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Review

# Biological pathways to adaptability – interactions between genome, epigenome, nervous system and environment for adaptive behavior

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**Because living systems depend on their environment, the evolution of environmental adaptability is inseparable from the evolution of life itself (Pross 2003). In animals and humans, environmental adaptability extends further to adaptive behavior. It has recently emerged that individual adaptability depends on the interaction of adaptation mechanisms at diverse functional levels. This interaction enables the integration of genetic, epigenetic and environmental factors for coordinated regulation of adaptations. In this review, we first present the basis for the regulation of adaptation mechanisms across functional levels. We then focus on neuronal activity-regulated adaptation mechanisms that involve the regulation of genes, noncoding DNA (ncDNA), ncRNAs and proteins to change the structural and functional properties of neurons. Finally, we discuss a selection of these important neuronal activity-regulated molecules and their effects on brain structure and function and on behavior. Most of the evidence so far is based on sampling of animal tissue or post-mortem studies in humans. However, we also present techniques that combine genetic with behavioral and neurophysiological measures in humans (e.g. genetic imaging) and discuss their potential and limitations. We argue that we need to understand how neuronal activity-dependent adaptation mechanisms integrate genetic, epigenetic and experience-dependent signals in order to explain individual variations in behavior and cognitive performance.**

Keywords: Adaptability, cognition, imaging, immediate early genes, neuron, plasticity, regulation, transcription factors

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## On the origin of adaptability

The evolution of adaptability was central for the evolution of life (Pross 2003) because living systems depend on the environment to maintain their thermodynamic nonequilibrium state. Adaptability is in itself a highly dynamic process and incompatible with stable systems in a state of thermodynamic equilibrium. Adaptability requires self-regulated variation that relies on mechanisms for active change. Which mechanisms can generate such self-regulated variation? Errors during self-replication (Table 1) can produce exponential diversity as long as the net effect of replication is positive (Lifson 1987). Such an imperfect self-replication mechanism has been proposed to be at the origin of diversification and selection of systems with teleonomic properties (Lifson 1987). Because imperfect self-replication creates self-variation, adaptability and individuality seem to owe their origin to this mechanism. Self-replication forms less stable products (higher organized molecules) from more stable chemical precursors (lower organized molecules). This is a thermodynamically unfavorable reaction that is counterbalanced through its coupling with a dissipative reaction by exploiting some environmental source of energy (Pross 2003).

Increasing structural and functional complexity of living systems enhances their capability to replicate through a variety of catalytic effects and increases the energy demand (Pross 2003). Increasing complexity also increases the number of errors during self-replication leading to increased variability. The positive selection of changes that improve the energy gathering reaction thus enables the further increase of complexity, replication capability (or reproduction ability) as well as the variability during imperfect self-replication. This circularity implies the coevolution of imperfect self-replication, energy gathering reaction and structural/functional complexity. For these reasons imperfect self-replication is a diversification mechanism for natural selection that can explain the importance of the dynamic interaction between living systems and their environment in the evolution of complexity and metabolism (Lifson 1987; Pross 2003).

The evolution of multicellular complexity has been supported by the superior energy yield of aerobic metabolism that evolved with the development of an oxygenic environment (Koch & Britton 2008). This switch to the more efficient aerobic metabolism in multicellular systems demonstrates how tightly the changes of living systems and environment are connected. Supported by improved energy supply, more

**Table 1:** Glossary of key terms

**Chromatin remodeling:** Changes in the interaction between DNA and histones by chromatin remodeling proteins, for example, by histone modification enzymes and multiprotein chromatin remodeling complexes.
**Cis-acting element:** (e.g. CRE-element) The target sequence of the regulated sequence/molecule (e.g. BDNF gene promoter) to which the regulator binds with its trans-acting element/sequence (e.g. CREB).
**Complexity:** Depends on the number and individual functions/structures of all units and their interactions. Biological complexity – structural, organizational and informational complexity, for example, genes that control each other and form networks → emergence of new properties.
**Dissipative reaction:** The released free energy, when reactants change from a higher to lower energy state, can be used for the replication reaction, such reactions toward the equilibrium are thermodynamically preferred. The availability of reactants for the dissipative reaction from the environment limits the self-replication.
**Editing of DNA:** Deamination of cytidine by AID or APOBECS results in uridine thus transforming C-G base pairs into U-G/T-G mispairs. In this way deamination can mediate DNA sequence changes if not detected and correctly repaired by DNA excision repair or mismatch repair pathways.
**Editing of RNA:** Changes the nucleotide sequence of an RNA after its transcription but before its processing, there are various types of editing, for example, nucleotide substitutions (common are adenosine-to-inosine (decoded as guanosine) and cytidine to uridine (decoded as thymidine)), editing targets are coding (e.g. pre-mRNA) as well as various noncoding sequences (e.g. t-RNAs, pre-miRNA, UTR, transposon-driven RNA), RNA editing creates transcript diversity, likely counteracts RNA interference pathways and may contribute to heterochromatic silencing. AID, APOBECS, ADARs (adenosine deaminases acting on RNA) and ATARs (adenosine deaminases acting on tRNA) are capable of RNA editing.
**EVH1 domain:** Binds proline-rich sequences acting as molecular adaptor.
**Neuroplasticity:** The adaptability of neurons in response to signals for which they are receptive. Neuronal adaptations range from instant to long-lasting and from molecular to morphological/structural changes.
**Noncoding RNA (ncRNA):** RNA transcribed from DNA that does not encode amino acid sequences and instead serves as diverse types of RNA a variety of functions, for example, micro RNA.
**Positive rate of net replication:** The number of replicating elements that are produced exceeds the number of those that are decomposed.
**Proteome:** The total of proteins expressed.
**Selection:** Persistence or survival of a specific functional or structural property (phenotype, e.g. affinity of an enzyme to its substrate) or an entire living system (individual, specie or group of species) within its specific functional environment, the functional environment comprises interactions within one functional level, e.g. molecular interactions and interactions across functional levels, e.g. interactions between molecular, cellular, and systemic levels.
**Self-replication:** Autocatalytic process whereby the self-replicating element accelerates its own reproduction, this process exhibits enormous kinetic power (exponential growth), if the self-replication is imperfect the newly produced self-replicating element is a modified copy → mechanism for self-variation, the energy and material to produce more of the self-replicating element is supplied by reactants that leave the reaction as thermodynamically more stable waste → dissipative reaction (toward the state of equilibrium), thus the replication reaction (away from the thermodynamic equilibrium) becomes possible and continues as long as enough reactants are available.
**Sumoylation:** Post-translational covalent binding of small ubiquitin-like modifier proteins (SUMO) directed by an enzymatic cascade, many functions including transcriptional regulation and regulation of nucleocytoplasmic transport (e.g. by sumolyation of GTPase-activating proteins).
**Teleonomic:** Character of life is manifest in its purposeful organization and behavior, for example, the replicating molecule has a structure that enables replication (Lifson 1987; Pross 2003).
**Ternary factors:** Form three-molecule complexes.
**Transcriptome:** The total of DNA transcribed into RNAs.
**Translatome:** The total of mRNAs translated into amino acid sequences.

complex organisms with diverse functional levels evolved and were capable of intra- and trans-generational adaptability via multiple self-variation mechanisms at each functional level.

There is a difference between the ability to adapt and being well adapted. Complex organisms possess more and more complex regulatory mechanisms and thus increased adaptability. For example the nervous (NS), immune, endocrine or cardio-vascular systems all possess adaptive mechanisms. Furthermore adaptations occur at multiple functional levels (molecular, cellular, systemic and behavioral). A single cell organism possesses none of these complex regulatory systems and only a reduced number of functional levels. However, this reduced adaptive capacity or potential for adaptation does not imply that less complex systems are less adapted than more complex systems. The range of possible variations supported by adaptation mechanisms (adaptive potential) mirrors the range of condition changes possibly encountered by the system's adaptation mechanisms. In short, adaptability aims at maintaining functionality of the system and its replication or reproduction by generating self-variation and by the regulation of this self-variation according to external and internal influences.

Intra-generational adaptability is the ability of one individual to adapt (e.g. regulation of gene expression, cellular/systemic structure/function and behavior).

Trans-generational adaptability is the ability of individuals to adapt across generations/self-replications by genetic, epigenetic, behavioral and cultural mechanisms. Self-variation mechanisms range from imperfect self-replication (e.g. recombination, mutation or copy errors in DNA transmitted through replication) to changes of the epigenome, protein expression, morphology, physiology and behavior.

With increasing complexity and in particular with the increasing number of functional levels the need for the coordinated regulation of adaptations increased as well, leading to the evolution of adaptation systems that include regulatory noncoding (nc) DNA sequences, epigenetic mechanisms, intra- and extra-cellular signaling and nervous systems (NSs). The coordinated regulation of adaptations at these different functional levels depends on the interactions between self-variation mechanisms that are responsive to internally or environmentally driven changes. Increased demand of energy during replication is an example of internal change, whereas increased competition for energy or space are examples of environmentally driven change. The response of self-variation (adaptation) mechanisms converts the change of an internal or external condition into a signal and entails modifications to maintain functionality (achieve a specific goal) under changing conditions. How adaptation mechanisms interact across functional levels to regulate adaptations and thus control the adaptability of an individual during its own lifetime and also across generations is a core question of contemporary research.

## Nervous systems – self-variation systems for the interaction with the environment

The complexity of NSs correlates with the environmental complexity and diversity to which species are adapted (Emes *et al*. 2008; Shumway 2008; Silk 2007). NSs enable the temporal and spatial regulation of the interaction between individual and environment by coupling adaptation mechanisms at the organism's molecular, cellular, neural network and behavioral levels. The regulation and variation mechanisms at those different functional levels as well as their interactions increase the adaptability of an individual. Gaining insight into these adaptation mechanisms and their interaction at the functional levels involved will help to unravel how interactions between heritable and environment-dependent differences between individuals lead to interindividual differences in behavior.

## Genetic and epigenetic adaptability

Variations of the genome or epigenome can only affect phenotypic variation if they modify the genome's output by changing the transcriptome and/or translatome. Such changes in gene expression can be initiated by variation of the genome via change of DNA sequence including single nucleotide polymorphisms (SNPs), structural variation ranging from a few base pairs to whole genome sequence rearrangement, deletion, insertion and repetition, DNA recoding by DNA repair/editing enzymes, as well as by variation of the epigenome via changes of DNA configuration including chromatin remodeling, DNA-methylation, histone modifications or genome output regulators including noncoding RNAs, transcription factors, hormones or enzymes. All these different modes of change can interact with each other (Ooi & Wood 2008). Factors that regulate the genome's output through these variation mechanisms can influence the timing and location of genetic and epigenetic changes and thus allow phenotypic adaptation in response to the specific selective pressure (Rando & Verstrepen 2007). In the following sections we will present evidence for the regulation of epigenetic and genetic adaptations in response to internally and environmentally driven signals. This evidence, some of which is still preliminary, supports the view that genetic and epigenetic changes are not purely random.

### *Epigenetic adaptation mechanisms*

Epigenetics refers to anything exclusive of DNA sequence that could be passed on from mother to daughter cells during meiosis and/or mitosis (Jaenisch & Bird 2003). Such potentially heritable items include molecules [e.g. RNAs (Brennecke *et al*. 2008), proteins (Marmorstein 2001)] and subcellular structures (e.g. mitochondria) (Wallace & Fan 2010) as well as the dynamic spatial configuration of DNA (the configuration of nucleotides, histones, nonhistone-chromatin proteins and chromatin) (Gibney & Nolan 2010). Cells with the same gene sequence can thus have different epigenomes, which are more plastic and dynamic than genomes. The mechanisms involved in the mitotic and meiotic heritability of epigenomes are not well understood. Besides the role of epigenetic mechanisms in trans-generational adaptability epigenetic mechanisms also confer intragenerational adaptability (Whitelaw & Whitelaw 2006). The time, location and stability of epigenetic changes depends on the integration of multiple internal (e.g. genome, developmental state) and environmental (stress, toxins, social interactions) signals across the lifetime. Epigenetic changes are based on the switching of alternative functional or structural states (see examples below) and result in the adaptation of cellular expression patterns during proliferation, differentiation or plastic changes in the adult organism (Borrelli *et al*. 2008).

