Cellular diversity of the somatosensory cortical map plasticity

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Abstract

Sensory maps are representations of the sensory epithelia in the brain. Despite the intuitive explanatory power behind sensory maps as being neuronal precursors to sensory perception, and sensory cortical plasticity as a neural correlate of perceptual learning, molecular mechanisms that regulate map plasticity are not well understood. Here we perform a meta-analysis of transcriptional and translational changes during altered whisker use to nominate the major molecular correlates of experience-dependent map plasticity in the barrel cortex. We argue that brain plasticity is a systems level response, involving all cell classes, from neuron and glia to non-neuronal cells including endothelia. Using molecular pathway analysis, we further propose a gene regulatory network that could couple activity dependent changes in neurons to adaptive changes in neurovasculature, and finally we show that transcriptional regulations observed in major brain disorders target genes that are modulated by altered sensory experience. Thus, understanding the molecular mechanisms of experience-dependent plasticity of sensory maps might help to unravel the cellular events that shape brain plasticity in health and disease.

Introduction

Neurons along the sensory axis in the brain are responsible for the processing and incorporation of inputs originating from the peripheral organs, granting the organism the ability to sense. As the incoming sensory information is often highly complex, the nervous system has to deal with a high-dimensional space in a time-varying manner. For over a century, it has been known that neurons within sensory areas display so-called 'receptive fields' which are temporally varying representations of the sensory periphery in individual neurons (Sherrington, 1906). Neurons in the primary visual cortex, for instance, are known to possess orientation selectivity: they respond strongly to visual stimuli of a given specific angle but lose their responsiveness to the same stimulus when it is rotated further away from their preferred angle (Hubel and Wiesel, 1968). Similarly, neurons in the primary auditory cortex respond preferentially to stimuli at a given frequency although their selectiveness diminishes as the loudness of the sound increases (Guo et al., 2012). Sensory cortices are typically organized so that neurons that have similar receptive fields are located in each other's vicinity thus forming sensory maps in the neocortex (**Figure 1**).

Receptive fields are not hard-wired, but adapt to ongoing changes in the statistics of the incoming sensory information. This process, also known as experience-dependent plasticity (EDP), is believed to underlie cortical map plasticity. Experiments across sensory modalities have shown as a general rule that preferential use of a sensory organ, or passive exposure to a select stimulus feature, results in the expansion of the sensory organ, or stimulus representation in the cortex (**Figure 1**). Synaptic and network mechanisms of EDP are increasingly well understood (Feldman, 2009; Feldman and Brecht, 2005; Fox and Wong, 2005; Froemke, 2015), and commonly studied in the context of changes in electrophysiological properties of neurons and synaptically coupled networks. As long-lasting changes in synaptic organization require molecular regulation in individual cells, there is a growing interest in systematic identification of molecular pathways that control EDP to mechanistically understand how experience alters neural networks and shapes behavior. Here, focusing on the map plasticity in the primary somatosensory cortex, we review the state-of-art of molecular correlates of EDP, and perform a meta-analysis of transcriptional and translational changes observed upon altered whisker use. We argue that experience alters gene regulation not only in neurons but in other types of cells in the brain, although the time-course, the dynamics (e.g. up- vs downregulation) and the pathways of plasticity are at least partially cell-type specific. Linking the synaptic activation in neurons and the subsequent regulation of releasable molecules to changes in neurovasculature, we further address how systems level brain plasticity can be modulated.

1) The whisker-barrel system as a model system to study neuroplasticity

Cortical representations of rodent whiskers in the barrel cortex, a subfield of the somatosensory cortex (Van der Loos and Woolsey, 1973) have become one of the leading animal models to study experience-dependent plasticity. They possess several distinct advantages over other models of EDP, including: (1) whiskers are organized in an orderly manner on the rodent's snout, with ~32

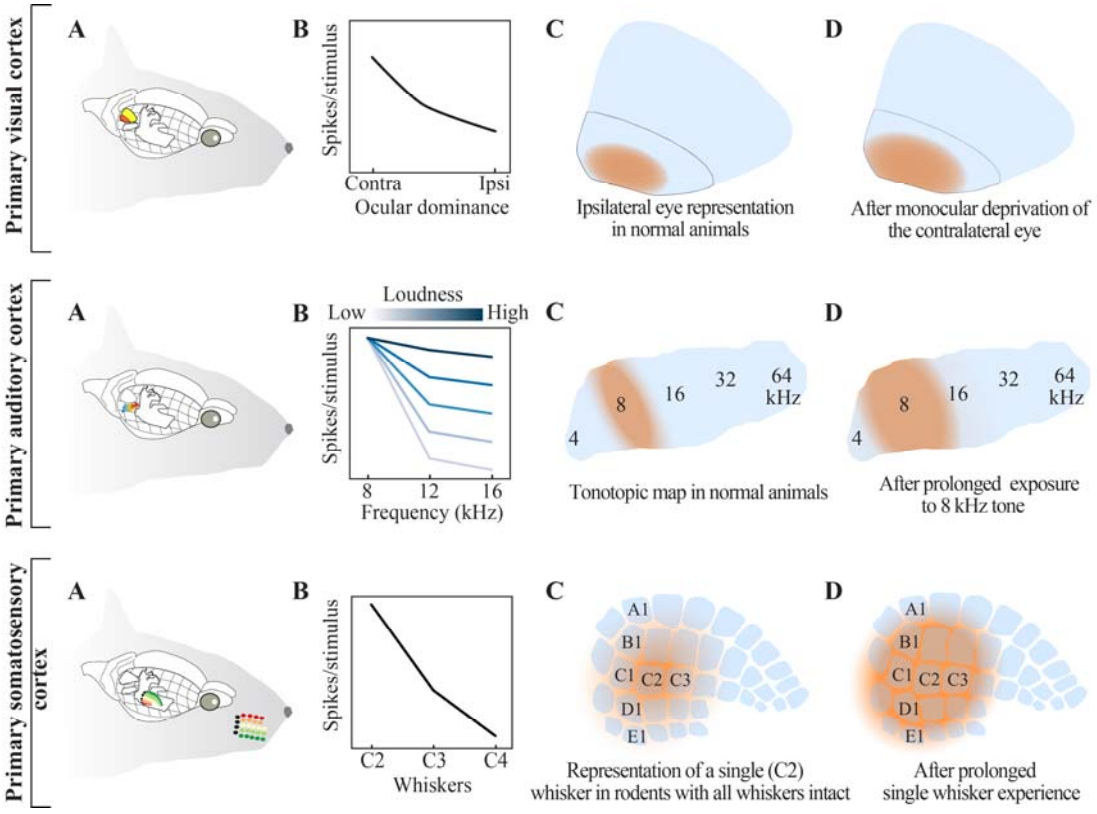


Figure 1. Receptive field plasticity and map reorganization across primary sensory cortices in rodents. (**A**) Relative locations of visual, auditory and somatosensory cortices in the rodent brain; areal designations and locations are approximated. Note that, for clarity, the ipsilateral cortices are shown whereas input mainly originates from the contralateral sensory organs. (**B**) Receptive field organization across the three cortices. Top row: The visual cortex can be subdivided into monocular and binocular region. Middle row: Auditory cortical neurons have a 'preferred frequency'. As the loudness of the auditory stimulus increases receptive fields are broadened, and neurons respond to stimuli across frequencies. Bottom row: Neurons in the somatosensory cortex are organized in a columnar fashion. Neurons in a column share a common principal whisker to which they preferentially respond. The response amplitude is reduced with increased distance between the principal whisker and the deflected (neighboring) whisker. (**C**) Cortical representations of the ipsilateral eye in the monocular region, a select tonal frequency and a whisker under normal conditions. (**D**) Upon sustained manipulation of sensory input (i.e. monocular deprivation (Gordon and Stryker, 1996), exposure to select tonal frequency(de Villers-Sidani et al., 2007) or whisker deprivation (Fox, 2002)) the sensory maps are reorganized. Independent from the sensory modality, increased use of a sensory organ, or exposure to a specific stimulus, results in expansion of cortical representations in an experience-dependent manner.

macro vibrissae (i.e. whiskers) spanning across 5 rows (named A-to-E; color coded on the figurine) and 4-8 arcs, and topographically represented by neighboring cortical columns in the barrel cortex (**Figure 1C, bottom**). This discrete topographic map allows easy and reproducible identification of the neural circuits that are altered by differential sensory organ use. (2) just like fingers

they are represented as somatosensory and motor maps in the cortex, but unlike fingers, whiskers can be reversibly deprived, providing a unique opportunity to study map reorganization during sensory deprivation and recovery from sensory organ loss. (3) whisker deprivation can be applied with ease and is relatively mild compared to other sensory deprivation paradigms such as ocular closure or digit amputation, and to some degree belongs to the rodents' natural sensory experience. Whiskers, like other hairs, undergo a hair-cycle, which results in spontaneous whisker loss, and rodents often pull their own whiskers while grooming and commonly barber each other's whiskers during social interaction (Sarna et al., 2000). Whisker deprivation is therefore likely to be less stressful for experimental animals, compared to the other established deprivation protocols across sensory modalities. Whisker plucking or clipping also differs markedly from follicle ablation, ocular removal, cochlea removal, follicle lesioning or nerve severance, which not only irreversibly eliminate peripheral sensory input, but also lead to nerve degeneration, nerve regeneration and cell death, which on their own could influence neuronal responses (Hámori et al., 1986; Waite and Cragg, 1982). These characteristics make the rodent whisker-to-barrel system ideally suited for the study of cortical EDP and as such it is widely used for this purpose.

2) Types of receptive field plasticity in the barrel cortex

As originally shown in the barrel cortex (Hand, 1982), sensory deprivation induced by transient whisker trimming is sufficient to perturb receptive field organization both during development and in adulthood (Kossut, 1985; Land and Simons, 1985). The extent of plasticity depends on the nature and duration of sensory deprivation as well as the age of the animal. Synaptic competition for sensory input is hypothesized to be a major driving force for cortical map plasticity (Fox, 2002; Song et al., 2000) and can readily be introduced through a wide range of deprivation protocols. Trimming all whiskers, but one, for example, results in expansion of the spared whisker's representation (**Figure 2B**) (Fox, 1992) while depriving all whiskers except two neighboring ones, fuses the representation of the two spared whiskers (**Figure 2C**) (Diamond et al., 1994). Other methods of deprivation range from single or multiple row sparing(Broser et al., 2008; Finnerty et al., 1999; Kaliszewska et al., 2012) or deprivation(Allen et al., 2003) and single whisker deprivation (**Figure 2D**) (Celikel et al., 2004) to more complex deprivation protocols (e.g. chessboard pattern deprivation, where every other whisker is deprived (Trachtenberg et al., 2002; Wallace and Fox, 1999)). Independent from the type of the deprivation protocol employed, these studies commonly concluded that experience-dependent changes in receptive field plasticity can be summarized by increased representation of the spared, and decreased representation of the deprived whisker. However, receptive field plasticity can also be induced by allowing animals to explore novel (or otherwise enriched) environments (Polley et al., 2004) (**Figure 2E**) or simply by passive whisker stimulation (Welker et al., 1992) (**Figure 2F**). These observations suggest that there are multiple forms of receptive field plasticity that could be modulated by contextual and top-down processes even in the absence of altered sensory organ use.

The majority of the studies on receptive field plasticity (and in brain plasticity in general) have focused on neurons. Glial cells can be found in high numbers in the

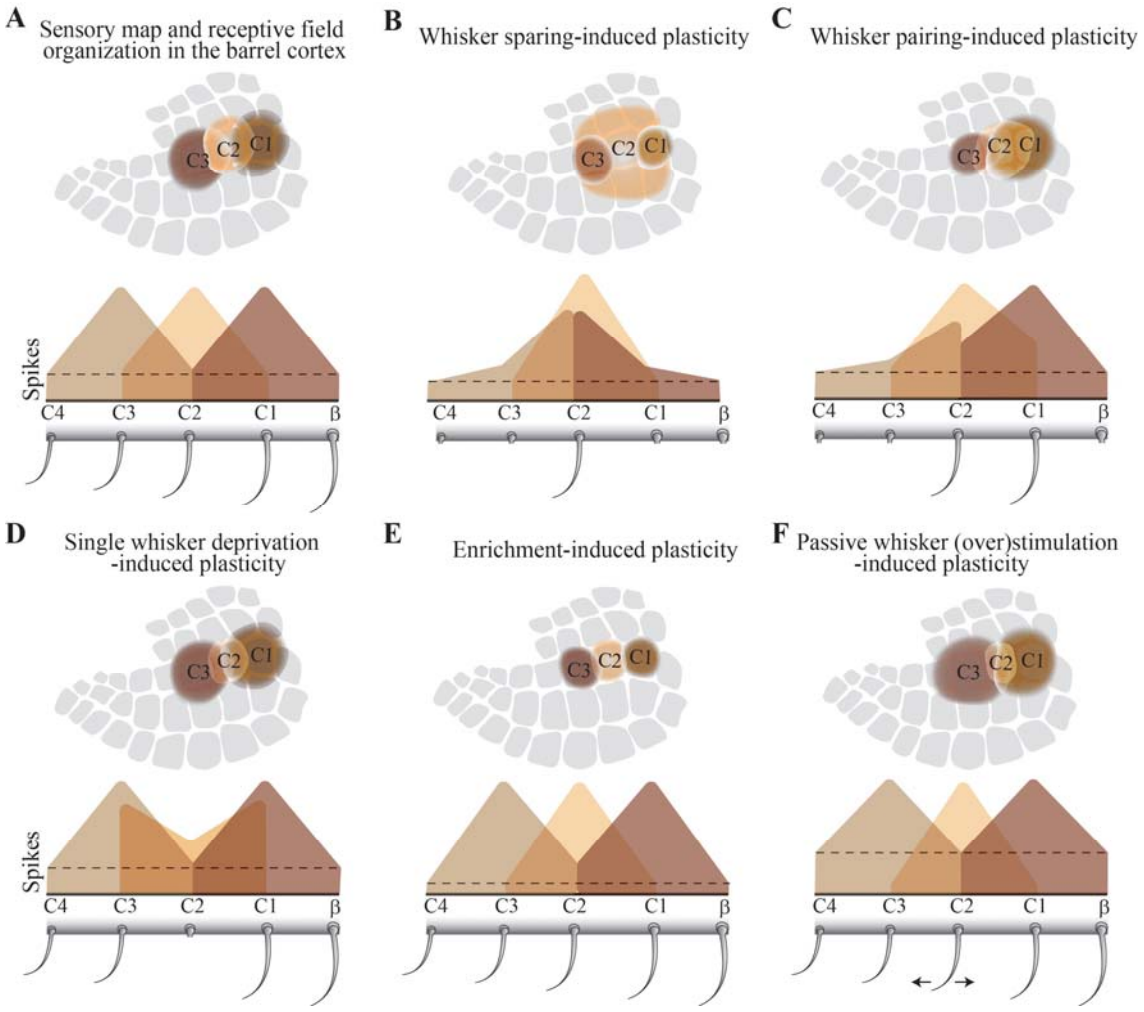


Figure 2. Known types of plasticity in the barrel cortex. Schematic representation of the sensory deprivation/experience condition, representative single neuron receptive fields in the supragranular layers of the barrel cortex, and the presumed map organization in the same layers across five different plasticity induction protocol. (**A**) Neurons in the barrel cortex respond to deflection of multiple whiskers. The whisker that evokes the largest number of action potentials is named as principal whisker, and the others are referred to as surround whiskers. In the absence of any whisker deprivation, perceptual training or environmental enrichment, the receptive field organization follows a topographical mapping where neurons in neighbouring cortical columns have neighbouring whiskers on the periphery as their principal whiskers. Neighboring whisker representations only partially overlap preserving the topographic mapping of the sensory periphery at the level of cortical circuits. (**B**) When all whiskers, but one, are removed, neural responses to the spared whisker are potentiated in neighbouring barrel columns(Fox, 1992), resulting in spared whisker representation to expand into the neighbouring cortical columns whose principal whiskers have been deprived. (**C**) Sparing two neighbouring whiskers causes their receptive fields to merge (Diamond et al., 1994), as spared whisker representations' increasingly overlap. (**continued on next page**)

