From c-Fos to MMP-9: In control of synaptic plasticity to produce healthy and diseased mind, a personal view

ABSTRACT

C-Fos is a component of AP-1 transcription factor. Three lines of evidence support pivotal role of c-Fos in learning and memory: (i) learning experience markedly enhances its expression; (ii) blocking od c-Fos impairs, while optogenetic activation of c-Fos expressing neurons supports learning and memory; (iii) c-Fos/AP-1 gene targets in activated neurons, encoding tissue inhibitor of metalloproteinases-1 (TIMP-1) and matrix metalloproteinase 9 (MMP-9) play a major role in synaptic plasticity that underlies learning and memory. TIMP-1 and MMP-9 compose an extracellularly operating enzymatic system active locally around excitatory synapses to modulate their morphology, molecular content and efficacy. Animal studies have implicated MMP-9 in a variety of neuropsychiatric conditions, e.g., epileptogenesis, autism spectrum disorders, development of addiction, and depression. In humans, MMP-9 contributes to epilepsy, alcohol and cocaine addiction, Fragile X Syndrome, schizophrenia and bipolar disorder. In aggregate, all those conditions can be considered as reflecting either healthy or diseased mind.

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Abbreviations: BA – Basal Amygdala, CaM – cell adhesion molecules, cLTP – chemical LTP, DG – dentate gyrus, ECM – extracellular matrix, FXS – fragile X syndrome, KO – knockout, LTP – long-term potentiation, MMP-9 – matrix metalloproteinase 9, TIMP-1 – tissue inhibitor of metalloproteinases-1

C-FOS AS THE FIRST LEARNING-ACTIVATED GENE DISCOVERED

In 1986, after postdoctoral studies on molecular biology of cell proliferation, I joined the Nencki Institute with an idea to initiate investigations into the mind in the brain. My research started with a few assumptions:

- learning and memory offer a window into the mind, and because they can be veridically studied in experimental animals, this is particularly opportune;
- molecular biology provides the most powerful toolbox to approach biological questions;
- cell activation of various kinds follows a partially uniform path, involving enhanced expression of selective genes, such as nuclear proto-oncogenes.

The first two assumptions appear obvious nowadays, so let me comment on the third one. It was discovered in the late 1970s and early 1980s that oncogenes (the genes that give rise to cancer, e.g., *via* oncogenic retroviruses) have normal, cellular counterpart genes called proto-oncogenes, which are involved in control of the cell division cycle in healthy cells [1,2]. In fact, we demonstrated that the protein c-Myc, encoded by a nuclear proto-oncogene (i.e., protooncogenic protein with the cell nucleus localization), was capable of initiating the cell division cycle [3]. Because c-Myc was found in the cell nuclei, it was immediately hypothesized that this and similarly located protooncogenic proteins (such as c-Fos) might have an impact on gene regulation, thus affecting lasting cellular responses. On other hand, it was shown in the 1960s that inhibitors of *de novo* protein synthesis, when introduced into the brains of animals, prevented the formation of memories lasting longer than a few hours [4,5]. This led to the conclusion that certain proteins that were produced during the process of learning were crucial for long-term memory. Soon thereafter, it was demonstrated that a similar inhibitory effect on memory was also exerted by substances that block RNA synthesis (i.e. inhibiting gene expression) [5].

Considering those two independent lines of research, a review paper on proto-oncogenes in the cell cycle, proposed that proto-oncogenes might also play a pivotal role in other biological processes thought to involve gene expression [6]. Soon thereafter, the idea suggesting its relevance also to learning and memory was explicitly put forward [7]. Other researchers expressed similar views at that time [8,9]. Therefore, we were encouraged to seek out which genes were activated in the brain under the influence of external stimuli, capable to activate neurons. We initially showed that when glutamic acid, an important neurotransmitter that stimulates neurons to fire and had already been recognized as piv-

otal for learning and memory, was introduced into the rat brain, it very quickly (within 15 min) and transiently (the effect was gone by 45 min) caused the activation of the gene encoding the c-Fos protein, as measured by the levels of its mRNA [10]. Other studies demonstrated that excessive neuronal activity, such as produced by seizures, also markedly elevated c-Fos expression in the rat brain [11,12], and Hunt *et al*. [13] reported that physiological stimulation of rat primary sensory neurons caused the expression of c-Fos in the spinal cord.

