Brain-Derived Neurotrophic Factor (BDNF), Orthodenticle Homeobox 2 homeoprotein (Otx2), myelin-related Nogo Receptor (NgR), Insulin-like Growth Factor-1 (IGF-1), Paired immunoglobulin-like receptor B (PirB) etc. (Tropea, Van Wart et al. 2009, Nabel and Morishita 2013, Berardi, Sale et al. 2015). Recently, epigenetic mechanisms were proposed to be part of the interface between environmental stimuli experienced during early life critical periods and the sustained molecular, cellular and complex behavioral phenotypes (Fagiolini, Jensen et al. 2009). Based on these findings, several attempts have been made to reopen plasticity in adulthood by pharmacological intervention e.g. selective serotonin reuptake inhibitors (SSRI), histone deacetylase inhibitor (HDACI), chondroitinase ABC inhibitors (ChABCI), acetylcholine-esterase inhibitors (AChEI) etc. and altered environmental stimulation e.g. deprivation by dark exposure or environmental enrichment (Jon 2012, Nabel and Morishita 2013). Unfortunately however, the exact interaction between these factors, the temporal succession of critical periods encoding distinct sensorimotor skills, and whether these factors also translate to higher cognitive skills such as speech learning, the establishment of social relationships, reading, mathematics etc., still remains obscure.

Bridging information from developmental studies in rodents, ferrets and cats, Olaverria and coworkers (2012) discuss the possibility of using Diffusion Tensor Imaging (DTI; Table 1) as a reliable marker to evaluate the timing of critical periods in early brain development by mapping the effects of experience-dependent plasticity on cortico-cortical connectivity within the neural tissue encoding sensory skills such as the visual system (Jaime, Andrew et al. 2012). A practical example in this context can be found in a study by Chan et al. (2012), who assessed the effects of early visual impairment i.e. monocular enucleation and monocular deprivation –a popular model for critical period ocular dominance plasticity– in rodents by combining DTI and Manganese Enhanced MRI (MEMRI; Table 1). They reported a reduced fractional anisotropy (FA) in the anterior and posterior retinal pathways in the monocular enucleated and deprived group compared to control, indicative of respectively degeneration and immaturity of the tracts. Interestingly, the non-deprived eye was characterized by a higher FA compared to control rats (Chan, Cheng et al. 2012). Besides its use in probing structural connectivity, DTI is sensitive to microstructural rearrangements and changing myelin content as well, both factors known to be implicated in limiting neuroplasticity. Remarkably, to our knowledge only a limited number of studies reported on targeting critical period plasticity with non-invasive imaging tools. Certain biological mechanisms setting boundaries on critical period plasticity e.g. formation of PNNs, excitation-inhibition balance mediated through GABA etc. could possibly be targeted by *in vivo* MRI and are extremely likely to play a role in recovery from functional losses or several pathologies e.g. impact of PNN abnormalities in Schizophrenia (Berretta,

Pantazopoulos et al. 2015), in adulthood as well. Using MEMRI, Chan and colleagues were able to track axonal projections originating in the retinal ganglion cells and distinguish alterations to retinal and callosal projections resulting from early visual impairment. They succeeded in demarcating the contralateral cortical projection area and found a significantly increased volume in early blinded rats and mice compared to controls. The brains' response to monocular enucleation in early postnatal life has also been tackled by *in vivo* Magnetic Resonance Spectroscopy (MRS; Table 1). Three weeks after surgery, Chow and colleagues (2011) found a significant reduction in the Taurine (Tau) and N-acetyl Aspartate (NAA) levels in the visual cortex contralateral to the enucleated eye indicative of neuronal loss and axonal damage (Chow, Zhou et al. 2011). Glutamate (Glu), Choline (Cho) and myo-Inositol concentrations were not affected. These observations are in line with previous histological studies (Ribak and Robertson 1986, Robertson, Höhmann et al. 1988).

Interestingly, Ben-Ari and coworkers describe the role of GABA in directing cortical brain maturation by tightly controlling the excitation/inhibition balance and how dysregulation of GABA might give rise to neurodevelopmental disorders such as Autism Spectrum Disorder and epilepsy (Ben-Ari, Khalilov et al. 2012). In addition, research on the visual system in rats describes GABA as a decisive determinant in imposing brakes on critical period plasticity (Deidda, Allegra et al. 2015). Most of these findings, however, were discovered by invasive and highly localized molecular tools. MRS, on the other hand, can be regarded as an exceptional tool to evaluate critical period plasticity given its sensitivity to estimate the neurochemical signature of metabolites such as GABA in the living brain. Stagg (2014) nicely reviews how MRS can be applied in research aimed at tackling the role GABA in cortical plasticity focused on the primary motor cortex. In addition, Stagg briefly touches upon the effects of acute neuromodulation of glutamate and GABA by noninvasive stimulation protocols such as Transcranial Magnetic Stimulation (TMS), and how this relates to the MRS GABA readout (Stagg 2014). Besides focusing on GABA, also other MRS-detectable metabolites infer neuroplastic events possibly related to the establishment of higher cognitive learned skills. Based on a prior functional MRI (fMRI; Table 1) study (Pugh, Landi et al. 2013), Pugh et al. (2014) acquired MRS spectra in children at two time points throughout the development of the neural circuitry involved in reading. Focusing on NAA, Cho, Glu and GABA levels, they found inverse correlations between Cho and Glu levels and reading and linguistic performance in the occipital lobes. Fascinatingly, Glu levels at the first measurement were predictive of reading performance assessed during a behavioral follow up 24 months later (Pugh, Frost et al. 2014).

A more unusual animal model displaying striking similarities to the process of human speech learning might shed light on the translational character of critical period determinants to higher cognitive functions. Indeed, similar to humans, songbirds –especially close-ended learners such as zebra finches– learn the song of their

father (tutor) during two partly overlapping critical periods early in life (for review (Doupe and Kuhl 1999)). After closure of the critical periods for vocal learning, the song will be crystallized. Therefore, male birds sing only one stereotypic zebra finch song which –under normal circumstances– never changes again. A very interesting advantage of songbirds in neuroplasticity research is that their song directly reflects the specific stage of vocal learning. Moreover, songs can be easily recorded, quantified and related to the observed functional and structural changes. Of particular interest with regards to critical period plasticity, recently, the appearance of parvalbumin-positive interneurons and PNNs have been studied throughout the process of vocal learning (Balmer, Carels et al. 2009). Fascinatingly, song maturity correlated to the percentage of parvalbuminergic cells surrounded by PNNs in a brain area in control of song learning and production. Moreover, depriving juvenile male zebra finches of tutor song resulted in a decreased level of parvalbumine-positive interneurons and PNNs (Balmer, Carels et al. 2009). In line with observations from critical period of sensorimotor functions, if no proper stimulation i.e. tutor song, is heard during the critical period for vocal learning, the deprived males will not be able to sing a typical zebra finch song in adult life (Feher, Wang et al. 2009). In addition, another study by the same group showed that the distribution of perineuronal nets is highly sexually dimorphic in specific components of the song control circuitry i.e. the brain circuitry in control of singing (Meyer, Boroda et al. 2014). This was confirmed by others as well (Cornez, ter Haar et al. 2015). Interestingly, only male zebra finches sing, while both sexes memorize the tutor song. Consequently, the neural substrate in control of the motoric aspect of song production displays a differential density in PNNs in females as compared to males. Both findings strongly suggest that the sexually dimorphic and developmental evolution of expression of PNNs in the zebra finch brain might be correlated to critical period plasticity. In order to confirm or disprove these hypothetical presumptions a causal relationship between behavioral changes i.e. song output, and localized reorganization of the extracellular matrix needs to be established. Interestingly, in theory, it might be possible to track the formation of PNNs with *in vivo* imaging tools sensitive to microstructural rearrangements e.g. DTI. Moreover, changing myelin contents and GABA levels can also be measured, making critical period plasticity highly fascinating to address with *in vivo* MRI.

~~*3.1.1.2. Maladaptive critical period plasticity*~~

~~Recent evidence suggests that the pathological basis of many neurodevelopmental disorders can be found in maladaptive critical period plasticity (Johnston 2004, Johnston 2009). Berger and colleagues hypothesize that the behavioral phenotype of autism spectrum disorder might result from a delicate interplay of genetic predisposition along with premature closing of the critical period for integration of sensory input, language and social skills (Berger, Rohn et al. 2013). Likewise, the pathological profile of several~~

neurodevelopmental conditions e.g. Down and Rett syndrome (Fernandez and Garner 2007), schizophrenia (Morishita, Kundakovic et al. , Bitanihirwe and Woo 2014), epilepsy (Coghlan, Horder et al. 2012), fragile X syndrome (Kim, Gibboni et al. 2013) etc. have all been linked to improper critical period plasticity.

Regardless of genetic predisposition, early life rearing conditions are essential for proper brain development. Indeed, deprivation studies (Bengoetxea, Ortuzar et al. 2012, Erzurumlu and Gaspar 2012) and rare case studies (Fromkin, Krashen et al. 1974) show that if environmental stimuli are only experienced prior to or post opening or closure of the critical period encoding a specific skill, the skill will not be mastered as proficiently as in normal circumstances (Berardi, Pizzorusso et al. 2000). This implies that critical periods might be interpreted as 'windows of opportunity' i.e. the brain is only compliant to particular stimulation or environmental input at the respective maturational time frame. Another argument illustrating the vital importance of early life experiences can be found in adverse rearing conditions or early traumatic experiences. Bogart and colleagues (2014) investigated the consequences of different rearing conditions of brain morphology and found profound differences in global white to grey matter volume ratio, depth of cortical folds and grey matter thickness when comparing mother- and nursery-reared chimpanzees (Bogart, Bennett et al. 2014). A similar study has been performed in the clinic, studying the effects of childhood emotional maltreatment on brain structure. The most striking differences were found in the medial prefrontal cortex, the brain area in control of cognitive and emotional dysfunctioning. Interestingly, both human (Vaiserman 2015) and animal evidence (Gudsnuk and Champagne 2012) suggests that the long-lasting consequences of early life stress and altered social experience might be mediated through epigenetic mechanisms and, what is more, epigenetic mechanisms are believed to pass these effects on to the next generation.

3.1.2. Adulthood

Yin and Yuang review the existence of a balance between Hebbian and homeostatic plasticity in adult life (Yin and Yuan 2015). Hebbian plasticity challenges existing functional and structural networks aimed at a constant refinement of current abilities and the corresponding neural substrate. Homeostatic plasticity, on the other hand, tries to maintain neuronal homeostasis and previously established connectivity by constraining network activity within physiological ranges. Several mechanisms in control of maintaining the balance between flexibility and stability of the brain have been identified (for review (Yin and Yuan 2015)), however, the tightly regulated interaction between these factors, the resulting large-scale effects on brain function and structure, and the corresponding behavior remain obscure. Insights into this matter might be obtained from studies assessing the biological base of memory acquisition and retention, and recovery from trauma in adulthood. In addition, also the visual system has proven to be an interesting model in the context of studying adult neuroplasticity (Wandell and Smirnakis 2009).

3.1.2.1. Learn and retain memory in adulthood

'*Cells that fire together, wire together*'. Donald Hebb was one of the first neuroscientists describing what we today refer to as the result of Long-Term Potentiation (LTP) (Hebb 1949, Bliss and Lømo 1973), often defined as the physiological basis or '*cellular consolidation*' of memory (LYNCH 2004, Mednick, Cai et al. 2011). LTP is a very clear example of experience-dependent plasticity since it mediates the reconfiguration of intrinsic homeostatic properties of individual neurons by sensitizing synapses, but also triggers large-scale network-wide adaptations based on environmental input. Indeed recently, parallel electrophysiological and fMRI recordings have targeted the acute effects of (artificial) induction of LTP on long-range global functional connectivity in adult rats (Canals, Beyerlein et al. 2009). This study was the first to reliably detect the rapid effects of LTP by fMRI, a technique that allows investigating widespread activation patterns of entire networks using a whole-brain approach. Remarkably, comparing BOLD activation maps while stimulating the perforant path between rats before (control) and after (potentiated) induction of LTP, they noted a significant enlargement of the activated network recruiting more distantly connected brain areas. In the potentiated condition, the cluster displaying voxels activated by stimulation encompassed the entire hippocampal formation i.e. hippocampus proper, subiculum and entorhinal cortex, also extending to the hippocampus of the contralateral hemisphere and involving extrahippocampal brain areas such as the perirhinal cortex, prefrontal cortex, nucleus accumbens and the anterior olfactory nucleus (ipsilateral hemisphere) (Canals, Beyerlein et al. 2009). Especially the latter observations uncovered an entire network of increased functional recruitment possibly reflecting intensified functional connectivity, extending beyond previously established areas of involvement known from electrophysiology and molecular studies. A follow up study revealed the effects of different stimulation paradigms and, using high-resolution functional imaging, they were able to specify the specific sub-locations of LTP-mediated effects in the hippocampus (Alvarez-Salvado, Pallares et al. 2014) (Fig 1).

In addition to the functional repercussions of induction of LTP, also the local biochemical environment is affected. For example, LTP results in a modulation of pre- and post-synaptic strength mediated through neurotransmitters such as glutamate, and their receptors e.g. NMDA-receptors. Moreover, a study in rats showed that LTP-like plasticity can only be successfully elicited after decreasing GABA levels in the motor cortex (Trepel and Racine 2000). In theory, since both GABA and glutamate can be detected by *in vivo* spectroscopy, MRS might be able to detect LTP-mediated plasticity directly if it includes a sufficiently large brain area (partial volume effect).