Epigenetic changes include the methylation/demethylation of cytosine (Wu & Zhang, 2010), modifications of histones (Barth & Imhof 2010) and chromatin structure (nucleosome structure and composition) (Li & Reinberg 2011) as well as various RNA-based mechanisms (e.g. regulation of monoallelic expression of imprinted genes (Royo & Cavaille 2008), X-chromosome inactivation (Chow & Heard 2009), inhibition of translation and transcriptional gene silencing (Collins & Penny 2009)). As we will explain below these epigenetic mechanisms are a toolbox for integrating internal and environmental signals that are important for the regulation of expression, processing, localization and degradation of transcripts and proteins.

Epigenetic adaptations regulate the genome's output and depend on the interactive effects of internally and environmentally driven signals. Internal signals are conditioned by the cellular genome (Surani *et al*. 2007), lineage (Hemberger *et al*. 2009), development (Hirabayashi & Gotoh 2010) and

aging (Fraga *et al*. 2005; Jaenisch & Bird 2003). Environmental signals are conditioned by various types of experiences encountered by an individual cell, cellular system or organism, for example, nutrients (Kaati *et al*. 2007), pathogens (De Santa *et al*. 2007), stress (Murgatroyd *et al*. 2009), social interactions (Fish *et al*. 2004; McGowan *et al*. 2009) and learning (Alarcon *et al*. 2004).

Various epigenetic adaptation mechanisms like chromatin remodeling (Schaefer *et al*. 2009), histone modifications (Alarcon *et al*. 2004; Bredy *et al*. 2007; Chwang *et al*. 2006), DNA-de-/methylation (Feng *et al*. 2010; Levenson *et al*. 2006; Miller & Sweatt 2007) and microRNA-based mechanisms (Krol *et al*. 2010; Rajasethupathy *et al*. 2009; Schratt *et al*. 2006) are involved in the temporal, spatial, qualitative and quantitative regulation of transcripts and proteins in response to neuronal activity. These mechanisms support the functional and structural adaptation of neurons needed to adapt neural networks activated during learning, memory, sensory and emotional experiences. Specific interactions between histone deacetylases (HDACs), neurotrophic factors and $Ca^{2+}$-dependent signaling proteins [e.g. TrkB, mitogen-activated protein kinase (MAPK) and $Ca^{2+}$/calmodulin-dependent kinases (CaMKs)] and neuronal activity-dependent transcription factors, such as myocyte enhancer factor 2 (MEF2), mediate neuroplasticity via epigenetic regulation (e.g. changes in chromatin structure and transcription of regulatory micro RNAs) (Fiore *et al*. 2009; Potthoff & Olson 2007).

In some cases it has been possible to unravel the entire cascade from environmental influences to behavioral adaptation, for example through linking changes in histone acetylation, hippocampal synaptic plasticity and spatial memory performance (Fischer *et al*. 2007). Furthermore pharmacological manipulations of histone acetylation and DNA-methylation have been used to regulate formation of long-term memory and fear conditioning responses (Levenson *et al*. 2006; Lubin *et al*. 2008; Sweatt 2009). Another example is the link between maternal care and estrogen receptor function. Methylation of estrogen receptor $\alpha$ promoter sites, transcriptional activity as well as brain region-specific expression of estrogen receptor $\alpha$ gene, estrogen sensitivity and maternal care behavior in adulthood have all been associated with the level of self-experienced maternal care during infancy (Champagne 2008). Another example is the activity-dependent regulation of growth factors in the adult hippocampus. Neuronal activity-dependent initialization of DNA excision repair-based demethylation of the brain-derived neurotrophic factor (BDNF)-IX and FGF1B promoters by 5-methylcytosine hydroxylase (TET1) and apolipoprotein B mRNA-editing enzyme complex 1 (APOBEC1) has been demonstrated in dentate gyrus neurons (Guo *et al*. 2011). Demethylation of these two promoters correlated with increased levels of the respective mRNAs. These examples illustrate how diverse epigenetic mechanisms can integrate genetic and environmental signals to adapt the genome output and hence contribute to individual adaptation at the molecular, neuronal, neural systems and behavioral level. In this way epigenetic adaptability can generate individually adapted phenotypes (e.g. cognitive and emotional behaviors) from a single genotype (Johnson & Tricker 2010).

Epigenetic variations are nonrandomly distributed within and between genomes (Bock *et al*. 2008). It has been suggested that epigenetic variations might precede genetic variations to facilitate the adaptation and evolution of phenotypes in response to selective pressures (Johnson & Tricker 2010). Moreover the regulating function of the epigenome may be particularly suited to facilitate the evolution of complex phenotypes (Johnson & Tricker 2010). However, the transgenerational inheritance of specific epigenetic adaptations in mammals remains an open question and may depend on the type of epigenetic adaptation. Genome-wide DNA-methylation for example has been shown to be reduced to as little as 10% in primordial germ cells of mice (Popp *et al*. 2010). Such elimination of the majority of previous DNA methylation might re-establish pluripotency.

### *Genetic adaptation mechanisms*

The nonrandom distribution of SNPs in the genome suggests selection differences between regions, which may result from differences in selective pressures between phenotypes (Rando & Verstrepen 2007). Phenotypes under high selective pressure seem to be more variable than phenotypes under no or low selective pressure. Recent observations point to a correlation between genetic variation mechanisms, phenotypic variability and the variability of the acting selective pressures (Rando & Verstrepen 2007). For example DNA sequences that control the expression of cell-surface antigens in pathogenic micro-organisms are hypervariable, and hypermutation of immunoglobulin genes increases the diversity of an immune cell's antigen-binding regions (Rando & Verstrepen 2007). Another example is the observation that a genetic change responsible for the adaptation of camouflage in mice coincided with the color change of the mice's habitat (Linnen *et al*. 2009). This suggests the existence of genetic adaptation mechanisms to generate phenotypic variation in response to environmental change. Certain mutations show a higher frequency under positive selection as long as the selective pressure is nonlethal (Shapiro 1995; Wood *et al*. 2009). The spectrum of sequence changes differs during unselected and selected exponential growth in bacteria (Rosenberg *et al*. 1994). For example, amino acid-specific starvation of *E. coli* was associated with transcriptional activation and increased mutation rates of the genes involved in the synthesis of this amino acid (Wright *et al*. 1999). Such increased fitness-affecting variability may support survival (Perfeito *et al*. 2007). The SOS signaling pathway inhibits cell division and activates DNA mutation, recombination and repair-related genes in starving cells (McKenzie *et al*. 2000). In addition, homologous recombination and plasmid gene transfer have been shown to induce genetic changes to adapt metabolic functions in response to the change of metabolic substrates in bacteria (Foster & Trimarchi 1995; Radicella *et al*. 1995). Hence cells are equipped with mechanisms to change their DNA in response to selective pressures on phenotypes like metabolism (Shapiro 1995).

#### *The role of transposons*

A significant part (>40%) of human DNA (Lander *et al*. 2001) consists of the small, repetitive, mobile DNA control

elements (transposons) that were discovered by McClintock (1951). Most of these transposons are retrotransposons (Lander *et al*. 2001) that if transcribed and translated catalyze target-primed reverse transcription. This copy–modify–paste mechanism allows to copy and potentially modify a DNA segment via an RNA-intermediate (involving formation of an RNA–protein complex) that is transcribed into DNA before being pasted into a new position in the genome (Ostertag & Kazazian 2001).

Those retrotransposons that encode all essential proteins required for retrotransposition are called autonomous (Kazazian 2004). Only about 80–100 of such retrotransposons that belong to the LINE-1 (long interspersed nuclear elements) family are estimated to still be functional in any human genome today and transpositions occur at very low frequencies (Babushok & Kazazian 2007; Ostertag & Kazazian 2001). The remaining transposons (including retro- and DNA transposons) are considered to be genetic 'fossils' that have lost their functionality in the course of evolution (Ostertag & Kazazian 2001). If activated, LINE-1 elements catalyze modifications ranging from small DNA sequence changes to large genomic rearrangements that could contribute to phenotypic diversity including individual variability in susceptibility to complex diseases (Muotri *et al*. 2009; Ostertag & Kazazian 2001).

Retrotransposons do not only catalyze retrotransposition of the transcripts that encoded them but at lower frequency move several kilo bases of DNA sequence into other positions by extending transcription of their own sequences into adjacent sequences (Goodier *et al*. 2000; Moran *et al*. 1999; Ostertag & Kazazian 2001). Although some of the LINE-1 proteins (RNA-binding protein, and protein with endonuclease and reverse transcriptase activity) are more efficient in catalyzing retrotransposition of mRNA that encoded them in the first place, they sometimes target other coding and noncoding RNAs as template for reverse transcription (Kazazian & Goodier 2002). In this way, coding (Esnault *et al*. 2000) as well as noncoding transcripts, including Alu elements (short interspersed elements) (Dewannieux *et al*. 2003), SVA elements (SINE-VNTR-Alu) (Ostertag *et al*. 2003) and uracil-rich small RNAs (snRNAs) (Buzdin *et al*. 2002; Garcia-Perez *et al*. 2007) that may or may not include LINE-1 sequence, can be reversely transcribed. So called pseudogenes result from retrotransposition of RNAs that lag retrotranscript sequence (Esnault *et al*. 2000). Combinations of retrotranscript and nonretrotransposon sequence are referred to as chimeric (retro)transcripts (Buzdin *et al*. 2002). Genetic innovations have been shown to arise via such sequence recombinations, for example, construction of a new gene family (Xing *et al*. 2006). It has been estimated that at least 35% of human genome sequence has been generated by these LINE-1-dependent mechanisms (Lander *et al*. 2001). *De novo* LINE-1 retrotransposition predominantly occurs in somatic cells (Kano *et al*. 2009), suggesting that it contributes to intraindividual adaptability and interindividual variability. Although LINE-1 RNA is transmitted from one generation of germ cells to the next the genome of these cells is rarely affected by LINE-1 retrotransposition events (Kano *et al*. 2009). Instead LINE-1 reintegration into the genome follows fertilization enabling mosaicism in somatic and germ line tissues (Kano *et al*. 2009). In this way, LINE-1 retrotransposition can generate differences between the genomes of individual cells that originated from a single zygote (with a single genome). However, persistence of LINE-1 RNA has been observed in embryonic cells after embryo implantation and at low level in adult tissues. Retrotransposon-mediated polymorphisms thus represent a substantial source for intra- and interindividual genomic variability (Ewing & Kazazian 2010).

Independent of retrotransposition effects on gene function or expression, LINE-1 promoter-driven transcription has been shown to alter expression of cellular genes (Speek 2001). Otherwise retrotransposons have been shown to prevent changes in DNA-methylation at gene promoters thus precluding changes in gene expression (Estecio *et al*. 2010). LINE-1 dependent modifications vary in magnitude and frequency and comprise changes in quantity, stability and composition of DNA or RNA (Cordaux & Batzer 2009).

Clusters of LINE-1 and LINE-1-mediated reintegration into the genome that have been found more often than one would expect by chance may be related to the transcriptional state of their target sites (Graham & Boissinot 2006). Chromosome 4 and the X-chromosome have a particularly high frequency of recent LINE-1 insertions. LINE-1 elements might be important for the regulation of genes with monoallelic expression, which have been located in LINE-1 element-rich regions (Allen *et al*. 2003). They may also function to increase the distance between loci in the absence of recombination, thus facilitating selection by reducing interference between genetic effects (Graham & Boissinot 2006).