(**continuation of previous page**) (**D**) Depriving one (row of) whiskers result in neurons in the deprived cortical column to acquire a new principal whisker (Celikel et al., 2004); while deprived whisker representation shrinks, the spared surrounding whisker representations expand to drive stimulus evoked representations in the deprived whisker's column. (**E**) Enriched environment experience leads to sharpened receptive fields and whisker representations in the barrel cortex (Polley et al., 2004). (**F**) Chronic (over)stimulation of a single whisker results in a shrunken receptive field in neurons of the corresponding barrel column while the receptive fields of the non-stimulated whisker tend to broaden (Welker et al., 1992). Single whisker representations are believed to expand upon non-stimulated whiskers, and shrink after stimulated whisker's deflection, reflecting increased topographic precision of the sensory map.

mammalian brain and are indispensable for proper brain function (Azevedo et al., 2009; Jäkel and Dimou, 2017). Neuroglial cells include astrocytes, microglia and oligodendrocytes, which together are involved in, for example, myelination, neurotransmitter recycling, response to brain damage and pathogens, and neurovascular coupling (also see the section on "*From synaptic activity to vascular plasticity*"). Glial cell morphology and activity can be modulated in an experience dependent manner (Barrera et al., 2013; Bergles and Richardson, 2015; Mangin et al., 2012; Stogsdill and Eroglu, 2017). For example, astrocytes' morphology and abundance are altered upon environmental enrichment, while the number of astrocytic contacts with synapses increase (Black et al., 1987; Diamond et al., 1964; Jones and Greenough, 1996). As astro-neuronal cannabinoid signaling is critical for long-term depression of cortical synapses (Min and Nevian, 2012), sensory deprivation induced synaptic depression might involve both neuronal and glial processes. Both oligodendrocyte morphology and axonal myelination by oligodendrocytes are modulated by recent sensory experience; social isolation or disruption of oligodendrocyte neuregulin signaling reduce axonal myelination and cognitive performance in select long-term memory paradigms (Makinodan et al., 2012); conversely, activity-dependent myelination and oligodendrogenesis improve task performance (Gibson et al., 2014). Microglia are classically known to be involved in the defense against pathogens, but are also involved in synaptogenesis during learning and memory, and respond to sensory input by increasing their contact with dendritic spines and synapses (Parkhurst et al., 2013; Sipe et al., 2016; Tremblay et al., 2010). Given their tight coupling to their neuronal counterparts, it is not surprising that glial cells have a preferred stimulus in the visual cortex (Schummers et al., 2008). Thus, (plasticity of) receptive fields are unlikely to be restricted to neurons, although non-neuronal plasticity in the barrel cortex is not commonly studied.

3) Molecular correlates of plasticity

Studies describing the cellular mechanisms underlying experience-dependent plasticity in the barrel cortex system, typically by electrophysiological means, are plentiful (see e.g (Allen et al., 2003; Celikel et al., 2004; Cheetham et al., 2007; Chittajallu and Isaac, 2010; Finnerty et al., 1999; Fox, 1992; Greenhill et al., 2015; Hardingham et al., 2008; Harris and Woolsey, 1981; House et al., 2011; Kätzel and Miesenböck, 2014; Kossut, 1985; Lendvai et al., 2000; L. Li et al., 2009; P. Li et al., 2009; Margolis et al., 2012; Micheva and Beaulieu, 1995;

Miquelajauregui et al., 2015; Nicolelis et al., 1991; Simons and Land, 1994, 1987; Stern et al., 2001; Wang and Zhang, 2008; Welker et al., 1989; Zembrzycki et al., 2013)). There has been, however, a surprising lack of experimental studies to unveil the molecular mechanisms that underlie the observed changes in neuronal responses in response to (altered) sensory experience. Single molecules, particularly those that had been previously shown to modulate synaptic plasticity, such as the Ca^{2+}/calmodulin-dependent protein kinase (CaMK), the transcription factor Cre-Response Element Binding (CREB), the growth factor Brain-derived Neurotrophic Factor (BDNF) and nitric oxide (Dachtler et al., 2012; Glazewski et al., 1999, 1996; Rocamora et al., 1996) have been studied in some detail, however technologies now allow for systematically addressing the molecular correlates of map plasticity throughout the transcriptome and proteome. Changes in transcripts' abundance can be quantified through the use of microarrays and RNA sequencing, while the proteome can be surveyed through, for example, tandem mass spectrometry. These techniques provide valuable information on the molecular processes and pathways that are required to establish, maintain and adapt the neural circuit organization in response to sensory experience. Moreover, these data can now also be obtained in cellular and subcellular resolution as individual cells can be sorted and their RNA subsequently sequenced (Zeisel et al., 2015).

3.1) Input-dependent and cell type specific effects of brief enhanced sensory experience on barrel cortex transcriptome

In a pioneering study that employed microarrays to quantitatively address transcriptional regulation in the barrel cortex, Vallès and colleagues studied animals upon exposure to an enriched environment (EEE) (Vallès et al., 2011). Adult rats in the experimental group were subjected to 30 minutes of EEE in a dark room filled with novel objects and toys. The control group was kept in the dark for the same duration but in their own home cages. Animals were sacrificed, either immediately after EEE or following a 4 hour period spent in their home cages, before isolation of barrel cortical RNA which was subjected to microarray analysis, thereby identifying EEE-induced changes in the transcriptome.

A common way to interpret large-scale molecular datasets is through the use of gene ontology (GO) terms. Gene ontologies entail defined cellular components, molecular functions or biological processes to which genes (or rather, their protein products) contribute(Gene Ontology Consortium, 2008). Gene ontology analyses determine whether gene sets that are differentially regulated belong to distinct GO terms and if their co-regulation is significant. GO classification of the differentially expressed transcripts in the Valles et al dataset has shown that gene transcription rapidly changes upon EEE (**Figure 3**), with a time course similar to whisker deprivation-induced regulation of gene transcription (Bisler et al., 2002). The majority of transcriptional regulation after EEE can be linked to general cellular processes (**Figure 3A, Supplemental Tables 1 and 2**), although the direction of the transcriptional regulation, i.e. up- vs down-regulation, depends on the sensory history; immediately after EEE the vast majority of differentially expressed transcripts are up-regulated (170 upregulated, 31 downregulated), whereas in the 4h group downregulated genes are more prevalent (29 upregulated, 98 downregulated). Lack of the sustained upregulation of gene transcription in this group might reflect the fact that animals

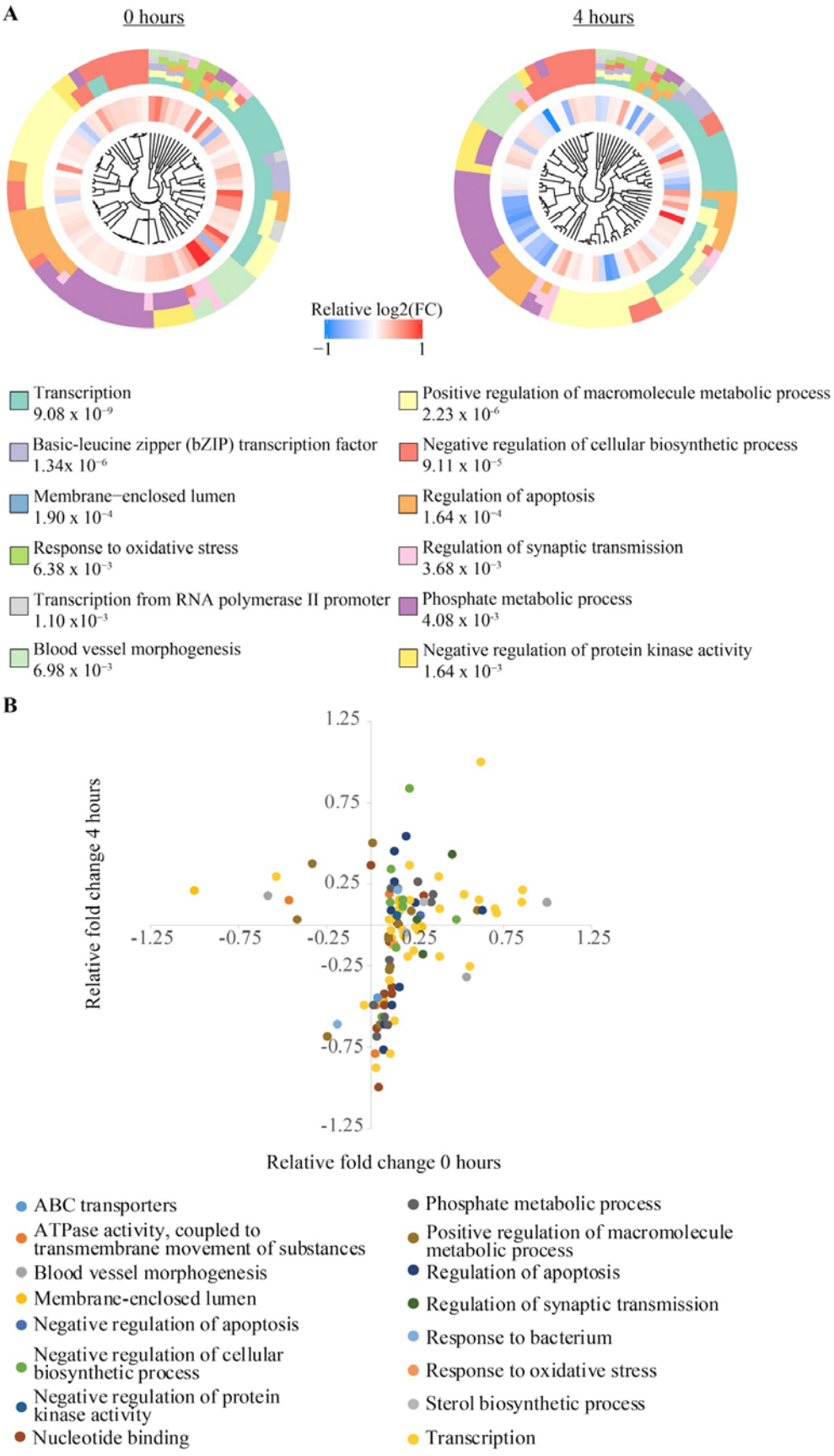
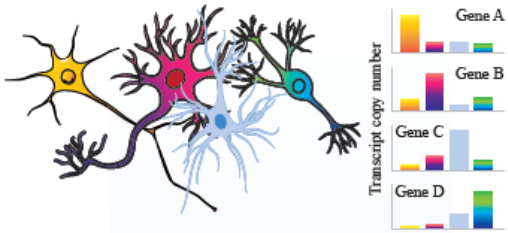


Figure 3 (previous page). **Gene ontology of differentially expressed genes after exposure to an enriched environment.** (**A**) Twelve most significant GO terms based on the transcriptional changes after EEE in the barrel cortex (data from (Vallès et al., 2011)). Transcripts are clustered by their respective GO term, numbers indicate p-values. Note that most genes are commonly classified under multiple GO terms. (**B**) Relative (with respect to control condition) expression values of all differentially regulated transcripts at 0 or 4 hours. The color code denotes GO terms. Those transcripts that appear in multiple GO terms are plotted only once; the cluster membership is ranked. As such only the most differentially regulated GO term is displayed for those transcripts that are classified under multiple GO terms. The majority of transcripts (n=103) are upregulated following EEE, half of which remain upregulated in the 4h group (upper right quadrant, n=52), the other half is downregulated (lower right quadrant, n=51). Only few genes have steady downregulation (lower left quadrant, n=2), or temporally delayed upregulation (upper left quadrant, n=6). Thus exposure to an enriched environment triggers temporally varying transcriptional regulation. The direction of change in single gene transcription can be used to classify transcriptional dynamics and relate it to behavioral context.

were returned to their home cage, i.e. an environmentally impoverished environment, before tissue collection for a period of 4h. Expected reduction in the utilization of the somatosensory input to explore animals' familiar environment might in turn diminish synaptic transmission and, consequently, the rate of metabolism, thus obviating upregulation of transcripts. If an enriched environment modulates gene expression in an activity-dependent manner, one might predict that longer EEE would result in sustained transcript up- or downregulation lasting until the network has accommodated to the enhanced sensory input. This was confirmed in a follow-up study in which rats were subjected to EEE for 28 days, after which only 29 genes were found to be differentially expressed, likely reflecting the 'steady-state' of the cortical reorganization upon chronic alteration in incoming sensory information (Vallès et al., 2014).

The overrepresented GO terms identified after EEE are not specific to neurons or synapses. They mostly represent general cellular processes such as transcription, metabolism and cell signaling, which suggests that after EEE, gene expression changes might not be restricted to neurons. Neuronal plasticity might possibly cause, or otherwise contribute to these observed changes in other cell types in the brain. Although the term 'regulation of synaptic transmission' (which specifically refers to communication through chemical synapses) was found to be overrepresented, other differentially regulated genes were strongly related to blood vessel morphogenesis. Sustained increased neuronal activity leads to heightened energy consumption and thus elevates oxygen consumption (Shetty et al., 2012). Increased metabolic rate and subsequent hypoxia could also elevate reactive oxygen species, which have been shown to induce oxidative stress and ultimately neuronal death (Friberg et al., 2002). Thus, overrepresentation of GO terms such as 'response to oxidative stress' and 'blood vessel morphogenesis' point to an important role for vascular endothelial cells in experience-dependent plasticity, serving to accommodate increased energy consumption (also see



1. Calculate Cell Enrichment Index (CEI)

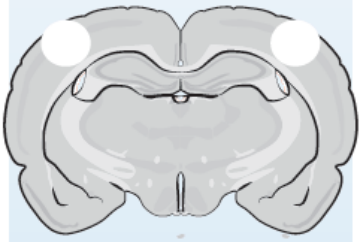
Single-cell RNA sequencing data from Zeisel et al (2015)

$$CEI_{Transcript} = \frac{\text{Average copy number per cell class}}{\text{Total copy number across cell classes}}$$

2. Determine which transcripts are preferentially expressed in cortical cell classes

e.g. preferential expression in Cell Class A if:

$$\frac{CEI_{Transcript}\,(\text{Cell Class A})}{CEI_{Transcript}\,(\text{Cell Class B:F})} > 1.1$$



3. Classify transcripts based on their differential expression profile upon altered sensory experience

Data from Vallès et al. (2011)

Whole tissue punch following EEE

Cell class enriched transcripts whose transcription is differentially regulated in an experience-dependent manner

Figure 4. The bioinformatics workflow. See Supplemental Table 3 for calculated CEIs per transcript.

the section "From synaptic activity to vascular plasticity" below). This also suggests that the transcriptomes of distinct cell types might be differentially regulated by EEE. To explore the possibility, using publicly available single-cell transcriptomics data from experimentally naïve juvenile mouse somatosensory cortex (Zeisel et al., 2015), we calculated a cell enrichment index (CEI; **Figure 4**, **Supplemental Table 3**). The CEI was calculated by dividing the average copy number of each transcript within each cell class by the total copy number of the same transcript averaged across all cell classes. From the list of differentially expressed transcripts identified by Vallès and colleagues (2011), we then selected transcripts that were enriched by >10% (i.e. had a >10% increased CEI based on the Zeisel dataset) in one cell type compared to the five others, which showed that most differentially expressed transcripts were preferentially expressed in interneurons, whereas astrocytes were the least represented cell class in the Valles dataset (**Figure 5A**).