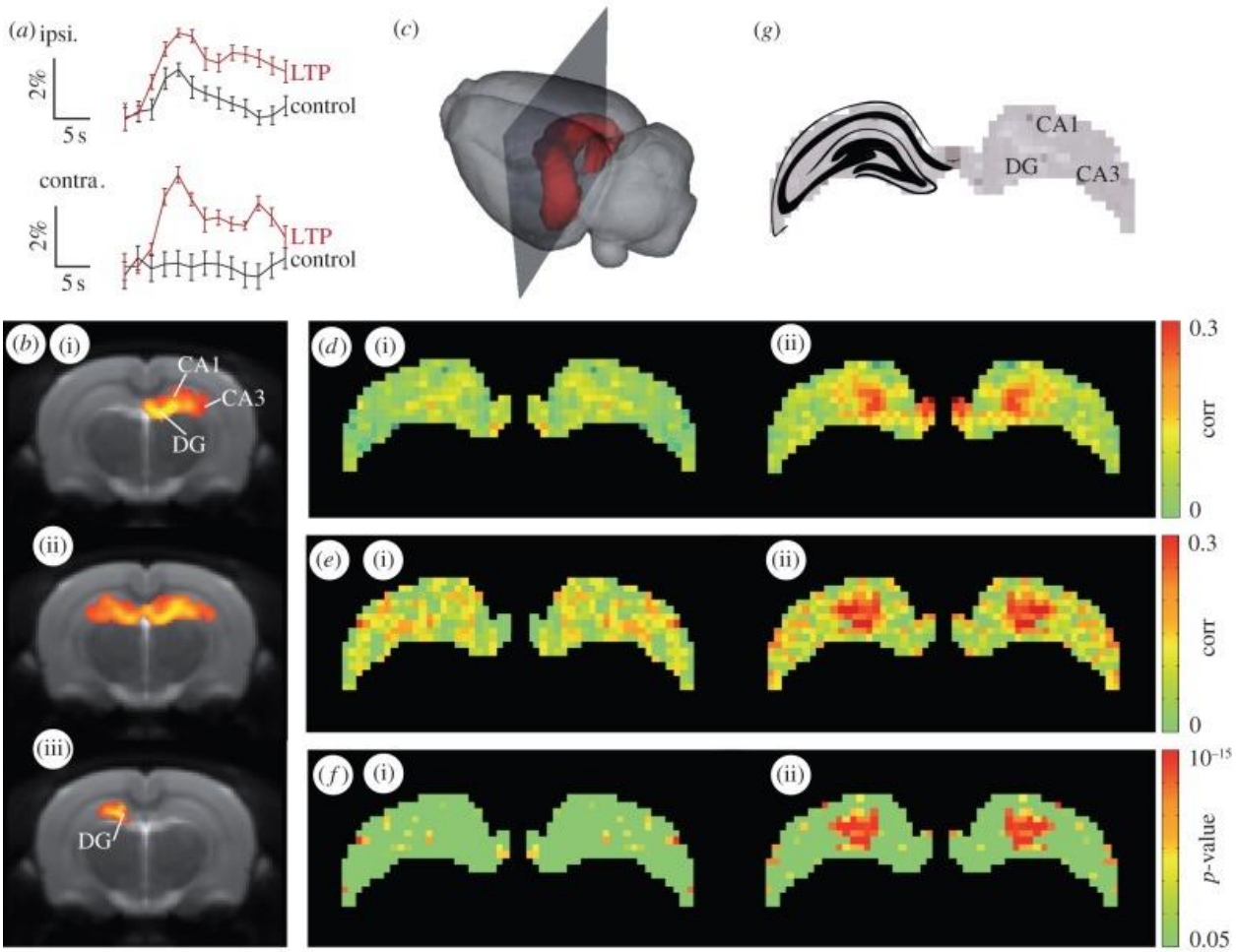

Figure 1: LTP elicits enhanced bilateral coupling detected by fMRI. **(a)** temporal evolution of the BOLD signal in the ipsi- and contralateral dorsal hippocampus before (black) and 3 h after induction of LTP (red). **(b)** Statistical maps indicating voxels activated upon electrical stimulation pre (i) and post (ii) LTP induction (n=4, $p<0.001$). Statistical map indicating the difference in activation when comparing fMRI maps before and after induction of LTP ($p<0.01$). Only the hippocampus is included in the analysis. **(c)** Three-dimensional reconstruction of the hippocampus and its relative position in the rat brain. **(d)** Group and **(e)** individual statistical maps indicating the cross-correlations of the BOLD-time courses before (i) and 3 h after (ii) induction of LTP. **(f)** Maps indicating significantly correlated voxels pre (i) and post (ii) induction of LTP. The color code of the statistical significance and correlation coefficients can be found on the right. **(g)** Schematic legend of the hippocampal territories on a grey-scaled cross-correlation map. Reprinted from (Alvarez-Salvado, Pallares et al. 2014) with permission from The Philosophical Transactions of Royal Society of London, Series B Biological Sciences.

Associative learning and conditioning

Besides tracing BOLD changes in response to LTP, fMRI has also been used intensively to visualize brain activation patterns over the course of associative learning e.g. to expose the neural substrate tuned by eye-blink conditioning in rabbits (Miller, Chen et al. 2003). The advantage of fMRI in this context is that it allows to evaluate the spatial location and possible hemispheric lateralization, magnitude and time course of BOLD activity across different stages. Evidence in favor of using small animals as a translational model

to study mechanisms underlying associative learning is provided by a clinical study on human subjects where fMRI data was acquired while performing an associative memory training (Small, Nava et al. 2001). Interestingly, the observations could be replicated in mice (Kent, Hess et al. 2007). Moreover, by studying CA3 NMDA receptor knock-out mice, Kent and colleagues could prove the involvement of NMDA receptors in the CA3 subregion of the hippocampus by showing an experience-dependent shift in hippocampal activity instigated by the learning task (Kent, Hess et al. 2007).

In addition to functional imaging, biochemical profiling has been used to study neuroplastic adaptations resulting from a learning task. Zhou and coworkers (2012) explored the use of MRS to assess acute and early effects of fear conditioning –model for post-traumatic stress disorder– on the brains of adult C57BL/6 mice. They reported a reduction in NAA, 1 day post conditioning in the hippocampus which persisted but slightly regressed throughout the first week post fear training. In addition, choline levels were lower the first day post conditioning, but this did not persist towards the 7 days' time point. In the cingulate cortex, only an acute reduction in NAA could be detected which did not last until one week post conditioning (Zhou, Ding et al. 2012).

Motor and Spatial learning

Probably the most extensively investigated subtype of learning and memorization can be found in motor and spatial learning. In contrast to most conditioning paradigms, motor and spatial learning are more difficult to assess by fMRI given the need for appropriate stimulation, the physical limitations of performing (complex) motor tasks in the MR scanner and the necessity to sedate animals during data acquisition (except for awake imaging after habituation training). Consequently, the impact of motor and/or spatial learning on microstructural remodeling of the brain has been studied extensively in both humans and animals (Imfeld, Oechslin et al. 2009, Blumenfeld-Katzir, Pasternak et al. 2011, Sagi, Tavor et al. 2012, Hofstetter, Tavor et al. 2013, Sampaio-Baptista, Scholz et al. 2014), for review (Dayan and Cohen 2011, Thomas and Baker 2013). In most cases, significant differences were found a few days or weeks after the motor training or learning paradigms had been completed. Indeed, most structural phenomena such as neurogenesis and network rearrangement are expected to be realized or at least detectable in the longer term. Sagi et al. (2012), however, succeeded in detecting acute experience-dependent microstructural remodeling of the hippocampus following spatial navigational learning (Sagi, Tavor et al. 2012). Fascinatingly, they observed significant microstructural changes reflected in altered mean diffusion (MD) values in human brains after only 2 hours of playing a virtual car race game and confirmed these observations in a rat study. Additional histological analyses of the hippocampal tissue of the rat brains displayed an upregulated synaptophysin immunoreactivity which is indicative of an increased number of synaptic vesicles, and revealed increased

levels of BDNF. Since BDNF is commonly regarded as a marker for LTP (Lu, Nagappan et al. 2014), the authors hypothesized that changes in MD might be indicative of the neural substrate where LTP was triggered by the learning task. This was previously already proposed by (Blumenfeld-Katzir, Pasternak et al. 2011) in a similar experimental setting, however, only combined MRI and electrophysiological measures can prove or disprove this statement (Alvarez-Salvado, Pallares et al. 2014). BDNF and synaptic vesicles are expected to be responsible for only a minor contribution of the observed MD changes. The authors also found an increased GFAP immunoreactivity which suggests the active involvement of astrocytes. This might concern cell swelling and remodeling of glial processes that result in a change of volume of the intra- versus extracellular compartment. In addition, synaptogenesis, morphometric adaptations of axons, dendrites and glial processes, and alterations in cell body size are likely to take part of the biological correlate of the DTI parameter readout. Importantly, the magnitude of change in MD in the right parahippocampal tissue could be correlated to behavioral performance i.e. task improvement is directly related to the change in tissue microarchitecture. Therefore, it leaves no surprise that intensive long-term training results in significant volume changes in these brain areas as previously observed by (Draganski, Gaser et al. 2004) and (Lerch, Yiu et al. 2011) in humans and rodents respectively. A related example investigating neuroplastic changes along the course of a single-food pellet reaching training in adult rats using *ex vivo* DTI, revealed differences in FA and MD in several white matter fiber-containing structures i.e. the cingulum, external capsule and parts of the corpus callosum in the hemisphere contralateral to the trained paw. The imaging findings were confirmed by *post mortem* histology testing for myelin. This paper was one of the first studies focusing on experience-dependent changes in white matter tracts instead of detecting alterations to volumes or microstructural reorganizations upon the acquisition of a particular motor task (Sampaio-Baptista, Khrapitchev et al. 2013). Another study aimed at finding rapid microstructural adaptations in response to a learning task was performed by the group of Wu (2013). Using voxel-based statistics, they found altered FA in the hippocampus, amygdala and cingulum as early as 1 hour and 1 day after fear conditioning (Ding, Li et al. 2013). These brain areas are known to be involved in processing of fearful experiences. Similar findings have been published in humans suffering post-traumatic stress disorder (Van Boven, Harrington et al. 2009).

Also the acquisition of more advanced motor learning tasks has been examined thoroughly by *in vivo* imaging. Quallo and coworkers (2009) found that macaque monkeys displayed volume alterations in the superior temporal sulcus, the second somatosensory sulcus, intraparietal sulcus and lobule 5 of the cerebellar hemisphere (bilaterally) after learning to retrieve food rewards using a rake. Moreover, motor performance could be correlated to the extent of change observed on MRI in individual monkeys and the effects were more pronounced in the right hemisphere compared to the left (Quallo, Price et al. 2009). A similar study

was performed by Hihara et al. (2006) and described results of a tract tracing light microscopy analysis on the brains of adult monkeys after 3 weeks of tool-use training to retrieve food placed out of reach. Using anterograde tracers, they found differential connectivity originating from the temporo-parietal junction projecting to the intraparietal junction in trained monkeys compared to untrained controls i.e. trained monkeys displayed a robust projection connecting both brain areas, whereas controls only showed a very weak connection. This observation involved the same brain areas as detected by *in vivo* voxel-based morphometry, suggesting that the tool-use training gave rise to strengthening of this sparse but existing pathway (Hihara, Notoya et al. 2006).

3.1.2.2. The inverse relationship between age and recovery from functional loss

The brains' ability to overcome injury is highest in childhood and adolescence but is not completely abolished towards adulthood (Nahmani and Turrigiano). Interesting in this context is the involvement of experience to promote rehabilitation e.g. daily music listening to improve functional outcome after stroke (Hannan 2014, Särkämö, Ripollés et al. 2014).

A remarkable feature characteristic to specific cases of brain or peripheral nervous system trauma can be found in paradoxical functional facilitation (PFF) when direct or indirect neural damage may result in the reinforcement of particular behavioral functions (Kapur 1996). In general two main subtypes of PFF can be discerned i.e. (i) restorative PFF, where after damage to an intact brain area improved or even normalized performance of a previously abnormal level of functioning can be found e.g. the Sprague effect (Sprague 1966), and (ii) cross-modal plasticity i.e. a coping mechanism of the brain where cortical circuitries previously encoding a particular skill or ability are re-assigned to process a new function after loss of the original one e.g. after peripheral deafferentiation or congenital blindness (Bavelier and Hirshorn 2010, Urbanski, Coubard et al. 2014). Cross-modal plasticity has been thoroughly examined in blind subjects, where the onset of blindness i.e. congenital, early or old age, strongly predicts the behavioral outcome (for review (Lazzouni and Lepore 2014, Urbanski, Coubard et al. 2014)). Indeed, Voss (2013) discusses the existence of sensitive windows (similar to critical periods) during which compensatory changes might exert the largest effects, specifically focusing on insights obtained from investigations of impairments to the visual system (Voss 2013). Complementary to this review, Nahmani and Turrigiano, (2014) comprehensively list the similarities and dissimilarities in plasticity-related mechanisms in recovery from acute cortical trauma or ischemia in adulthood compared to neuroplasticity triggered by deprivation in early development. The authors explain that disinhibition is one of the primary mediators to release the brakes on cortical excitability and thus functional and structural plasticity, both in early as well as later life. They conclude that the capacity of the brain to '*functionally rewire*' is indeed strongly reliant on the maturational stage of the organism, and –in order to achieve a full understanding of the underlying neuroplastic mechanisms– combined multi-level

assessments investigating both localized circuitry rewiring, expression of plasticity-related factors and behavioral tests assessing functional recovery need to be conducted. Especially since behavioral performance is the only reliable indicator of the functional success of the underlying neuroplastic adaptation (Nahmani and Turrigiano 2014).

Functional imaging techniques provide great advantage in evaluating the functional reallocation of cortical areas and cortical responsiveness to peripheral sensorimotor and/or cognitive stimulation. Indeed, Endo et al. (2007) showed a biphasic modulation of the BOLD response when comparing the acute versus long-term effects of complete thoracic spine transection in rats. The brain area activated upon stimulation partly invaded the adjacent sensory-deprived hind limb cortical territory (Fig 2). Moreover, the biphasic evolution of the fMRI response to forelimb stimulation was echoed by enhanced gene expression of BDNF, NgR and LINGO-1, generally considered as neuroplasticity markers. When comparing their findings to previous reports, the authors concluded that the extent of cortical reorganization strongly depends on the type and severity of spinal cord injury (Endo, Spenger et al. 2007). However, since only adult animals were considered in this context, no assumptions on possible age-dependency could be made. In addition, fMRI upon visual stimulation has been used frequently to investigate population receptive field topographic maps both in humans (Papanikolaou, Keliris et al. 2014) and animals (Shao, Keliris et al. 2013). Several other experimental models displaying cross-modal plasticity have been investigated using fMRI and resting state fMRI (rsfMRI; Table 1) (Pelled, Chuang et al. 2007, Pawela, Biswal et al. 2010, Yu, Wang et al. 2010, Li, Hettinger et al. 2013) or DTI to shed light on alterations in structural connectivity e.g. (Ramu, Herrera et al. 2008, Wrigley, Gustin et al. 2009). In addition, MEMRI is also an interesting tool to inspect cortical projection areas. Furthermore, the effects of stroke on the functional reorganization of the brain have been explored extensively (Dijkhuizen, van der Marel et al. 2012). Besides functional and structural imaging, the biochemical profile of cross-modal coping mechanisms following blindness have been researched exhaustively with MRS in both humans (Weaver, Richards et al. 2013, Kupers and Ptito 2014) and animals (Chan, Cheung et al. 2010).