Immediately afterwards, we raised the question of whether evoking long-term potentiation, LTP (that is an electrophysiological model of mechanisms underlying learning and memory) by electrical stimulation in the brain *in vivo*, as well as exposing a rat to a behavioral, learning episode, might also produce the same effects on gene expression. Indeed that proved to be the case [14-22]. Importantly elevated *c-fos* mRNA expression was observed only when the animals were learning a new task, but not when they vigorously performed already learned behavior [18]. Similar experiments were also carried out by K.V. Anokhin and colleagues, arriving at similar results (activation of the gene encoding c-Fos [23,24]. Over the following years, it has been repeatedly demonstrated that the protein c-Fos appears in nerve cells only when a given neuron is stimulated under conditions making it prone to synaptic plasticity [25] and even specific links of c-Fos expression to long-lasting memories were reported [26].

Despite the wealth of correlative data implicating c-Fos in learning and memory, the functional role of the protein in these phenomena has only recently been proven unequivocally. Using a behavioral paradigm, in which mice had to learn to discriminate sounds of two different frequencies—a task known to rely on functionally intact auditory cortex—we have demonstrated that acquisition of this behavior was greatly impaired when c-Fos was downregulated specifically in this brain area (in result of lentivector-mediated, shRNA-driven blocking of the protein synthesis) [27]. Notably, also auditory discrimination-evoked synaptic plasticity was impaired under those conditions [27]. Synaptic plasticity refers to modifications of synaptic efficacy within vast neuronal network of the brain that processes, in a malleable way, incoming information to produce behaviors that change because of the associated past stimuli and their reinforcing value.

This result is in line with the previous studies on c-Fos knockout and antisense oligonucleotides that negatively affected c-Fos levels [28,29]. However, we shall stress that those previous data suffered from limited specificity, probably because the tools employed diminished basal neuronal activity (that was found intact under our experimental conditions, see de Hoz *et al*. [27]). Most importantly, very elegant studies have conversely shown that artificial, optogenetic stimulation of neurons that expressed c-Fos in response to a learning experience maintain physiological memory traces and even create synthetic ones [30-32]. Thus, it has been found that neurons with transient, learning-evoked c-Fos expression are both necessary and sufficient to support the memory trace.

Finally, the last line of evidence pointing to c-Fos role in learning and memory comes from the investigation of its target genes. We have demonstrated that c-Fos activates the gene encoding TIMP-1 (tissue inhibitor of matrix metalloproteinases, Jaworski *et al*. [33]), a protein capable of blocking the activity and thus controlling the extracellular enzyme MMP-9 (matrix metalloptoteinase-9). This, in turn, shifted our attention to MMP-9 as being targeted by TIMP-1. Interestingly, numerous evidence outside the nervous system suggested that also MMP-9 might be regulated by c-Fos/AP-1 [34]. In fact, we have shown that this is the case also in the brain, after behavioral training of fear conditioning and in BDNF-activated neurons in culture [35,36].

MMP-9: AN EXTRACELLULAR PROTEASE

MMP-9, matrix metalloproteinase-9 is a protease that operates predominantly extracellularly. It belongs to a larger family of enzymes (metalloproteinases) that together with other similar molecules form an abundant class of metzincins (including also astacins, ADAMs, ADAMTSs, etc., see for review: [37,38]). Originally, we have reported that MMP-9 undergoes a massive activation in the dentate gyrus (DG) of the hippocampus in response to treatment with kainate [39]. This result was very surprising, since until then multiple studies implicated MMP-9 in pro-neurodegenerative, pathological responses, easily associated with excessive, tissue detrimental proteolysis [40-42]. Although kainate treatment produces CA1 and CA3 hippocampal cell loss, the DG remains spared and even is a subject of massive, albeit aberrant synaptic plasticity [43]. Even more surprising was our discovery that increases in MMP-9 in dendritic tree area of DG concerned not only the protein and enzymatic activity, but also mRNA, suggestive of its translocation towards synapses that were undergoing plastic reorganization. In result, we have put forward hypotheses of possible role of MMP-9 in dendritic remodeling and synaptic plasticity, as well as of local, dendritic/synaptic translation of MMP-9 during plasticity [39].