Genes that displayed the most robust expression changes in response to EEE were preferentially expressed not only in pyramidal cells but also in endothelial cells and microglia. Transcripts found mostly in astrocytes, interneurons and oligodendrocytes, by contrast, showed modest changes after EEE (**Figure 5A,B**). Comparing gene expression across 0h or 4h showed that the majority of transcripts were reduced in their abundance at the 4h interval across all cell types, often returning (close) to baseline levels (**Figure 5B**). These changes were most diverse (albeit only marginally) in pyramidal cells (7 up-, 22 downregulated, 6 no change) while endothelial cells had relative abundance of genes whose transcription is upregulated after 4 hours (**Figure 5B**). Despite the fact that we calculated the CEI based on cells obtained from experimentally naïve juvenile mice and use it to address the plausible cellular diversity in adult rodents, these results argue that sensory experience might affect gene expression in a cell type-specific manner. If so, cellular signaling pathways upstream of differential gene

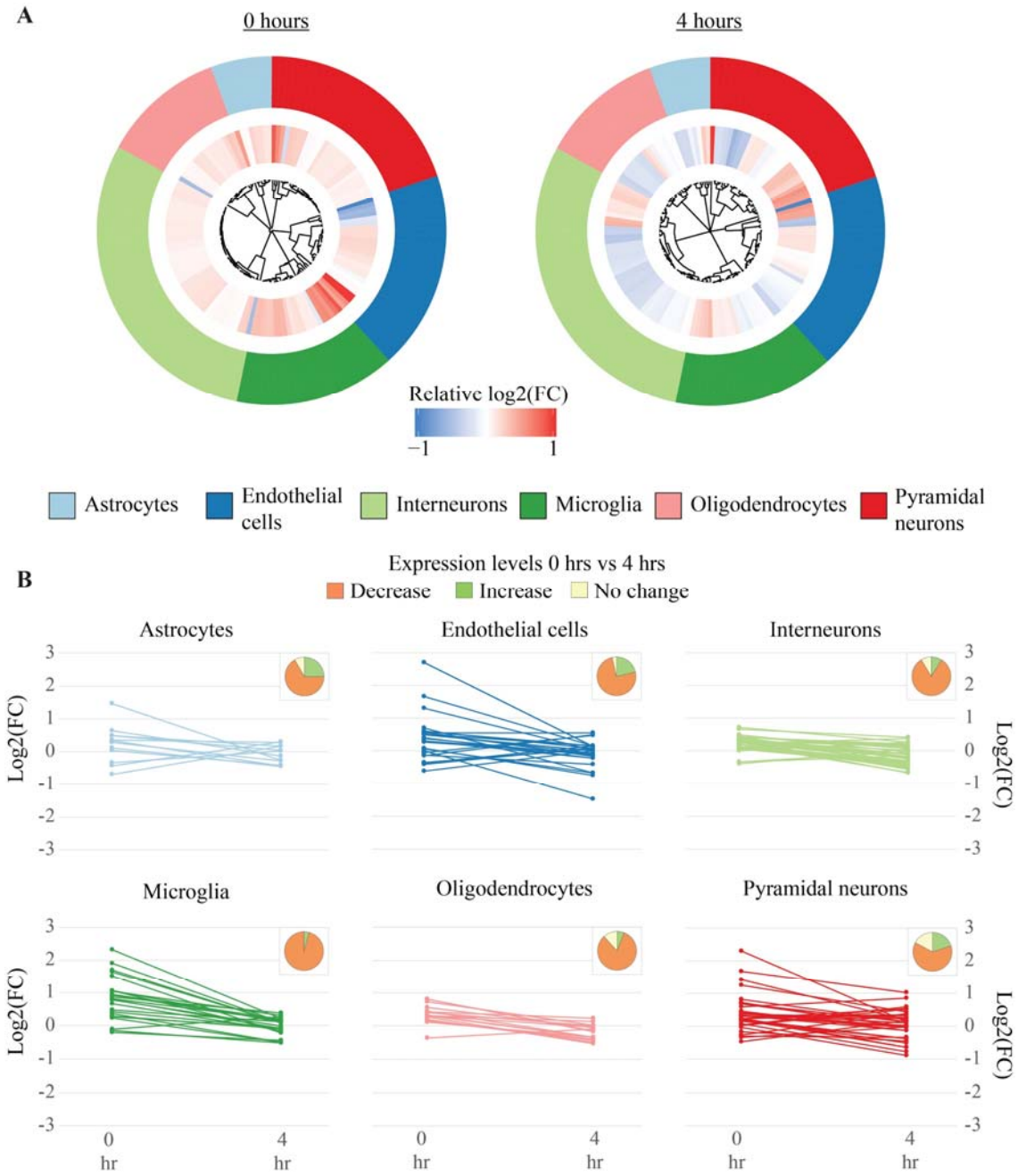


Figure 5. Cell type-specific gene expression profiles after exposure to an enriched environment. Genes that are preferentially expressed in a cell-type specific manner was determined using single-cell RNAseq data ((Zeisel et al., 2015); see main text for details). (**A**) Distribution of differentially expressed genes 0 or 4 hours after EEE across identified cell classes. (**B**) Temporal changes in gene transcription across cell types. Each data point represents a unique transcript identified as differentially expressed following enriched environment experience (EEE) (Vallès et al., 2011). Pie charts represent the relative percentage of genes whose transcription is downregulated (in orange), upregulated (in green) or non-regulated (in yellow) when the normalized transcription levels in 4h group were compared to 0h.

expression are also likely to be distinct for each cell class. A systematic analysis of the mouse transcriptome upon altered sensory organ use will help to unravel the cellular diversity and molecular pathways associated with experience-dependent plasticity.

3.2) Extended sensory stimulation and deprivation and their effects on synaptic proteins

Transcriptional modulation by sensory experience will alter structural and functional organization of neural circuits only if the changes are reflected in the proteome. Because RNA translation into protein is not a linear process, and controlled by posttranscriptional regulatory mechanisms (Keene, 2007), proteomic studies will be required to mechanistically address the molecular pathways associated with expression of plasticity. Currently the only proteomics study available in barrel cortex was performed by Butko and colleagues (Butko et al., 2013), who either clipped or brushed the whisker pads of rats for a period of 30 days, starting from P4, and subsequently prepared synaptoneurosomes from barrel cortex. Using tandem mass spectrometry Butko and colleagues identified systematic downregulation of translation for various ion channels (e.g. inward rectifying potassium channels KCNJ3 and KCNJ6, calcium-activated potassium channel KCNN2), neurotransmitter receptors (e.g. AMPA and NMDA receptor subunits GluA1, GluA2, GLuN1, GluN2A/B), cytoskeletal proteins (e.g. Catenins) and signaling proteins (e.g. adenylyl cyclase, protein kinase C) in whisker deprived rats. These alterations in protein levels are likely to be the cause of electrophysiological changes in receptive field and sensory map representations.

4) From synaptic activity to vascular plasticity

If brain plasticity is a systems level response to change, as argued above, there must be molecular players that could couple changes in one cell type to another. For example, changes in neuronal activity might be coupled to neurovascularization, helping to control both the neural activity as well as the dynamics of the blood flow in an experience dependent manner (Kole, 2015).

Short-term changes in local blood flow are associated with neuronal activity and modulated by astrocyte-mediated vasodilation, vasoconstriction (McCaslin et al., 2011; Takano et al., 2006) and cholinergic signaling (Lecrux et al., 2017); inhibitory neurons are also implicated in neurovascular coupling as specific subsets of interneurons can have different effects on vascular tone (Cauli et al., 2004). They can induce vasoconstriction through vasoactive proteins such as neuropeptide Y and somatostatin, whereas vasodilation can be achieved through secretion of vasoactive intestinal polypeptide or nitric oxide (NO), a potent vasodilatory molecule. Dynamic modulation of the cerebrovasculature thus involves a wide range of neuronal and non-neuronal cell types.

Besides short-term adaptation, long-term effects on the neurovasculature also have been observed. Already over two decades ago, in the visual cortex of young and adult rats synaptogenesis was found to be accompanied by angiogenesis (i.e. the formation of new blood vessels) following EEE (Black et al., 1989, 1987). More recent research has shown that during a critical postnatal developmental period, excessive stimulation induces a reduction of blood vessel sprouting and endothelial proliferation in the somatosensory,

auditory and motor cortices (Whiteus et al., 2014). These anti-angiogenic effects were associated with hypoxic conditions in the corresponding overstimulated brain regions, which in turn was accompanied dendritic spine loss. A separate study (Lacoste et al., 2014) employed both enhanced and decreased whisker experience, and found that blood vessel patterning in barrel cortex was modulated as a result: vascular density and branching were diminished in response to whisker deprivation whereas the same metrics were enhanced upon whisker stimulation. These findings indicate that the organization of the neurovascular bed is modulated in the wake of sensory experience, and suggest that brain oxygen levels (which are a derivative of brain vascularization) can in fact form a limiting factor to synaptic plasticity.

Despite the clear demonstrations of the impact of sensory experience on the neurovasculature, it is currently unknown which molecular components might orchestrate experience-dependent blood vessel patterning in the neocortex. To establish potential cellular signaling pathways involved in this process, we identified the top ten most differentially regulated genes after EEE (Vallés et al., 2011). We specifically focused on the genes that are in the GO term 'Vasculature development' and whose transcript was differentially regulated ≥ 10% beyond control both in 0h and 4h groups (see **Supplemental Table 2 and 4**). These transcripts include *Cyr61*, *Plat*, *Jun*, *Junb*, *Verge*, *Egr1*, *Egr3*, *Nr4a1*, *Nr4a3* and *Hspb1*. The products of these ten genes, discussed in detail below, are involved in a variety of functions that would enable neurovascular plasticity ranging from induction of vessel sprouting and cell migration to alterations in vessel permeability.

4.1) Molecules of neurovascular plasticity

Cysteine-rich angiogenic inducer 61 (Cyr61) codes for a secreted extracellular matrix (ECM) protein involved in processes involving cell migration, adhesion, differentiation and mitogenesis (Lau and Lam, 1999). In cortical neurons, mechanical strain and BDNF have been shown to induce transcriptional activity of Serum Response Factor (SRF), which in turn is involved in regulating *Cyr61* promoter activity (Hanna et al., 2009; Kalita et al., 2006); A third way that *Cyr61* expression could be regulated by neuronal activity is through muscarinic acetylcholine receptors (mAChRs) and NMDA receptors (Albrecht et al., 2000; Ito et al., 2007).

The tissue plasminogen activator (Plat) is involved in ECM degradation, a critical step in angiogenesis that serves to clear the way for migration of vasculature-associated cells. Its gene product has been shown to be secreted by vascular endothelial cells in response to fluid shear stress, linking its function to neuronal activity resulting in increased blood flow (Diamond et al., 1990). Mechanical stretch induced expression of vascular endothelial growth factor (VEGF) and angiotensin (AGT) requires activation by PLAT (Teng et al., 2012). Its gene product is also involved in mediating synaptic growth, increasing NMDAR-mediated Ca2+ influx and cleaving proBDNF into BDNF and hence also has functions related to neuronal plasticity (Baranes et al., 1998; Nicole et al., 2001; Pang et al., 2004).

Activator protein 1 (AP-1) is a transcription factor regulating various cellular processes such as cell proliferation, differentiation, apoptosis, and cell migration (Angel and Karin, 1991; Karin et al., 1997). It consists of homo or heterodimers of Jun proteins, among which are JUN and JUNB, the transcripts of which were differentially expressed

following EEE (Vallès et al., 2011). Inhibition of AP-1 results in reduced vascular smooth muscle cell proliferation and diminished migration and tubule formation by ECs. In addition, inhibited microvascular endothelial cell proliferation and was observed, as well as reduced vasculature formation by ECs after cerebral ischemia (Ennis et al., 2005; Murata et al., 2012; Zhan et al., 2002; Zhang et al., 2004). *Jun* and *Junb* have both been shown to be induced by increased neuronal activity and plasticity (Abraham et al., 1991; Nedivi et al., 1993; Sonnenberg et al., 1989).

The product of the vascular early response gene *(*Verge or Apold1*)* accumulates at the periphery of endothelial cells, where it functions to regulate cell permeability by remodeling the cells' cytoskeleton, allowing substances to pass through endothelial cell layers (Regard et al., 2004). A knockout of this gene is shown to exacerbate outcomes after stroke in mice (Mirza et al., 2013). Conditions inducing its expression has been studied in various tissues, and include hypoxia, ischemia, physical activity and hypertonicity (Liu et al., 2012; Maallem et al., 2008; Regard et al., 2004; Simonsen et al., 2010)). A putative mechanism linking neuronal activity to Verge expression entails tumor necrosis factor (TNF) and fibroblast growth factor (FGF) signaling, which are expressed in response to glutamate and oxygen-glucose deprivation by neurons and astrocytes (Hurtado et al., 2002; Pechán et al., 1993).

Intracellular signaling pathways activate cellular processes downstream of membrane receptors. Prkx codes for a cAMP-dependent protein kinase involved in transcriptional regulation through interaction with and/or phosphorylation of its downstream targets (Zimmermann et al., 1999). Several downstream targets of PRKX are involved in vascular functions such as maintenance of blood vessel integrity and (inhibition of) angiogenesis (Kim et al., 2000; Li et al., 2011; Zhou et al., 2007). Indeed, Prkx expression has been shown to be involved in vascular endothelial cell proliferation, migration, vascular-like structure formation and morphogenesis (Li et al., 2011, 2002). The neuronal function of PRKX is has not been studied in detail, hence as of yet it is unknown whether its regulation can be modulated through increased neuronal activity.

Egr1 and *Egr3* code for zinc finger transcription factors. They are immediate early genes, as such their expression can be swiftly regulated in response to stimuli. Befitting this characteristic, these two genes are upregulated immediately after EEE (Vallès et al., 2011). They are important for growth factor expression and -signaling; upon *Egr1* knock-down, not only EC replication, migration and tubule network formation was reduced but also expression of FGF was impaired (Fahmy et al., 2003). EGR3 on the other hand is involved in VEGF signaling, as its perturbation is paired with impaired VEGF-induced migration, proliferation and tube formation by endothelial cells (Liu et al., 2008; Suehiro et al., 2010). EGR proteins are upregulated in response to various growth factors (Biesiada et al., 1996; Fang et al., 2013; Mayer et al., 2009; Tsai et al., 2000).

Members of the Nuclear Receptor Subfamily, *Nr4a1* and *Nr4a3* are involved in vascular function through regulation of VEGF signaling (Rius et al., 2006; Zeng et al., 2006), thus helping to control microvessel permeability (Zhao et al., 2011) and endothelial and vascular smooth muscle cell proliferation (Nomiyama et al., 2006; Rius et al., 2006).