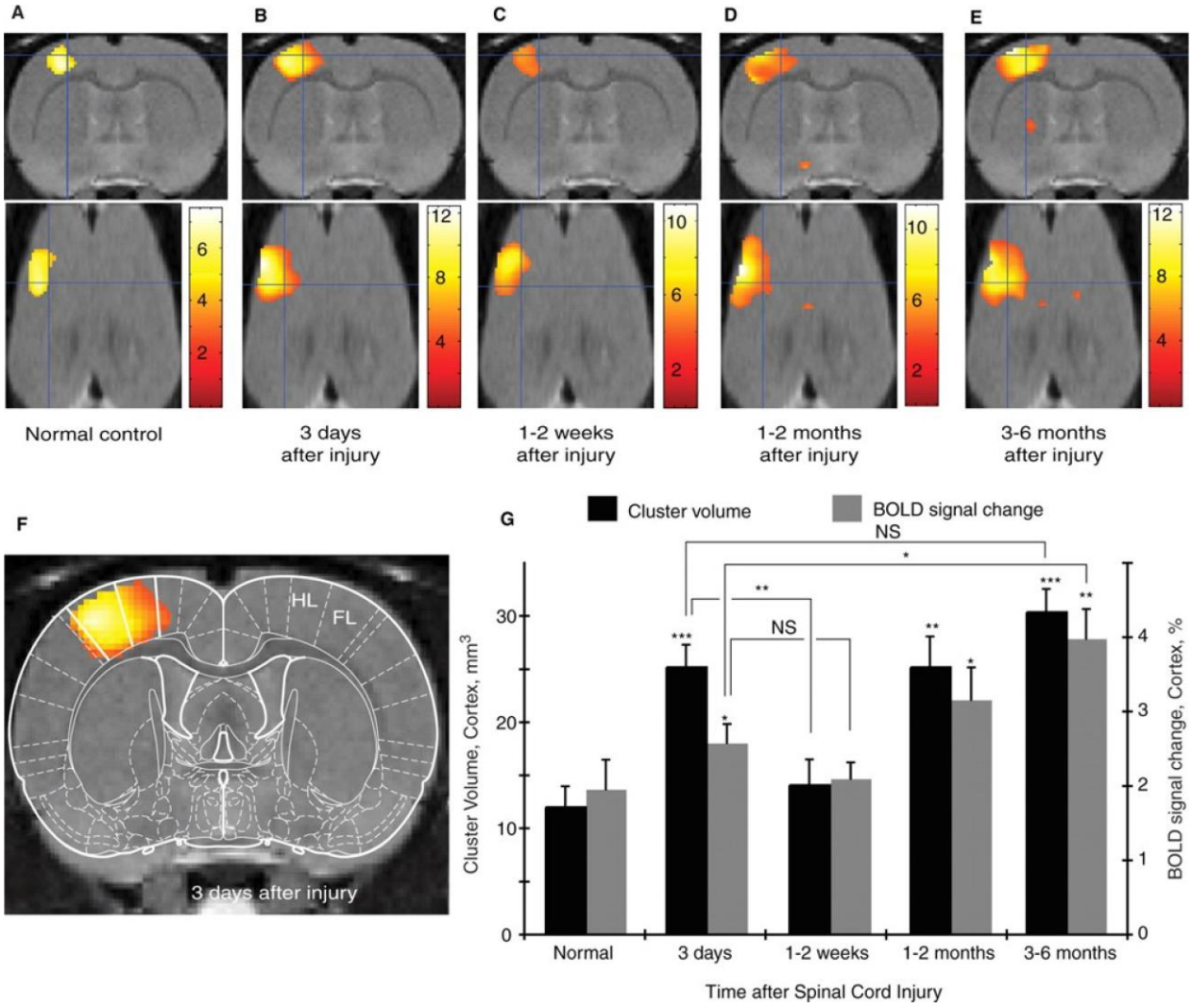

Figure 2: Temporal evolution of the fMRI activation of the primary sensory cortex upon contralateral forelimb stimulation after (complete) spinal cord transection. **A**: Cluster activated in control rats. **B-E**: Functional activation in injured animals at 3 days (B), 1-2 weeks (C), 1-2 months (D) and 3-6 months (E) post transection. The crosshair indicates exactly the same anatomical position in all panels. Interestingly, besides the 1-2 weeks post injury time point, all fMRI activation maps extend more caudal and medial compared to the control group. **(F)** Coronal slice illustrating the statistical map 3 days after spine transection overlaid on the Paxinos and Watson atlas indicating a medial but not lateral extension of the activated cluster. (HL: hind limb territory of primary somatosensory cortex; FL: forelimb territory) (G) Cluster volume and BOLD signal change (%) of activation in the primary somatosensory cortex at different time-points post transection and in healthy controls (n = 12 rats per group). Data are represented as mean ± SEM, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; NS: non-significant. Reprinted from (Endo, Spenger et al. 2007) with permission from Oxford University Press Journals.

The adaptive response of the brain to injury or trauma can be beneficial so that functionality can be (almost fully) regained, unfortunately however, in some cases neuroplasticity is maladaptive in that it triggers pathogenesis (for review we refer to the special issue of Neuroscience December 26, 2014 'Compensation Following Injury to the Adult Brain: Always for Good?'). Also in this field of research, MRI has proven to be a valuable non-invasive probe to trace the physiological fingerprint of pathology. A very well-known

example in this context can be found in (acquired) epilepsy. Gröhn et al. (2011) reviews the use of combined MR measures to set up the pathological profile of disease ontogenesis and progression of epilepsy (Gröhn, Sierra et al. 2011). For example, MEMRI hyperintensities in the early stages after induction of *status epilepticus* have been correlated to mossy fiber sprouting in the dentate gyrus of the hippocampus (Nairismägi, Pitkänen et al. 2006), DTI revealed sites of axonal reorganization and myelin damage (Laitinen, Sierra et al. 2010) where voxel-based processing of DTI datasets unveiled novel loci implicated in the pathogenic process (Sierra, Laitinen et al. 2011), Arterial Spin Labeling (ASL) identified sites of hypo/hyperperfusion (Choy, Cheung et al. 2010, Choy, Wells et al. 2010), intravascular contrast agents shed light onto alterations in the vascular architecture (Hayward, Ndode-Ekane et al. 2010) etc. Gröhn explains that *in vivo* MRI has great potential in becoming a crucial tool for personalized medicine given its ability to infer disease ontogenesis and progression, which is of vital importance to evaluate individual rehabilitation programs and find novel targets for treatment (Gröhn, Sierra et al. 2011).

3.2. Hormones are powerful modulators of brain structure and function

Hormones and brain plasticity are bidirectionally linked (Institute 2009). Mounting evidence can be found in favor of this statement. To name a few: (i) Hormones are indispensable during normal brain development and partly drive sexual differentiation. (ii) Neuroplasticity is dramatically down-regulated during adolescence towards adulthood, a period in life characterized by major fluctuations in hormonal homeostasis. (iii) Changing hormone levels during the menstrual cycle have been correlated to rapid structural (Pletzer, Kronbichler et al. 2010, Hagemann, Ugur et al. 2011) and functional (Arelin, Mueller et al. 2015) neuroplastic adaptations (for review (Barth, Villringer et al. 2015)). (iv) Animal studies have revealed the protective effect of estrogens on age-associated cognitive decline related to neurodegeneration (Daniel 2013, Lan, Zhao et al. 2015). (v) The entire CNS is copiously sprinkled with hormone receptors and enzymes converting inactive pre-hormone molecules into their active counterpart, and vice versa.

Besides its well-known effects on behavior, previous research on animals revealed sex hormone-mediated changes in gliagenesis, vasculature, neurogenesis and synaptic remodeling (Woolley and McEwen 1992, Yankova, Hart et al. 2001). Some of them occur very rapidly e.g. a 32% decrease in synaptic density of hippocampal neurons 24 h after the onset of estrus in rats (Woolley and McEwen 1992), for a more recent review by the same lab we refer to (Woolley 2007). Interestingly, voxel-based morphometry has been applied to explore the effects of hormones on the brains of menopausal women (Boccardi, Ghidoni et al. 2006, Wnuk, Korol et al. 2012) or the effect of the menstrual cycle on hippocampal morphology (Protopopescu, Butler et al. 2008). In addition, also the effects of altered testosterone (Höfer, Lanzenberger

et al. 2013) and thyroid (Cooke, Mullally et al. 2013) levels on the brain have been studied by *in vivo* imaging.

Not only mammals, but also songbirds have proven to be an extremely valuable model to study the effects of (sex) hormone treatments on structural brain anatomy and higher cognitive functioning e.g. song-related contextual processing, both acutely and in the longer term, in ontogeny as well as more advanced life stages (Bottjer and Johnson 1997). Songbirds are the living proof that the environment, hormonal status and behavior can have a huge impact on the overall organization of the brain, both in terms of function and structure. Vocal communication –in this case birdsong– is a complex communicative tool, acquired by learning, shared by only a few species, conveys meaning and is subject to interpretation by the audience (Petkov and Jarvis 2012). Each year again seasonal songbirds go through a de- and recrudescence of the gonads together with a remarkable reorganization of the song control system in the brain i.e. the volume and interconnectivity between distinct song control system components dramatically increases in anticipation of the breeding season, preparing birds to sing. Interestingly, this photoperiod-driven change in hormone levels directly affects overall anatomy including the brain, but also drives singing behavior (Tramontin and Brenowitz 2000) and affects auditory perception of song (De Groof, Poirier et al. 2013). In addition, most seasonal species are capable of adapting and extending their song repertoire on a yearly basis. These specific properties make songbirds an extremely attractive model to gain understanding of the effects of experience-dependent or activity-induced plasticity, possibly related to hormonal status, on a higher cognitive skill. So far, most studies mainly used invasive readouts such as histology and immediate early gene assays (Mello, Velho et al. 2004, Thompson 2011, Clayton 2013) and only sparsely made use of *in vivo* imaging. For example, DTI and MEMRI to assess volume sizes of and structural connectivity between brain areas over different seasons in canaries (Van Meir, Pavlova et al. 2006) and starling (De Groof and Van der Linden 2010) or upon hormone-treatment (Van Meir, Verhoye et al. 2004), and auditory fMRI to reveal seasonally changing activation patterns and right hemispheric dominance in processing songs with distinct social relevance (De Groof, Poirier et al. 2013). Another study by the same group showed that also rsfMRI can be used to detect hemispheric lateralization in songbirds and pigeons (Jonckers, Güntürkün et al. 2015). Figure 3 nicely illustrates how DTI and MEMRI can be used to investigate neuroplasticity in a seasonal setting.

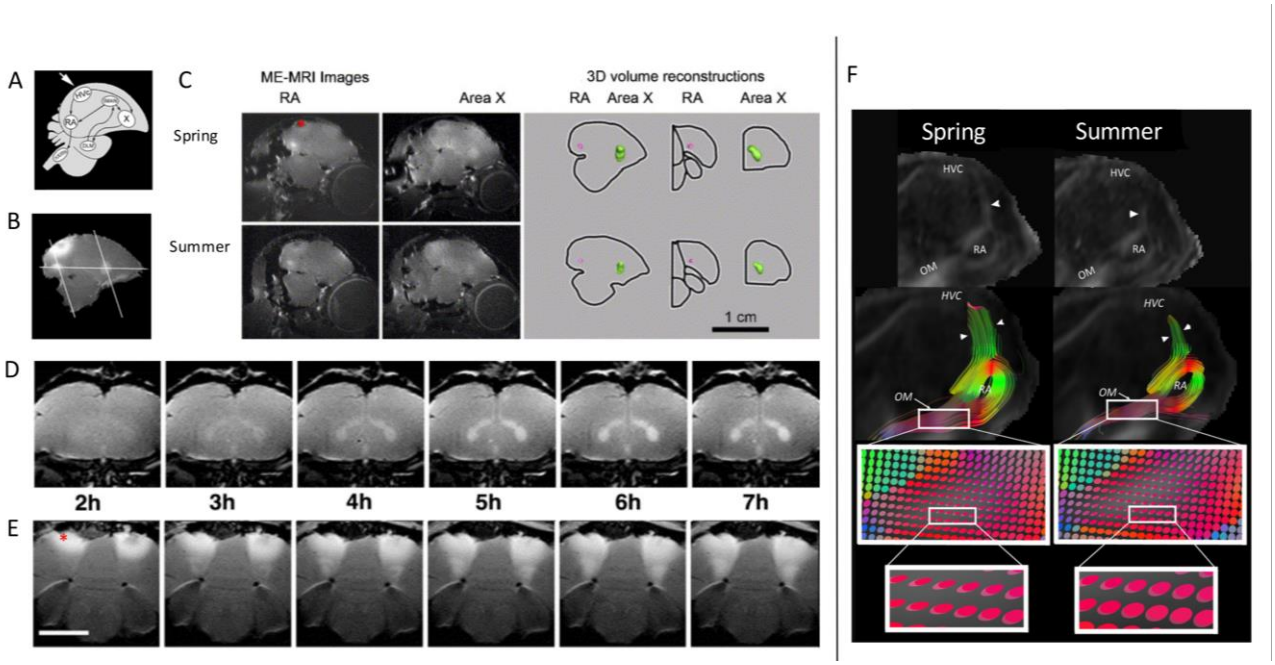

Figure 3: **MEMRI and DTI to explore song control system plasticity in a seasonal songbird. (A)** Simplified schematic overview of the song control system in songbirds. **(B)** Sagittal sections in which both the $MnCl_2$ injection site (HVC indicated by *) and the downstream nuclei (RA and Area X) can be found. The right panels provide a 3-dimensions view of the volume difference picked up by MEMRI when comparing spring to summer. **(C)** Changes in signal intensity at 2, 3, 4, 5, 6 and 7 hours post $MnCl_2$ injection in the brain of a female starling. Over time a hyperintense signal can be colocalized with Area X and RA (not shown). **(D)** Top image shows a sagittal section through the starling brain atlas (De Groof, George et al. 2015) in which the song control nuclei are visible. The region of the insert in shown underneath were seasonal changes in the connectivity of the telencephalic vocal motor circuit are observed using DTI. The upper row presents sagittal FA maps (right is caudal) of the same subject in different seasons. The arrowhead shows the HVC-to-RA connection. The second row of images presents fiber-tracking with RA as the seed point. The inserts show the individual diffusion tensors of the OM tract. Notice that they are broader in Summer than in Spring indicating a potential change in myelination. Reprinted from (Van Meir, Pavlova et al. 2006) and (Van der Linden, Verhoye et al. 2002) with permission from Elsevier and from (De Groof, Verhoye et al. 2008) with permission from John Wiley and sons.