Another potential role for retrotransposons is in the regulation of gene silencing. Chow *et al*. found silent LINE-1 regions to assist Xist RNA in forming a heterochromatic nuclear compartment and suggested a distinct set of transcribed LINE-1 elements to play a role in the extension of X chromosome inactivation into active regions (Chow *et al*. 2010). This study gives an example for LINE-1-assisted regulation of gene silencing in differentiating cells during embryonic development and could explain why LINE-1 density and its proximity to genes is correlated with the efficiency of gene silencing (Bailey *et al*. 2000; Chow *et al*. 2010; Lyon 1998).

Cells possess multiple mechanisms to regulate LINE-1 activity, with a trend to increase their activity in response to stressful conditions (Farkash & Luning Prak 2006). In bacteria the frequency of transpositions is regulated in response to environmental signals, which suggests an adaptive function (Hall 1999). Small interfering RNAs, another type of ncRNA, can be generated from transposons and convergent transcripts (van Rij & Berezikov 2009). These ncRNAs together with proteins contribute to the regulation of transposon mobility and gene expression in somatic and germ cells (van Rij & Berezikov 2009).

Retrotransposon transcription can be activated through the regulation of histone phosphoacetylation dependent on the MAPK signaling pathway and HDAC activation (Brunmeir *et al*. 2010). The MAPK signaling pathway is also present in neurons and one of its downstream targets is methyl CpG binding protein 2 (MeCP2), a neuronal activity-regulated transcription factor involved in DNA and chromatin modification. Neuronal activity has been shown to

activate LINE-1 retrotransposition in neuronal progenitor cells suggesting a role of these elements in experience-dependent neuroplasticity (Muotri *et al*. 2009). Recently Muotri *et al*. have shown that MeCP2 contributes to the regulation of LINE-1 activity in neurons (Muotri *et al*. 2010).

LINE-1 retrotransposons are active in humans during developmental and adult neurogenesis (Singer *et al*. 2010). Because environmental (e.g. stress) and internal (e.g. hormones) factors have been found to activate LINE-1 retrotranspositions this mechanism for the generation of genetic variations could be important for individual adaptability (Singer *et al*. 2010).

Although the understanding of the regulatory mechanisms involved in transposon-mediated variation of the genome and the transcriptome is still at its beginning the preliminary evidence available thus far supports our view of transposons as molecular adaptors involved in genetic and epigenetic adaptations that result in phenotypic variability in response to both internally and externally driven changes.

*Recoding of DNA or RNA*

Another mechanism that has been suggested to generate environmentally-driven DNA/RNA sequence variability in protein-coding and ncRNA-coding sequences of immune (Hamilton *et al*. 2010) and NS cells is the editing or recoding of DNA or RNA (Mattick & Mehler 2008).

After hydroxylation of 5-methylcytosine (5-mC) by TET1 (5-mC hydroxylase), 5-hydroxymethylcytosine (5hmC) is converted to 5-hydroxymethyluracil (5hmU) by APOBEC1 (apolipoprotein B mRNA-editing enzyme complex 1) cytidine deaminase (Guo *et al*. 2011). In the final step 5hmU is exchanged with unmethylated cytosine by 5hmU glycosylase-mediated base excision repair. Recent studies suggest that this DNA demethylation mechanism is regulated by neuronal activity and involved in the transcriptional regulation of plasticity-related genes in adult neurons (Guo *et al*. 2011; Ma *et al*. 2009). Absent or incorrect base excision repair would leave base mispairs and thus lead to deamination-induced genetic mutations instead of epigenetic changes. These and similar DNA editing mechanisms mediated by cytidine deaminases thus either modify only the DNA methylation pattern (if correctly repaired) or additionally change the DNA sequence (Morgan *et al*. 2004). Such modifications are known to be important for epigenetic remodeling, regulation of transposon activity, and immune functions (Chahwan *et al*. 2010; Di Noia & Neuberger 2007; Hamilton *et al*. 2010; Muckenfuss *et al*. 2006). Dysregulated or malfunctioning DNA editing has devastating effects including neoplasms, immunodeficiency and neurodegeneration (Pham *et al*. 2005; Smith 2011; Weissman *et al*. 2007). Genes encoding DNA/RNA editing enzymes accordingly show signs of strong positive selection in the human genome (Mattick & Mehler 2008). RNA editing is most active in the brain, and humans show a twofold increase of editing compared to mice (Mattick & Mehler 2008). In a genome-wide analysis of RNA editing sites high levels of editing within coding sequences were identified for metabotropic glutamate and GABA receptor genes in human frontal cortex (Li *et al*. 2009). However identified editing sites of genes related to neuroplasticity, for example, VAMP4, CaMKI and HTR2C were also located within noncoding RNA sequence. This finding points to the importance of noncoding sequences as targets for RNA-editing in neuroplasticity-related genes. For example, RNA editing at five sites generates numerous isoforms of the 5-$HT_{2C}$ receptor, which vary in serotonin binding affinity and efficiency of receptor-G-protein interaction (Nishikura 2010). The glutamatergic AMPA receptor is also affected by RNA editing. Calcium permeability of neuronal AMPA receptors differs according to GluR2 subunit pre-mRNA editing at the Q/R site by the adenosine deaminase acting on RNA 2 (ADAR2) (Geiger *et al*. 1995; Peng *et al*. 2006). Such RNA editing-dependent adaptations of receptor properties appear to be particularly relevant during brain development (Lomeli *et al*. 1994; Wahlstedt *et al*. 2009). Expression of ADAR2 is regulated by cAMP response element binding protein (CREB) (Peng *et al*. 2006), a synaptic activity-regulated transcription factor (Benito & Barco 2010). Moreover ADAR1-mediated RNA editing has been shown to regulate the activity of the glycosylase NEIL1 involved in DNA base excision repair (Yeo *et al*. 2010), with both enzymes apparently also active in human brain (Simmons *et al*. 2010). RNA editing could thus be an important molecular mechanism for the regulation of neural development and plasticity, for example, by modifying sequences and biophysical properties of glutamate receptor subunits to modulate synaptic strength and neural network connectivity (Mattick & Mehler 2008). Through their connection with intracellular signaling pathways, the activity of RNA editing enzymes appears to be influenced by environmental experience and behavior. This has led to the speculation that the coordinated coupling of RNA and DNA editing among synapses, neurons and neural networks through signaling would allow the genetic encoding of environmentally-driven changes in neural structure and function during brain development and cognitive plasticity (Mattick & Mehler 2008).

In summary genetic and epigenetic adaptation mechanisms are extraordinarily versatile and are regulated in response to internal and environmental signals. If genetic changes can be regulated, that is, induced or suppressed in response to the presence or absence of selective pressures, they belong into the 'toolbox' of complex individual adaptability.

## Interaction of adaptation mechanisms across functional levels

Sensory, cognitive, emotional, social or motor experiences or behaviors that modulate the activity of specific neural networks can drive activity-dependent changes at the molecular, synaptic and cellular level (Fig. 1). Such reorganization processes are presumably required for the updating of past with new experiences, increasing processing efficiency and capacity for learning and memory (Dudai 2004; Miyashita *et al*. 2008). The ongoing adaptation process within individual neurons as well as neural networks depends on the interaction between adaptation mechanisms at the molecular, cellular, network and behavioral level for the dynamic integration of signals driven by internal and/or environmental changes. How this interaction is coordinated at the molecular,

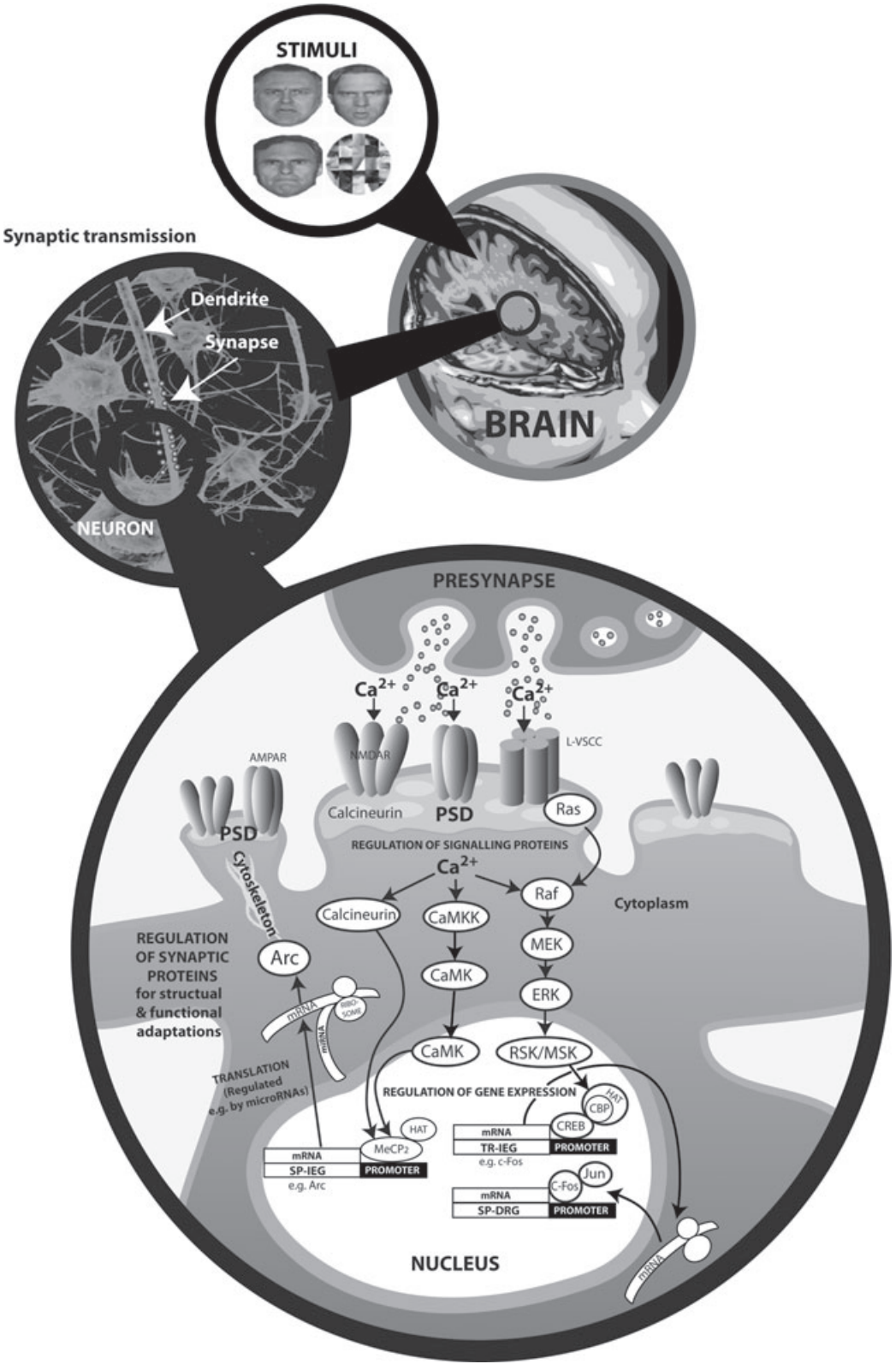


**Figure 1: Legend on next page.**

cellular network and behavioral level to enable learning and memory processes is far from being understood (Citri & Malenka 2008).

The regulation of the transcriptome, translatome and proteome contribute significantly to neuroplasticity. Collectively the various cell types of the NS express 80% of the coding genome, exceeding the gene expression of any other organ (Ooi & Wood 2008). The transcription-dependent neuroplasticity that occurs during learning and memory formation is regulated by RNAs and proteins involved in neuronal activity-dependent intracellular and intra-nuclear signaling and neuronal activity-dependent epigenetic mechanisms (Flavell & Greenberg 2008). Adaptation mechanisms involved in learning and memory like synaptic strength (Barco *et al*. 2002; Plath *et al*. 2006) and dendritic growth (Wayman *et al*. 2006; Yuste & Bonhoeffer 2004; Zhou *et al*. 2006) have been shown to depend on the coordinated expression of multiple genes in response to neuronal activity. Neuroplasticity that depends on DNA expression requires more time, energy and regulation but increases adaptability compared with neuroplasticity restricted to post-transcriptional or post-translational regulation.