Nr4a1 also has neuronal functions, as it controls surface expression of the NMDAR subunit NR2B (Zhang et al., 2016) while also regulating spine density in hippocampal excitatory neurons in an activity-dependent manner (Chen et al., 2014). Interestingly, an important upstream regulator of Nr4a receptors, cAMP-response element-binding protein (CREB) (Volakakis et al., 2010), is a key molecule in plasticity induction (Benito and Barco, 2010) but also regulates cellular responses to hypoxia (Leonard et al., 2008; Shneor et al., 2017), suggesting a dual role for the NR4A protein family in neurons as well as the vasculature. Activity-dependent secretion of growth factors, e.g. upregulation of *Nr4a1* and *Nr4a3* upon EEE, could have important functions in, for instance, neuron-to-vasculature signaling (see **Figure 6** and the section *Linking synaptic activity to vasculature change through releasable molecules*)

A member of the heat shock proteins, *Hspb1* is ubiquitously expressed and plays important roles in apoptosis (Concannon et al., 2003) but also in smooth muscle cell migration (Hedges et al., 1999) and protection against ischemic injury (Martin et al., 1997). The latter suggests important functional roles for HSPB1 in the vasculature plausibly via its phosphorylation by VEGF (Evans et al., 2008). Modulation of the (neuro)vasculature is likely to include anti-angiogenic cues, as runaway angiogenesis is commonly associated with tumor development (De Palma et al., 2017). HSPB1 might also act as a negative regulator of angiogenesis through its interaction with VEGF upon its release from endothelial cells (Lee et al., 2012). With strong, long-lasting upregulation upon EEE, HSPB1 could orchestrate vascular responses to increased neuronal activity.

Although not most strongly regulated, several other genes among the genes upregulated upon EEE have known functions in the vasculature, see e.g molecules involved in PDGF-B signaling (**Supplemental Table 4**). PDGF-B (upregulated upon EEE; (Vallès et al., 2011)) can induce expression of *Egr1*, *Fos*, *Jun*, *Junb*, *Cyr61*, *Rap1b* and *Klf2*, (O'Brien et al., 1990; Quarck et al., 1996; Rothman et al., 1994; Wu et al., 2008) the latter of which has been shown to have, among others, *ET-1* as a downstream regulatory target (Dekker et al., 2005). ET-1, in turn, may exert its vascular functions by inducing the expression and release of vasodilatory or vasoconstrictory molecules (Hynynen and Khalil, 2006; Ihara et al., 1991). PDGF-BB-mediated induction of chemotaxis and mitogenesis in vascular smooth muscle cells requires PLAT, linking PDGF-B to yet another vasculature modulator (Herbert et al., 1997). Because these genes are expressed in an activity-dependent manner (based on (Vallès et al., 2011)), pathways such as these could well orchestrate blood vessel patterning to suit the needs of neuronal circuits (Lacoste et al., 2014; Whiteus et al., 2014).

4.2) Linking synaptic activity to vasculature change through releasable molecules

The genes outlined above are shown to contribute to neurovascularization, however it is not known whether synaptic activity could regulate their transcription, and whether there are downstream protein-protein interactions that could link plasticity of synaptic communication to the organization of the neurovascular bed. Because experience dependent plasticity of neural activity is the primary mechanism by which receptive fields and sensory representations in the brain reorganize, we addressed the upstream

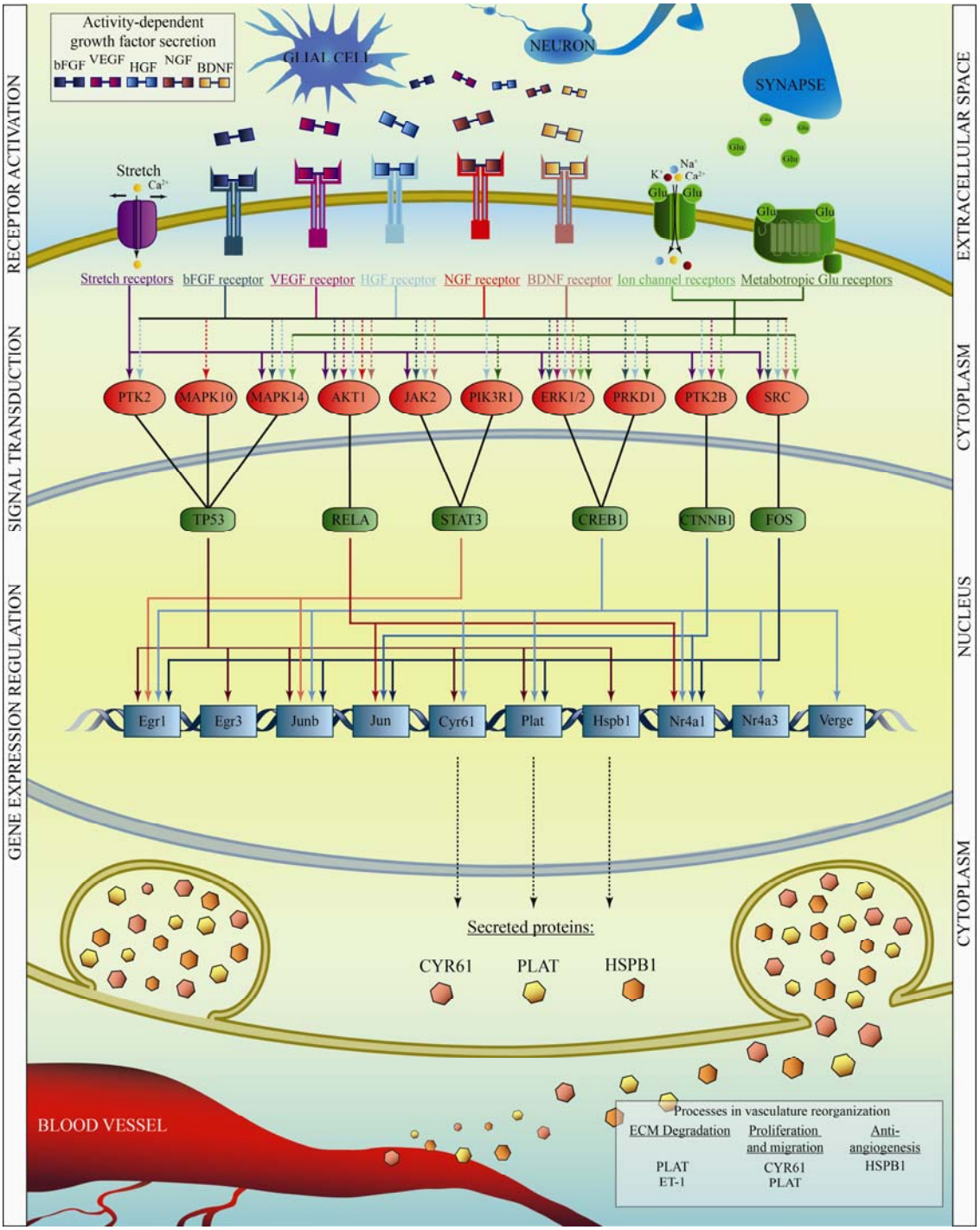


Figure 6. Linking synaptic activation to neurovascular reorganization. See main text for details.

pathways that link that these genes to the synapse. To this end, we utilized the Ingenuity® Pathway Analysis (IPA®, Qiagen) to investigate the potential regulatory pathways in which the genes of interest are involved. In pathway reconstruction we only included experimental data from neurons, astrocytes, endothelial cells, fibroblasts, smooth muscle cells (as these three can

be found in blood vessels), the CNS and CNS cell lines. Molecules were only included if they are expressed in these cell types; interactions between molecules were allowed to be indirect or direct but always filtered for activating relationships between receptors, kinases and transcription factors (e.g. kinases activating downstream transcription factors). Between transcription factors and downstream genes, relationships were filtered for 'expression' or 'transcription'. Since we aimed to provide an overview of common pathways, only transcription factors that target at least two of the ten analyzed genes were used in pathway reconstruction. This approach yielded an overview of the inferred pathways that may be activated as a result of stretch, growth factor and glutamate receptor stimulation and ultimately drive expression of genes involved in remodeling of the neurovasculature (**Figure 6**).

Mechanoreceptors can be found in vasculature-related cells and astrocytes, where they can be activated as a result of increased blood flow, leading to an influx of calcium (Morita et al., 1994; Ostrow et al., 2011; Zheng et al., 2008). Among the mechanoreceptors, downstream of AGTR1 and TRPc5 (Barauna et al., 2013) (Shen et al., 2015) we find PTK2, MAPK10, MAPK14, AKT1, JAK2, PIK3R1, ERK1/2, PTK2B and SRC as downstream kinases which in turn allow transcriptional regulation of the genes of interest (**Figure 5**). Note that NMDA receptors were recently found to be activated by mechanical stress (Maneshi et al., 2017), suggesting a (partial) overlap between stretch and ionotropic glutamate receptor pathways suggested herein. In the growth factor pathway we included basic fibroblast growth factor (bFGF) , hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), brain derived neurotrophic factor (BDNF), and nerve growth factor (NGF) which show enhanced expression in an activity dependent manner in neurons and/or astrocytes (Pechán et al., 1993; Tyndall and Walikonis, 2007);(Bengoetxea et al., 2008);(Matsuda et al., 2009);(Bruno and Cuello, 2006; Pechán et al., 1993). Particularly AKT1 and ERK1/2 are downstream of these receptors. The glutamate receptor pathways include ionotrophic, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-Methyl-D-aspartic acid (NMDA) receptors, activation of which lead to influx of Ca^{2+}, K^{+} and/or Na^{+}, as well as metabotropic glutamate receptors (mGluRs). The pathway analysis showed that glutamate receptor activation is likely to induce activation of particularly ERK1/2, PRKD1, MAPK14 and SRC kinases, leading to activation of CREB1, TP53 and FOS (**Figure 6**).

The most inclusive transcriptional regulators, suggested by this "synaptic activity to neurovascularization" pathway, are CREB1, FOS and TP53, which together can potentially regulate all our genes of interest with the exception of KLF2. *Fos* was also found by Vallès et al to be upregulated along with *Trp53rk* (TP53 regulating kinase), which increases the likelihood of FOS and TP53 involvement in the predicted pathways. Surprisingly, activating protein 1 (AP-1) was not found to have any role in any of the three pathways, even though two of its subunits were found to be upregulated after EEE (*Jun*, *Junb*) (Vallès et al., 2011) and have many potential upstream transcription factors (**Figure 6**). This suggests that the role of AP-1 either lays in the regulation of genes with vasculature-unrelated functions or that its upstream pathway involves synaptic receptors mapped herein. Lastly, no regulators were found upstream of *Prkx* and *Rap1b* that fit in the obtained

pathways, suggesting that there is at least another class of upstream regulators that could link the synaptic activity to neurovascularization. Several genes (namely Egr3, Hsbp1, Nr4a3 and Verge) are downstream to only one transcription factor in our pathway. Given that the current pathways are purposely comprised of only the most prominent candidates, expression of these genes is likely regulated by other transcription factors that were excluded in the current analysis.

5) From synaptic plasticity to synaptic disorders

Neuronal communication deficits are likely to be central to the pathology of various brain disorders, including, but not limited to neurodevelopmental, neurodegenerative and memory disorders. Therefore, it is feasible that genes whose transcription are regulated by sensory experience might be dysregulated in select neurological disorders. In agreement with this proposition, perturbation of the plasticity-related proteins BDNF, Neuregulin 1 or mGluR1 is shown to result in a schizophrenia-like phenotype (Angelucci et al., 2005; Brody et al., 2003; O'Tuathaigh et al., 2008). Suppression of *Pak3* expression (associated with X-linked intellectual disability) in rats disrupts hippocampal plasticity (Boda et al., 2004) and when synapsin 1-3, which are involved in synaptic neurotransmitter release, are knocked out in mice, the animals display Autism Spectrum Disorder-related phenotypes of social impairments (Greco et al., 2013). While Synapsin 3 is also linked to schizophrenia-like behaviour (Porton et al., 2010), aberrant phosphorylation of eukaryotic Initiation Factor 2 (eIF2) can cause memory impairments, and its suppression reduces synaptic plasticity and memory impairments in Alzheimer's disease model mice (Ma et al., 2013).

Moving beyond animal models, many genome-wide association (GWA) and population studies are focused on discerning the underlying genetic causes of (and predispositions to) neurological disorders. We therefore asked whether EDP-related transcripts and proteins identified in the studies by Vallès *et al* (Vallès et al., 2011) and Butko *et al* (Butko et al., 2013) are differentially regulated in neurological disorders. We used the Disease and Gene Annotations (DGA) database (Peng et al., 2013), which entails documented relationships between genes and diseases/disorders (such as altered protein or mRNA levels, single-nucleotide polymorphisms and mutations). Although the transcripts and proteins that Butko and Vallès identified as differentially regulated hardly overlap, the disorders with which they have been associated by population studies show a striking similarity, despite the divergent protein classes they encompass **(Figure 7**). This could be explained in part by the notion that these particular disorders are studied heavily.