3.3. Physical activity and environmental complexity promote neuroplasticity

The intricate balance between Hebbian and homeostatic plasticity can be easily disrupted by activity or experience. Indeed, substantial clinical evidence illustrates the flexibility of the adult brain upon physical or cognitive challenges, or –by combining both– the enhancement of cognitive functioning upon physical exercise (Hötting and Röder 2013). This not only relates to healthy subjects, patients suffering stroke or other neurotrauma and specific neurodegenerative disorders benefit significantly from physical workout and active participation to cognitive tasks (Ahlskog, Geda et al. 2011). Also in animal studies, the link between physical exercise and performance in spatial learning and memory tests has been demonstrated extensively both in health and disease (Johansson 2004) and has shown great resemblance in mechanistic pathways between animal and human plasticity (Voss, Vivar et al. 2013). A popular model used to mimic increased physical and cognitive challenges in a research environment is found in housing animals in an enriched

environment i.e. accommodate animals in large cages equipped with species-specific needs such as running wheels, labyrinths etc. of which the composition and arrangement within the cage is changed regularly (Baumans 2005). Environmental enrichment promotes physical workout, provides more complexity as animals might need to overcome specific challenges to forage food or find its way back through the obstacles and encourages social interaction. Berardi and coworkers (2015) nicely review how environmental enrichment affects molecular plasticity-related (epi)genetic modulators, based on research dedicated mainly to the visual system (Berardi, Sale et al. 2015).

3.3.1. Beyond critical periods: activity and experience are still able to shape the adult brain to a certain extent

In healthy animals, environmental enrichment and complex training paradigms have often been related to improved learning, memory and overall cognitive performance (van Praag, Kempermann et al. 2000, Nithianantharajah and Hannan 2006, Simpson and Kelly 2011). Interestingly, Sholz and colleagues (2015) used Manganese-enhanced MRI –to improve anatomical contrast– to inspect macrostructural brain plasticity upon housing adult mice in an enriched environment. Previous studies reported that after around three weeks of enrichment neuroplastic adaptations are established and can be observed (van Praag, Kempermann et al. 2000, Nithianantharajah and Hannan 2006). Therefore, Scholz acquired manganese-enhanced anatomical datasets before, after three weeks of enriched housing conditions and after 4 weeks of enrichment combined with one week of Barnes maze training (to test spatial learning and memory). In addition, to evaluate whether a change of environment evokes acutely detectable brain changes, they performed high-resolution *ex vivo* measurements of mouse brains which experienced 24h of enrichment (without application of $MnCl_2$). Using deformation-based morphometry, they found volumetric changes in the hippocampal formation and sensorimotor cortices after three weeks of enrichment and could observe a similar –but not significant– trend in the acute phase. The volumetric differences found in this study clearly show the malleability of the brain to experiencing a more complex and stimulating environment. The involvement of the hippocampus in learning and memory associated with navigation, exploration and locomotion, is in line with another study where Morris Water Maze training revealed differences in apparent diffusion coefficient of the hippocampus (Blumenfeld-Katzir, Pasternak et al. 2011). When relating housing conditions to performance in the Barnes maze, Scholz et al. confirmed that mice housed in a more stimulating environment learned the location of the escape box faster, but no differences in memory (during the probe trial) could be detected between the stimulated and control group (Scholz, Allemang-Grand et al. 2015). Connected to this study, the same research group used high-resolution *ex vivo* 3-dimensional datasets and deformation-based morphometry to evaluate rapid structural modifications evoked by different maze

learning procedures each mimicking a specific type of learning (Lerch, Yiu et al. 2011), and by rotarod training (Scholz, Niibori et al. 2015).

Biedermann and colleagues (2012) used high-resolution T_2-weighted datasets to inspect local volumetric alterations combined with MRS spectra including information on GABA and glutamate levels. Interestingly, they observed an inverse relationship between hippocampal volume (increase upon voluntary wheel running) and glutamate concentration (decrease) pointing towards the active involvement of glutamatergic system in aerobic exercise-induced neuroplasticity (Biedermann, Fuss et al. 2012) (Fig 4). This training-induced alteration in metabolic profile was also found in a previous study in humans where they detected acutely increased Glx (combined glutamate and glutamine signal) in the visual cortex after 10 min of vigorous exercise (Maddock, Casazza et al. 2011). Other studies in humans used MRS to deduce metabolic changes resulting from endurance-training in middle-aged subjects (Gonzales, Tarumi et al. 2013), fast GABA level alterations were observed in the sensorimotor cortex due to motor-learning (Floyer-Lea, Wylezinska et al. 2006) and increased NAA (relative to creatine and choline) levels in the left posterior hippocampus related to rote learning (Roche, Mullally et al. 2009), etc.

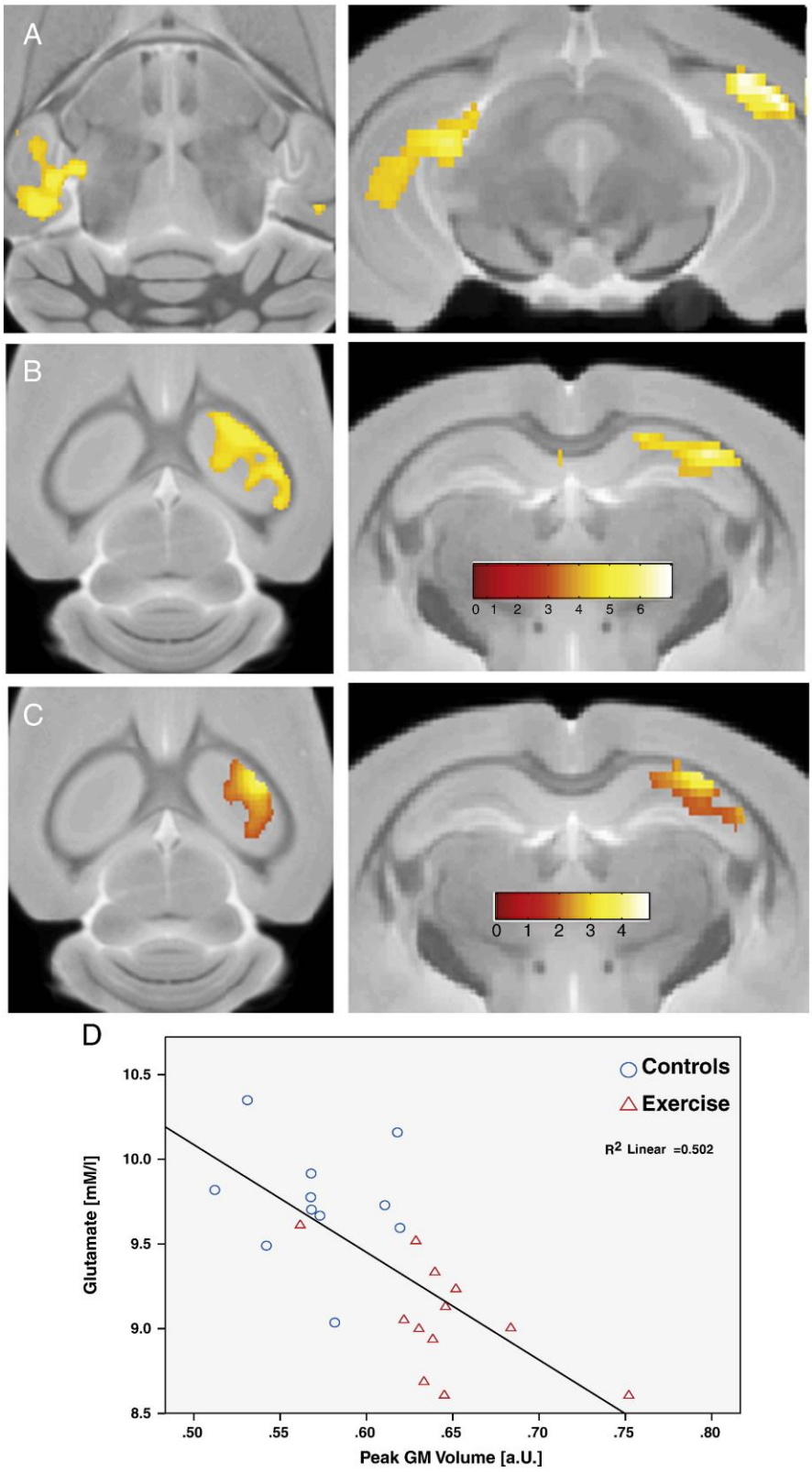

Figure 4: Results of voxel-based morphometric analysis comparing exercising and sedentary mice, and correlation of morphometric results to Glutamate levels as detected by MRS obtained from the right hippocampus. **(A-B)** Statistical map indicating clusters where increased grey matter was found co-localized with the left and right hippocampus ($p < 0.001$ uncorrected, 200 voxel cluster

size). **(C)** Cluster in the hippocampus which are significantly negatively correlated with Glu levels. The color-bars show the T-values of the statistical tests. **(D)** Glutamate levels represented in function of mean volume change in both sedentary and running mice. Reprinted from (Biedermann, Fuss et al. 2012) with permission from Elsevier.

3.3.2. Activity-induced neuroplasticity to slow down disease progression or facilitate recovery

The beneficial effects of environmental enrichment on neurodegenerative disorders has been described in Huntington's' (van Dellen, Blakemore et al. 2000, Lazic, Grote et al. 2006), Parkinson's' (Faherty, Raviie Shepherd et al. 2005), Alzheimer's' (Görtz, Lewejohann et al. 2008) disease etc. Nithianantharajah and colleagues (2006) and Svensson et al. (2014) nicely review the effects of physical exercise on disease progression, inflammation, behavior etc. in neurodegenerative disorders, concluding to what extent preclinical research involving animal models can be translated to the human brain (Nithianantharajah and Hannan 2006, Svensson, Lexell et al. 2014). A particularly interesting preclinical example can be found in a (preliminary) study by Little et al. (2012). Based on rsfMRI measures, they found an increased functional connectivity between CA1 and cortical areas when housing transgenic mice in environmental enriched conditions (Little, Foxely et al. 2012). These findings could be linked to previously established results revealing increased hippocampal neurogenesis under similar experimental settings using a different transgenic mouse model for Alzheimer pathology (Herring, Ambree et al. 2009). Furthermore, Golub and coworkers (2011) showed that mice suffering post-traumatic stress disorder displayed a volume reduction of the left hippocampus and right amygdala. When the same stressor was applied in mice housed in a more stimulating environment, both a change in hippocampal volume and fear-related behavior could be observed. The authors concluded that environmental enrichment counteracted the post-traumatic volume loss of the hippocampus and led to a decrease in contextual fear and arousal compared to traumatized mice kept in standard housing conditions. Interestingly, the timing of enrichment i.e. before, after or continuous seemed to have similar effects on the behavior, however, enrichment after foot shock appeared to be more effective in inhibiting hippocampal, but not amygdaloid, volume loss. In order to gain a more extensive understanding of the mechanisms resulting in the structural findings, Golub and colleagues performed *post mortem* ultramicroscopy to validate hippocampal volume changes, and Western Blotting tests to assess GAP43 (Growth Associated Protein 43) expression levels in the hippocampus and cerebellum. GAP43 is an axonal plasticity marker localized in the presynaptic terminal of axons and linked to neurite outgrowth. They found a reduction in hippocampal GAP43 expression after experiencing a foot shock and an increase in hippocampal GAP43 expression in mice housed in a stimulating environment greatly resembling the MRI findings. Interestingly, up-and down-regulation of GAP43 expression points to a respective pruning and strengthening of neuronal interconnectivity in response to traumatizing or complex stimulating experiences and is very likely part of the biological mechanisms responsible for the observed volume differences (Golub,

Kaltwasser et al. 2011). Likewise, Zhang (2014) and He (2014) found independently that treadmill pre-training reduced cerebral edema in case of ischemic stroke. They hypothesized that it was probably partially instigated by improved mitochondrial function (Zhang, He et al. 2014) and the down-regulation of aquaporin 4 (He, Wang et al. 2014). In addition, Jenks et al., (2013) reported improved spatial learning, memory performance and sociability in a rat model displaying severe malformations in cortical development, when the rat pups were raised in a maximally stimulating environment or allowed increased training time. Interestingly, after environmental enrichment, both control and cortical malformation groups outperformed the groups lacking a stimulating environment (Jenks, Lucas et al. 2013).

3.3.3. Role of the Vasculature

Aerobic exercise enhances blood flow. Consequently, the biological base responsible for the beneficial effects of physical exercise on neuroplasticity and cognition might be partially found in its effects on the vasculature. Indeed, Mariotti and coworkers (2014) tested the effect of forced mild physical training (treadmill running) in 25 month old mice. The old mice underwent imaging sessions before and after training during which multislice anatomical datasets, T_2 maps and contrast-enhanced relative Cerebral Blood Volume (rCBV) scans were acquired to test for resp. volumetry, microstructural rearrangements and the assessment of relative blood volume. They found a significant effect of training on rCBV in the old mice, but no differences in cortical thickness measured at the hippocampus and motor cortex, nor in relaxation properties reflecting water distribution, were detected. These observations suggest that mild aerobic exercise can induce regionally specific changes in perfusion (similar to (Pereira, Huddleston et al. 2007)), without causing edema or detectable volume changes in motor cortex and hippocampus. Interestingly, when testosterone was administered weekly during the entire motor training period, no additional differences were observed compared to the training group (Mariotti, Fattoretti et al. 2014). This finding excluded the additional effect of exogenous testosterone on activity-induced increases in cerebral perfusion as was first hypothesized. Likewise, a study in rhesus monkeys revealed an inverse relation between CBV and age and a positive correlation between CBV and memory performance in a delayed nonmatching-to-sample task. Interestingly, both effects were strictly confined to the dentate gyrus of the hippocampus. This indicates that non-neuronal factors that take part in neuroplasticity also behave differently in an age- and regionally specific manner. To exclude biologically irrelevant observations due to age-related changes in biophysical properties of the vasculature which might obscure the actual biological effect, and to account for the fact that hemodynamic imaging only indirectly relates to brain function and metabolism, a parallel *in situ* hybridization (ISH) experiment was performed in rats. Arc –immediately early gene that becomes upregulated in neurons that participate to a specific behavior– RNA expression was evaluated in young,

middle-aged and old rats after being briefly exposed to a novel environment (2 x 5 min). Interestingly, again a correlation between the number of Arc-positive cells (activated upon experiencing novel environment) and age could be observed exclusively in the dentate gyrus of the hippocampus. They concluded that the dentate gyrus is most significantly affected by aging and might be partially responsible for cognitive impairment related to advanced age (Small, Chawla et al. 2004). Based on these observations, Blau and colleagues (2012) explored the presence of a link between age-related deficits in LTP and changes in vasculature in healthy rats, assessing both blood flow and blood-brain barrier (BBB) permeability. Using a combination of *in vivo* MRI techniques, histology and flow cytometry of hippocampal tissue, they found a negative correlation between T_2 relaxation time, activated microglia expressing CD11b and CD68 mRNA and the ability to sustain LTP in the hippocampus, together with an age-related decrease in cerebral perfusion and increased BBB permeability. They hypothesized that reduced cerebral blood flow (and thus lowered tissue oxygenation) and impaired BBB permeability might destabilize local tissue homeostasis, which in combination with deregulated microglia may be a crucial determinant in sustaining neuroinflammatory activity affecting synaptic functioning and the resulting cognitive decline (Blau, Cowley et al. 2012).