MMP-9 IN SYNAPTIC PLASTICITY, LEARNING AND MEMORY

The hypothesis of an MMP-9 role in physiological plasticity was positively verified by Nagy *et al*. [44] as well as Meighan *et al*. [45] who demonstrated, by various means that MMP-9 was indispensable for late (over half an hour) phase of hippocampal (CA3-CA1) LTP, as well as for hippocampal learning and memory (contextual fear conditioning, water maze), as shown unequivocally with MMP-9 knockout (KO) mice, along other less specific means. Furthermore, increases in MMP-9 protein and enzymatic activity levels under those conditions were also demonstrated [44,45]. Soon thereafter, these observations were extended to other experimental systems of LTP, learning and memory that all involved the hippocampus [46-52]; for review: [53-55].

Surprisingly, formation of aversive memories that relies on lateral amygdala (LaA) apparently does not require MMP-9 activity [44,56], and LTP might be evoked on the external capsule-LaA pathway, even when MMP-9 is miss-

ing [57]. An important role of MMP-9 in synaptic function underlying postnatal and even adult cortical plasticity has also been shown for the visual and somatosensory cortex [58-62]. Similarly, requirement for MMP-9 has also been demonstrated for chemical LTP (cLTP) in hippocampal cultures [63-66].

CENTRAL NUCLEUS OF THE AMYGDALA AS A HUB FOR APPETITIVE PLASTICITY, LEARNING AND MEMORY

Amygdala is a heterogeneous brain structure (at least 13 sub-regions can be easily discerned) that is well known for its pivotal role in emotional and motivational behaviors. Almost 20 years ago we have demonstrated that c-Fos expression in this brain region can be very precisely associated with specific behaviors [67], indicating functional heterogeneity of amygdalar sub-regions. To follow on this finding, we then reported that the central nucleus of the amygdala is strongly c-Fos labeled after appetitive training, but virtually missing c-Fos after acquisition of aversive behaviors in rats and mice [68]. Reviewing all of the existing literature on this topic further reinforced such a notion [69]. Incidentally, we have also found that c-Fos expression in this brain region is conspicuously related to a phenomenon of emotional contagion, a simple form of empathy [70], but is neither associated with acquisition nor extinction of fear behavior [71].

Considering the c-Fos—MMP-9—synaptic plasticity link we have established, we have next investigated whether indeed MMP-9, especially in the central amygdala is critical for appetitive learning and memory. Knapska *et al*. [56] provided very strong support for such a notion. In particular, we have shown that global KO of MMP-9 impairs appetitive, but not aversive learning and memory and then, selective inhibition of MMP-9 extracellularly within the central amygdala results in the same phenotype – impairs appetitive learning, leaving intact aversive learning and memory [56]. Interestingly, LTP from Lateral Amygdala to Basal Amygdala (BA) and from BA to medial Central Amygdala are greatly impaired when MMP-9 activity is not available [57]. Thus, MMP-9 is not universally mandatory for synaptic plasticity, learning and memory. Nevertheless, activity of this molecule is an obligatory component for specific forms of those phenomena, especially in the hippocampus and central amygdala.

Most recently, Lebitko and colleagues (submitted) have found that selective blocking of c-Fos in the central amygdala by lentivirally delivered specific shRNA (used previously by de Hoz *et al*., 2018 [27]) impairs specifically preparatory but not consummatory appetitive behaviors. These results go against a mainstream view of central amygdala as playing important role solely in aversive learning, acting as a relay station towards the brain stem. On the other hand, recent data from Tonegawa laboratory have supported our results [72,73], appreciably acknowledging our pioneering findings.

LOCAL TRANSLATION OF MMP-9

We have also followed the hypothesis of local translation of MMP-9 at/around activated excitatory synapses. It should be noted that our other studies clearly pointed to MMP-9 presence on dendritic spines that harbor postsynaptic areas of excitatory synapses. On other hand, to MMP-9 remained non-detectable at either presynaptic domains or GABA-ergic synapses [74,75]. Konopacki *et al*. [76], using fluorescent in situ hybridization combined with immunofluorescent protein detection, reported on a patchy MMP-9 mRNA accumulation in DG dendrites in response to kainate treatment. This result reinforced the idea of MMP-9 mRNA being translocated, after kainate, towards excitatory synapses. Dziembowska *et al*. [77] and Janusz *et al*. [78] provided a number of experimental data clearly showing that indeed MMP-9 mRNA can undergo local synaptic translation to produce the protein after activation of excitatory synapses. These experiments have also revealed that MMP-9 production, release and synaptic availability after synaptic activation occurs within a few minutes following treatment with glutamate (see also [79]). Importantly, our results have been confirmed and even extended to human brain tissue [80]. Incidentally, another interesting layer of MMP-9 regulation at the mRNA stability level has recently been revealed by Zybura-Broda *et al*. [81].