Neuronal plasticity is altered in various neurological disorders, including schizophrenia (Voineskos et al., 2013), intellectual disability (Ramakers et al., 2012), autism (Pardo and Eberhart, 2007) and bipolar disorder (Schloesser et al., 2008). Targets from both molecular datasets discussed in this review can be linked to many of common neurological disorders including Alzheimer's disease, autism spectrum disorder and schizophrenia (**Figure 7**). Some molecules are currently not known to be affected in multiple disorders, which seems to be particularly the case with transcripts or proteins related to schizophrenia, while others are affected in

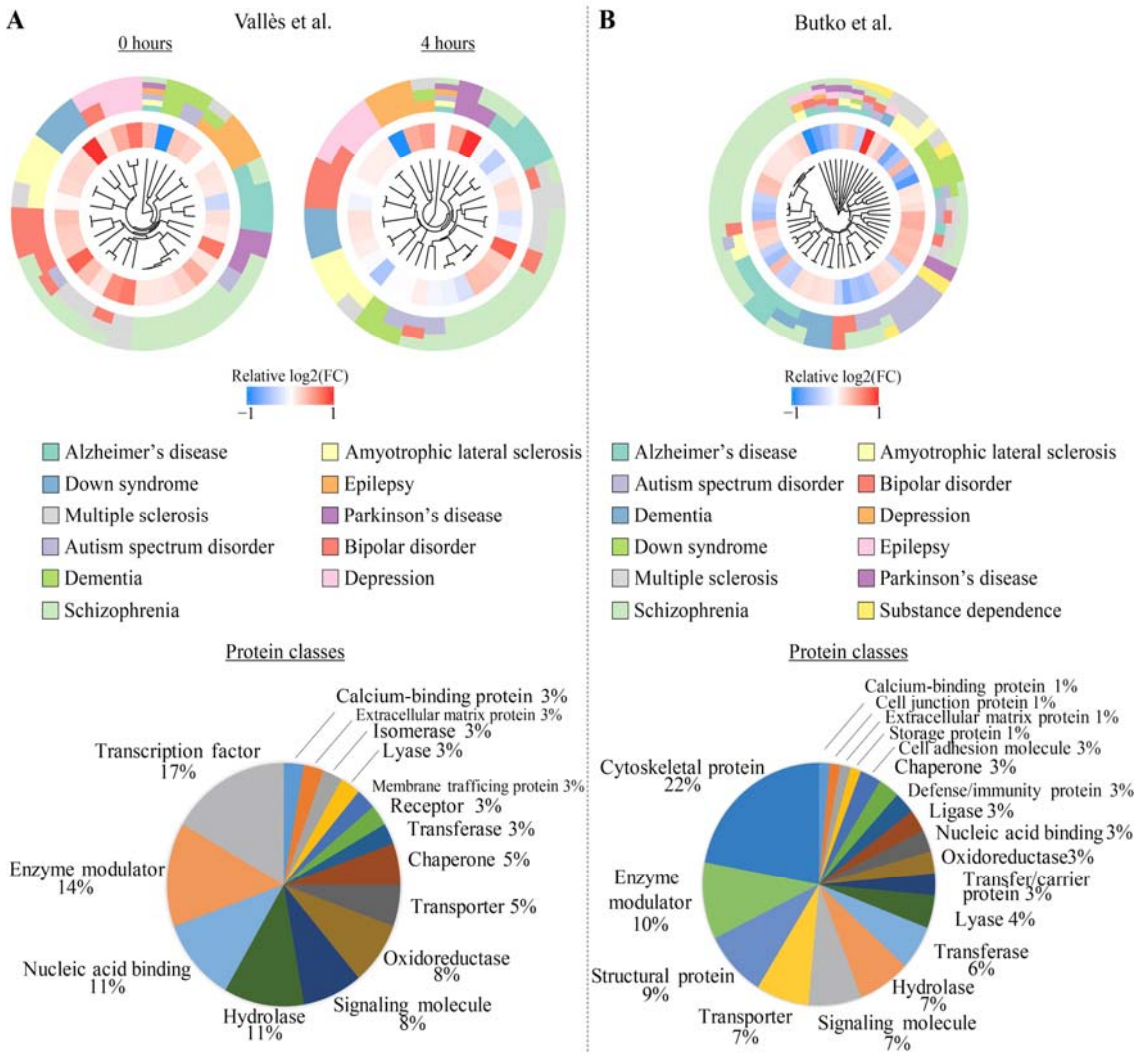


Figure 7. Experience-dependent plasticity and select brain disorders share common molecular targets. Top: Neurological disorders associated with differentially expressed transcripts after exposure to an enriched environment (left, data from (Vallès et al., 2011)) or proteins (right, data from (Butko et al., 2013)); genes are clustered by disorder. Bottom: Protein classes of transcripts (left) or proteins (right) associated with neurological diseases (Based on Panther Database).

up to seven distinct brain disorders. For example, GRIN2B is associated with Alzheimer's disease (Hohman et al., 2016), autism (Hu et al., 2016), bipolar disorder (Kato, 2007), Parkinson's disease (Lee et al., 2009) and schizophrenia. Since GRIN2B is an NMDA receptor subunit, this observation likely reflects its central role in plasticity and neurological function in general. Due to the difference in sample isolation procedures in the studies by Vallès and Butko, i.e. whole tissue punch vs synaptoneurosomes, respectively, the molecules linked to brain disorders also differ substantially in the protein classes they encompass (**Figure 7**). For example, cytoskeletal proteins make up a large portion of the disease-related targets identified by Butko *et al* (Butko et al., 2013) and transcription factors are not found, whereas the reverse

is true for the targets based on Vallès *et al* (Vallès et al., 2011).

An important caveat of the observations is that the links that can be established can only be as numerous as the observations that they are based on. Nevertheless, complementing GWA or population studies with experimental evidence such as those obtained from transcriptomics or proteomics studies can facilitate identification of underlying causes of neurological disorders or understand how symptoms during disease progression arise. Although transcriptome- or proteome-wide studies provide direction for research, in particular when combined with expression data obtained from patients, functional studies remain indispensable to fully understand the molecular bases of health and disease. As experience dependent plasticity and a large number of brain disorders involve similar transcriptional and translational targets, experience dependent plasticity in sensory circuits could help to unravel the molecular pathways associated with brain disorders.

6) Future directions for molecular studies of experience-dependent plasticity

Transcriptomic and proteomic big data have an outstanding promise to usher the field of experience-dependent plasticity to a new era where differential transcriptional regulation of genes are linked to neural network reorganization through large-scale molecular pathway analysis, causally linking molecules to network organization and ultimately to behaviour.

EDP requires the interaction of the numerous different cell types that exist in the brain, from excitatory (Allen et al., 2003) and inhibitory (Foeller et al., 2005) neurons to glia (Perez-Alvarez et al., 2014) and even the epithelial and muscle cells of blood vessels (Lacoste et al., 2014; Whiteus et al., 2014). A major unanswered question is how the vastly diverse cortical cellular population orchestrates EDP and which of the molecules that underlie it are common across (all) cell types and which are critical to a select few. Current technologies allow for the isolation of individual cells, possibly in combination with fluorescent labeling of molecularly defined cell classes, from which RNA (Zeisel et al., 2015) or (although still in need of development) proteins (Heath et al., 2016) can be harvested and subsequently analyzed. Using currently available datasets, it is possible to infer *post hoc* which cell types most robustly changed their transcriptomic make-up following sensory experience, as we have exemplified above. Nonetheless, applying single-cell technologies in combination with sensory experience manipulations would enable the study of molecules critical for EDP with unprecedented precision.

A further benefit would come from the collection of samples in a cortical layer-specific manner. Electrophysiologically, cortical lamina have since long been shown to display distinct phenotypes in cortical map plasticity (Diamond et al., 1994), stemming from the organization of their thalamic and cortical inputs and their cellular populations (Molyneaux et al., 2007). Cortical laminae can be readily identified through molecular markers, showing their distinct molecular identities (Belgard et al., 2011; Molyneaux et al., 2007), which likely shows the coherence between a layer's functional role and the molecules required to exert it. This stresses the importance of anatomical resolution when studying experience-dependent plasticity on either the electrophysiological and molecular level.

Both Vallès (Vallès et al., 2011) and Butko (Butko et al., 2013) and their colleagues have examined, through *in situ* hybridization or immunostainings, the distribution of a subset of identified targets across cortical lamina, revealing tight spatial restrictions on their expression in cellular populations. Such *post-hoc* approaches however are of low throughput, and future studies should strive to obtain lamina-specific tissues (much like in Belgard et al., 2011; Kole et al., 2017a, 2017b) and use these for subsequent processing and analysis. This will allow for a large-scale screening of layer-specific manifestations of experience-dependent plasticity at the molecular level.

The most recent transcriptome and proteome studies employ environmental enrichment or all-whisker stimulation or trimming, which induce homeostatic plasticity in barrel cortex. Homeostatic and Hebbian plasticity work in coherence to establish cortical maps, but their mechanisms differ significantly (Feldman and Brecht, 2005; Gainey and Feldman, 2017; Keck et al., 2017). Alternative deprivation or stimulation methods, such as single-row whisker deprivation or single-whisker experience (Allen et al., 2003; Celikel et al., 2004; Clem et al., 2008; Foeller et al., 2005), result in electrophysiologically well-defined plasticity phenotypes, the molecular mechanisms of which have been poorly studied and still require elucidation.

The ultimate goal will have to be to systematically study experience-dependent plasticity in a cell, cell-type, node (e.g. cortical layer) specific manner, across the many forms of experience (see **Figure 2**) and perceptual learning-induced. This will allow researchers to create an all-inclusive molecular map of the transcriptome and proteome, that will lead to causal experiments to unravel the molecules that control brain plasticity plasticity (Kole et al., 2017a; Kole et al., 2017b). The whisker system, with its modular organization along the whisker-to-barrel pathway as well as the rich behavioral repertoire of whisker dependent tasks (e.g. (Filipkowski et al., 2000; Guic-Robles et al., 1992; Jabłońska and Skangiel-Kramska, 1995; Jacobs and Juliano, 1995);(Celikel and Sakmann, 2007; Clem et al., 2008; Cohen and Castro-Alamancos, 2010; Galvez et al., 2007; Grion et al., 2016; Guic et al., 2008; Juczewski et al., 2016; Krupa et al., 2001; Miceli et al., 2017; Miyashita and Feldman, 2013; O'Connor et al., 2010; Rosselet et al., 2011; Safaai et al., 2013; Topchiy et al., 2009; Troncoso et al., 2007; Voigts et al., 2015; Waiblinger et al., 2015)), will likely lead the way.

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Bibliography

Abraham, W.C., Dragunow, M., Tate, W.P., 1991. The role of immediate early genes in the stabilization of long-term potentiation. Mol Neurobiol 5, 297–314.

Albrecht, C., von Der Kammer, H., Mayhaus, M., Klaudiny, J., Schweizer, M., Nitsch, R.M., 2000. Muscarinic acetylcholine receptors induce the expression of the immediate early growth regulatory gene CYR61. J Biol Chem 275, 28929–28936. doi:10.1074/jbc.M003053200

Allen, C.B., Celikel, T., Feldman, D.E., 2003. Long-term depression induced by sensory deprivation during cortical map plasticity in vivo. Nat Neurosci 6, 291–299. doi:10.1038/nn1012

Angel, P., Karin, M., 1991. The role of Jun, Fos and the AP-1 complex in cell-proliferation and transformation. Biochim Biophys Acta 1072, 129–157.

Angelucci, F., Brenè, S., Mathé, A.A., 2005. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry 10, 345–352. doi:10.1038/sj.mp.4001637

Azevedo, F.A.C., Carvalho, L.R.B., Grinberg, L.T., Farfel, J.M., Ferretti, R.E.L., Leite, R.E.P., Jacob Filho, W., Lent, R., Herculano-Houzel, S., 2009. Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol 513, 532–541. doi:10.1002/cne.21974

Baranes, D., Lederfein, D., Huang, Y.Y., Chen, M., Bailey, C.H., Kandel, E.R., 1998. Tissue plasminogen activator contributes to the late phase of LTP and to synaptic growth in the hippocampal mossy fiber pathway. Neuron 21, 813–825.

Barauna, V.G., Magalhaes, F.C., Campos, L.C.G., Reis, R.I., Kunapuli, S.P., Costa-Neto, C.M., Miyakawa, A.A., Krieger, J.E., 2013. Shear stress-induced Ang II AT1 receptor activation: G-protein dependent and independent mechanisms. Biochem Biophys Res Commun 434, 647–652. doi:10.1016/j.bbrc.2013.04.005

Barrera, K., Chu, P., Abramowitz, J., Steger, R., Ramos, R.L., Brumberg, J.C., 2013. Organization of myelin in the mouse somatosensory barrel cortex and the effects of sensory deprivation. Dev Neurobiol 73, 297–314. doi:10.1002/dneu.22060

Belgard, T.G., Marques, A.C., Oliver, P.L., Abaan, H.O., Sirey, T.M., Hoerder-Suabedissen, A., García-Moreno, F., Molnár, Z., Margulies, E.H., Ponting, C.P., 2011. A transcriptomic atlas of mouse neocortical layers. Neuron 71, 605–616. doi:10.1016/j.neuron.2011.06.039

Bengoetxea, H., Argandoña, E.G., Lafuente, J.V., 2008. Effects of visual experience on vascular endothelial growth factor expression during the postnatal development of the rat visual cortex. Cereb Cortex 18, 1630–1639. doi:10.1093/cercor/bhm190

Benito, E., Barco, A., 2010. CREB's control of intrinsic and synaptic plasticity: implications for CREB-dependent memory models. Trends Neurosci 33, 230–240. doi:10.1016/j.tins.2010.02.001

Bergles, D.E., Richardson, W.D., 2015. Oligodendrocyte development and plasticity. Cold Spring Harb Perspect Biol 8, a020453. doi:10.1101/cshperspect.a020453

Biesiada, E., Razandi, M., Levin, E.R., 1996. Egr-1 activates basic fibroblast growth factor transcription. Mechanistic implications for astrocyte proliferation. J Biol Chem 271, 18576–18581.

Bisler, S., Schleicher, A., Gass, P., Stehle, J.H., Zilles, K., Staiger, J.F., 2002. Expression of c-Fos, ICER, Krox-24 and JunB in the whisker-to-barrel pathway of rats: time course of induction upon whisker stimulation by tactile exploration of an enriched environment. J Chem Neuroanat 23, 187–198.

Black, J.E., Polinsky, M., Greenough, W.T., 1989. Progressive failure of cerebral angiogenesis supporting neural plasticity in aging rats. Neurobiol Aging 10, 353–358.

Black, J.E., Sirevaag, A.M., Greenough, W.T., 1987. Complex experience promotes capillary formation in young rat visual cortex. Neurosci Lett 83, 351–355.

Boda, B., Alberi, S., Nikonenko, I., Node-Langlois, R., Jourdain, P., Moosmayer, M., Parisi-Jourdain, L., Muller, D., 2004. The mental retardation protein PAK3 contributes to synapse formation and plasticity in hippocampus. J Neurosci 24, 10816–10825. doi:10.1523/JNEUROSCI.2931-04.2004

Brody, S.A., Conquet, F., Geyer, M.A., 2003. Disruption of prepulse inhibition in mice lacking mGluR1. Eur J Neurosci 18, 3361–3366.

Broser, P., Grinevich, V., Osten, P., Sakmann, B., Wallace, D.J., 2008. Critical period plasticity of axonal arbors of layer 2/3 pyramidal neurons in rat somatosensory cortex: layer-specific reduction of projections into deprived cortical columns. Cereb Cortex 18, 1588–1603. doi:10.1093/cercor/bhm189

Bruno, M.A., Cuello, A.C., 2006. Activity-dependent release of precursor nerve growth factor, conversion to mature nerve growth factor, and its degradation by a protease cascade. Proc Natl Acad Sci U S A 103, 6735–6740. doi:10.1073/pnas.0510645103

Butko, M.T., Savas, J.N., Friedman, B., Delahunty, C., Ebner, F., Yates, J.R., Tsien, R.Y., 2013. In vivo quantitative proteomics of somatosensory cortical synapses shows which protein levels are modulated by sensory deprivation. Proc Natl Acad Sci U S A 110, E726-35. doi:10.1073/pnas.1300424110

Cauli, B., Tong, X.-K., Rancillac, A., Serluca, N., Lambolez, B., Rossier, J., Hamel, E., 2004. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. J Neurosci 24, 8940–8949. doi:10.1523/JNEUROSCI.3065-04.2004

Celikel, T., Sakmann, B., 2007. Sensory integration across space and in time for decision making in the somatosensory system of rodents. Proc Natl Acad Sci U S A 104, 1395–1400. doi:10.1073/pnas.0610267104

Celikel, T., Szostak, V.A., Feldman, D.E., 2004. Modulation of spike timing by sensory deprivation during induction of cortical map plasticity. Nat Neurosci 7, 534–541. doi:10.1038/nn1222

Cheetham, C.E.J., Hammond, M.S.L., Edwards, C.E.J., Finnerty, G.T., 2007. Sensory experience alters cortical connectivity and synaptic function site specifically. J Neurosci 27, 3456–3465. doi:10.1523/JNEUROSCI.5143-06.2007

Chen, Y., Wang, Y., Ertürk, A., Kallop, D., Jiang, Z., Weimer, R.M., Kaminker, J., Sheng, M., 2014. Activity-induced Nr4a1 regulates spine density and distribution pattern of excitatory synapses in pyramidal neurons. Neuron 83, 431–443. doi:10.1016/j.neuron.2014.05.027

Chittajallu, R., Isaac, J.T.R., 2010. Emergence of cortical inhibition by coordinated sensory-driven plasticity at distinct synaptic loci. Nat Neurosci 13, 1240–1248. doi:10.1038/nn.2639

Clem, R.L., Celikel, T., Barth, A.L., 2008. Ongoing in vivo experience triggers synaptic metaplasticity in the neocortex. Science 319, 101–104. doi:10.1126/science.1143808

Cohen, J.D., Castro-Alamancos, M.A., 2010. Detection of low salience whisker stimuli requires synergy of tectal and thalamic sensory relays. J Neurosci 30, 2245–2256. doi:10.1523/JNEUROSCI.5746-09.2010

Concannon, C.G., Gorman, A.M., Samali, A., 2003. On the role of Hsp27 in regulating apoptosis. Apoptosis 8, 61–70.