Rapidly induced post-translational modification and trafficking of pre-existing proteins and other functional molecules appear to be important for regulation and maintenance of molecular functions. Neuronal adaptation by regulation of pre-existing mRNA is limited to the type and quantity of available mRNAs. Fonseca *et al*. have suggested that the strength of neuronal activity determines the dependency of long-term potentiation (LTP) on protein synthesis (Fonseca *et al*. 2006). The neuronal activity-dependent regulation of translation in dendrites is important for the rapid enhancement of neurotransmission (Kang & Schuman 1996), late-phase LTP (Bradshaw *et al*. 2003; Kelleher *et al*. 2004), LTD (Huber *et al*. 2000) and morphological changes of synapses (Bailey & Chen 1983; Vanderklish & Edelman 2002). Protein synthesis-dependence appears to be limited to the time needed to synthesize the proteins and establish synaptic changes (Sutton & Schuman 2006). Whether and for how long these changes persist depends on interactions at the molecular, cellular and systems-levels (Sutton & Schuman 2006).

The regulation of these molecular plasticity mechanisms in neurons is coordinated by intracellular signaling systems and depends on neuronal activity. Intracellular signaling systems can amplify signals to operate as a biochemical switch from low to maximal activation, realize time and location-dependent integration of diverse extracellular signals, induce transient or long-lasting activation of effector molecules and respond to positive or negative feedback mechanisms (Adams & Sweatt 2002). Thus, intracellular signaling systems can coordinate the type and duration of adaptations at the molecular, synaptic and neuronal level with high input-specificity.

## Functional and structural adaptation of neurons

Developmental and activity-dependent adaptation of neuronal structure and function depends on the processing of extracellular signals (conveyed mainly by neurotransmitters, neurotrophins, hormones and cytokines) that regulate the adaptation of the neuronal protein network via intracellular signaling systems. The coordination of specific signaling pathways mediates input-specific modifications. Intracellular signaling can have local effects on the function of pre-existing synaptic molecules (e.g. mRNA, proteins) or, if converted into an intranuclear signal, on gene expression. The conversion of an extracellular signal (first messenger) into an intracellular signal (second messenger) depends on the signal and receptor properties. Receptors coupled to intracellular second messenger systems can regulate the activity of enzymes (e.g. protein kinases/phosphatases, phospholipases), which regulate target proteins (e.g. structural proteins, signaling enzymes, ion channels/pumps and transcription factors/cofactors). For example the $Ca^{2+}$-second messenger system involves $Ca^{2+}$-binding proteins (e.g. phospholipase C and $A_2$, protein kinase A/C, calmodulin, calcineurin). These proteins can regulate $Ca^{2+}$-dependent signaling enzymes, for example, CaMKs that can recruit transcription factors and cofactors to the promoters of neuronal activity-dependent genes (Greer & Greenberg 2008; West *et al*. 2001).

### *Transcription factor regulation of immediate and delayed response genes*

Transcription factors that regulate activity-dependent gene expression, like CREB, MEF2, nuclear factor of activated T cells (NFAT), MeCP2 and serum response factor (SRF), can be a part of the transcription machinery and/or involved in chromatin remodeling (Cohen & Greenberg 2008; West *et al*. 2001). Transcription factors can change the activity-dependent expression of their target genes within minutes. Such target genes include those coding for activity-induced transcription factors, like *c-Fos* and *nerve growth factor-inducible protein A* (*NGFI-A*) (Cole *et al*. 1989) and for a large range of cellular function proteins, for example,

**Figure 1: Extracellular stimuli activate intra-neuronal signaling proteins, mediated by $Ca^{2+}$.** Depending on the $Ca^{2+}$-signal, signaling proteins regulate and coordinate the adaptation of neuronal properties by changing pre-existing proteins, mRNA translation and gene expression. Changes of gene expression require the regulation of transcription factors (TR) inside the nucleus. These neuronal activity-regulated transcription factors regulate immediate early genes (IEGs) that can encode other transcription factors or synaptic proteins. microRNAs can regulate the transport and translation of mRNA for transcription factors or synaptic proteins. *De novo* synthesis of IEG transcription factors is required to regulate the gene expression of delayed response genes (DRGs) that encode synaptic proteins. These molecular adaptation mechanisms lead to structural and functional changes of neurons, thus providing the basis for neuroplasticity and short-or long-lasting functional adaptations of neuronal properties. The adaptation of neuronal properties allows the functional adaptation of neural networks to regulate adaptations of the behavioral response, for example, the memorizing of certain stimuli.

activity-regulated cytoskeleton-associated protein (*Arc*) (Link *et al*. 1995), *Homer 1a* (Brakeman *et al*. 1997) and *BDNF* (Zafra *et al*. 1990). Expression of these immediate-early genes (IEGs) is independent of *de novo* protein synthesis or transcription of other genes (Miyashita *et al*. 2008). Activity-induced IEGs that encode transcription factors in turn regulate the transcription of delayed response genes (DRGs) (Miyashita *et al*. 2008). DRGs encode proteins for long-term changes in neuronal functions, for example, neurotransmitter and hormone receptor genes. Activity-regulated genes are expressed with distinct kinetics, differences in stimulus-responsiveness, cell-type and region-specificity (Chaudhuri *et al*. 1997; Guzowski *et al*. 1999; Vazdarjanova *et al*. 2002) and this activity-dependent regulation of gene expression patterns in neural networks has been found to distinguish stages of learning and memory (Guzowski *et al*. 2001). Furthermore the combined expression of learning state-independent and learning state-dependent IEGs (Miyashita *et al*. 2008) may increase the range and thus the input-specificity of synaptic modifications. Neuronal activity-regulated proteins play central roles in the adaptation of metabolism, cytoskeleton changes, signaling pathways, neurotransmitter exocytosis, neuronal morphology and survival, number and properties of synapses and receptors. These molecular, synaptic and cellular adaptations can modify the properties of neuronal networks to facilitate behavioral adaptability.

### *Gene output regulation by noncoding RNA*

In addition to regulatory proteins, various types of noncoding RNAs (ncRNAs) regulate genes and proteins involved in neuroplasticity (Mehler & Mattick 2006). These ncRNAs contain regulatory sequences instead of protein-coding sequences and are transcribed from DNA together with protein-coding sequences, mostly UTRs and introns or independently of protein-coding sequence, for example, from intergenic regions or antisense strands. Regulatory ncRNAs dispose of cis- and/or trans-acting elements to engage in RNA–RNA, RNA–DNA and RNA–protein interactions (Mattick & Gagen 2001). In this way they can regulate chromatin remodeling, transcription, mRNA processing, translation, mRNA stability and subcellular location, protein stability, activity and secretion (Costa 2007, Mattick & Makunin 2006, Szymański *et al*. 2003). Among the numerous regulatory ncRNAs expressed in the brain recent investigations have started to unveil the functions of neuronal microRNAs (miRNAs) (Klein *et al*. 2005). Activity-regulated microRNAs are similar to IEGs in that they are expressed in response to synaptic activity. They regulate the translation of synaptic proteins involved in structural plasticity, for example dendritic growth (Vo *et al*. 2005; Wayman *et al*. 2008a). By binding to cis-acting elements in 3′UTR with varying sequence compatibility, miRNAs can regulate the transport and translatability of mRNA targets in both developing and mature neurons (Kosik 2006). Information on the functional impact of neuronal ncRNAs is still extremely limited. Nevertheless the evidence for a role of microRNAs in various forms of neuroplasticity has certainly enhanced the interest in interactions between ncRNAs and neuronal structure and function.

## Neuronal activity-regulated proteins and microRNAs involved in neuroplasticity

Signal processing at the molecular level underlies the neuronal adaptations that mediate neural network plasticity involved in learning and adaptive behavior. The following overview (Fig. 2) summarizes the molecular adaptations through which genes, proteins and ncRNAs that can be regulated by neuronal activity influence the neuron's structural and functional properties and hence behavior and neuropathology. We present in more detail five such regulatory genes, proteins and ncRNAs that are interconnected and relay adaptations between the molecular, neuronal, neural network and behavioral level. In addition we provide a table (Table 2) and four figures (Figs 3–6) to summarize this information.

### *Activity-regulated synaptic cytoskeleton protein*

Neuronal-activity dependent transient transcription and translation of the IEG *Arc/Arg3.1* (Fig. 3) has been reported for many brain regions such as hippocampus, amygdala, neocortex and striatum (Miyashita *et al*. 2008). NMDA receptor-mediated LTP can initiate the transient expression of *Arc* within 1–2 min (Guzowski *et al*. 1999). Binding of the transcription factors SRF, MEF2 and CREB to the synaptic activity-responsive element (SARE) is required and sufficient for activity-dependent *Arc* transcription (Kawashima *et al*. 2009). Newly synthesized, *Arc* mRNA is trans-located to activated excitatory post-synapses (Steward *et al*. 1998; Steward & Worley 2001) for consecutive protein synthesis (Moga *et al*. 2004). Dendritic synthesis of Arc is up-regulated by BDNF (Yin *et al*. 2002). The neuronal activity-dependent synthesis of Arc protein involves the phosphorylation of translation factor eukaryotic initiation factor 4E (eIF4E) by MAPK integrating kinase-1 (MNK1) dependent on MAPK-signaling as well as phosphorylated elongation factor 2 (eEF2) (Bramham *et al*. 2010).

Arc protein situated in the postsynaptic density (PSD) of glutamatergic neurons interacts with signaling, cytoskeleton and endocytosis proteins (Miyashita *et al*. 2008) thereby enhancing dendritic growth (Donai *et al*. 2003) and restricting AMPA receptor numbers (Chowdhury *et al*. 2006; Rial Verde *et al*. 2006; Shepherd *et al*. 2006). Intriguingly, activation of AMPA receptors has been shown to down-regulate the activity-dependent expression of *Arc* without affecting *Arc* translation or Arc protein turnover (Rao *et al*. 2006). This indicates a mutual negative feedback mechanism that may serve homeostatic regulation of both AMPA receptor-dependent and *Arc* transcription-dependent changes.

Arc protein has been associated with hippocampal late LTP and LTD-dependent memory formation (Plath *et al*. 2006). Brief activation of metabotropic glutamate receptors (mGluRs) in hippocampal neurons induces LTD associated with increased mGluR1 endocytosis and long-term increases in AMPA receptor endocytosis rate that both rely on dendritic *de novo* synthesis of Arc (Waung *et al*. 2008). Together these findings indicate the requirement of Arc synthesis for both the enhancement and the attenuation of synaptic contacts.