MMP-9 IN STRUCTURAL AND FUNCTIONAL SYNAPTIC PLASTICITY – THE MECHANISMS

The evidence for pivotal role of MMP-9 in structural plasticity of dendritic spines comes from hippocampal cultures and slices, as well as the brain *in vivo* (see [55,82,83] for review). Two major observations have been made. First, excessive abundance of MMP-9 produces elongation and thinning of the spines [84,85]. On the other hand, physiologically and locally available MMP-9 evokes conversion of small spines to larger, more efficacious mushroom ones [66,86]. We have recently explained this apparent paradox, by finding that the full function of MMP-9 requires first its activity, followed by subsequent inhibition, exerted physiologically by TIMP-1 [87]. We have also found that excessive MMP-9 in transgenic rats with neuronal overexpression of the enzyme [74] results in higher, than in the wild-type rats, proportion of silent synapses and lower AMPA/NMDA receptor ratio, along with impaired LTP. Treatment with MMP inhibitors in those transgenics normalized (i.e., enhanced) LTP as well as unsilenced the synapses, and finally resulted in increased AMPA/NMDA receptor ratio [87].

Using hippocampal cultures subjected to cLTP we have found that this form of synaptic plasticity correlates with growth of small spines into larger mushroom ones, concomitantly with synaptic accumulation of GluA1 AMPA receptors that are at same time less mobile at the synapses [66]. All these major attributes of synaptic plasticity were lost when cLTP treatment was carried under MMP inhibition, i.e., neither spine growth, nor GluA1 accumulation and immobilization at the synapses could be observed under such conditions [66].

Several other reports supported important role of MMP-9 in structural plasticity of dendritic spines, also *in vivo*. Sidhu *et al*. [88] observed that MMP-9 KO mice displayed larger spine head areas in the hippocampus at 1-2 weeks postnatally (at later times this value became the same as in the wild type animals). Interestingly, Aujla and Huntley [89] found

that levels of MMP-9 peaked in the hippocampus more or less at the same time. Murase et al. [90] showed that MMP-9 KO mice had unaltered spine density in the hippocampus of adult animals, however, there was increase in proportion of mushroom spine on the expense of thin ones. Kelly *et al*. [62], while studying ocular dominance plasticity in the mouse visual cortex, observed no change in the morphology of existing dendritic spines in MMP-9 KO, however, spine dynamics were altered and KO mice showed increased turnover of dendritic spines over a period of 2 days. Fragkouli et al. [91] constructed mice overexpressing MMP-9 and reported on increased spine density in the hippocampus and somatosensory cortex after behavioral training of adult animals.

SYNAPTIC CELL ADHESION MOLECULES AS MAJOR NEURONAL MMP-9 TARGETS

It may appear obvious that MMP-9 should cleave components of the extracellular matrix (ECM) surrounding the synapses. In fact, Tsien [92] has proposed that such a cleavage may relieve the synapses/dendritic spines from local environmental constraints limiting their growth, any by this virtue allowing them to undergo plastic changes supporting learning and memory. It should be noted that disruption of ECM may indeed affect synaptic plasticity [93-96]. Although, possible role of MMP-9 in ECM remodeling has been suggested by studies on the cerebellum, no clear MMP-9 substrate has emerged, and in fact we have failed to demonstrate that MMP-9 cleaves suspected substrate, tenascin-C [97,98]. Similarly, it remains as an attractive, though unproven possibility that MMP-9 might cleave CD44 that may anchor hyaluronic acid-based ECM at the neuronal cell membrane [99].

Notably, treatment with excessive exogenous MMP-9 did not produce any gross alteration of ECM in hippocampal cultures [100]. Furthermore, no ECM proteins surrounding synapses have been identified as MMP-9 substrates. In fact, most of such substrates belong to the category of cell adhesion molecules (CAMs, [101-103]). Even more interestingly, all of them are CAMs that are located postsynaptically. The group includes: β-dystroglycan, ICAM-5, neuroligin-1, SynCAM2 (synaptic cell adhesion molecule-2 also known as necl-3) and nectin-3 [79,104-108]. All of those proteins may form trans-synaptic adhesive apparatus with their presynaptic binding partners (β-dystroglycan and neuroligin-1 with neurexins, nectin-3 with nectin-1, ICAM-5 with ICAM-5, SynCAM2 with SynCam1). Other neuronal MMP-9 substrates identified to date are collapsin response mediator protein-2 (CRMP-2, [109]), NGF [110] and pro-BDNF [111].