3.3.4. Role of Neurogenesis

Numerous studies revealed an up-regulation or increased survival of newly generated neurons in response to physical exercise (van Praag, Christie et al. 1999, van Praag, Shubert et al. 2005), complex environmental stimulation (Kempermann, Kuhn et al. 1997, Olson, Eadie et al. 2006), and after mastering an effortful learning task such as eye-blink conditioning (Curlik, DiFeo et al. 2014), etc. Moreover, both in humans and rodents it has been shown that hormones e.g. estrogen and progestin (McEwen, Alves et al. 1997, Luine, Richards et al. 1998), promote neurogenesis and are linked to improved hippocampal-dependent learning and cognitive performance. A review by Jessberger and Gage (2014) discusses research dedicated to adult neurogenesis performed during the last few decades including the similarities and dissimilarities between animal-based research and clinical investigation, current methods to assess neurogenesis *in vivo* in the adult rodent and human brain, the interplay between neurogenesis and neuroplasticity, and the cellular and molecular mechanisms in control of adult neurogenesis (Jessberger and Gage 2014).

In order to detect neurogenesis and especially the migration pattern of newly generated cells longitudinally in the living brain, the use of different non-invasive imaging tools have been tested including bioluminescence, PET and MRI-based methods such as MRI reporter genes and iron oxide particles (for review: (Couillard-Despres, Vreys et al. 2011)). Most *in vivo* imaging tools label stem and/or progenitor

cells derived from the subventricular zone and trace their travel along the rostral migration stream towards the olfactory bulb. In contrast, neural progenitor cells originating from the dentate gyrus migrate only a very short distance to the subgranular zone of the hippocampus. Unfortunately, this falls far beyond the accuracy of *in vivo* MRI or PET (Coquery, Blesch et al. 2012).

Direct labelling of stem and/or progenitor cells cannot be applied in all experimental designs which illustrates the need for indirect *in vivo* measures of neurogenesis. For example, Manganas et al. (2007) suggested the 1.28 ppm peak to be a biomarker for neurogenesis (Manganas, Zhang et al. 2007). Follow up studies, however, found that the spectroscopic signal (1.28 ppm peak) correlated more to the presence of mobile lipids droplets within cells and apoptosis regardless of the cell type (Ramm, Couillard-Despres et al. 2009). Therefore, the 1.28 ppm peak might reflect neurogenic niches rather than echoing neurogenesis *per se* (Couillard-Despres, Vreys et al. 2011). Pereira et al. (2007) showed a positive link between neurogenesis and an increased cerebral blood volume (CBV) in the dentate gyrus of the hippocampus, the brain area most prone to activity-induced neurogenesis, and confirmed this finding by *post mortem* histology staining for BrdU (neurogenesis). Moreover they also found similar results in a parallel study on humans, where the increased CBV in the hippocampus could be correlated to both improved cardiopulmonary and cognitive function (Pereira, Huddleston et al. 2007). Other *post mortem* investigations confirmed neurogenesis as major factor underlying *in vivo* detected changes in grey matter volume in response to motor training (Biedermann, Fuss et al. 2012). Interestingly, Fuss and colleagues performed *in vivo* volumetric imaging and deduced the possible involvement of neurogenesis as underlying effect mediating hippocampal volume increases upon physical exercise by the experimental design i.e. focal irradiation of the hippocampal formation blocks neurogenesis. Irradiated mice failed to show hippocampal volume increases due to physical exercise compared to non-irradiated control mice (Fuss, Biedermann et al. 2014). A different study by the same group evaluated the effects of voluntary wheel running on adult mice with and without focal irradiation of the hippocampus to interfere with local adult neurogenesis, and performed regressive analyses between volumetric MRI measurements and histological investigations testing for neurogenesis, proliferating and pyknotic cells, blood vessel density and arborization, glial cells, microglia, neuronal activation. They found that irradiated mice that had access to the running wheel did not show any differences in histological markers compared to the sedentary non-irradiated group. The sham-irradiated running group displayed higher grey matter volume affecting the entire hippocampus compared to all other experimental groups. Interestingly, by utilizing a regression model testing for a relationship between whole hippocampal volume and the histological parameters, DCX-labeled newborn neurons correlated best and are most plausibly underlying the activity-dependent hippocampal volume increase (Biedermann, Fuss et al. 2012).

However, one should note that indirect measures lack specificity and can only be held partially responsible for the underlying biology. For example, volumetric changes might be attributable by cell swelling and/or infiltration of glia cells, both of which are often more likely to occur. The location and time course of these changes can also be indicative of the observed changes e.g. cell swelling can take place acutely, whereas neurogenesis and migration of newly generated cells can occupy days to weeks.

4. Conclusion

Using invasive methods, several mechanisms directing neuroplastic responses upon experience, training or treatment are unmasked which led to the identification of general principles (excitation/inhibition balance etc.), major factors (GABA, BDNF etc.) and genetic elements (Lynx-1, NogoR etc.). However, information is still relatively fragmented and generalization between different systems is suggested but still not fully proven. More in depth insights can only be realized by carefully designed animal experiments where *in vivo* imaging can guide in-depth *ex vivo* methods such as histology and genetic testing to decipher the involvement of and interaction between crucial mediators among different systems –ranging from basic sensorimotor to higher cognitive skills– and different species. Numerous histological methods and localized punching techniques combined with highly sensitive molecular assays allow to zoom in on the (epi-) genetic background driving the observed changes in highly localized brain niches. This strategy allows the establishment of cause-consequence relationships describing links between systems which might uncover targets to '*unlock the brain*' (Jon 2012).

Still, this will be a challenging quest since many internal and external factors are able to influence the neuroplastic outcome. For example, the menstrual cycle affects the (micro-) structure of the brain, small differences in early age significantly interfere with the outcome of specific behavioral tests etc. This all stresses the need to carefully control the experimental conditions. Moreover, ample studies have illustrated that timing is crucial. This not only relates to critical period plasticity in ontogeny, but also to the brain's adaptability following brain injury or to the effects of physical exercise on cognitive performance. Understanding the temporal profile of neuroplastic changes along the acquisition of specific skills over different training sessions or post trauma requires non-invasive translational imaging tools which allow to dynamically map functional, structural and metabolical events in the same subject. Indeed, a few exemplary studies have focused on the temporal progression of neuroplastic changes directly related to a specific training or learning paradigm (Taubert, Draganski et al. 2010, Ma, Narayana et al. 2011, Taubert, Lohmann et al. 2011, Hamzei, Glauche et al. 2012), for review (Taubert, Villringer et al. 2012). However, more research is still highly necessary and will lead to fundamental insights into the dynamics of learning and

memory, but will also shed light on how to predict motor outcome or improvements in behavioral performance after a specific learning paradigm (Pugh, Frost et al. 2014, Sampaio-Baptista, Scholz et al. 2014) which is of crucial importance when e.g. choosing specific rehabilitation strategies after brain injury (Choy, Cheung et al. 2010). Moreover, additional information on the behavioral outcome of this subject is the only reliable measure to 'quantify' the success of rehabilitation programs or learning paradigms. Fascinatingly, several imaging studies have been able to correlate the behavioral test scores to specific MRI parameter readouts. These findings illustrate the power of *in vivo* imaging to effectively uncover the neural substrate encoding specific skills responsible for specific behavioral functions. Many studies have already shown the added value of MRI in neuroplasticity research, however, still many opportunities and possibilities to investigate the brains' response upon change using MRI remain relatively unexplored. Combining several MRI contrasts might help in establishing a detailed profile of functional, structural and biochemical alterations which leads to a more complete picture of the underlying biology responsible for a specific behavioral readout. In addition, having this information, additional measures can be chosen more judiciously.

To conclude, with this review we hope to convince you that (small animal) MRI enables a powerful top-down imaging-guided research strategy in which a spatio-temporal profile of neuroplastic adaptations related to specific behavioral events can be targeted with more localized invasive methods which will lead to the disentanglement of the observed neuroplastic events up to the molecular level and will eventually deepen our understanding of human brain function.

Acknowledgments

This research was supported by grants from the Research Foundation—Flanders (FWO, Project No. G030213N and G044311N), the Hercules Foundation (Grant No. AUHA0012), Concerted Research Actions (GOA Funding) from the University of Antwerp and Interuniversity Attraction Poles (IAP) ('PLASTOCINE': P7/17) to AVdL. JH is a PhD student supported by the University of Antwerp. GDG is a Postdoctoral Fellow of the Research Foundation-Flanders (FWO).

5. References

Aguado, L. (2003). "Neuroscience of Pavlovian Conditioning: A Brief Review." The Spanish Journal of Psychology **6**(02): 155-167.

Ahlskog, J. E., Y. E. Geda, N. R. Graff-Radford and R. C. Petersen (2011). "Physical Exercise as a Preventive or Disease-Modifying Treatment of Dementia and Brain Aging." Mayo Clinic Proceedings **86**(9): 876-884.

Albani, S. H., M. M. Andrawis, R. J. H. Abella, J. T. Fulghum, N. Vafamand, A. N. Kim and T. C. Dumas (2015). "Behavior in the elevated plus maze is differentially affected by testing conditions in rats under and over three weeks of age." Frontiers in Behavioral Neuroscience **9**.

Alvarez-Salvado, E., V. Pallares, A. Moreno and S. Canals (2014). "Functional MRI of long-term potentiation: imaging network plasticity." Philos Trans R Soc Lond B Biol Sci **369**(1633): 20130152.

Álvarez-Salvado, E., V. Pallarés, A. Moreno and S. Canals (2014). Functional MRI of long-term potentiation: imaging network plasticity.

Arelin, K., K. Mueller, C. Barth, P. V. Rekkas, J. Kratzsch, I. Burmann, A. Villringer and J. Sacher (2015). "Progesterone mediates brain functional connectivity changes during the menstrual cycle - A pilot resting state MRI study." Frontiers in Neuroscience **9**.

Balmer, T. S., V. M. Carels, J. L. Frisch and T. A. Nick (2009). "Modulation of Perineuronal Nets and Parvalbumin with Developmental Song Learning." The Journal of Neuroscience **29**(41): 12878-12885.

Barth, C., A. Villringer and J. Sacher (2015). "Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods." Frontiers in Neuroscience **9**.

Baumans, V. (2005). "Environmental Enrichment for Laboratory Rodents and Rabbits: Requirements of Rodents, Rabbits, and Research." ILAR Journal **46**(2): 162-170.

Bavelier, D. and E. Hirshorn (2010). "I see where you're hearing: how cross-modal plasticity may exploit homologous brain structures." Nature Neuroscience **13**(11): 1309-1311.

Ben-Ari, Y., I. Khalilov, K. T. Kahle and E. Cherubini (2012). "The GABA Excitatory/Inhibitory Shift in Brain Maturation and Neurological Disorders." The Neuroscientist **18**(5): 467-486.

Bengoetxea, H., N. Ortuzar, S. Bulnes, I. Rico-Barrio, J. V. Lafuente and E. G. Argandoña (2012). "Enriched and Deprived Sensory Experience Induces Structural Changes and Rewires Connectivity during the Postnatal Development of the Brain." Neural Plasticity **2012**: 305693.

Bengtsson, S. L., Z. Nagy, S. Skare, L. Forsman, H. Forssberg and F. Ullen (2005). "Extensive piano practicing has regionally specific effects on white matter development." Nat Neurosci **8**(9): 1148-1150.

Berardi, N., T. Pizzorusso and L. Maffei (2000). "Critical periods during sensory development." Current Opinion in Neurobiology **10**(1): 138-145.

Berardi, N., A. Sale and L. Maffei (2015). "Brain structural and functional development: genetics and experience." Developmental Medicine & Child Neurology **57**: 4-9.

Berger, J. M., T. T. Rohn and J. T. Oxford (2013). Autism as the Early Closure of a Neuroplastic Critical Period Normally Seen in Adolescence.

Berretta, S., H. Pantazopoulos, M. Markota, C. Brown and E. T. Batzianouli (2015). "Losing the sugar coating: Potential impact of perineuronal net abnormalities on interneurons in schizophrenia." Schizophrenia Research(0).

Biedermann, S., J. Fuss, L. Zheng, A. Sartorius, C. Falfán-Melgoza, T. Demirakca, P. Gass, G. Ende and W. Weber-Fahr (2012). "In vivo voxel based morphometry: Detection of increased hippocampal volume and decreased glutamate levels in exercising mice." NeuroImage **61**(4): 1206-1212.

Bitanihirwe, B. K. Y. and T.-U. W. Woo (2014). "Perineuronal nets and schizophrenia: The importance of neuronal coatings." Neuroscience & Biobehavioral Reviews **45**(0): 85-99.

Blau, C. W., T. R. Cowley, J. O'Sullivan, B. Grehan, T. C. Browne, L. Kelly, A. Birch, N. Murphy, A. M. Kelly, C. M. Kerskens and M. A. Lynch (2012). "The age-related deficit in LTP is associated with changes in perfusion and blood-brain barrier permeability." Neurobiology of Aging **33**(5): 1005.e1023-1005.e1035.