Dachtler, J., Hardingham, N.R., Fox, K., 2012. The role of nitric oxide synthase in cortical plasticity is sex specific. J Neurosci 32, 14994–14999. doi:10.1523/JNEUROSCI.3189-12.2012

De Palma, M., Biziato, D., Petrova, T.V., 2017. Microenvironmental regulation of tumour angiogenesis. Nat Rev Cancer 17, 457–474. doi:10.1038/nrc.2017.51

de Villers-Sidani, E., Chang, E.F., Bao, S., Merzenich, M.M., 2007. Critical period window for spectral tuning defined in the primary auditory cortex (A1) in the rat. J Neurosci 27, 180–189. doi:10.1523/JNEUROSCI.3227-06.2007

Dekker, R.J., van Thienen, J.V., Rohlena, J., de Jager, S.C., Elderkamp, Y.W., Seppen, J., de Vries, C.J.M., Biessen, E.A.L., van Berkel, T.J.C., Pannekoek, H., Horrevoets, A.J.G., 2005. Endothelial KLF2 links local arterial shear stress levels to the expression of vascular tone-regulating genes. Am J Pathol 167, 609–618. doi:10.1016/S0002-9440(10)63002-7

Diamond, M.C., Krech, D., Rosenzweig, M.R., 1964. The effects of an enriched environment on the histology of the rat cerebral cortex. J Comp Neurol 123, 111–120.

Diamond, M.E., Huang, W., Ebner, F.F., 1994. Laminar comparison of somatosensory cortical plasticity. Science 265, 1885–1888.

Diamond, S.L., Sharefkin, J.B., Dieffenbach, C., Frasier-Scott, K., McIntire, L.V., Eskin, S.G., 1990. Tissue plasminogen activator messenger RNA levels increase in cultured human

endothelial cells exposed to laminar shear stress. J Cell Physiol 143, 364–371. doi:10.1002/jcp.1041430222

Ennis, B.W., Fultz, K.E., Smith, K.A., Westwick, J.K., Zhu, D., Boluro-Ajayi, M., Bilter, G.K., Stein, B., 2005. Inhibition of tumor growth, angiogenesis, and tumor cell proliferation by a small molecule inhibitor of c-Jun N-terminal kinase. J Pharmacol Exp Ther 313, 325–332. doi:10.1124/jpet.104.078873

Evans, I.M., Britton, G., Zachary, I.C., 2008. Vascular endothelial growth factor induces heat shock protein (HSP) 27 serine 82 phosphorylation and endothelial tubulogenesis via protein kinase D and independent of p38 kinase. Cell Signal 20, 1375–1384. doi:10.1016/j.cellsig.2008.03.002

Fahmy, R.G., Dass, C.R., Sun, L.-Q., Chesterman, C.N., Khachigian, L.M., 2003. Transcription factor Egr-1 supports FGF-dependent angiogenesis during neovascularization and tumor growth. Nat Med 9, 1026–1032. doi:10.1038/nm905

Fang, F., Shangguan, A.J., Kelly, K., Wei, J., Gruner, K., Ye, B., Wang, W., Bhattacharyya, S., Hinchcliff, M.E., Tourtellotte, W.G., Varga, J., 2013. Early growth response 3 (Egr-3) is induced by transforming growth factor-β and regulates fibrogenic responses. Am J Pathol 183, 1197–1208. doi:10.1016/j.ajpath.2013.06.016

Feldman, D.E., 2009. Synaptic mechanisms for plasticity in neocortex. Annu Rev Neurosci 32, 33–55. doi:10.1146/annurev.neuro.051508.135516

Feldman, D.E., Brecht, M., 2005. Map plasticity in somatosensory cortex. Science 310, 810–815. doi:10.1126/science.1115807

Filipkowski, R.K., Rydz, M., Berdel, B., Morys, J., Kaczmarek, L., 2000. Tactile experience induces c-fos expression in rat barrel cortex. Learn Mem 7, 116–122.

Finnerty, G.T., Roberts, L.S., Connors, B.W., 1999. Sensory experience modifies the short-term dynamics of neocortical synapses. Nature 400, 367–371. doi:10.1038/22553

Foeller, E., Celikel, T., Feldman, D.E., 2005. Inhibitory sharpening of receptive fields contributes to whisker map plasticity in rat somatosensory cortex. J Neurophysiol 94, 4387–4400. doi:10.1152/jn.00553.2005

Fox, K., 1992. A critical period for experience-dependent synaptic plasticity in rat barrel cortex. J Neurosci 12, 1826–1838.

Fox, K., 2002. Anatomical pathways and molecular mechanisms for plasticity in the barrel cortex. Neuroscience 111, 799–814. doi:10.1016/S0306-4522(02)00027-1

Fox, K., Wong, R.O.L., 2005. A comparison of experience-dependent plasticity in the visual and somatosensory systems. Neuron 48, 465–477. doi:10.1016/j.neuron.2005.10.013

Friberg, H., Wieloch, T., Castilho, R.F., 2002. Mitochondrial oxidative stress after global brain ischemia in rats. Neurosci Lett 334, 111–114.

Froemke, R.C., 2015. Plasticity of cortical excitatory-inhibitory balance. Annu Rev Neurosci 38, 195–219. doi:10.1146/annurev-neuro-071714-034002

Gainey, M.A., Feldman, D.E., 2017. Multiple shared mechanisms for homeostatic plasticity in rodent somatosensory and visual cortex. Philos Trans R Soc Lond, B, Biol Sci 372. doi:10.1098/rstb.2016.0157

Galvez, R., Weible, A.P., Disterhoft, J.F., 2007. Cortical barrel lesions impair whisker-CS trace eyeblink conditioning. Learn Mem 14, 94–100. doi:10.1101/lm.418407

Gene Ontology Consortium, 2008. The Gene Ontology project in 2008. Nucleic Acids Res 36, D440-4. doi:10.1093/nar/gkm883

Gibson, E.M., Purger, D., Mount, C.W., Goldstein, A.K., Lin, G.L., Wood, L.S., Inema, I., Miller, S.E., Bieri, G., Zuchero, J.B., Barres, B.A., Woo, P.J., Vogel, H., Monje, M., 2014. Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. Science 344, 1252304. doi:10.1126/science.1252304

Glazewski, S., Barth, A.L., Wallace, H., McKenna, M., Silva, A., Fox, K., 1999. Impaired experience-dependent plasticity in barrel cortex of mice lacking the alpha and delta isoforms of CREB. Cereb Cortex 9, 249–256.

Glazewski, S., Chen, C.M., Silva, A., Fox, K., 1996. Requirement for alpha-CaMKII in experience-dependent plasticity of the barrel cortex. Science 272, 421–423.

Gordon, J.A., Stryker, M.P., 1996. Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. J Neurosci 16, 3274–3286.

Greco, B., Managò, F., Tucci, V., Kao, H.-T., Valtorta, F., Benfenati, F., 2013. Autism-related behavioral abnormalities in synapsin knockout mice. Behav Brain Res 251, 65–74. doi:10.1016/j.bbr.2012.12.015

Greenhill, S.D., Ranson, A., Fox, K., 2015. Hebbian and homeostatic plasticity mechanisms in regular spiking and intrinsic bursting cells of cortical layer 5. Neuron 88, 539–552. doi:10.1016/j.neuron.2015.09.025

Grion, N., Akrami, A., Zuo, Y., Stella, F., Diamond, M.E., 2016. Coherence between Rat Sensorimotor System and Hippocampus Is Enhanced during Tactile Discrimination. PLoS Biol 14, e1002384. doi:10.1371/journal.pbio.1002384

Guic, E., Carrasco, X., Rodríguez, E., Robles, I., Merzenich, M.M., 2008. Plasticity in primary somatosensory cortex resulting from environmentally enriched stimulation and sensory discrimination training. Biol Res 41, 425–437. doi:/S0716-97602008000400008

Guic-Robles, E., Jenkins, W.M., Bravo, H., 1992. Vibrissal roughness discrimination is barrelcortex-dependent. Behav Brain Res 48, 145–152.

Guo, W., Chambers, A.R., Darrow, K.N., Hancock, K.E., Shinn-Cunningham, B.G., Polley, D.B., 2012. Robustness of cortical topography across fields, laminae, anesthetic states, and neurophysiological signal types. J Neurosci 32, 9159–9172. doi:10.1523/JNEUROSCI.0065-12.2012

Hámori, J., Savy, C., Madarász, M., Somogyi, J., Takács, J., Verley, R., Farkas-Bargeton, E., 1986. Morphological alterations in subcortical vibrissal relays following vibrissal follicle destruction at birth in the mouse. J Comp Neurol 254, 166–183. doi:10.1002/cne.902540203

Hand, P.J., 1982. Plasticity of the rat barrel system, in: Changing Concepts of the Nervous System. Academic Press, New York, N.Y., pp. 49–68.

Hanna, M., Liu, H., Amir, J., Sun, Y., Morris, S.W., Siddiqui, M.A.Q., Lau, L.F., Chaqour, B., 2009. Mechanical regulation of the proangiogenic factor CCN1/CYR61 gene requires the combined activities of MRTF-A and CREB-binding protein histone acetyltransferase. J Biol Chem 284, 23125–23136. doi:10.1074/jbc.M109.019059

Hardingham, N., Wright, N., Dachtler, J., Fox, K., 2008. Sensory deprivation unmasks a PKA-dependent synaptic plasticity mechanism that operates in parallel with CaMKII. Neuron 60, 861–874. doi:10.1016/j.neuron.2008.10.018

Harris, R.M., Woolsey, T.A., 1981. Dendritic plasticity in mouse barrel cortex following postnatal vibrissa follicle damage. J Comp Neurol 196, 357–376. doi:10.1002/cne.901960302

Heath, J.R., Ribas, A., Mischel, P.S., 2016. Single-cell analysis tools for drug discovery and development. Nat Rev Drug Discov 15, 204–216. doi:10.1038/nrd.2015.16

Hedges, J.C., Dechert, M.A., Yamboliev, I.A., Martin, J.L., Hickey, E., Weber, L.A., Gerthoffer, W.T., 1999. A role for p38(MAPK)/HSP27 pathway in smooth muscle cell migration. J Biol Chem 274, 24211–24219. doi:10.1074/jbc.274.34.24211

Herbert, J.M., Lamarche, I., Carmeliet, P., 1997. Urokinase and tissue-type plasminogen activator are required for the mitogenic and chemotactic effects of bovine fibroblast growth factor and platelet-derived growth factor-BB for vascular smooth muscle cells. J Biol Chem 272, 23585–23591.

Hohman, T.J., Bush, W.S., Jiang, L., Brown-Gentry, K.D., Torstenson, E.S., Dudek, S.M., Mukherjee, S., Naj, A., Kunkle, B.W., Ritchie, M.D., Martin, E.R., Schellenberg, G.D., Mayeux, R., Farrer, L.A., Pericak-Vance, M.A., Haines, J.L., Thornton-Wells, T.A., Alzheimer's Disease Genetics Consortium, 2016. Discovery of gene-gene interactions across multiple independent data sets of late onset Alzheimer disease from the Alzheimer Disease Genetics Consortium. Neurobiol Aging 38, 141–150. doi:10.1016/j.neurobiolaging.2015.10.031

House, D.R.C., Elstrott, J., Koh, E., Chung, J., Feldman, D.E., 2011. Parallel regulation of feedforward inhibition and excitation during whisker map plasticity. Neuron 72, 819–831. doi:10.1016/j.neuron.2011.09.008

Hu, C., Chen, W., Myers, S.J., Yuan, H., Traynelis, S.F., 2016. Human GRIN2B variants in neurodevelopmental disorders. J Pharmacol Sci 132, 115–121. doi:10.1016/j.jphs.2016.10.002

Hubel, D.H., Wiesel, T.N., 1968. Receptive fields and functional architecture of monkey striate cortex. J Physiol (Lond) 195, 215–243.

Hurtado, O., Lizasoain, I., Fernández-Tomé, P., Alvarez-Barrientos, A., Leza, J.C., Lorenzo, P., Moro, M.A., 2002. TACE/ADAM17-TNF-alpha pathway in rat cortical cultures after exposure to oxygen-glucose deprivation or glutamate. J Cereb Blood Flow Metab 22, 576–585. doi:10.1097/00004647-200205000-00009

Hynynen, M.M., Khalil, R.A., 2006. The vascular endothelin system in hypertension--recent patents and discoveries. Recent Pat Cardiovasc Drug Discov 1, 95–108.

Ihara, M., Fukuroda, T., Saeki, T., Nishikibe, M., Kojiri, K., Suda, H., Yano, M., 1991. An endothelin receptor (ETA) antagonist isolated from Streptomyces misakiensis. Biochem Biophys Res Commun 178, 132–137.

Ito, T., Hiraoka, S., Kuroda, Y., Ishii, S., Umino, A., Kashiwa, A., Yamamoto, N., Kurumaji, A., Nishikawa, T., 2007. Effects of schizophrenomimetics on the expression of the CCN1 (CYR 61) gene encoding a matricellular protein in the infant and adult neocortex of the mouse and rat. Int J Neuropsychopharmacol 10, 717–725. doi:10.1017/S1461145707007882

Jabłońska, B., Skangiel-Kramska, J., 1995. Sensory conditioning and sensory stimulation do not affect GABAA receptor binding in the barrel field of mice. Acta Neurobiol Exp (Wars) 55, 289–293.

Jacobs, S.E., Juliano, S.L., 1995. The impact of basal forebrain lesions on the ability of rats to perform a sensory discrimination task involving barrel cortex. J Neurosci 15, 1099–1109.

Jäkel, S., Dimou, L., 2017. Glial Cells and Their Function in the Adult Brain: A Journey through the History of Their Ablation. Front Cell Neurosci 11, 24. doi:10.3389/fncel.2017.00024

Jones, T.A., Greenough, W.T., 1996. Ultrastructural evidence for increased contact between astrocytes and synapses in rats reared in a complex environment. Neurobiol Learn Mem 65, 48–56. doi:10.1006/nlme.1996.0005

Juczewski, K., von Richthofen, H., Bagni, C., Celikel, T., Fisone, G., Krieger, P., 2016. Somatosensory map expansion and altered processing of tactile inputs in a mouse model of fragile X syndrome. Neurobiol Dis 96, 201–215. doi:10.1016/j.nbd.2016.09.007

Kaliszewska, A., Bijata, M., Kaczmarek, L., Kossut, M., 2012. Experience-dependent plasticity of the barrel cortex in mice observed with 2-DG brain mapping and c-Fos: effects of MMP-9 KO. Cereb Cortex 22, 2160–2170. doi:10.1093/cercor/bhr303

Kalita, K., Kharebava, G., Zheng, J.-J., Hetman, M., 2006. Role of megakaryoblastic acute leukemia-1 in ERK1/2-dependent stimulation of serum response factor-driven transcription by BDNF or increased synaptic activity. J Neurosci 26, 10020–10032. doi:10.1523/JNEUROSCI.2644-06.2006

Karin, M., Liu, Z. g, Zandi, E., 1997. AP-1 function and regulation. Curr Opin Cell Biol 9, 240–246.