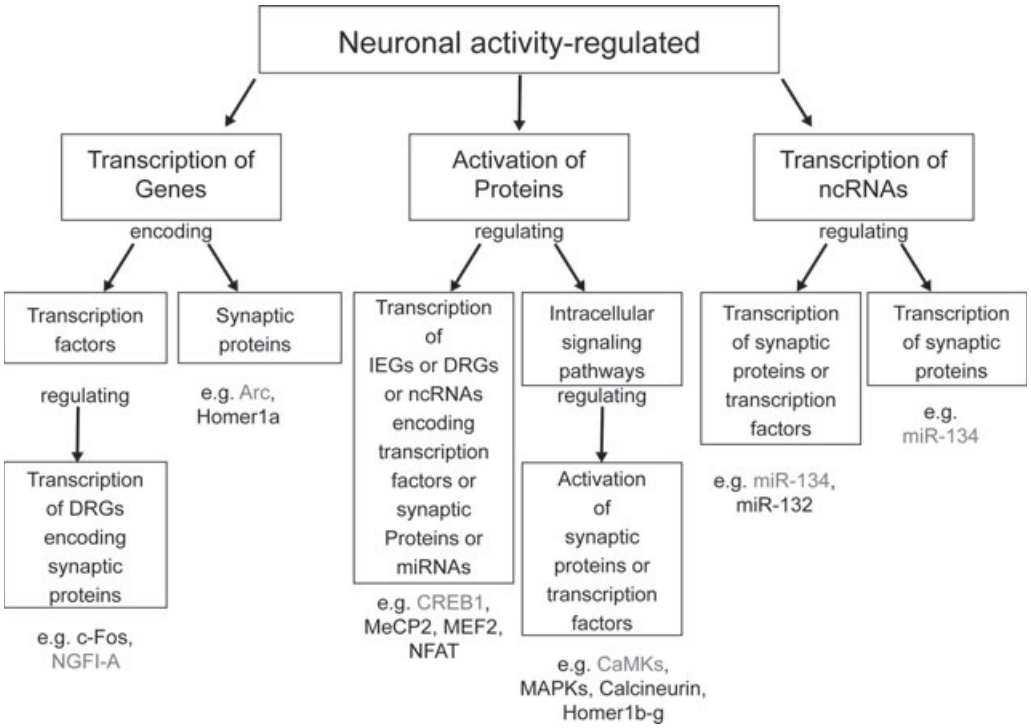


**Figure 2: Summary of the molecular mechanisms involved in the regulation of functional and structural neuroplasticity by neuronal activity-regulated genes, proteins and ncRNAs.**

The expression of *Arc* in mature neurons of primary visual cortex has been demonstrated to depend on the specific orientation of visual stimuli (Wang *et al*. 2006b), which may indicate that Arc inhibits neurons responding with low orientation selectivity to enhance orientation-selective processing (Wang *et al*. 2006b).

Temporal and spatial regulation of Arc function involves targeting of intron sequences within 3'UTR of *Arc* mRNA by eukaryotic initiation factor 4AIII (eIF4AIII), a core component of the exon junction complex during pre-mRNA splicing (Georgi *et al*. 2007). This complex mediates translation-dependent decay of *Arc* mRNA in cortical and hippocampal neurons after the first round of *Arc* mRNA translation for the precise control of Arc protein synthesis (Georgi *et al*. 2007). Arc protein degradation is enhanced by E3 ubiquitin ligase (Ube3A) (Greer *et al*. 2010). Neuronal activity-dependent transcription of Ube3A may be under the influence of MEF2 (Greer *et al*. 2010). Because Arc facilitates AMPA receptor endocytosis, Ube3A expression thus enhances AMPA receptor numbers (Greer *et al*. 2010). Subregion-specific changes of hippocampal *Arc* transcription and *Arc* promoter methylation in response to novel environment experience have been reported to be age-dependent (Penner *et al*. 2011).

In summary *Arc* transcription, mRNA localization and synthesis are regulated in response to neuronal activation changes to modulate AMPA receptor numbers, cytoskeletal dynamics involved in dendritic growth, and LTP and LTD thus contributing to sensory processing and learning.

### *cAMP response element binding protein (CREB/CREB1)*

The transcription factor CREB (Fig. 4) can bind to the cAMP response element (CRE) in promoter and enhancer sequences of DNA encoding proteins or miRNAs involved in neuroplasticity (Kim *et al*. 2010a; Montminy & Bilezikjian 1987; Sheng *et al*. 1990; Vo *et al*. 2005; Wayman *et al*. 2008a). Binding of CREB depends on chromatin conformation at CRE sites and the binding of cofactors to CRE flanking sequences (Cha-Molstad *et al*. 2004; Mayr & Montminy 2001; Mayr *et al*. 2005). CREB binding can occur with and without CREB-activation (Conkright *et al*. 2003; Mayr & Montminy 2001; Richards *et al*. 1996), can vary with neuronal activation, and contributes to the recruitment of cofactors and protein complexes required for RNA synthesis (Kim *et al*. 2010b). Activation of CREB, which can be modified at multiple sites, is regulated by $Ca^{2+}$-, cAMP- and receptor tyrosine kinase-dependent signaling pathways and involves the regulation of CREB coactivators (Johannessen *et al*. 2004; Lonze & Ginty, 2002; Meitzen *et al*. 2011). For example CREB-binding protein (CBP) exhibits intrinsic histone acetyltransferase activity (HAT) to remodel chromatin, recruit and stabilize RNA polymerase II (Flavell & Greenberg 2008). The recruitment of mitogen- and stress-activated protein kinase 1 (MSK1) to phosphorylate histone H3 at the *c-Fos* promoter for the induction of *c-Fos* transcription is CREB dependent (Shimada *et al*. 2010). CREB and CaMK activity influence the transcription of *c-Fos*, *BDNF*, *CPG15/neuritin, wnt-2* and *miR-132*, which likely mediate

**Table 2:** Activity-regulated proteins and miRNA

| **Regulator** (subcellular functions and locations can differ between protein isoforms) | **Expression in the brain** (can differ between protein isoforms) | **Neuronal adaptations, affected behaviors, neuropathologies** |
|---|---|---|
| **Arc** – activity-regulated IEG encoding synaptic cytoskeleton protein regulates synaptic proteins | hippocampus, amydala, insula, entorhinal cortex, anterior cingulate cortex (ACC), DLPFC, orbital frontal cortex, ventral tegmental area, substantia nigra, caudate, putamen, nucleus accumbens, sensory and motor cortices | – structural, functional, neuronal survival<br>– memory, learning, stress adaptation<br>– stress disorders (Kozlovsky *et al*. 2008; Molteni *et al*. 2010), depression (de Foubert *et al*. 2007), addiction (Bramham *et al*. 2010; Pandey *et al*. 2008), cognitive (Wang *et al*. 2006a) and emotional memory impairment (Eriksson *et al*. 2011) |
| **CREB1/CREB** – activity-regulated transcription factor cAMP response element binding protein 1 regulates IEGs for transcription factors and synaptic proteins | hippocampus, amygdala, entorhinal cortex, insula, PFC, occipital cortex, nucleus accumbens, ventral tegmental area | – structural, functional, promotes neuronal survival<br>– memory, learning, emotion, stress response<br>– major depression (Yuan *et al*. 2010), addiction (McClung & Nestler 2003), anxiety (Wallace *et al*. 2009), cognitive impairment (Bourtchuladze *et al*. 1994), sexual behavior (Barrot *et al*. 2005), schizophrenia (Kawanishi *et al*. 1999), Rubinstein-Taybi syndrome (Alarcon *et al*. 2004), Alzheimer's disease (Liang *et al*. 2007; Smith *et al*. 2009), Huntington's disease (Okamoto *et al*. 2009) |
| **CaMKs** – $Ca^{2+}$/calmodulin-dependent kinases, activity-regulated signaling protein isoforms, regulate multiple proteins in synapse, cytoplasm and nucleus | DLPFC, hippocampal formation, ACC, caudate, putamen, thalamus, hypothalamus, midbrain and visual cortex | – structural, functional, promotes neuronal survival<br>– memory, learning<br>– Alzheimer's disease (Gu *et al*. 2009; Steiner *et al*. 1990; Ly & Song 2011), addiction (Licata & Pierce 2003; Kim *et al*. 2009; Marin *et al*. 2009; Pierce & Kalivas 1997) |
| **NGFI-A** – Nerve Growth Factor-Inducible protein A = Zif268/EGR-1/Krox-24/TIS8/ZENK, activity-regulated IEG and continuously expressed gene encoding transcription factor, regulates expression of DRGs | hippocampus, amygdala, basal ganglia, thalamus, hypothalamus, visual cortex, somatosensory cortex, cingulate, brainstem, cerebellum, raphe nucleus, and auditory cortices | – functional and structural and may neuronal survival<br>– short and long-term memory, sensory information processing, arousal, motivation, emotion, stress responses, exploratory behavior<br>– maternal depression affects NGFI-A-regulated glucocorticoid receptor expression and stress-response (cortisol level) in neonates (Oberlander *et al*. 2008)<br>– down-regulation of NGFI-A mRNA in hippocampus of patients with major depression compared with healthy controls (Alt *et al*. 2010) |
| **miR-134-** expression temporally and spatially regulated by extra-cellular signals, regulates translation of synaptic proteins | primary cortex, cerebellum, hippocampus | – structural<br>– Alzheimer's disease (Hebert & De Strooper 2009)<br>– schizophrenia (Santarelli *et al*. 2011) |

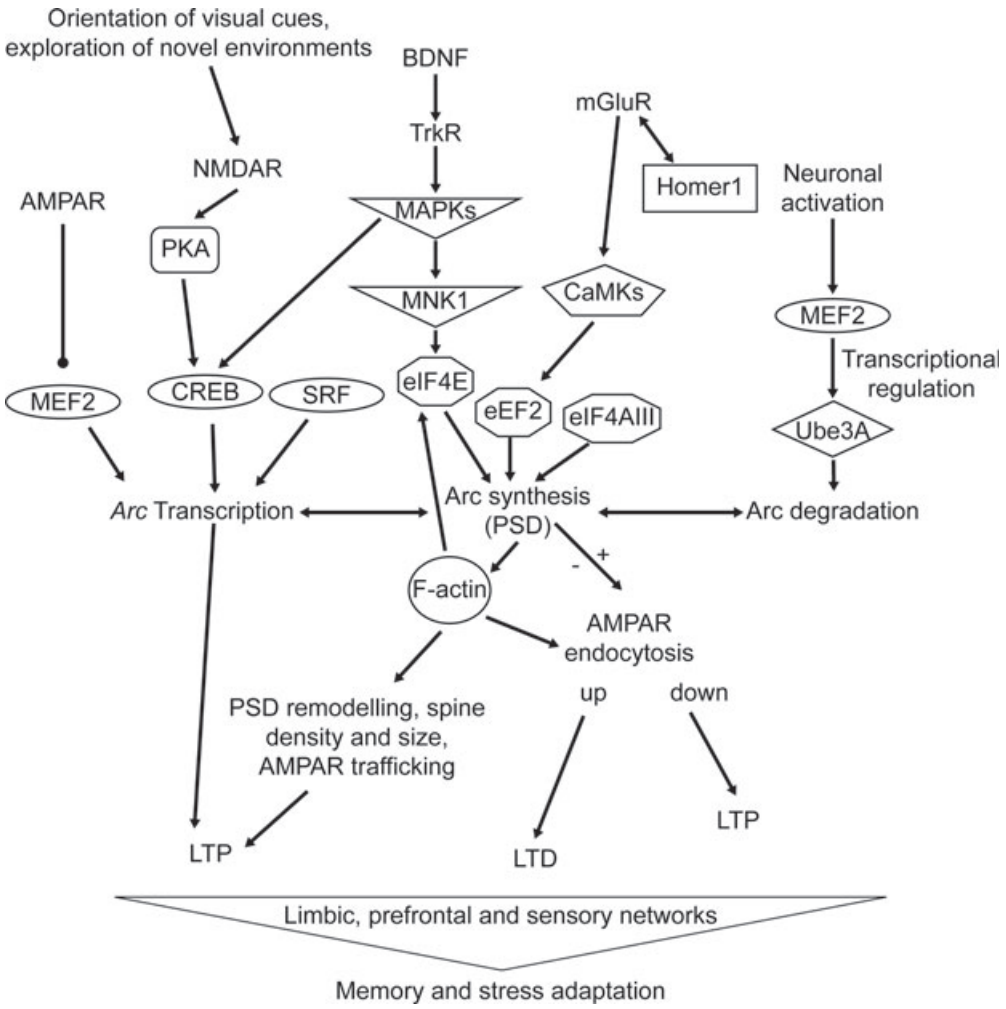


**Figure 3: Overview of the functions of Arc. The figure shows the pathways for the regulation of Arc transcription and the synthesis and degradation of its protein product, and their downstream consequences for neural plasticity.** For abbreviations see Supporting Information: Appendix S1. −/+ signs refer to decrease or increase of function, for example, a minus sign next to an pointing arrow indicates decreased activation while a minus sign next to stumping arrow indicates decreased inhibition. Similar conventions are followed in Figs 4–6.

neuronal activity-dependent dendritic outgrowth (Flavell & Greenberg 2008). CREB has also been implicated in the stress response as one of the regulators of corticotropin-releasing hormone (CRH) gene transcription (Liu *et al*. 2008). Gene expression of two transcriptional regulators of defense genes, NR4A orphan nuclear receptor also called nerve growth factor-inducible protein B (NGFI-B) or Nur77 (an activity-regulated IEG transcription factor that negatively regulates cell survival and growth) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1$\alpha$), has been shown to depend on CREB activation to mediate neuronal survival in response to neuronal stresses (Volakakis *et al*. 2010). *Nur77* transcription can be repressed by sumoylated MEF2 protein binding to the MEF2 response elements (MREs) on the *Nur77* promoter and recruiting of transcriptional repressors (Lam *et al*. 2009). The specificity of CREB regulated transcription thus depends on stimulus type, types of signaling proteins that interact or converge to regulate CREB activity (various protein kinases and phosphatases) and other transcription factors interacting with CREB or CREB targets. The translation of CREB mRNA is negatively regulated by miR-134 (Gao *et al*. 2010).