Bliss, T. V. P. and T. Lømo (1973). "Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path." The Journal of Physiology **232**(2): 331-356.
Blumenfeld-Katzir, T., O. Pasternak, M. Dagan and Y. Assaf (2011). "Diffusion MRI of Structural Brain Plasticity Induced by a Learning and Memory Task." PLoS ONE **6**(6): e20678.
Boccardi, M., R. Ghidoni, S. Govoni, C. Testa, L. Benussi, M. Bonetti, G. Binetti and G. B. Frisoni (2006). "Effects of hormone therapy on brain morphology of healthy postmenopausal women: a Voxel-based morphometry study." Menopause **13**(4): 584-591.
Bogart, S. L., A. J. Bennett, S. J. Schapiro, L. A. Reamer and W. D. Hopkins (2014). "Different early rearing experiences have long-term effects on cortical organization in captive chimpanzees (Pan troglodytes)." Developmental Science **17**(2): 161-174.
Bookstein, F. L. (2001). ""Voxel-Based Morphometry" Should Not Be Used with Imperfectly Registered Images." NeuroImage **14**(6): 1454-1462.
Bottjer, S. W. and F. Johnson (1997). "Circuits, hormones, and learning: Vocal behavior in songbirds." Journal of Neurobiology **33**(5): 602-618.
Boyke, J., J. Driemeyer, C. Gaser, C. Büchel and A. May (2008). "Training-Induced Brain Structure Changes in the Elderly." The Journal of Neuroscience **28**(28): 7031-7035.
Brabant, G., J. Cain, A. Jackson and I. Kreitschmann-Andermahr (2011). "Visualizing hormone actions in the brain." Trends in Endocrinology & Metabolism **22**(5): 153-163.
Butz, M., F. Wörgötter and A. van Ooyen (2009). "Activity-dependent structural plasticity." Brain Research Reviews **60**(2): 287-305.
Canals, S., M. Beyerlein, H. Merkle and N. K. Logothetis (2009). "Functional MRI Evidence for LTP-Induced Neural Network Reorganization." Current Biology **19**(5): 398-403.
Chan, K. C., J. S. Cheng, S. Fan, I. Y. Zhou, J. Yang and E. X. Wu (2012). "In vivo evaluation of retinal and callosal projections in early postnatal development and plasticity using manganese-enhanced MRI and diffusion tensor imaging." NeuroImage **59**(3): 2274-2283.
Chan, K. C., M. M. Cheung and E. X. Wu (2010). "IN VIVO MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF RODENT VISUAL SYSTEM." Journal of Integrative Neuroscience **09**(04): 477-508.
Chow, A. M., I. Y. Zhou, S. J. Fan, K. W. Y. Chan, K. C. Chan and E. X. Wu (2011). "Metabolic changes in visual cortex of neonatal monocular enucleated rat: a proton magnetic resonance spectroscopy study." International Journal of Developmental Neuroscience **29**(1): 25-30.
Choy, M., K. K. Cheung, D. L. Thomas, D. G. Gadian, M. F. Lythgoe and R. C. Scott (2010). "Quantitative MRI predicts status epilepticus-induced hippocampal injury in the lithium–pilocarpine rat model." Epilepsy Research **88**(2–3): 221-230.
Choy, M., J. A. Wells, D. L. Thomas, D. G. Gadian, R. C. Scott and M. F. Lythgoe (2010). "Cerebral blood flow changes during pilocarpine-induced status epilepticus activity in the rat hippocampus." Experimental Neurology **225**(1): 196-201.
Clayton, D. F. (2013). "The Genomics of Memory and Learning in Songbirds." Annual Review of Genomics and Human Genetics **14**(1): 45-65.
Coghlan, S., J. Horder, B. Inkster, M. A. Mendez, D. G. Murphy and D. J. Nutt (2012). "GABA system dysfunction in autism and related disorders: From synapse to symptoms." Neuroscience & Biobehavioral Reviews **36**(9): 2044-2055.
Cooke, G. E., S. Mullally, N. Correia, S. M. O'Mara and J. Gibney (2013). "Hippocampal Volume Is Decreased in Adults with Hypothyroidism." Thyroid **24**(3): 433-440.
Coquery, N., A. Blesch, A. Stroh, F. Fernández-Klett, J. Klein, C. Winter and J. Priller (2012). "Intrahippocampal transplantation of mesenchymal stromal cells promotes neuroplasticity." Cytotherapy **14**(9): 1041-1053.
Cornez, G., S. M. ter Haar, C. A. Cornil and J. Balthazart (2015). "Anatomically Discrete Sex Differences in Neuroplasticity in Zebra Finches as Reflected by Perineuronal Nets." PLoS ONE **10**(4): e0123199.

Couillard-Despres, S., R. Vreys, L. Aigner and A. Van Der Linden (2011). "In vivo monitoring of adult neurogenesis in health and disease." Frontiers in Neuroscience **5**.
Curlik, I., Daniel Martin, G. DiFeo and T. J. Shors (2014). "Preparing for Adulthood: Thousands Upon Thousands of New Cells are Born in the Hippocampus During Puberty and Most Survive with Effortful Learning." Frontiers in Neuroscience **8**.
Daniel, J. M. (2013). "Estrogens, estrogen receptors, and female cognitive aging: The impact of timing." Hormones and Behavior **63**(2): 231-237.
Davatzikos, C. (2004). "Why voxel-based morphometric analysis should be used with great caution when characterizing group differences." NeuroImage **23**(1): 17-20.
Dayan, E. and Leonardo G. Cohen (2011). "Neuroplasticity Subserving Motor Skill Learning." Neuron **72**(3): 443-454.
De Groof, G., I. George, S. Touj, M. Stacho, E. Jonckers, H. Cousillas, M. Hausberger, O. Güntürkün and A. Van der Linden (2015). "A three-dimensional digital atlas of the starling brain." Brain Structure and Function: 1-11.
De Groof, G., C. Poirier, I. George, M. Hausberger and A. Van der Linden (2013). "Functional changes between seasons in the male songbird auditory forebrain." Front Behav Neurosci **7**: 196.
De Groof, G. and A. Van der Linden (2010). "Love songs, bird brains and diffusion tensor imaging." NMR in Biomedicine **23**(7): 873-883.
De Groof, G., M. Verhoye, V. Van Meir, J. Balthazart and A. Van der Linden (2008). "Seasonal rewiring of the songbird brain: an in vivo MRI study." European Journal of Neuroscience **28**(12): 2475-2485.
Dedovic, K., R. Renwick, N. K. Mahani, V. Engert, S. J. Lupien and J. C. Pruessner (2005). "The Montreal Imaging Stress Task: using functional imaging to investigate the effects of perceiving and processing psychosocial stress in the human brain." Journal of Psychiatry and Neuroscience **30**(5): 319-325.
Deidda, G., M. Allegra, C. Cerri, S. Naskar, G. Bony, G. Zunino, Y. Bozzi, M. Caleo and L. Cancedda (2015). "Early depolarizing GABA controls critical-period plasticity in the rat visual cortex." Nat Neurosci **18**(1): 87-96.
Delgado, M. R., A. Olsson and E. A. Phelps (2006). "Extending animal models of fear conditioning to humans." Biological Psychology **73**(1): 39-48.
Dijkhuizen, R., K. van der Marel, W. Otte, E. Hoff, J. van der Zijden, A. van der Toorn and M. A. van Meer (2012). "Functional MRI and Diffusion Tensor Imaging of Brain Reorganization After Experimental Stroke." Translational Stroke Research **3**(1): 36-43.
Ding, A. Y., Q. Li, I. Y. Zhou, S. J. Ma, G. Tong, G. M. McAlonan and E. X. Wu (2013). "MR Diffusion Tensor Imaging Detects Rapid Microstructural Changes in Amygdala and Hippocampus Following Fear Conditioning in Mice." PLoS ONE **8**(1): e51704.
Doupe, A. J. and P. K. Kuhl (1999). "BIRDSONG AND HUMAN SPEECH: Common Themes and Mechanisms." Annual Review of Neuroscience **22**(1): 567-631.
Draganski, B., C. Gaser, V. Busch, G. Schuierer, U. Bogdahn and A. May (2004). "Neuroplasticity: Changes in grey matter induced by training." Nature **427**(6972): 311-312.
Draganski, B. and A. May (2008). "Training-induced structural changes in the adult human brain." Behavioural Brain Research **192**(1): 137-142.
Endo, T., C. Spenger, T. Tominaga, S. Brene and L. Olson (2007). "Cortical sensory map rearrangement after spinal cord injury: fMRI responses linked to Nogo signalling." Brain **130**(Pt 11): 2951-2961.
Erzurumlu, R. S. and P. Gaspar (2012). "Development and critical period plasticity of the barrel cortex." European Journal of Neuroscience **35**(10): 1540-1553.
Fagiolini, M., C. L. Jensen and F. A. Champagne (2009). "Epigenetic influences on brain development and plasticity." Current Opinion in Neurobiology **19**(2): 207-212.
Faherty, C. J., K. Raviie Shepherd, A. Herasimtschuk and R. J. Smeyne (2005). "Environmental enrichment in adulthood eliminates neuronal death in experimental Parkinsonism." Molecular Brain Research **134**(1): 170-179.

Feher, O., H. Wang, S. Saar, P. P. Mitra and O. Tchernichovski (2009). "De novo establishment of wild-type song culture in the zebra finch." Nature **459**(7246): 564-568.
Fernandez, F. and C. C. Garner (2007). "Over-inhibition: a model for developmental intellectual disability." Trends in Neurosciences **30**(10): 497-503.
Fledelius, H. C., E. Goldschmidt, B. Haargaard and H. Jensen (2014). "Human parallels to experimental myopia? A literature review on visual deprivation." Acta Ophthalmologica: n/a-n/a.
Floyer-Lea, A., M. Wylezinska, T. Kincses and P. M. Matthews (2006). Rapid Modulation of GABA Concentration in Human Sensorimotor Cortex During Motor Learning.
Fowler, J. S., N. D. Volkow, C. A. Kassed and L. Chang (2007). "Imaging the Addicted Human Brain." Science & Practice Perspectives **3**(2): 4-16.
Frasnelli, J., O. Collignon, P. Voss and F. Lepore (2011). Crossmodal plasticity in sensory loss.
Fromkin, V., S. Krashen, S. Curtiss, D. Rigler and M. Rigler (1974). "The development of language in genie: a case of language acquisition beyond the "critical period"." Brain and Language **1**(1): 81-107.
Fuss, J., S. V. Biedermann, C. Falfán-Melgoza, M. K. Auer, L. Zheng, J. Steinle, F. Hörner, A. Sartorius, G. Ende, W. Weber-Fahr and P. Gass (2014). "Exercise boosts hippocampal volume by preventing early age-related gray matter loss." Hippocampus **24**(2): 131-134.
Golub, Y., S. F. Kaltwasser, C. P. Mauch, L. Herrmann, U. Schmidt, F. Holsboer, M. Czisch and C. T. Wotjak (2011). "Reduced hippocampus volume in the mouse model of Posttraumatic Stress Disorder." Journal of Psychiatric Research **45**(5): 650-659.
Gonzales, M., T. Tarumi, S. Kaur, N. Nualnim, B. Fallow, M. Pyron, H. Tanaka and A. Haley (2013). "Aerobic Fitness and the Brain: Increased N-Acetyl-Aspartate and Choline Concentrations in Endurance-Trained Middle-Aged Adults." Brain Topography **26**(1): 126-134.
Görtz, N., L. Lewejohann, M. Tomm, O. Ambrée, K. Keyvani, W. Paulus and N. Sachser (2008). "Effects of environmental enrichment on exploration, anxiety, and memory in female TgCRND8 Alzheimer mice." Behavioural Brain Research **191**(1): 43-48.
Gröhn, O., A. Sierra, R. Immonen, T. Laitinen, K. Lehtimäki, A. Airaksinen, N. Hayward, J. Nairismagi, L. Lehto and A. Pitkänen (2011). "Multimodal MRI assessment of damage and plasticity caused by status epilepticus in the rat brain." Epilepsia **52**: 57-60.
Gudsnuk, K. and F. A. Champagne (2012). "Epigenetic Influence of Stress and the Social Environment." ILAR Journal **53**(3-4): 279-288.
Hagemann, G., T. Ugur, E. Schleussner, H.-J. Mentzel, C. Fitzek, O. W. Witte and C. Gaser (2011). "Changes in Brain Size during the Menstrual Cycle." PLoS ONE **6**(2): e14655.
Hamzei, F., V. Glauche, R. Schwarzwald and A. May (2012). "Dynamic gray matter changes within cortex and striatum after short motor skill training are associated with their increased functional interaction." NeuroImage **59**(4): 3364-3372.
Hannan, A. J. (2014). "Review: Environmental enrichment and brain repair: harnessing the therapeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity." Neuropathology and Applied Neurobiology **40**(1): 13-25.
Hayward, N. M. E. A., X. E. Ndode-Ekane, N. Kutchiashvili, O. Gröhn and A. Pitkänen (2010). "Elevated cerebral blood flow and vascular density in the amygdala after status epilepticus in rats." Neuroscience Letters **484**(1): 39-42.
He, Z., X. Wang, Y. Wu, J. Jia, Y. Hu, X. Yang, J. Li, M. Fan, L. Zhang, J. Guo and M. C. P. Leung (2014). "Treadmill Pre-Training Ameliorates Brain Edema in Ischemic Stroke via Down-Regulation of Aquaporin-4: An MRI Study in Rats." PLoS ONE **9**(1): e84602.
Hebb, D. (1949). The Organization of Behavior: A Neuropsychological Theory, Wiley.
Hensch, T. K. (2004). "CRITICAL PERIOD REGULATION." Annual Review of Neuroscience **27**(1): 549-579.
Herring, A., O. Ambree, M. Tomm, H. Habermann, N. Sachser, W. Paulus and K. Keyvani (2009). "Environmental enrichment enhances cellular plasticity in transgenic mice with Alzheimer-like pathology." Exp Neurol **216**(1): 184-192.