Kato, T., 2007. Molecular genetics of bipolar disorder and depression. Psychiatry Clin Neurosci 61, 3–19. doi:10.1111/j.1440-1819.2007.01604.x

Kätzel, D., Miesenböck, G., 2014. Experience-dependent rewiring of specific inhibitory connections in adult neocortex. PLoS Biol 12, e1001798. doi:10.1371/journal.pbio.1001798

Keck, T., Toyoizumi, T., Chen, L., Doiron, B., Feldman, D.E., Fox, K., Gerstner, W., Haydon, P.G., Hübener, M., Lee, H.-K., Lisman, J.E., Rose, T., Sengpiel, F., Stellwagen, D., Stryker, M.P., Turrigiano, G.G., van Rossum, M.C., 2017. Integrating Hebbian and homeostatic plasticity: the current state of the field and future research directions. Philos Trans R Soc Lond, B, Biol Sci 372. doi:10.1098/rstb.2016.0158

Keene, J.D., 2007. RNA regulons: coordination of post-transcriptional events. Nat Rev Genet 8, 533–543. doi:10.1038/nrg2111

Kole, K., 2015. Experience-dependent plasticity of neurovascularization. J Neurophysiol 114, 2077–2079. doi:10.1152/jn.00972.2014

Kole, K., Komuro, Y., Provaznik, J., Pistolic, J., Benes, V., Tiesinga, P., Celikel, T., 2017a. Transcriptional mapping of the primary somatosensory cortex upon sensory deprivation. Gigascience 6, 1–6. doi:10.1093/gigascience/gix081

Kole, K., Lindeboom, R.G.H., Baltissen, M.P.A., Jansen, P.W.T.C., Vermeulen, M., Tiesinga, P., Celikel, T., 2017b. Proteomic landscape of the primary somatosensory cortex upon sensory deprivation. Gigascience 6, 1–10. doi:10.1093/gigascience/gix082

Kossut, M., 1985. Effects of sensory denervation and deprivation on a single cortical vibrissal column studied with 2-deoxyglucose. Physiol Bohemoslov 34 Suppl, 79–83.

Krupa, D.J., Matell, M.S., Brisben, A.J., Oliveira, L.M., Nicolelis, M.A., 2001. Behavioral properties of the trigeminal somatosensory system in rats performing whisker-dependent tactile discriminations. J Neurosci 21, 5752–5763.

Lacoste, B., Comin, C.H., Ben-Zvi, A., Kaeser, P.S., Xu, X., Costa, L. da F., Gu, C., 2014. Sensory-related neural activity regulates the structure of vascular networks in the cerebral cortex. Neuron 83, 1117–1130. doi:10.1016/j.neuron.2014.07.034

Land, P.W., Simons, D.J., 1985. Metabolic activity in SmI cortical barrels of adult rats is dependent on patterned sensory stimulation of the mystacial vibrissae. Brain Res 341, 189–194.

Lau, L.F., Lam, S.C., 1999. The CCN family of angiogenic regulators: the integrin connection. Exp Cell Res 248, 44–57. doi:10.1006/excr.1999.4456

Lecrux, C., Sandoe, C.H., Neupane, S., Kropf, P., Toussay, X., Tong, X.-K., Lacalle-Aurioles, M., Shmuel, A., Hamel, E., 2017. Impact of altered cholinergic tones on the neurovascular coupling response to whisker stimulation. J Neurosci 37, 1518–1531. doi:10.1523/JNEUROSCI.1784-16.2016

Lee, J.-Y., Lee, E.K., Park, S.S., Lim, J.-Y., Kim, H.J., Kim, J.S., Jeon, B.S., 2009. Association of DRD3 and GRIN2B with impulse control and related behaviors in Parkinson's disease. Mov Disord 24, 1803–1810. doi:10.1002/mds.22678

Lee, Y.-J., Lee, H.-J., Choi, S.-H., Jin, Y.B., An, H.J., Kang, J.-H., Yoon, S.S., Lee, Y.-S., 2012. Soluble HSPB1 regulates VEGF-mediated angiogenesis through their direct interaction. Angiogenesis 15, 229–242. doi:10.1007/s10456-012-9255-3

Lendvai, B., Stern, E.A., Chen, B., Svoboda, K., 2000. Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. Nature 404, 876–881. doi:10.1038/35009107

Leonard, M.O., Howell, K., Madden, S.F., Costello, C.M., Higgins, D.G., Taylor, C.T., McLoughlin, P., 2008. Hypoxia selectively activates the CREB family of transcription factors in the in vivo lung. Am J Respir Crit Care Med 178, 977–983. doi:10.1164/rccm.200712-1890OC

Li, L., Bender, K.J., Drew, P.J., Jadhav, S.P., Sylwestrak, E., Feldman, D.E., 2009. Endocannabinoid signaling is required for development and critical period plasticity of the whisker map in somatosensory cortex. Neuron 64, 537–549. doi:10.1016/j.neuron.2009.10.005

Li, P., Rudolph, U., Huntsman, M.M., 2009. Long-term sensory deprivation selectively rearranges functional inhibitory circuits in mouse barrel cortex. Proc Natl Acad Sci U S A 106, 12156–12161. doi:10.1073/pnas.0900922106

Liu, D., Evans, I., Britton, G., Zachary, I., 2008. The zinc-finger transcription factor, early growth response 3, mediates VEGF-induced angiogenesis. Oncogene 27, 2989–2998. doi:10.1038/sj.onc.1210959

Liu, F., Turtzo, L.C., Li, J., Regard, J., Worley, P., Zeevi, N., McCullough, L.D., 2012. Loss of vascular early response gene reduces edema formation after experimental stroke. Exp Transl Stroke Med 4, 12. doi:10.1186/2040-7378-4-12

Ma, T., Trinh, M.A., Wexler, A.J., Bourbon, C., Gatti, E., Pierre, P., Cavener, D.R., Klann, E., 2013. Suppression of eIF2α kinases alleviates Alzheimer's disease-related plasticity and memory deficits. Nat Neurosci 16, 1299–1305. doi:10.1038/nn.3486

Maallem, S., Wierinckx, A., Lachuer, J., Kwon, M.H., Tappaz, M.L., 2008. Gene expression profiling in brain following acute systemic hypertonicity: novel genes possibly involved in osmoadaptation. J Neurochem 105, 1198–1211. doi:10.1111/j.1471-4159.2008.05222.x

Makinodan, M., Rosen, K.M., Ito, S., Corfas, G., 2012. A critical period for social experience-dependent oligodendrocyte maturation and myelination. Science 337, 1357–1360. doi:10.1126/science.1220845

Maneshi, M.M., Maki, B., Gnanasambandam, R., Belin, S., Popescu, G.K., Sachs, F., Hua, S.Z., 2017. Mechanical stress activates NMDA receptors in the absence of agonists. Sci Rep 7, 39610. doi:10.1038/srep39610

Mangin, J.-M., Li, P., Scafidi, J., Gallo, V., 2012. Experience-dependent regulation of NG2 progenitors in the developing barrel cortex. Nat Neurosci 15, 1192–1194. doi:10.1038/nn.3190

Margolis, D.J., Lütcke, H., Schulz, K., Haiss, F., Weber, B., Kügler, S., Hasan, M.T., Helmchen, F., 2012. Reorganization of cortical population activity imaged throughout long-term sensory deprivation. Nat Neurosci 15, 1539–1546. doi:10.1038/nn.3240

Martin, J.L., Mestril, R., Hilal-Dandan, R., Brunton, L.L., Dillmann, W.H., 1997. Small heat shock proteins and protection against ischemic injury in cardiac myocytes. Circulation 96, 4343–4348.

Matsuda, N., Lu, H., Fukata, Y., Noritake, J., Gao, H., Mukherjee, S., Nemoto, T., Fukata, M., Poo, M.-M., 2009. Differential activity-dependent secretion of brain-derived neurotrophic factor from axon and dendrite. J Neurosci 29, 14185–14198. doi:10.1523/JNEUROSCI.1863-09.2009

Mayer, S.I., Rössler, O.G., Endo, T., Charnay, P., Thiel, G., 2009. Epidermal-growth-factor-induced proliferation of astrocytes requires Egr transcription factors. J Cell Sci 122, 3340–3350. doi:10.1242/jcs.048272

McCaslin, A.F.H., Chen, B.R., Radosevich, A.J., Cauli, B., Hillman, E.M.C., 2011. In vivo 3D morphology of astrocyte-vasculature interactions in the somatosensory cortex: implications for neurovascular coupling. J Cereb Blood Flow Metab 31, 795–806. doi:10.1038/jcbfm.2010.204

Miceli, S., Nadif Kasri, N., Joosten, J., Huang, C., Kepser, L., Proville, R., Selten, M.M., van Eijs, F., Azarfar, A., Homberg, J.R., Celikel, T., Schubert, D., 2017. Reduced Inhibition within Layer IV of Sert Knockout Rat Barrel Cortex is Associated with Faster Sensory Integration. Cereb Cortex 27, 933–949. doi:10.1093/cercor/bhx016

Micheva, K.D., Beaulieu, C., 1995. An anatomical substrate for experience-dependent plasticity of the rat barrel field cortex. Proc Natl Acad Sci U S A 92, 11834–11838.

Min, R., Nevian, T., 2012. Astrocyte signaling controls spike timing-dependent depression at neocortical synapses. Nat Neurosci 15, 746–753. doi:10.1038/nn.3075

Miquelajauregui, A., Kribakaran, S., Mostany, R., Badaloni, A., Consalez, G.G., Portera-Cailliau, C., 2015. Layer 4 pyramidal neurons exhibit robust dendritic spine plasticity in vivo after input deprivation. J Neurosci 35, 7287–7294. doi:10.1523/JNEUROSCI.5215-14.2015

Mirza, M.A., Capozzi, L.A., Xu, Y., McCullough, L.D., Liu, F., 2013. Knockout of vascular early response gene worsens chronic stroke outcomes in neonatal mice. Brain Res Bull 98, 111–121. doi:10.1016/j.brainresbull.2013.07.011

Miyashita, T., Feldman, D.E., 2013. Behavioral detection of passive whisker stimuli requires somatosensory cortex. Cereb Cortex 23, 1655–1662. doi:10.1093/cercor/bhs155

Molyneaux, B.J., Arlotta, P., Menezes, J.R.L., Macklis, J.D., 2007. Neuronal subtype specification in the cerebral cortex. Nat Rev Neurosci 8, 427–437. doi:10.1038/nrn2151

Morita, T., Kurihara, H., Maemura, K., Yoshizumi, M., Nagai, R., Yazaki, Y., 1994. Role of Ca2+ and protein kinase C in shear stress-induced actin depolymerization and endothelin 1 gene expression. Circ Res 75, 630–636.

Murata, Y., Fujiwara, N., Seo, J.H., Yan, F., Liu, X., Terasaki, Y., Luo, Y., Arai, K., Ji, X., Lo, E.H., 2012. Delayed inhibition of c-Jun N-terminal kinase worsens outcomes after focal cerebral ischemia. J Neurosci 32, 8112–8115. doi:10.1523/JNEUROSCI.0219-12.2012

Nedivi, E., Hevroni, D., Naot, D., Israeli, D., Citri, Y., 1993. Numerous candidate plasticity-related genes revealed by differential cDNA cloning. Nature 363, 718–722. doi:10.1038/363718a0

Nicole, O., Docagne, F., Ali, C., Margaill, I., Carmeliet, P., MacKenzie, E.T., Vivien, D., Buisson, A., 2001. The proteolytic activity of tissue-plasminogen activator enhances NMDA receptor-mediated signaling. Nat Med 7, 59–64. doi:10.1038/83358

Nicolelis, M.A., Chapin, J.K., Lin, R.C., 1991. Thalamic plasticity induced by early whisker removal in rats. Brain Res 561, 344–349.

Nomiyama, T., Nakamachi, T., Gizard, F., Heywood, E.B., Jones, K.L., Ohkura, N., Kawamori, R., Conneely, O.M., Bruemmer, D., 2006. The NR4A orphan nuclear receptor NOR1 is induced by platelet-derived growth factor and mediates vascular smooth muscle cell proliferation. J Biol Chem 281, 33467–33476. doi:10.1074/jbc.M603436200

Ostrow, L.W., Suchyna, T.M., Sachs, F., 2011. Stretch induced endothelin-1 secretion by adult rat astrocytes involves calcium influx via stretch-activated ion channels (SACs). Biochem Biophys Res Commun 410, 81–86. doi:10.1016/j.bbrc.2011.05.109

O'Brien, T.P., Yang, G.P., Sanders, L., Lau, L.F., 1990. Expression of cyr61, a growth factor-inducible immediate-early gene. Mol Cell Biol 10, 3569–3577.

O'Connor, D.H., Clack, N.G., Huber, D., Komiyama, T., Myers, E.W., Svoboda, K., 2010. Vibrissa-based object localization in head-fixed mice. J Neurosci 30, 1947–1967. doi:10.1523/JNEUROSCI.3762-09.2010

O'Tuathaigh, C.M.P., O'Connor, A.-M., O'Sullivan, G.J., Lai, D., Harvey, R., Croke, D.T., Waddington, J.L., 2008. Disruption to social dyadic interactions but not emotional/anxiety-related behaviour in mice with heterozygous "knockout" of the schizophrenia risk gene neuregulin-1. Prog Neuropsychopharmacol Biol Psychiatry 32, 462–466. doi:10.1016/j.pnpbp.2007.09.018

Pang, P.T., Teng, H.K., Zaitsev, E., Woo, N.T., Sakata, K., Zhen, S., Teng, K.K., Yung, W.-H., Hempstead, B.L., Lu, B., 2004. Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. Science 306, 487–491. doi:10.1126/science.1100135

Pardo, C.A., Eberhart, C.G., 2007. The neurobiology of autism. Brain Pathol 17, 434–447. doi:10.1111/j.1750-3639.2007.00102.x

Parkhurst, C.N., Yang, G., Ninan, I., Savas, J.N., Yates, J.R., Lafaille, J.J., Hempstead, B.L., Littman, D.R., Gan, W.-B., 2013. Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155, 1596–1609. doi:10.1016/j.cell.2013.11.030

Pechán, P.A., Chowdhury, K., Gerdes, W., Seifert, W., 1993. Glutamate induces the growth factors NGF, bFGF, the receptor FGF-R1 and c-fos mRNA expression in rat astrocyte culture. Neurosci Lett 153, 111–114.