Because of its neuronal activity-dependent effects on the transcription of neuroplasticity-related genes CREB has been proposed as a major contributor to the molecular transition from short- to long-term plasticity through the regulation of intrinsic neuronal excitability (e.g. membrane resistance, firing rate, after-hyperpolarization via changes of number or function of voltage-gated ion channels) (Benito & Barco 2010) and by facilitating late-LTP at hippocampal synapses (Barco *et al*. 2002). Furthermore, the positive regulation of synaptic NMDA receptor numbers but not AMPA receptors

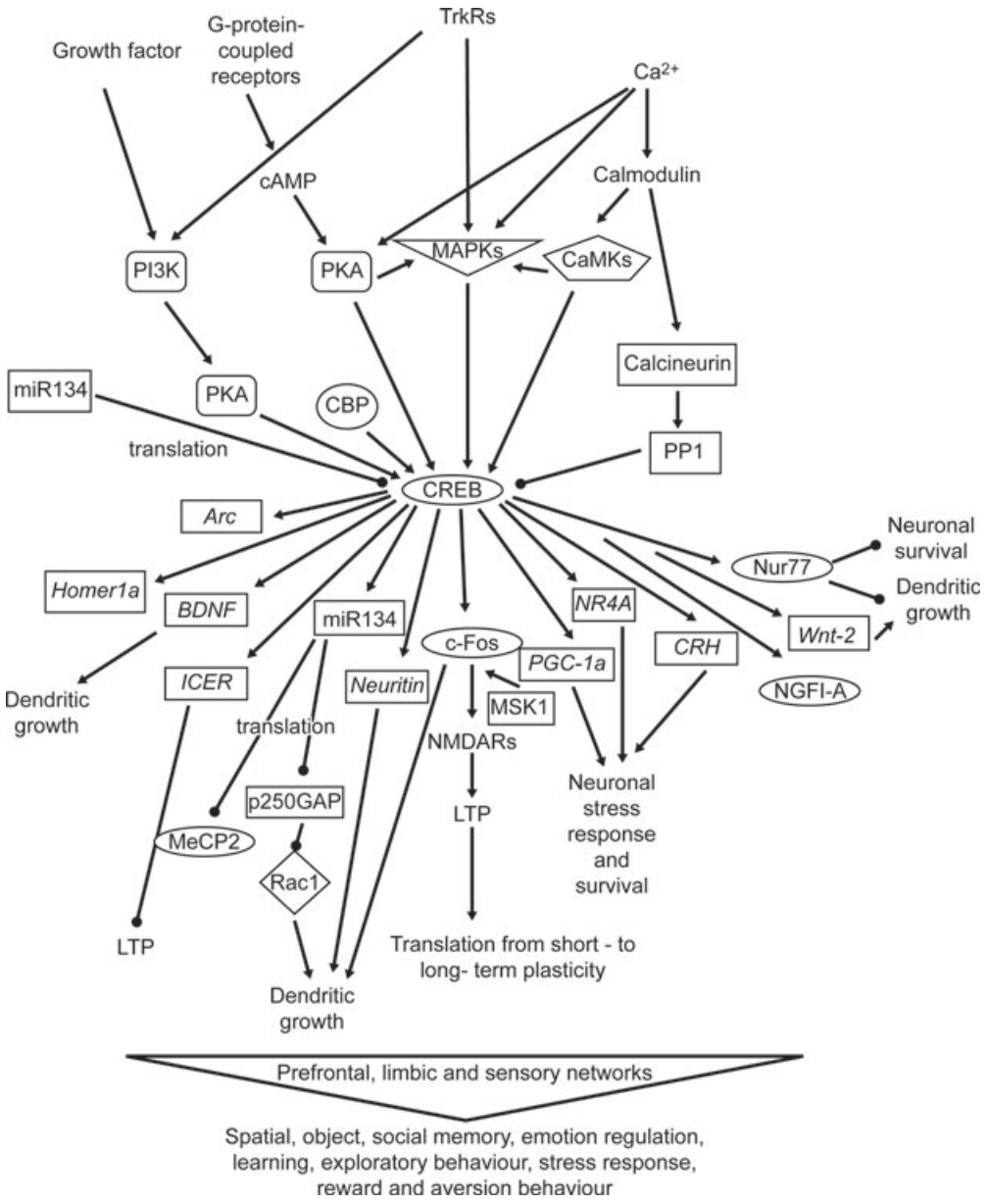


**Figure 4: The central position of CREB in the regulation of plasticity genes.** The major second messenger pathways converge onto CREB, which in turn can regulate most of the other genes discussed in this paper.

combined with increased spine density in the hippocampus induced through CREB over-expression resulted in neurons with new naïve synapses (Marie *et al*. 2005). Containing exclusively NMDA receptors, such synapses are activated at depolarized membrane potentials that drive LTP but not at hyperpolarized membrane potentials unless there has been LTP-dependent introduction of AMPA receptors. Although this addition of new naïve synapses was based on CREB over-expression and not directly CREB activation it suggests a contribution of CREB and its regulated genes to future circuit adaptations. The responsiveness of neurons in the nucleus accumbens is also modulated by CREB; elevation of CREB activity enhances and reduction decreased activity of the nucleus accumbens (Dong *et al*. 2006; Wallace *et al*. 2009). Changes in CREB activity or expression have been implicated in object (Hotte *et al*. 2006) and social recognition memory (Kogan *et al*. 2000), emotional reactions, reward processing, anxiety and depressive-like behaviors (Barrot *et al*. 2002, 2005; Carlezon *et al*. 2005; Dinieri *et al*. 2009), and suicide risk (Dwivedi *et al*. 2003). Enhancement of glucocorticoid receptor stimulation subsequently increased phosphorylated CREB. CREB activation led to increased

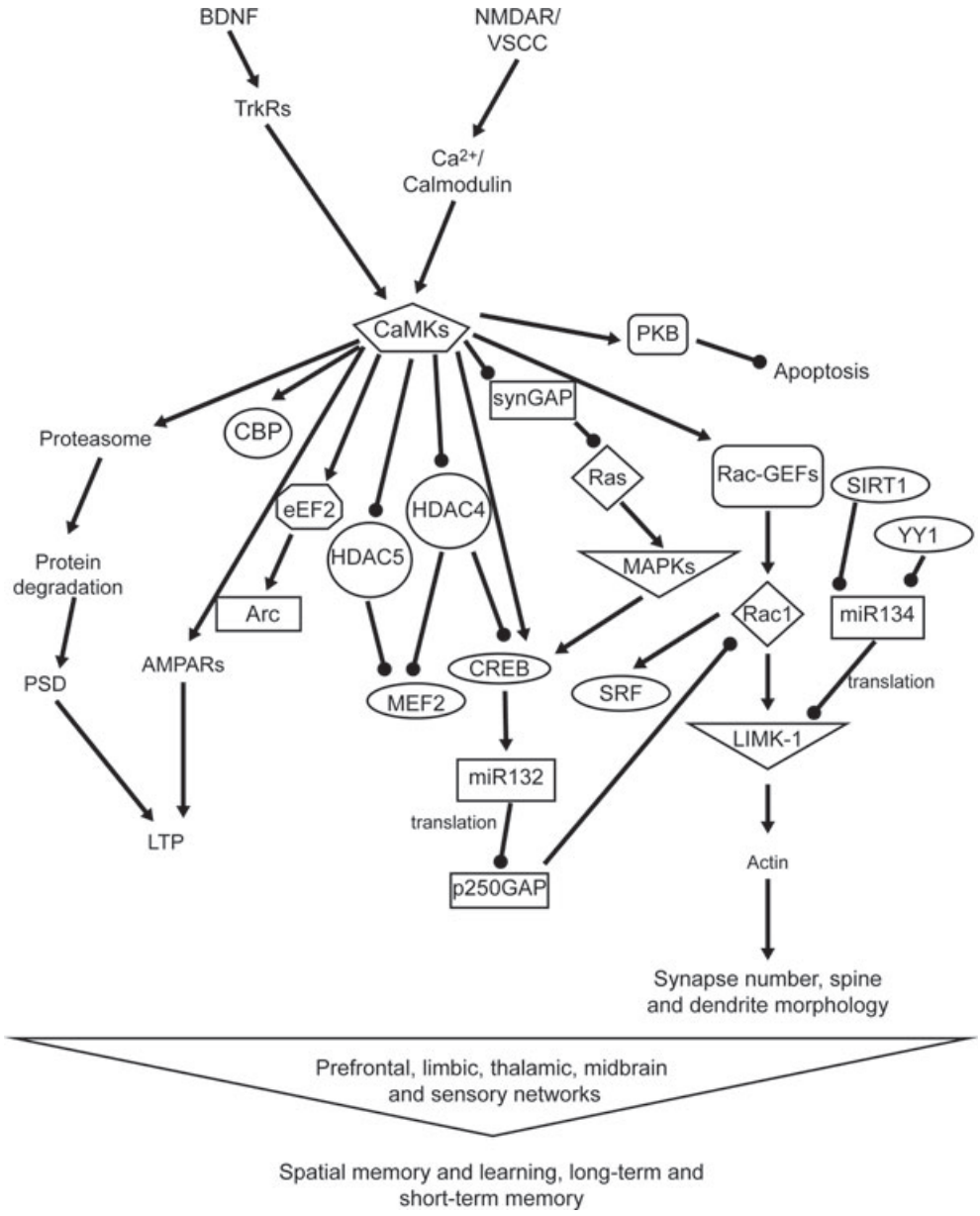


**Figure 5: CaMK signaling pathways regulate activity-dependent transcription factors and proteins involved in function and structural neuroplasticity.**

histone acetylation that was shown to have positive effects on insular cortex-dependent long-term memory for object recognition and hippocampus-dependent long-term memory for object location (Roozendaal *et al*. 2010). This study underlines the importance of brain region-specific epigenetic regulation and its interaction with the CREB pathway for behavioral adaptations during learning. The levels of CREB as well as several proteins in one of the pathways that regulate CREB-dependent transcription – the ERK/MAPK signaling pathway – were diminished in the frontal cortex of patients with schizophrenia and major depression (Yuan *et al*. 2010).

In conclusion both neuronal activity-dependent CREB binding to its DNA-targets and CREB activation contribute to the transcriptional regulation of IEGs, DRGs and miRNAs which are involved in functional and structural neuroplasticity in prefrontal, limbic (Runyan & Dash 2005) and primary sensory cortical networks (Hong *et al*. 2008).