Hihara, S., T. Notoya, M. Tanaka, S. Ichinose, H. Ojima, S. Obayashi, N. Fujii and A. Iriki (2006). "Extension of corticocortical afferents into the anterior bank of the intraparietal sulcus by tool-use training in adult monkeys." Neuropsychologia **44**(13): 2636-2646.
Höfer, P., R. Lanzenberger and S. Kasper (2013). "Testosterone in the brain: Neuroimaging findings and the potential role for neuropsychopharmacology." European Neuropsychopharmacology **23**(2): 79-88.
Hofstetter, S., I. Tavor, S. Tzur Moryosef and Y. Assaf (2013). "Short-Term Learning Induces White Matter Plasticity in the Fornix." The Journal of Neuroscience **33**(31): 12844-12850.
Hötting, K. and B. Röder (2013). "Beneficial effects of physical exercise on neuroplasticity and cognition." Neuroscience & Biobehavioral Reviews **37**(9, Part B): 2243-2257.
Imfeld, A., M. S. Oechslin, M. Meyer, T. Loenneker and L. Jancke (2009). "White matter plasticity in the corticospinal tract of musicians: A diffusion tensor imaging study." NeuroImage **46**(3): 600-607.
Institute, L. M. G. S. C. M. N. L. C. (2009). Hormones and Brain Plasticity, Oxford University Press, USA.
Jaime, F. O., S. B. Andrew, A. L. Lindsey and D. K. Christopher (2012). "Deafferentation-Induced Plasticity of Visual Callosal Connections: Predicting Critical Periods and Analyzing Cortical Abnormalities Using Diffusion Tensor Imaging." Neural Plasticity **2012**.
Jenks, K. R., M. M. Lucas, B. A. Duffy, A. A. Robbins, B. Gimi, J. M. Barry and R. C. Scott (2013). "Enrichment and Training Improve Cognition in Rats with Cortical Malformations." PLoS ONE **8**(12): e84492.
Jessberger, S. and F. H. Gage (2014). "Adult neurogenesis: bridging the gap between mice and humans." Trends in Cell Biology **24**(10): 558-563.
Johansson, B. B. (2004). "Functional and cellular effects of environmental enrichment after experimental brain infarcts." Restorative Neurology and Neuroscience **22**(3): 163-174.
Johnston, M. V. (2004). "Clinical disorders of brain plasticity." Brain and Development **26**(2): 73-80.
Johnston, M. V. (2009). "Plasticity in the developing brain: Implications for rehabilitation." Developmental Disabilities Research Reviews **15**(2): 94-101.
Jon, J. B. (2012). "Neurodevelopment: unlocking the brain." Nature **487**(7405): 24-26.
Jonckers, E., O. Güntürkün, G. De Groof, A. van der Linden and V. P. Bingman (2015). "Network structure of functional hippocampal lateralization in birds." Hippocampus: n/a-n/a.
Jones, D. K., M. R. Symms, M. Cercignani and R. J. Howard (2005). "The effect of filter size on VBM analyses of DT-MRI data." NeuroImage **26**(2): 546-554.
Kapur, N. (1996). Paradoxical functional facilitation in brain-behaviour research.
Kempermann, G., H. G. Kuhn and F. H. Gage (1997). "More hippocampal neurons in adult mice living in an enriched environment." Nature **386**(6624): 493-495.
Kent, K., K. Hess, S. Tonegawa and S. A. Small (2007). "CA3 NMDA receptors are required for experience-dependent shifts in hippocampal activity." Hippocampus **17**(10): 1003-1011.
Kim, H., R. Gibboni, C. Kirkhart and S. Bao (2013). "Impaired Critical Period Plasticity in Primary Auditory Cortex of Fragile X Model Mice." The Journal of Neuroscience **33**(40): 15686-15692.
Kral, A. (2013). "Auditory critical periods: A review from system's perspective." Neuroscience **247**(0): 117-133.
Kupers, R. and M. Ptito (2014). "Compensatory plasticity and cross-modal reorganization following early visual deprivation." Neuroscience & Biobehavioral Reviews **41**(0): 36-52.
Laitinen, T., A. Sierra, A. Pitkänen and O. Gröhn (2010). "Diffusion tensor MRI of axonal plasticity in the rat hippocampus." NeuroImage **51**(2): 521-530.
Lan, Y.-L., J. Zhao and S. Li (2015). "Update on the Neuroprotective Effect of Estrogen Receptor Alpha Against Alzheimer's Disease." Journal of Alzheimer's Disease **43**(4): 1137-1148.
Lazic, S. E., H. E. Grote, C. Blakemore, A. J. Hannan, A. van Dellen, W. Phillips and R. A. Barker (2006). "Neurogenesis in the R6/1 transgenic mouse model of Huntington's disease: effects of environmental enrichment." European Journal of Neuroscience **23**(7): 1829-1838.

Lazzouni, L. and F. Lepore (2014). "Compensatory plasticity: time matters." Frontiers in Human Neuroscience **8**.
Lerch, J. P., A. P. Yiu, A. Martinez-Canabal, T. Pekar, V. D. Bohbot, P. W. Frankland, R. M. Henkelman, S. A. Josselyn and J. G. Sled (2011). "Maze training in mice induces MRI-detectable brain shape changes specific to the type of learning." NeuroImage **54**(3): 2086-2095.
Levelt, C. N. and M. Hübener (2012). "Critical-Period Plasticity in the Visual Cortex." Annual Review of Neuroscience **35**(1): 309-330.
Li, R., P. C. Hettinger, J. A. Machol, X. Liu, J. B. Stephenson, C. P. Pawela, J.-G. Yan, H. S. Matloub and J. S. Hyde (2013). "Cortical plasticity induced by different degrees of peripheral nerve injuries: a rat functional magnetic resonance imaging study under 9.4 Tesla." Journal of Brachial Plexus and Peripheral Nerve Injury **8**: 4-4.
Little, D. M., S. Foxely and O. Lazarov (2012). "A preliminary study targeting neuronal pathways activated following environmental enrichment by resting state functional magnetic resonance imaging." J Alzheimers Dis **32**(1): 101-107.
Lockhart, S. and C. DeCarli (2014). "Structural Imaging Measures of Brain Aging." Neuropsychology Review **24**(3): 271-289.
Lu, B., G. Nagappan and Y. Lu (2014). BDNF and Synaptic Plasticity, Cognitive Function, and Dysfunction. Neurotrophic Factors. G. R. Lewin and B. D. Carter, Springer Berlin Heidelberg. **220:** 223-250.
Luine, V., S. Richards, V. Wu and K. Beck (1998). "Estradiol enhances learning and memory in a spatial memory task and effects levels of monoaminergic neurotransmitters." Hormones and behavior **34**(2): 149.
LYNCH, M. A. (2004). Long-Term Potentiation and Memory.
Ma, L., S. Narayana, D. A. Robin, P. T. Fox and J. Xiong (2011). "Changes occur in resting state network of motor system during 4 weeks of motor skill learning." NeuroImage **58**(1): 226-233.
Maddock, R. J., G. A. Casazza, M. H. Buonocore and C. Tanase (2011). "Vigorous exercise increases brain lactate and Glx (glutamate + glutamine): A dynamic 1H-MRS study." NeuroImage **57**(4): 1324-1330.
Manganas, L. N., X. Zhang, Y. Li, R. D. Hazel, S. D. Smith, M. E. Wagshul, F. Henn, H. Benveniste, P. M. Djurić, G. Enikolopov and M. Maletić-Savatić (2007). "Magnetic Resonance Spectroscopy Identifies Neural Progenitor Cells in the Live Human Brain." Science **318**(5852): 980-985.
Mariotti, R., P. Fattoretti, M. Malatesta, E. Nicolato, M. Sandri and C. Zancanaro (2014). "Forced mild physical training improves blood volume in the motor and hippocampal cortex of old mice." The journal of nutrition, health & aging **18**(2): 178-183.
May, A. (2011). "Experience-dependent structural plasticity in the adult human brain." Trends in Cognitive Sciences **15**(10): 475-482.
McConathy, J. and Y. I. Sheline (2015). "Imaging Biomarkers Associated With Cognitive Decline: A Review." Biological Psychiatry **77**(8): 685-692.
McEwen, B. S., S. E. Alves, K. Bulloch and N. G. Weiland (1997). "Ovarian steroids and the brain: Implications for cognition and aging." Neurology **48**(5 Suppl 7): 8S-15S.
Mednick, S. C., D. J. Cai, T. Shuman, S. Anagnostaras and J. Wixted (2011). "An opportunistic theory of cellular and systems consolidation." Trends in neurosciences **34**(10): 504-514.
Mello, C. V., T. A. F. Velho and R. Pinaud (2004). "Song-Induced Gene Expression: A Window on Song Auditory Processing and Perception." Annals of the New York Academy of Sciences **1016**(1): 263-281.
Meyer, C. E., E. Boroda and T. A. Nick (2014). "Sexually dimorphic perineuronal net expression in the songbird." Basal Ganglia **3**(4): 229-237.
Miller, M. J., N. K. Chen, L. Li, B. Tom, C. Weiss, J. F. Disterhoft and A. M. Wyrwicz (2003). "fMRI of the conscious rabbit during unilateral classical eyeblink conditioning reveals bilateral cerebellar activation." J Neurosci **23**(37): 11753-11758.

Morishita, H., M. Kundakovic, L. Bicks, A. Mitchell and S. Akbarian "Interneuron epigenomes during the critical period of cortical plasticity: Implications for schizophrenia." Neurobiology of Learning and Memory(0).
Moulton, E. A., I. Elman, L. R. Becerra, R. Z. Goldstein and D. Borsook (2014). "The cerebellum and addiction: insights gained from neuroimaging research." Addiction Biology **19**(3): 317-331.
Nabel, E. M. and H. Morishita (2013). "Regulating Critical Period Plasticity: Insight from the Visual System to Fear Circuitry for Therapeutic Interventions." Frontiers in Psychiatry **4**: 146.
Nagy, C. and G. Turecki (2012). "Sensitive periods in epigenetics: bringing us closer to complex behavioral phenotypes." Epigenomics **4**(4): 445-457.
Nahmani, M. and G. G. Turrigiano "Adult cortical plasticity following injury: Recapitulation of critical period mechanisms?" Neuroscience(0).
Nahmani, M. and G. G. Turrigiano (2014). "Adult cortical plasticity following injury: Recapitulation of critical period mechanisms?" Neuroscience **283**(0): 4-16.
Nairismägi, J., A. Pitkänen, S. Narkilahti, J. Huttunen, R. A. Kauppinen and O. H. J. Gröhn (2006). "Manganese-enhanced magnetic resonance imaging of mossy fiber plasticity in vivo." NeuroImage **30**(1): 130-135.
Niccolini, F. and M. Politis (2014). "Neuroimaging in Huntington's disease." World Journal of Radiology **6**(6): 301-312.
Nithianantharajah, J. and A. J. Hannan (2006). "Enriched environments, experience-dependent plasticity and disorders of the nervous system." Nat Rev Neurosci **7**(9): 697-709.
O'Doherty, D. C. M., K. M. Chitty, S. Saddiqui, M. R. Bennett and J. Lagopoulos "A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder." Psychiatry Research: Neuroimaging.
Olson, A. K., B. D. Eadie, C. Ernst and B. R. Christie (2006). "Environmental enrichment and voluntary exercise massively increase neurogenesis in the adult hippocampus via dissociable pathways." Hippocampus **16**(3): 250-260.
Papanikolaou, A., G. A. Keliris, T. D. Papageorgiou, Y. Shao, E. Krapp, E. Papageorgiou, K. Stingl, A. Bruckmann, U. Schiefer, N. K. Logothetis and S. M. Smirnakis (2014). "Population receptive field analysis of the primary visual cortex complements perimetry in patients with homonymous visual field defects." Proceedings of the National Academy of Sciences **111**(16): E1656-E1665.
Parvaz, M. A., N. Alia-Klein, P. A. Woicik, N. D. Volkow and R. Z. Goldstein (2011). "Neuroimaging for drug addiction and related behaviors." Reviews in the neurosciences **22**(6): 609-624.
Pawela, C. P., B. B. Biswal, A. G. Hudetz, R. Li, S. R. Jones, Y. R. Cho, H. S. Matloub and J. S. Hyde (2010). "Interhemispheric neuroplasticity following limb deafferentation detected by resting-state functional connectivity magnetic resonance imaging (fcMRI) and functional magnetic resonance imaging (fMRI)." NeuroImage **49**(3): 2467-2478.
Pelled, G. (2011). MRI of Neuronal Plasticity in Rodent Models. Magnetic Resonance Neuroimaging. M. Modo and J. W. M. Bulte, Humana Press. **711:** 567-578.
Pelled, G., K.-H. Chuang, S. J. Dodd and A. P. Koretsky (2007). "Functional MRI detection of bilateral cortical reorganization in the rodent brain following peripheral nerve deafferentation." NeuroImage **37**(1): 262-273.
Pereira, A. C., D. E. Huddleston, A. M. Brickman, A. A. Sosunov, R. Hen, G. M. McKhann, R. Sloan, F. H. Gage, T. R. Brown and S. A. Small (2007). "An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus." Proceedings of the National Academy of Sciences **104**(13): 5638-5643.
Petkov, C. I. and E. Jarvis (2012). "Birds, Primates and Spoken Language Origins: Behavioral Phenotypes and Neurobiological Substrates." Frontiers in Evolutionary Neuroscience **4**.
Pletzer, B., M. Kronbichler, M. Aichhorn, J. Bergmann, G. Ladurner and H. H. Kerschbaum (2010). "Menstrual cycle and hormonal contraceptive use modulate human brain structure." Brain Research **1348**(0): 55-62.