Considering trans-synaptic adhesive apparatus as a major MMP-9 target and taking into account other aforementioned information, one may suggest that following glutamate stimulation, especially by NMDA receptors, MMP-9 is released from small dendritic spines around postsynaptic domains of excitatory synapses. Next, MMP-9 destabilizes synaptic structure by breaking trans-synaptic connections through limited cleavage of postsynaptically originating proteins bound to their presynaptic partners. This way, the post-synapse and its dendritic spine carrier are allowed to expand and maybe search for a new presynaptic partner. As soon as MMP-9 is inhibited by endogenous TIMP-1, the pre-postsynaptic connection is re-established, however in a modified, possible more efficacious form. Such a scenario is in a perfect agreement with the available experimental data and provides a good explanation for MMP-9 pivotal role in the synaptic plasticity, learning and memory.

However, the molecular mechanisms delineated above, although plausible are not proven yet. Thus, either alternative or complementary modes of MMP-9 function in synaptic plasticity have to be considered. Especially intriguing is partial cleavage of pro-BDNF to produce its mature form [111] as well repeatedly described mediation of MMP-9 synaptic effects via integrins, in particular integrin β1 [44,63,85,86].

MMP-9 AS EXECUTOR OF C-FOS FUNCTION IN SYNAPTIC PLASTICITY, LEARNING AND MEMORY?

Considering the aforementioned evidence implicating c-Fos in synaptic plasticity in learning, and its function in regulating MMP-9 and TIMP-1 gene expression, we hypothesize that c-Fos role in these phenomena might in fact be executed *via* MMP-9 and TIMP-1. A following molecular scenario might be even considered here. During learning experience, glutamate activates NMDA receptors to release MMP-9 and TIMP-1 to control the synaptic plasticity as described above. Since both proteins are released outside the cell and cannot be recuperated, there is a need to replenish them. MMP-9 activity, e.g., by converting pro-BDNF to its mature form (mBDNF) produces a signal that through TrkB receptors and ERK kinases is delivered to SRF transcription factor that is the major upregulator of *c-fos* gene expression in activated neurons. Next, the protein product, c-Fos in a form of AP-1, enhances transcription of MMP-9 gene.

MMP-9 IN NEUROPSYCHIATRIC DISORDERS: A CASE OF ABERRANT SYNAPTIC PLASTICITY?

Besides being pivotal for physiological synaptic plasticity, as described above, MMP-9 has also been implicated in aberrant plasticity that may contribute to a variety of neuropsychiatric conditions [55,112]. A particular strong case has been presented for epileptogenesis (for review: [55,113]), *i.e.,* development of epilepsy. In particular, Wilczynski *et al*. [74] reported that MMP-9 KO mice were deficient in developing epilepsy in a model of chemical kindling of seizure phenotype, whereas rats overexpressing MMP-9 selectively in neurons were more prone to this phenotype. This genetic proof-of-concept for MMP-9 in epileptogenesis was further supported by studies on chemical inhibitors of the enzyme and other animal models [111,114-116]. Recently, Pijet *et al*. [117] have employed traumatic brain injury-evoked epileptogenesis, clinically relevant mouse model, to demonstrate important contribution of MMP-9 to epilepsy development. Most interestingly, elevated MMP-9 was found in human epileptic brain samples [118-121]. Furthermore, Zybura-Broda *et al.* [121] implicated progressive increase in MMP-9 levels, possibly dependent on its gene promoter demethylation, in human epilepsy and rat epileptogenesis.

Similarly, addiction to substances of abuse has repeatedly been linked to MMP-9 levels [122-132]. Our recent study has demonstrated that MMP-9 in the central amygdala controls synaptic plasticity, as well as motivation to seek alcohol in addicted mice and, furthermore, in humans MMP-9 gene polymorphism leading to higher MMP-9 levels supports motivation towards alcohol [132].