### *$Ca^{2+}$/calmodulin-dependent kinases*

$Ca^{2+}$/calmodulin-dependent kinases (Fig. 5) are Serine/Threonine protein kinases that phosphorylate Ser/Thr residues of their protein substrates (Wayman *et al*. 2008b;

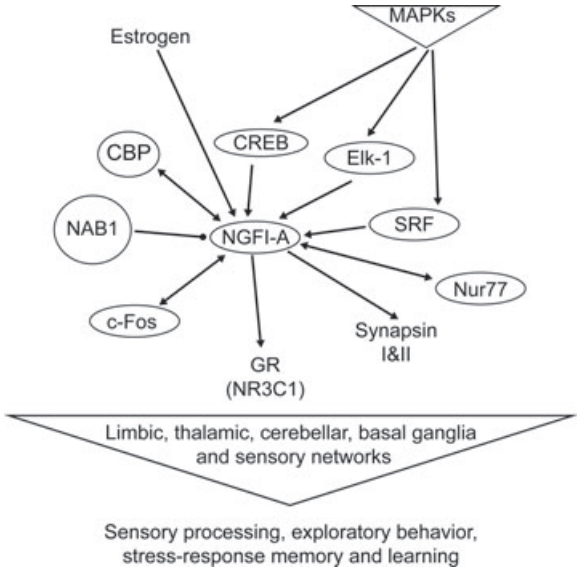


**Figure 6: NGFI-A mediates interactions between endocrine and neuronal functions for the adaptation of behavior.**

White *et al*. 1998). Because the recognition motifs of their substrates commonly overlap (Lee *et al*. 1994), the colocalization of CaMKs with their substrates within multiprotein signaling complexes like PSD or subcellular compartments like the nucleus or membranes determines their signaling specificity and activation kinetics (Bayer *et al*. 2006; Enslen & Soderling 1994; Enslen *et al*. 1994; Inagaki *et al*. 2000; Tsui *et al*. 2005; Wayman *et al*. 2004). Various CaMK-family members and their isoforms contribute to the temporal and spatial regulation of neuronal activity-dependent transcription and translation. Increased activation of CaMKII promotes the synaptic expression of AMPA receptors (Rose *et al*. 2009) and the modulation of $\alpha$-CaMKII activity by NMDA receptor NR2B subunit can modify AMPA receptor function involved in LTP (Barria *et al*. 1997; Zhou *et al*. 2007). Mutation-induced interference with $\alpha$-CaMKII function impairs *N*-methyl-D-aspartate receptor (NMDAR)-dependent LTP in a cell type-specific manner affecting pyramidal but not interneuron dependent pathways in the hippocampus (Lamsa *et al*. 2007). Successful short-term memory retrieval depends on the learning-induced transient stability of $\alpha$-CaMKII activation state that corresponds to its degree of phosphorylation (Wang *et al*. 2008b). During this transient period following encoding, stability of $\alpha$-CaMKII activation state is probably required to transiently stabilize the pattern of potentiated synapses and initiate short-term memory representation (Wang *et al*. 2008b). The dynamic activity state of CaMKII can be regulated by autophosphorylation, hyperphosphorylation, dephosphorylation, autoinhibition and also involves NMDA receptor interactions (Chao *et al*. 2011; Chin & Means 2002; Lisman & McIntyre 2001). Rapid, neuronal activity-dependent translocation of $\alpha$-CaMKII can also act as a scaffold to recruit proteasomes and stimulate protein degradation in dendritic spines to allow activity-dependent changes of PSD composition (Bingol *et al*. 2010). Dysbindin-1, a regulator of synaptic plasticity (Papaleo & Weinberger 2011), has been shown to positively affect CaMKII protein levels probably by restricting the number of dopamine D2 receptors in medial prefrontal cortex (Iizuka *et al*. 2007; Papaleo *et al*. 2010).

Phosphorylation of LIM kinase 1 by CaMKK-CaMKIV signaling has been demonstrated to promote $Ca^{2+}$-dependent neurite outgrowth in cultured neurons (Takemura *et al*. 2009). Dendritic growth has also been found to be promoted by CaMKIV-induced CREB phosphorylation (Redmond *et al*. 2002).

CaMKK and CaMKI regulate axonal elongation or activity-dependent dendritic growth (Wayman *et al*. 2008b). $Ca^{2+}$-dependent CaMKK-CaMKI signaling stimulates MAPK/ERK signaling to induce NMDA receptor-dependent LTP (Schmitt *et al*. 2005). This involves the activation of CREB-dependent transcription of miR-132, which inhibits p250GAP (GTPase-activating protein) translation. The inhibition of p250GAP prevents GTP hydrolysis. This, in turn, promotes Rac1, a small Rac GTPase and positive regulator of dendritic structure (Saneyoshi *et al*. 2010). Distinct CaMKs regulate various guanine-nucleotide-exchange factors (GEFs) that regulate the small Rac GTPases (Rac-GEFs) through binding of either GTP or GDP (Penzes *et al*. 2008). Activation of CaMK-Rac-GEF pathways regulates structural neuroplasticity, for example spine density, synapse number, reorganization of actin cytoskeleton and interaction with scaffolding proteins. The output of a specific Rac-GEF pathway depends on the type of its activation (Penzes *et al*. 2008). It has been shown for example that activity-dependent activation and adhesion-dependent activation of a specific Rac-GEF pathway can have opposite effects on dendritic spine morphogenesis (Saneyoshi *et al*. 2008).

CaMKs have also been indicated as regulators of activity-dependent neuronal survival. The activation of CaMK-mediated pathways results in the phosphorylation of HDAC4 (histone deacetylase 4) and 5 that prevents HDAC4/HDAC5 trafficking from the cytoplasm to the nucleus (Linseman *et al*. 2003). Hyperpolarization of the resting membrane potential or inhibition of CaMKs provokes the localization of HDAC4 and 5 in the nucleus. Inside the nucleus HDAC4 and 5 interrupt transcription dependent on the activity-regulated transcription factors MEF2 and CREB likely resulting in the repression of pro-survival genes in neurons, which are under the regulation of these transcription factors (Bolger & Yao 2005; Linseman *et al*. 2003). Translocation of HDAC4 into the nucleus can occur in response to excitotoxic glutamate conditions (Bolger & Yao 2005). The negative effects of HDAC4 activation on neuronal survival can be reduced by small interfering RNAs (Bolger & Yao 2005).

Despite the strong evidence for the importance of neuronal CaMKs for brain structure and function from animal studies very few studies have reported effects in humans. These have linked variation in CAMK2 genes and cognitive functions in healthy humans (de Quervain & Papassotiropoulos 2006; Rasetti *et al*. 2007) and patients with schizophrenia (Need *et al*. 2009).

In sum, CaMKs are key regulators of neuronal activity-dependent intracellular signaling systems involved in temporal, spatial integration and amplification of signals. Through their interactions with ion channels, structural proteins and

other regulatory proteins or ncRNAs they can convert changes of neuronal activity into functional and structural adaptations of neurons to optimize the properties of neural networks required for learning and memory.

### *Nerve Growth Factor-Inducible Protein A*

Transcription of the IEG *NGFI-A* (Fig. 6) encoding the transcription factor NGFI-A, a zinc-finger protein, can be induced in response to neuronal activity or neurotrophic factors (Knapska & Kaczmarek 2004). The transcription of *NGFI-A* can be up-regulated by the MAPK/ERK pathway. This requires the activation of CREB, (SRF) and Est Like gene 1 transcription factor (Elk-1), which can bind to the *NGFI-A* promoter elements CRE and SRE. Additional response elements in the promoter exist for the transcriptional regulation of *NGFI-A* by estrogen (Slade & Carter 2000), auto-regulation by NGFI-A (Sakamoto *et al*. 1991; Schwachtgen *et al*. 2000) and inhibition by, for example, NGFI-A binding protein 1 (NAB1) (Russo *et al*. 1995). Temporal and local regulation of NGFI-A mRNA and protein expression contribute to the transcriptional regulation of multiple DRGs (Knapska & Kaczmarek 2004) encoding, for example, glucocorticoid receptor (GR) (Weaver *et al*. 2004) and the synaptic vesicle-cytoskeleton-associated proteins synapsin I and II (Thiel, 1993). NGFI-A also interacts with several other transcription factors, such as CBP (Silverman *et al*. 1998), c-Fos (Dragunow *et al*. 1994; Gius *et al*. 1990) and NGFI-B (Williams & Lau 1993). NGFI-A protein is expressed throughout the brain, for example, in thalamus, hypothalamus, striatum, amygdala, hippocampus and sensory cortices (Knapska & Kaczmarek 2004). Up-regulation of *NGFI-A* expression in sensory cortices has been observed in response to sensory stimulation, for example, through environmental enrichment (Pinaud *et al*. 2002; Wallace *et al*. 1995).

Region-specific dynamic regulation of *NGFI-A* mRNA expression has been observed in response to acute and repeated stress (Girotti *et al*. 2006). However the regulation of *NGFI-A* expression is influenced by a large spectrum of stimuli including seizures, hippocampal LTP-inducing stimuli and various types of learning (Knapska & Kaczmarek 2004).

Naturally occurring variation in the degree of maternal care (grooming and nursing behavior of rats) has been shown to regulate the expression of the GR gene (*NR3C1*) in the hippocampus of rat pups (Weaver 2007; Weaver *et al*. 2006, 2007). This involves the regulation of genome configuration on the NGFI-A transcription factor response element of the GR promoter via acetylation/deacetylation of specific histones and sequence methylation/demethylation. The methylation status of this promoter sequence appears to be mediated through serotonin signaling at hippocampal 5-$HT_7$ receptors activated in response to maternal care. Additional activity-dependent transcription factors and cofactors are also likely to participate in the regulation of GR gene transcription. Binding of the transcription factor NGFI-A depends thus on histone(s) acetylation status and methylation status of its response element in the GR promoter sequence. NGFI-A binding regulates the transcriptional activity of the GR gene and thus alters the expression of hippocampal glucocorticoid receptor levels (Weaver *et al*. 2007). The early-life maternal care-induced methylation status of the GR gene promoter sequence has been shown to persist and influence behavior and hypothalamic–pituitary–adrenal stress response of the offspring in adulthood and to be reversible with cross-fostering (Fish *et al*. 2004; Weaver *et al*. 2004). The offspring of dams exhibiting a high degree of maternal care showed enhanced learning, memory, and exploratory behavior and less stress reactivity.

In sum, NGFI-A is an IEG transcription factor that regulates genes involved in synaptic transmission and endocrine function directly or via interactions with other transcription factors.

### *MicroRNA-134 (miR-134)*

MicroRNA-134 (Fig. 5) is one of the small (ca. 22 nucleotides long) noncoding regulatory RNAs specifically expressed in the brain.

One of the BDNF-regulated mRNAs that contains a binding site for miR-134 within its 3′UTR is LIM-domain containing protein kinase 1 (Limk1) (Schratt *et al*. 2006). Binding of miR-134 contributes significantly to the reduction of Limk1 mRNA translation thereby reducing Limk1 protein levels at synapses unless BDNF cancels these effects (Schratt *et al*. 2006). Limk1 targeted to excitatory postsynapses within dendrites of hippocampal neurons regulates actin filament dynamics, and decrease of Limk1 protein reduces dendritic spine size (Schratt *et al*. 2006). Thus, BDNF promotes and miR-134 inhibits dendritic outgrowth that depends on Limk1 protein levels. Recently the translational downregulation of CREB in the hippocampus has been shown to involve the binding of miR-134 to 3′UTR regulatory elements of CREB mRNA (Gao *et al*. 2010). Another target of miR-134 is the mRNA of the translational repressor protein Pomilio 2 that promotes dendritogensis (Fiore *et al*. 2009).

The two transcription factors silent information regulator of transcription (Sirtuin 1/SIRT1) and Yin Yang 1 (YY1) restrict the transcription of miR-134 (Gao *et al*. 2010). Manipulation of the function of these transcription factors was accompanied by changes of hippocampal BDNF mRNA and protein levels, synaptophysin levels of presynapses, dendritic spine density of CA1 pyramidal neurons, LTP and memory (Gao *et al*. 2010). MEF2 induces the activity-dependent transcription of a miR-cluster that includes miR-134 (Fiore *et al*. 2009).

Increased levels of miR-134 have been observed in the DLPFC of patients with schizophrenia compared with healthy controls (Santarelli *et al*. 2011), suggesting an involvement of this activity-regulated micro-RNA in altered neuronal structure and function in schizophrenia.