Poldrack, R. A. (2000). "Imaging Brain Plasticity: Conceptual and Methodological Issues— A Theoretical Review." NeuroImage **12**(1): 1-13.
Protopopescu, X., T. Butler, H. Pan, J. Root, M. Altemus, M. Polanecsky, B. McEwen, D. Silbersweig and E. Stern (2008). "Hippocampal structural changes across the menstrual cycle." Hippocampus **18**(10): 985-988.
Pugh, K. R., S. J. Frost, D. L. Rothman, F. Hoeft, S. N. Del Tufo, G. F. Mason, P. J. Molfese, W. E. Mencl, E. L. Grigorenko, N. Landi, J. L. Preston, L. Jacobsen, M. S. Seidenberg and R. K. Fulbright (2014). "Glutamate and Choline Levels Predict Individual Differences in Reading Ability in Emergent Readers." The Journal of Neuroscience **34**(11): 4082-4089.
Pugh, K. R., N. Landi, J. L. Preston, W. E. Mencl, A. C. Austin, D. Sibley, R. K. Fulbright, M. S. Seidenberg, E. L. Grigorenko, R. T. Constable, P. Molfese and S. J. Frost (2013). "The relationship between phonological and auditory processing and brain organization in beginning readers." Brain and language **125**(2): 173-183.
Quallo, M. M., C. J. Price, K. Ueno, T. Asamizuya, K. Cheng, R. N. Lemon and A. Iriki (2009). "Gray and white matter changes associated with tool-use learning in macaque monkeys." Proceedings of the National Academy of Sciences **106**(43): 18379-18384.
Ramm, P., S. Couillard-Despres, S. Plötz, F. J. Rivera, M. Krampert, B. Lehner, W. Kremer, U. Bogdahn, H. R. Kalbitzer and L. Aigner (2009). "A Nuclear Magnetic Resonance Biomarker for Neural Progenitor Cells: Is It All Neurogenesis?" STEM CELLS **27**(2): 420-423.
Ramu, J., J. Herrera, R. Grill, T. Bockhorst and P. Narayana (2008). "Brain fiber tract plasticity in experimental spinal cord injury: Diffusion tensor imaging." Experimental Neurology **212**(1): 100-107.
Ribak, C. E. and R. T. Robertson (1986). "Effects of neonatal monocular enucleation on the number of GAD-positive puncta in rat visual cortex." Experimental Brain Research **62**(1): 203-206.
Ridgway, G. R., S. M. D. Henley, J. D. Rohrer, R. I. Scahill, J. D. Warren and N. C. Fox (2008). "Ten simple rules for reporting voxel-based morphometry studies." NeuroImage **40**(4): 1429-1435.
Robertson, R. T., C. F. Höhmann, J. L. Bruce and J. T. Coyle (1988). "Neonatal enucleations reduce specific activity of acetylcholinesterase but not choline acetyltransferase in developing rat visual cortex." Developmental Brain Research **39**(2): 298-302.
Roche, R. A., S. L. Mullally, J. P. McNulty, J. Hayden, P. Brennan, C. P. Doherty, M. Fitzsimons, D. McMackin, J. Prendergast, S. Sukumaran, M. A. Mangaoang, I. H. Robertson and S. M. O'Mara (2009). Prolonged rote learning produces delayed memory facilitation and metabolic changes in the hippocampus of the ageing human brain. **2009:** 136.
Sagi, Y., I. Tavor, S. Hofstetter, S. Tzur-Moryosef, T. Blumenfeld-Katzir and Y. Assaf (2012). "Learning in the Fast Lane: New Insights into Neuroplasticity." Neuron **73**(6): 1195-1203.
Salo, R. and C. Fassbender (2012). Structural, Functional and Spectroscopic MRI Studies of Methamphetamine Addiction. Brain Imaging in Behavioral Neuroscience. C. S. Carter and J. W. Dalley, Springer Berlin Heidelberg. **11:** 321-364.
Sampaio-Baptista, C., A. A. Khrapitchev, S. Foxley, T. Schlagheck, J. Scholz, S. Jbabdi, G. C. DeLuca, K. L. Miller, A. Taylor, N. Thomas, J. Kleim, N. R. Sibson, D. Bannerman and H. Johansen-Berg (2013). "Motor Skill Learning Induces Changes in White Matter Microstructure and Myelination." The Journal of Neuroscience **33**(50): 19499-19503.
Sampaio-Baptista, C., J. Scholz, M. Jenkinson, A. G. Thomas, N. Filippini, G. Smit, G. Douaud and H. Johansen-Berg (2014). "Gray matter volume is associated with rate of subsequent skill learning after a long term training intervention." NeuroImage **96**(0): 158-166.
Särkämö, T., P. Ripollés, H. Vepsäläinen, T. Autti, H. M. Silvennoinen, E. Salli, S. Laitinen, A. Forsblom, S. Soinila and A. Rodríguez-Fornells (2014). "Structural changes induced by daily music listening in the recovering brain after middle cerebral artery stroke: a voxel-based morphometry study." Frontiers in Human Neuroscience **8**.
Scholz, J., R. Allemang-Grand, J. Dazai and J. P. Lerch (2015). "Environmental enrichment is associated with rapid volumetric brain changes in adult mice." NeuroImage **109**(0): 190-198.

Scholz, J., Y. Niibori, P. W Frankland and J. P Lerch (2015). "Rotarod training in mice is associated with changes in brain structure observable with multimodal MRI." NeuroImage **107**(0): 182-189.
Shao, Y., G. A. Keliris, A. Papanikolaou, M. D. Fischer, D. Zobor, H. Jägle, N. K. Logothetis and S. M. Smirnakis (2013). "Visual cortex organisation in a macaque monkey with macular degeneration." European Journal of Neuroscience **38**(10): 3456-3464.
Sierra, A., T. Laitinen, K. Lehtimäki, L. Rieppo, A. Pitkänen and O. Gröhn (2011). "Diffusion tensor MRI with tract-based spatial statistics and histology reveals undiscovered lesioned areas in kainate model of epilepsy in rat." Brain Structure and Function **216**(2): 123-135.
Simpson, J. and J. P. Kelly (2011). "The impact of environmental enrichment in laboratory rats—Behavioural and neurochemical aspects." Behavioural Brain Research **222**(1): 246-264.
Small, S. A., M. K. Chawla, M. Buonocore, P. R. Rapp and C. A. Barnes (2004). "Imaging correlates of brain function in monkeys and rats isolates a hippocampal subregion differentially vulnerable to aging." Proceedings of the National Academy of Sciences of the United States of America **101**(18): 7181-7186.
Small, S. A., A. S. Nava, G. M. Perera, R. DeLaPaz, R. Mayeux and Y. Stern (2001). "Circuit mechanisms underlying memory encoding and retrieval in the long axis of the hippocampal formation." Nat Neurosci **4**(4): 442-449.
Sprague, J. M. (1966). "Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat." Science **153**(3743): 3.
Stagg, C. J. (2014). "Magnetic Resonance Spectroscopy as a tool to study the role of GABA in motor-cortical plasticity." NeuroImage **86**(0): 19-27.
Sumiyoshi, A., Y. Taki, H. Nonaka, H. Takeuchi and R. Kawashima (2014). "Regional gray matter volume increases following 7 days of voluntary wheel running exercise: A longitudinal VBM study in rats." NeuroImage **98**(0): 82-90.
Svensson, M., J. Lexell and T. Deierborg (2014). "Effects of Physical Exercise on Neuroinflammation, Neuroplasticity, Neurodegeneration, and Behavior: What We Can Learn From Animal Models in Clinical Settings." Neurorehabilitation and Neural Repair.
Svirsky, M. A., S. W. Teoh and H. Neuburger (2004). "Development of Language and Speech Perception in Congenitally, Profoundly Deaf Children as a Function of Age at Cochlear Implantation." Audiology and Neurotology **9**(4): 224-233.
Taubert, M., B. Draganski, A. Anwander, K. Müller, A. Horstmann, A. Villringer and P. Ragert (2010). "Dynamic Properties of Human Brain Structure: Learning-Related Changes in Cortical Areas and Associated Fiber Connections." The Journal of Neuroscience **30**(35): 11670-11677.
Taubert, M., G. Lohmann, D. S. Margulies, A. Villringer and P. Ragert (2011). "Long-term effects of motor training on resting-state networks and underlying brain structure." NeuroImage **57**(4): 1492-1498.
Taubert, M., A. Villringer and P. Ragert (2012). "Learning-Related Gray and White Matter Changes in Humans: An Update." The Neuroscientist **18**(4): 320-325.
Thomas, C. and C. I. Baker (2013). "Teaching an adult brain new tricks: A critical review of evidence for training-dependent structural plasticity in humans." NeuroImage **73**(0): 225-236.
Thompson, C. K. (2011). "Cell death and the song control system: A model for how sex steroid hormones regulate naturally-occurring neurodegeneration." Development, Growth & Differentiation **53**(2): 213-224.
Tramontin, A. D. and E. A. Brenowitz (2000). "Seasonal plasticity in the adult brain." Trends in Neurosciences **23**(6): 251-258.
Trepel, C. and R. J. Racine (2000). "GABAergic modulation of neocortical long-term potentiation in the freely moving rat." Synapse **35**(2): 120-128.
Tropea, D., A. Van Wart and M. Sur (2009). "Molecular mechanisms of experience-dependent plasticity in visual cortex." Philosophical Transactions of the Royal Society B: Biological Sciences **364**(1515): 341-355.
Urbanski, M., O. A. Coubard and C. Bourlon (2014). "Visualizing the blind brain: brain imaging of visual field defects from early recovery to rehabilitation techniques." Frontiers in Integrative Neuroscience **8**: 74.

Vaiserman, A. M. (2015). "Epigenetic programming by early-life stress: Evidence from human populations." Developmental Dynamics **244**(3): 254-265.
Van Boven, R. W., G. S. Harrington, D. B. Hackney, A. Ebel, G. Gauger, J. D. Bremner, M. D'Esposito, J. A. Detre, E. M. Haacke, C. R. Jack, W. J. Jagust, D. Le Bihan, C. A. Mathis, S. Mueller, P. Mukherjee, N. Schuff, A. Chen and M. W. Weiner (2009). "Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder." Journal of rehabilitation research and development **46**(6): 717-757.
van Dellen, A., C. Blakemore, R. Deacon, D. York and A. J. Hannan (2000). "Delaying the onset of Huntington's in mice." Nature **404**(6779): 721-722.
Van der Linden, A., N. Van Camp, P. Ramos-Cabrer and M. Hoehn (2007). "Current status of functional MRI on small animals: application to physiology, pathophysiology, and cognition." NMR in Biomedicine **20**(5): 522-545.
Van der Linden, A., V. Van Meir, T. Boumans, C. Poirier and J. Balthazart (2009). "MRI in small brains displaying extensive plasticity." Trends in Neurosciences **32**(5): 257-266.
Van der Linden, A., M. Verhoye, V. Van Meir, I. Tindemans, M. Eens, P. Absil and J. Balthazart (2002). "In vivo manganese-enhanced magnetic resonance imaging reveals connections and functional properties of the songbird vocal control system." Neuroscience **112**(2): 467-474.
Van Meir, V., D. Pavlova, M. Verhoye, R. Pinxten, J. Balthazart, M. Eens and A. Van der Linden (2006). "In vivo MR imaging of the seasonal volumetric and functional plasticity of song control nuclei in relation to song output in a female songbird." NeuroImage **31**(3): 981-992.
Van Meir, V., M. Verhoye, P. Absil, M. Eens, J. Balthazart and A. Van der Linden (2004). "Differential effects of testosterone on neuronal populations and their connections in a sensorimotor brain nucleus controlling song production in songbirds: a manganese enhanced-magnetic resonance imaging study." NeuroImage **21**(3): 914-923.
van Praag, H., B. R. Christie, T. J. Sejnowski and F. H. Gage (1999). "Running enhances neurogenesis, learning, and long-term potentiation in mice." Proceedings of the National Academy of Sciences **96**(23): 13427-13431.
van Praag, H., G. Kempermann and F. H. Gage (2000). "Neural consequences of enviromental enrichment." Nat Rev Neurosci **1**(3): 191-198.
van Praag, H., T. Shubert, C. Zhao and F. H. Gage (2005). "Exercise Enhances Learning and Hippocampal Neurogenesis in Aged Mice." The Journal of Neuroscience **25**(38): 8680-8685.
Van Reeth, E., I. W. K. Tham, C. H. Tan and C. L. Poh (2012). "Super-resolution in magnetic resonance imaging: A review." Concepts in Magnetic Resonance Part A **40A**(6): 306-325.
Viswanath, H., K. M. Velasquez, D. G. Y. Thompson Lake, R. Savjani, A. Q. Carter, D. M. Eagleman, P. R. Baldwin, R. De La Garza and R. Salas (2015). "Alterations in Interhemispheric Functional and Anatomical Connectivity are Associated with Tobacco Smoking in Humans." Frontiers in Human Neuroscience **9**.
Vorhees, C. V. and M. T. Williams (2014). "Assessing Spatial Learning and Memory in Rodents." ILAR Journal **55**(2): 310-332.
Voss, M. W., C. Vivar, A. F. Kramer and H. van Praag (2013). "Bridging animal and human models of exercise-induced brain plasticity." Trends in Cognitive Sciences **17**(10): 525-544.
Voss, P. (2013). "Sensitive and critical periods in visual sensory deprivation." Frontiers in Psychology **4**: 664.
Walf, A. A. and C. A. Frye (2007). "The use of the elevated plus maze as an assay of anxiety-related behavior in rodents." Nature protocols **2**(2): 322-328.
Wandell, B. A. and S. M. Smirnakis (2009). "Plasticity and stability of visual field maps in adult primary visual cortex." Nat Rev Neurosci **10**(12): 873-884.
Weaver, K. E., T. L. Richards, M. Saenz, H. Petropoulos and I. Fine (2013). "Neurochemical changes within human early blind occipital cortex." Neuroscience **252**(0): 222-233.
Wnuk, A., D. L. Korol and K. I. Erickson (2012). "Estrogens, hormone therapy, and hippocampal volume in postmenopausal women." Maturitas **73**(3): 186-190.

Woolley, C. and B. McEwen (1992). "Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat [published erratum appears in J Neurosci 1992 Oct;12(10):following table of contents]." The Journal of Neuroscience **12**(7): 2549-2554.
Woolley, C. S. (2007). "Acute Effects of Estrogen on Neuronal Physiology." Annual Review of Pharmacology and Toxicology **47**(1): 657-680.
Wrigley, P. J., S. M. Gustin, P. M. Macey, P. G. Nash, S. C. Gandevia, V. G. Macefield, P. J. Siddall and L. A. Henderson (2009). "Anatomical Changes in Human Motor Cortex and Motor Pathways following Complete Thoracic Spinal Cord Injury." Cerebral Cortex **19**(1): 224-232.
Yankova, M., S. A. Hart and C. S. Woolley (2001). "Estrogen increases synaptic connectivity between single presynaptic inputs and multiple postsynaptic CA1 pyramidal cells: A serial electron-microscopic study." Proceedings of the National Academy of Sciences of the United States of America **98**(6): 3525-3530.
Yin, J. and Q. Yuan (2015). "Structural homeostasis in the nervous system: A balancing act for wiring plasticity and stability." Frontiers in Cellular Neuroscience **8**.
Yu, X., S. Wang, D.-Y. Chen, S. Dodd, A. Goloshevsky and A. P. Koretsky (2010). "3D mapping of somatotopic reorganization with small animal functional MRI." NeuroImage **49**(2): 1667-1676.
Zatorre, R. J., R. D. Fields and H. Johansen-Berg (2012). "Plasticity in Gray and White: Neuroimaging changes in brain structure during learning." Nature neuroscience **15**(4): 528-536.
Zhang, L., Z. He, Q. Zhang, Y. Wu, X. Yang, W. Niu, Y. Hu and J. Jia (2014). "Exercise Pretreatment Promotes Mitochondrial Dynamic Protein OPA1 Expression after Cerebral Ischemia in Rats." International Journal of Molecular Sciences **15**(3): 4453-4463.
Zhou, I. Y., A. Y. Ding, Q. Li, G. M. McAlonan and E. X. Wu (2012). "Magnetic resonance spectroscopy reveals N-acetylaspartate reduction in hippocampus and cingulate cortex after fear conditioning." Psychiatry Research: Neuroimaging **204**(2–3): 178-183.