Moreover, functional role of MMP-9 has been demonstrated in fragile X syndrome (FXS) that offers a very interesting example of autistic conditions dependent on a single gene (encoding fragile X mental retardation 1 protein, FMRP). Bilousova *et al*. [84] was the first to show that FMRP KO mice displayed increased MMP-9 activity and then Janusz et al. [78] found that local translation of MMP-9 is negatively controlled by FMRP. Thus, FMRP deficiency releases MMP-9 local translation from this negative control, resulting in higher MMP-9 levels at the synapse. Similarly, Gkogkas *et al*. [80] found that the eukaryotic translation initiation factor P-eIF4E and MMP-9 expression were both elevated in the brains of human FXS patients and in FMRP deficient mice. Furthermore, Bilousova *et al*. [84] observed dendritic spine elongation in neuronal cultures that were derived from FMRP KO, a phenomenon that could be normalized by application of minocycline, which inhibited the enzymatic activity of MMP-9. Minocycline treatment also reduced anxiety in FMRP knockout mice [84] and reversed the deficit in ultrasonic vocalizations [133]. Finally, Sidhu *et al*. [88] crossed MMP-9 KO mice with FMRP KO mice, to alleviate all of the major symptoms of FXS that were observed in FMRP KO. Recently Wen *et al*. [134] reported that MMP-9 levels were elevated in P12-P18 auditory cortex of Fmr1 KO mice and genetic reduction of MMP-9 to WT levels restored the formation of perineuronal nets (a form of ECM) around parvalbumin expressing inhibitory interneurons. Moreover, *in vivo* single-unit recordings from auditory cortex neurons showed enhanced spontaneous and sound-driven responses in developing Fmr1 KO mice, which were normalized following genetic reduction of MMP-9. In aggregate, these results addressed abnormal sensory responses associated with FXS and autism spectrum disorders. Notably, the animal data strongly supported the consideration of minocycline as a treatment for FXS. Indeed, several clinical studies that have been conducted, offerring promising results [135-137] (for review, see [139]).

Finally there is also a growing list of findings highly suggestive of a role of MMP-9 in schizophrenia [140] and Lepeta *et al.* [141] have recently shown that MMP-9 gene polymorphism located in 3'UTR of its mRNA contributes to severity of delusional symptoms in humans suffering from schizophrenia, along with affecting local MMP-9 production at the dendritic spines as well as their morphology.

CONCLUDING REMARKS

The evidence for a role of c-Fos/TIMP-1/MMP-9 pathway in synaptic plasticity appears very compelling, indeed. The evidence derives from studies documenting enhanced c-Fos and MMP-9 levels in response to stimuli that evoke plasticity and, moreover, the MMP-9 increases occur in/around stimulated excitatory synapses. Furthermore, blocking of c-Fos and MMP-9 impairs the plasticity. These data seem to explain well the role of the c-Fos—MMP-9 pathway in learning and memory, and may be also reveal how MMP-9 contributes to major neuropsychiatric disorders.

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Od c-Fos do MMP-9 w kontroli plastyczności synaptycznej zdrowego i chorego umysłu, spojrzenie osobiste

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Słowa kluczowe: uczenie się i pamięć, cząsteczki adhezji komórkowej, padaczka, autyzm, schizofrenia, uzależnienia

STRESZCZENIE

c-Fos jest składnikiem czynnika transkrypcyjnego AP-1. Trzy linie dowodów wspierają kluczową rolę c-Fos w uczeniu się i pamięci: (i) uczenie się pobudza jego ekspresję; (ii) blokowanie c-Fos upośledza, podczas gdy optogenetyczna aktywacja neuronów wyrażających c-Fos wspomaga uczenie się i pamięć; (iii) docelowe geny dla c-Fos/AP-1 w pobudzonych neuronach, kodują tkankowy inhibitor metaloproteaz-1 (TIMP-1) oraz metaloproteazę macierzową 9 (MMP-9), które to białka odgrywają kluczową rolę w plastyczności synaptycznej, leżącej u podstaw uczenia się i pamięci. TIMP-1 i MMP-9 tworzą działający zewnątrzkomórkowo układ enzymatyczny, aktywny miejscowo wokół synaps pobudzających i modulujący ich morfologię, skład biochemiczny oraz efektywność. Badania na zwierzętach sugerują zaangażowanie MMP-9 w różnych stanach neuropsychicznych, np. rozwoju padaczki, zaburzeniach ze spektrum autyzmu, rozwoju uzależnienia i depresji. U ludzi MMP-9 przyczynia się do padaczki, uzależnienia od alkoholu i kokainy, zespołu łamliwego chromosomu X, schizofrenii i zaburzeń afektywnych dwubiegunowych. Łącznie wszystkie te sytuacje można uznać za przykładowe dla zdrowego lub chorego umysłu.