This example demonstrates that neuronal activity-dependent micro-RNAs are integrated in signaling pathways and regulate the translation of activity-dependent transcription factors and proteins involved in synaptic plasticity.

## Future research directions on individual adaptability

The heterogeneity of complex psychiatric disorders like schizophrenia is best accounted for by multifactorial models

that incorporate genetic, epigenetic and environmental influences. The dysregulation of gene expression, intra- and extra-neural signaling pathways, neural cell and neural network properties and behavior are common features of complex psychiatric disorders (McClung & Nestler 2008; Ramocki & Zoghbi 2008; Ross *et al*. 2006).

The effects of genetic variability not only depend on the interactions with other genes, proteins, epigenetic and environmental factors but are also influenced by neuronal activity driven by sensory, cognitive, emotional, social or motor experiences/behaviors. In order to account for the inconsistency and heterogeneity observed in genetic studies of schizophrenia we may therefore also require knowledge about how experience-driven neuronal activity contributes to changes in gene and protein expression to regulate neuroplasticity.

Responsiveness of genetic, epigenetic and neuronal adaptation mechanisms to environmental factors and individual experiences could also explain the impact of potential risk factors like stress, drugs, and infection in the manifestation of the genetic propensity to psychiatric disorders. Dysregulated adaptation mechanisms may thus be a common aspect of all complex psychiatric disorders.

### *What factors contribute to interindividual variability in neural and cognitive functions?*

Genetic variability is a key factor for the understanding of individual differences in behavioral or cognitive performance measures and their neurophysiological correlates (Ando *et al*. 2001; Blokland *et al*. 2008; Wolf *et al*. 2011). However, as described above genetic variability interacts with epigenetic variation and a large variety of regulatory factors that can mediate environmental influences and experience-dependent differences in neuronal activity. For example individual differences in working memory capacity likely depend on interactions between genetic, epigenetic and experience-dependent interindividual differences in neuronal activity that affect regulatory proteins and ncRNAs involved in short-term neuroplasticity.

The total interindividual variability of the genome sequence in humans is estimated at 0.2%, of which 40% are nucleotide variations (SNPs) and 60% structural changes (Sebat 2007). Structural variations contribute presumably at least 20% to the variability of gene expression (Hurles *et al*. 2008). Only a small proportion of the total DNA sequence variability will alter protein coding sequences because these make up only about 1% of the human genome (Church *et al*. 2009). Most of the interindividual genetic variability thus affects genome sequences that are transcribed into ncRNAs and untranscribed sequences that are presumably also regulatory. Adaptively evolving loci have been identified in noncoding sequence of the human genome that may also affect neuronal regulatory regions (Kelley & Swanson 2008).

Genetic and epigenetic variation within regulatory noncoding sequence is thus expected to be the major source for genetically driven individual differences and in addition interacts with environmentally driven regulation. Changes in regulative ncRNA sequences could result in subtle changes that contribute to interindividual variability of quantitative traits (Mattick & Makunin 2006). In addition comparative genome analysis has revealed that most evolutionary conserved sequences in mammalian genomes are noncoding (Lindblad-Toh *et al*. 2005). These noncoding sequences are often found close to genes that encode transcription factors (Canestro *et al*. 2007) and often contain cis-acting regulatory elements that regulate the transcription of adjacent genes (Woolfe *et al*. 2005). Through its cis- and trans-acting effects, nc-RNA is involved in gene and protein regulation. The variation and conservation of noncoding sequence may thus reflect its role in the diversification and maintenance of phenotypes during evolution. Most genes give rise to multiple mRNA transcripts for the regulation of translation to adapt the isoform, quantity or location of a protein. Differences in the 3′ and 5′UTRs are critical for mRNA processing as well as timing and location of translation via interaction with trans-acting factors. For example cytoplasmatic polyadenylation element binding protein 1 (CPEP1) is part of a multiprotein complex that binds to specific cis-acting elements of the 3′UTR to regulate mRNA transport, polyadenylation and translation of several synaptic plasticity proteins (Wayman *et al*. 2008b). The length of 3′UTR sequence of BDNF mRNA is thus important for the regulation of its transport, which has been shown to affect spine morphology and synaptic plasticity in hippocampal neurons (An *et al*. 2008). 3′UTR removal of $\alpha$-CaMKII mRNA prevents its translocation, reduces protein expression in PSD, late-LTP stability and memory (Wayman *et al*. 2008b). 3′UTR cis-acting elements signal the dendritic localization and translation of $\alpha$-CaMKII mRNA (Mayford *et al*. 1996; Mori *et al*. 2000). MicroRNA expression also modulates synaptic plasticity and can regulate mRNA translation in the human brain by interacting with target sequences in 3′UTR (Zhang & Su 2008). The variation of miRNAs themselves and their target sequences may increase variability in gene expression and thus influence phenotypic adaptability (Zhang & Su 2008).

In summary neuronal activity-regulated proteins and ncRNAs that are organized in complex molecular networks can integrate extracellular (neuronal activity-dependent) and intracellular signals (genetic, epigenetic) to regulate neuronal adaptations. Adaptations at the molecular level ranging from post-translational to transcriptional modifications are the basis of the functional and structural adaptation of neuronal properties. The bidirectional interactions between the neuronal and molecular level are increasingly well understood. How these molecular and neuronal adaptations adapt neural network properties that translate into adaptations of perceptual, cognitive and behavioral functions still needs to be investigated in more detail.

### *How can genetically driven alternations of brain function and behavior be detected?*

Methods interconnecting neuro-molecular, neuro-physiological and behavioral levels can reveal the impact of genetic variability to variations of brain functions and behavior. One technique with the capacity to cover this spectrum of functions is genetic neuroimaging, which combines neuroimaging technologies such as functional magnetic resonance imaging (fMRI) with molecular genetics. However

this technique is limited by two major constraints. First the analysis is restricted to DNA sequence variations because the genome is isolated from lymphocytes or other dispensable cells. For this reason genetic neuroimaging cannot provide information about the genome output variation in neurons. Functional MRI can localize and quantify the change of the hemodynamic signal at neural network level. By modeling the time course of the signal change as a function of the behavioral manipulation, for example, a memory task, this method provides a correlate of task-related neural activity. This, points to the second main limitation, which is the correlative nature of genetic neuroimaging. Prior knowledge regarding the effects of genetic variants on expression and function of neuronal activity-regulated proteins and ncRNAs is thus an advantage. Common genetic variants known to affect the expression or function of neuronal activity-regulated proteins and ncRNAs involved in neuroplasticity are rarely known. Mostly the genetic contribution to individual variation of neuronal network activity involved in cognitive functions has been investigated for genes encoding receptors or enzymes of several neurotransmitter systems as well as regulators of brain development (Egan *et al*. 2003; Goldberg & Weinberger 2004). The strengths of fMRI are its high sensitivity, reasonable spatial resolution and its capacity to provide maps of neural network plasticity of the whole brain in vivo. Moreover, the correlation between genetic and task-related imaging and performance data allows for the validation of effects across functional levels. There are high hopes for the identification of neuroimaging endophenotypes of neuropsychiatric disorders and their subsequent use in gene discovery studies (Glahn *et al*. 2007). A first application (although not based on a formally identified endophenotype) used the functional imaging signal from prefrontal cortex as quantitative traits for the genome-wide search for new candidate genes for schizophrenia (Potkin *et al*. 2009). This approach allows for the genome-wide discovery of genetic variants associated with imaged or otherwise quantified endophenotypes. Hence noninvasive genetic neuroimaging studies may help to quantify and specify the influence of genetic parameters on brain functions and behavior. However, in order to monitor signal changes dependent on genome output variation such approaches would require the application and measurement of noninvasive, reliable, short-lived and sequence-specific markers that are responsive to changes in neuronal activity-dependent genome expression.

A different version of genetic imaging operates at the cellular level. Advanced invasive methods like cellular compartment analysis of temporal activity by fluorescent *in situ* hybridization (catFISH) can localize, quantify and identify mRNAs and proteins within neuronal networks activated for distinct stages of learning and memory (Guzowski *et al*. 1999; Miyashita *et al*. 2008). Another invasive way of investigating *in vivo* molecular changes involved in the regulation of neuronal activity, synaptic and neuronal plasticity, for example, the regulation of IEG expression at the network level, is the transgenic or viral-introduction of neuronal activity-dependent fluorescent sensors (Barth 2007). The induction of light-sensitive proteins combined with an effector function can also be used to manipulate molecules involved in neuronal signaling (Deisseroth 2011).

These studies have provided new insight in the interactions between genes, neurons and behavior by showing neuronal activity-dependent initiation of new gene transcription. In vitro studies that use florescence makers to trace gene expression in combination with electrophysiology, for example, by time-lapse live-cell fluorescence imaging can identify neuronal activity-dependent changes in gene transcription (Kawashima *et al*. 2009).

The investigation of these mechanisms is crucial because they are involved in the regulation of neuroplasticity, such as neuronal activity-dependent synapse number (Flavell *et al*. 2006), dendritogenesis (Fiore *et al*. 2009) or adult hippocampal neurogenesis (Ma *et al*. 2009). Genetic manipulation of activity-dependent transcription factors that induce the transcription of immediate early genes (IEGs) has been shown to impair learning and memory through their effects on structural synaptic plasticity (Barbosa *et al*. 2008). Impairments in these neuronal activity-dependent regulation mechanisms have been linked to genetically complex mental disorders (Swanberg *et al*. 2009). The regulation of activity-dependent gene expression has also been shown to play an important role during the development of GABAergic synapses (Lin *et al*. 2008), which could be relevant for the pathogenesis of schizophrenia. Neuronal activity-responsive IEGs and their transcription factors are expressed in regions important for emotion and cognition such as prefrontal, orbitofrontal, occipital cortex, hippocampus and amygdala.

### *Outlook*

According to recent genome analysis results, protein-coding sequence makes up only about 1% of human DNA (Church *et al*. 2009). The remaining, noncoding, sequence likely plays an important regulatory role for the adaptive use of genes (in particular the regulation of gene expression). This suggests that variations in protein-coding sequences may be less relevant for phenotypic differences than variations in sequences that determine the when and where of gene expression (Cubas *et al*. 1999). At present the effects of genetic variability in noncoding sequence on the expression of neuronal activity-regulated noncoding RNAs or regulatory proteins are largely unknown. However, recent evidence suggests the importance of noncoding sequence for cis- and trans-binding interactions between RNAs and RNAs and proteins during the regulation of gene expression (Wang *et al*. 2008a). Variability in noncoding sequence that affects regulation of gene expression has been related to psychiatric disorders (Zhao *et al*. 2009), normal variation of cognition (Gosso *et al*. 2008), emotional and social behaviors (Hammock *et al*. 2005). Hence it would be interesting to investigate variability particularly in noncoding regulatory sequences (e.g. UTRs) that affects synaptic activity-regulated genes and proteins with genetic neuroimaging also with respect to psychiatric disorders. Other interesting targets for future genetic imaging studies are activity-regulated microRNAs. Because these micro-RNAs, proteins and genes regulate synaptic plasticity, genetic variation affecting these regulators may contribute to interindividual variability in cognitive functions as well as their dysfunction in disorders like schizophrenia. A recent genome-wide analysis detected a

strong association between schizophrenia and a SNP within an intron probably encoding miRNA-137 that is involved in neuronal development (Ripke *et al*. 2011). Furthermore, four genome-wide associated schizophrenia genes contain putative target sites for this miRNA. For one of these genes encoding the transcription factor 4, miRNA-137 effects were found on protein translation in neuronal culture.

Presently no noninvasive *in vivo*-technique is available to study neuronal activity and plasticity related genome output regulation during cognitive activities in humans. However interdisciplinary efforts that combine insights from invasive and noninvasive approaches to investigate the integration of adaptation mechanisms across functional levels have the power to elucidate the interplay between genome, epigenome, neurophysiology, behavior and environmental experiences for human adaptability and thus individuality.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1:** Abbreviations of molecule and disease terms

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