Peng, K., Xu, W., Zheng, J., Huang, K., Wang, H., Tong, J., Lin, Z., Liu, J., Cheng, W., Fu, D., Du, P., Kibbe, W.A., Lin, S.M., Xia, T., 2013. The Disease and Gene Annotations (DGA): an annotation resource for human disease. Nucleic Acids Res 41, D553-60. doi:10.1093/nar/gks1244

Perez-Alvarez, A., Navarrete, M., Covelo, A., Martin, E.D., Araque, A., 2014. Structural and functional plasticity of astrocyte processes and dendritic spine interactions. J Neurosci 34, 12738–12744. doi:10.1523/JNEUROSCI.2401-14.2014

Polley, D.B., Kvasnák, E., Frostig, R.D., 2004. Naturalistic experience transforms sensory maps in the adult cortex of caged animals. Nature 429, 67–71. doi:10.1038/nature02469

Porton, B., Rodriguiz, R.M., Phillips, L.E., Gilbert, J.W., Feng, J., Greengard, P., Kao, H.T., Wetsel, W.C., 2010. Mice lacking synapsin III show abnormalities in explicit memory and conditioned fear. Genes Brain Behav 9, 257–268. doi:10.1111/j.1601-183X.2009.00555.x

Quarck, R., Berrou, E., Magnier, C., Bobe, R., Bredoux, R., Tobelem, G., Enouf, J., Bryckaert, M., 1996. Differential up-regulation of Rap1a and Rap1b proteins during smooth muscle cell cycle. Eur J Cell Biol 70, 269–277.

Ramakers, G.J.A., Wolfer, D., Rosenberger, G., Kuchenbecker, K., Kreienkamp, H.-J., Prange-Kiel, J., Rune, G., Richter, K., Langnaese, K., Masneuf, S., Bösl, M.R., Fischer, K.-D., Krugers, H.J., Lipp, H.-P., van Galen, E., Kutsche, K., 2012. Dysregulation of Rho GTPases in the αPix/Arhgef6 mouse model of X-linked intellectual disability is paralleled by impaired structural and synaptic plasticity and cognitive deficits. Hum Mol Genet 21, 268–286. doi:10.1093/hmg/ddr457

Regard, J.B., Scheek, S., Borbiev, T., Lanahan, A.A., Schneider, A., Demetriades, A.-M., Hiemisch, H., Barnes, C.A., Verin, A.D., Worley, P.F., 2004. Verge: a novel vascular early response gene. J Neurosci 24, 4092–4103. doi:10.1523/JNEUROSCI.4252-03.2004

Rius, J., Martínez-González, J., Crespo, J., Badimon, L., 2006. NOR-1 is involved in VEGF-induced endothelial cell growth. Atherosclerosis 184, 276–282. doi:10.1016/j.atherosclerosis.2005.04.008

Rocamora, N., Welker, E., Pascual, M., Soriano, E., 1996. Upregulation of BDNF mRNA expression in the barrel cortex of adult mice after sensory stimulation. J Neurosci 16, 4411–4419.

Rosselet, C., Fieschi, M., Hugues, S., Bureau, I., 2011. Associative learning changes the organization of functional excitatory circuits targeting the supragranular layers of mouse barrel cortex. Front Neural Circuits 4, 126. doi:10.3389/fncir.2010.00126

Rothman, A., Wolner, B., Button, D., Taylor, P., 1994. Immediate-early gene expression in response to hypertrophic and proliferative stimuli in pulmonary arterial smooth muscle cells. J Biol Chem 269, 6399–6404.

Safaai, H., von Heimendahl, M., Sorando, J.M., Diamond, M.E., Maravall, M., 2013. Coordinated population activity underlying texture discrimination in rat barrel cortex. J Neurosci 33, 5843–5855. doi:10.1523/JNEUROSCI.3486-12.2013

Sarna, J.R., Dyck, R.H., Whishaw, I.Q., 2000. The Dalila effect: C57BL6 mice barber whiskers by plucking. Behav Brain Res 108, 39–45.

Schloesser, R.J., Huang, J., Klein, P.S., Manji, H.K., 2008. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology 33, 110–133. doi:10.1038/sj.npp.1301575

Schummers, J., Yu, H., Sur, M., 2008. Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex. Science 320, 1638–1643. doi:10.1126/science.1156120

Shen, B., Wong, C.-O., Lau, O.-C., Woo, T., Bai, S., Huang, Y., Yao, X., 2015. Plasma membrane mechanical stress activates TRPC5 channels. PLoS ONE 10, e0122227. doi:10.1371/journal.pone.0122227

Sherrington, C.S., 1906. Observations on the scratch-reflex in the spinal dog. J Physiol (Lond) 34, 1–50.

Shetty, P.K., Galeffi, F., Turner, D.A., 2012. Cellular Links between Neuronal Activity and Energy Homeostasis. Front Pharmacol 3, 43. doi:10.3389/fphar.2012.00043

Shneor, D., Folberg, R., Pe'er, J., Honigman, A., Frenkel, S., 2017. Stable knockdown of CREB, HIF-1 and HIF-2 by replication-competent retroviruses abrogates the responses to hypoxia in hepatocellular carcinoma. Cancer Gene Ther 24, 64–74. doi:10.1038/cgt.2016.68

Simons, D.J., Land, P.W., 1987. Early experience of tactile stimulation influences organization of somatic sensory cortex. Nature 326, 694–697. doi:10.1038/326694a0

Simons, D.J., Land, P.W., 1994. Neonatal whisker trimming produces greater effects in nondeprived than deprived thalamic barreloids. J Neurophysiol 72, 1434–1437.

Simonsen, M.L., Alessio, H.M., White, P., Newsom, D.L., Hagerman, A.E., 2010. Acute physical activity effects on cardiac gene expression. Exp Physiol 95, 1071–1080. doi:10.1113/expphysiol.2010.054858

Sipe, G.O., Lowery, R.L., Tremblay, M.È., Kelly, E.A., Lamantia, C.E., Majewska, A.K., 2016. Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex. Nat Commun 7, 10905. doi:10.1038/ncomms10905

Song, S., Miller, K.D., Abbott, L.F., 2000. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3, 919–926. doi:10.1038/78829

Sonnenberg, J.L., Macgregor-Leon, P.F., Curran, T., Morgan, J.I., 1989. Dynamic alterations occur in the levels and composition of transcription factor AP-1 complexes after seizure. Neuron 3, 359–365.

Stern, E.A., Maravall, M., Svoboda, K., 2001. Rapid development and plasticity of layer 2/3 maps in rat barrel cortex in vivo. Neuron 31, 305–315.

Stogsdill, J.A., Eroglu, C., 2017. The interplay between neurons and glia in synapse development and plasticity. Curr Opin Neurobiol 42, 1–8. doi:10.1016/j.conb.2016.09.016

Suehiro, J., Hamakubo, T., Kodama, T., Aird, W.C., Minami, T., 2010. Vascular endothelial growth factor activation of endothelial cells is mediated by early growth response-3. Blood 115, 2520–2532. doi:10.1182/blood-2009-07-233478

Takano, T., Tian, G.-F., Peng, W., Lou, N., Libionka, W., Han, X., Nedergaard, M., 2006. Astrocyte-mediated control of cerebral blood flow. Nat Neurosci 9, 260–267. doi:10.1038/nn1623

Teng, H., Chopp, M., Hozeska-Solgot, A., Shen, L., Lu, M., Tang, C., Zhang, Z.G., 2012. Tissue plasminogen activator and plasminogen activator inhibitor 1 contribute to sonic hedgehog-induced in vitro cerebral angiogenesis. PLoS ONE 7, e33444. doi:10.1371/journal.pone.0033444

Topchiy, I.A., Wood, R.M., Peterson, B., Navas, J.A., Rojas, M.J., Rector, D.M., 2009. Conditioned lick behavior and evoked responses using whisker twitches in head restrained rats. Behav Brain Res 197, 16–23. doi:10.1016/j.bbr.2008.07.032

Trachtenberg, J.T., Chen, B.E., Knott, G.W., Feng, G., Sanes, J.R., Welker, E., Svoboda, K., 2002. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420, 788–794. doi:10.1038/nature01273

Tremblay, M.-È., Lowery, R.L., Majewska, A.K., 2010. Microglial interactions with synapses are modulated by visual experience. PLoS Biol 8, e1000527. doi:10.1371/journal.pbio.1000527

Troncoso, J., Múnera, A., Delgado-García, J.M., 2007. Learning-dependent potentiation in the vibrissal motor cortex is closely related to the acquisition of conditioned whisker responses in behaving mice. Learn Mem 14, 84–93. doi:10.1101/lm.341807

Tsai, J.C., Liu, L., Guan, J., Aird, W.C., 2000. The Egr-1 gene is induced by epidermal growth factor in ECV304 cells and primary endothelial cells. Am J Physiol, Cell Physiol 279, C1414-24.

Tyndall, S.J., Walikonis, R.S., 2007. Signaling by hepatocyte growth factor in neurons is induced by pharmacological stimulation of synaptic activity. Synapse 61, 199–204. doi:10.1002/syn.20362

Vallès, A., Boender, A.J., Gijsbers, S., Haast, R.A.M., Martens, G.J.M., de Weerd, P., 2011. Genomewide analysis of rat barrel cortex reveals time- and layer-specific mRNA expression changes related to experience-dependent plasticity. J Neurosci 31, 6140–6158. doi:10.1523/JNEUROSCI.6514-10.2011

Vallès, A., Granic, I., De Weerd, P., Martens, G.J.M., 2014. Molecular correlates of cortical network modulation by long-term sensory experience in the adult rat barrel cortex. Learn Mem 21, 305–310. doi:10.1101/lm.034827.114

Van der Loos, H., Woolsey, T.A., 1973. Somatosensory cortex: structural alterations following early injury to sense organs. Science 179, 395–398.

Voigts, J., Herman, D.H., Celikel, T., 2015. Tactile object localization by anticipatory whisker motion. J Neurophysiol 113, 620–632. doi:10.1152/jn.00241.2014

Voineskos, D., Rogasch, N.C., Rajji, T.K., Fitzgerald, P.B., Daskalakis, Z.J., 2013. A review of evidence linking disrupted neural plasticity to schizophrenia. Can J Psychiatry 58, 86–92. doi:10.1177/070674371305800205

Volakakis, N., Kadkhodaei, B., Joodmardi, E., Wallis, K., Panman, L., Silvaggi, J., Spiegelman, B.M., Perlmann, T., 2010. NR4A orphan nuclear receptors as mediators of CREB-dependent neuroprotection. Proc Natl Acad Sci U S A 107, 12317–12322. doi:10.1073/pnas.1007088107

Waiblinger, C., Brugger, D., Schwarz, C., 2015. Vibrotactile discrimination in the rat whisker system is based on neuronal coding of instantaneous kinematic cues. Cereb Cortex 25, 1093–1106. doi:10.1093/cercor/bht305

Waite, P.M., Cragg, B.G., 1982. The peripheral and central changes resulting from cutting or crushing the afferent nerve supply to the whiskers. Proc R Soc Lond, B, Biol Sci 214, 191–211.

Wallace, H., Fox, K., 1999. The effect of vibrissa deprivation pattern on the form of plasticity induced in rat barrel cortex. Somatosens Mot Res 16, 122–138.

Wang, H., Zhang, Z., 2008. A critical window for experience-dependent plasticity at whisker sensory relay synapse in the thalamus. J Neurosci 28, 13621–13628. doi:10.1523/JNEUROSCI.4785-08.2008

Welker, E., Rao, S.B., Dörfl, J., Melzer, P., van der Loos, H., 1992. Plasticity in the barrel cortex of the adult mouse: effects of chronic stimulation upon deoxyglucose uptake in the behaving animal. J Neurosci 12, 153–170.

Welker, E., Soriano, E., Dörfl, J., Van der Loos, H., 1989. Plasticity in the barrel cortex of the adult mouse: transient increase of GAD-immunoreactivity following sensory stimulation. Exp Brain Res 78, 659–664.

Whiteus, C., Freitas, C., Grutzendler, J., 2014. Perturbed neural activity disrupts cerebral angiogenesis during a postnatal critical period. Nature 505, 407–411. doi:10.1038/nature12821

Wu, J., Bohanan, C.S., Neumann, J.C., Lingrel, J.B., 2008. KLF2 transcription factor modulates blood vessel maturation through smooth muscle cell migration. J Biol Chem 283, 3942–3950. doi:10.1074/jbc.M707882200

Zeisel, A., Muñoz-Manchado, A.B., Codeluppi, S., Lönnerberg, P., La Manno, G., Juréus, A., Marques, S., Munguba, H., He, L., Betsholtz, C., Rolny, C., Castelo-Branco, G., Hjerling-Leffler, J., Linnarsson, S., 2015. Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science 347, 1138–1142. doi:10.1126/science.aaa1934

Zembrzycki, A., Chou, S.-J., Ashery-Padan, R., Stoykova, A., O'Leary, D.D.M., 2013. Sensory cortex limits cortical maps and drives top-down plasticity in thalamocortical circuits. Nat Neurosci 16, 1060–1067. doi:10.1038/nn.3454

Zeng, H., Qin, L., Zhao, D., Tan, X., Manseau, E.J., Van Hoang, M., Senger, D.R., Brown, L.F., Nagy, J.A., Dvorak, H.F., 2006. Orphan nuclear receptor TR3/Nur77 regulates VEGF-A-induced angiogenesis through its transcriptional activity. J Exp Med 203, 719–729. doi:10.1084/jem.20051523

Zhan, Y., Kim, S., Yasumoto, H., Namba, M., Miyazaki, H., Iwao, H., 2002. Effects of dominant-negative c-Jun on platelet-derived growth factor-induced vascular smooth muscle cell proliferation. Arterioscler Thromb Vasc Biol 22, 82–88.

Zhang, G., Dass, C.R., Sumithran, E., Di Girolamo, N., Sun, L.-Q., Khachigian, L.M., 2004. Effect of deoxyribozymes targeting c-Jun on solid tumor growth and angiogenesis in rodents. J Natl Cancer Inst 96, 683–696.

Zhang, Y., Chen, G., Gao, B., Li, Y., Liang, S., Wang, X., Wang, X., Zhu, B., 2016. NR4A1 knockdown suppresses seizure activity by regulating surface expression of NR2B. Sci Rep 6, 37713. doi:10.1038/srep37713

Zhao, D., Qin, L., Bourbon, P.-M., James, L., Dvorak, H.F., Zeng, H., 2011. Orphan nuclear transcription factor TR3/Nur77 regulates microvessel permeability by targeting endothelial nitric oxide synthase and destabilizing endothelial junctions. Proc Natl Acad Sci U S A 108, 12066–12071. doi:10.1073/pnas.1018438108

Zheng, W., Christensen, L.P., Tomanek, R.J., 2008. Differential effects of cyclic and static stretch on coronary microvascular endothelial cell receptors and vasculogenic/angiogenic responses. Am J Physiol Heart Circ Physiol 295, H794-800. doi:10.1152/ajpheart.00343.2008

Supplemental material

Supplemental Table 1

Differentially expressed genes of GO terms shown in Figure 3 (data is from Vallès et al., 2011).

Supplemental Table 2

Functional clusters of Gene Ontology (GO) terms for the differentially expressed genes in the Vallès et al. (2011) dataset. Only clusters with an FDR of <0.05 and an enrichment score of >1.3 are included. The most significant term (with the lowest FDR) within each cluster is displayed.

Supplemental Table 3

Cellular Enrichment Indices (CEIs) of differentially expressed genes upon EEE. See Figure 4 for the details of the bioinformatics pathway.

Supplemental Table 4

List of differentially expressed transcripts within the GO term 'Vasculature Development' (see Supplemental Table 2). In bold are the transcripts that are most strongly regulated upon EEE and remain differentially transcribed for at least 4 hours (cutoff 10%). Transcripts in italics are those involved in PDGF-B signaling.