

Genetic Influences on Posttraumatic Stress Disorder (PTSD): Inspirations from a Memory-Centered Approach

The development of PTSD depends on environmental exposure to a traumatic experience. Moreover, PTSD vulnerability increases proportionally to the amount of traumatic events experienced (Kolassa et al. 2010a). Given the strong environmental contribution to PTSD risk, the idea of *patho-genetics* is counterintuitive at first. However, there exists a strong genetic contribution to PTSD etiology, which exerts behavioral effects especially at low levels of traumatic load, where some individuals develop a PTSD yet others display resilience (Kolassa et al. 2010b, Kolassa et al. 2010c). In this issue, Katharina Domschke provides an excellent overview on the vulnerability genes that have been discussed with respect to PTSD. In the following, we will introduce a memory-centered framework of PTSD which can inspire genetic as well as epigenetic research on this disorder.

Pathological Memories in PTSD Etiology

Research in different areas of war and conflict revealed similar patterns of PTSD symptoms all over the globe. This observation led to the proposition of a shared physiological origin of PTSD symptoms (Elbert & Schauer 2002). Memory impairment is a core characteristic of PTSD: Trauma survivors with PTSD struggle to deliberately recall the autobiographical context details (e.g. time and space) of the trauma in a chronological order. At the same time, they suffer from vivid, intrusive memories of the experienced events (Brewin 2011).

But how do such pathological memories develop? Insights can be derived from the model of Elbert and co-workers (Elbert & Schauer 2002, Kolassa & Elbert 2007, Rockstroh & Elbert 2010), which proposes that the emotional, sensory, cognitive and interoceptive elements of a trauma are stored in an associative, strongly interconnected memory structure termed *fear network*. This strong associative memory formation is intrinsically adaptive, as it should help the organism to recall cues that are associated with life threat in order to avoid future danger. However, in the case of multiple trauma exposure, each additional traumatic experience will activate the same fear memory, since important elements (e.g. blood, fear of death) overlap. Likewise, new elements will be added to the fear network, and its interconnections strengthen. Consequently, it becomes harder and harder for the trauma survivor to distinguish the autobiographical context information associated with the different events which merge in the fear network. Due to the associative nature of a fully developed fear network, a single trauma reminder is enough to activate the entire network, which results in the typical intrusive symptoms observed in PTSD.

From Pathological Memories to Patho-Genetics

From our memory-centered perspective, two conclusions are evident: First of all, the fear memory model clearly states how cumulative trauma exposure increases the risk of the development of pathological memories in a dose-dependent manner. This strong environmental predictor can simply not be neglected. To obtain valid results, genetic association studies on PTSD risk should investigate gene×environment interactions by modeling traumatic load quantitatively. Second, genetic factors which modulate PTSD risk most likely influence the way traumatic experiences are consolidated in a pathological fear memory structure. The anatomical structures which are involved in fear memory formation are well described and comprise the amygdala, the medial prefrontal cortex and the hippocampus. The interplay of these three structures is influenced by neuroendocrinological mediators, most prominently serotonin, dopamine, noradrenaline and cortisol (Johnson et al. 2012, Rodrigues et al. 2009). As described by Domschke in this issue, genetic association studies have predominantly focused on genes coding for receptors, transporters or enzymes involved in these neuromodulatory pathways. However, not the development of trauma memories as such, but their consolidation strength and persistence leads to the pathological features of PTSD (Brewin 2008). Important insights on the molecular cascades of memory consolidation stem from translational research (for a review, see Pape & Pare 2010). Animal studies identified a protein kinase cascade composed of calcium-dependent protein kinase pathways (Ca²⁺/calmodulin-dependent protein kinase II (CAMKII); Protein Kinase A (PKA); Protein Kinase C (PKC)) and mitogen-activated protein kinases (MAPKs). These cascades eventually activate transcription factors and promote enhanced protein synthesis of targets associated with memory stabilization (Pape & Pare 2010). The different agents of these pathways are crucially involved in the long-term stabilization of memories and would therefore constitute interesting targets for genetic association studies on PTSD. Yet, few studies have investigated genes involved in the strength and stability of pathological fear memories in PTSD.

The work of de Quervain and co-workers, however, contributes significantly to our understanding of genetic factors involved in memory consolidation and their contribution to PTSD etiology. This work group recently investigated 2005 variations spanning genes involved in the aforementioned protein kinase cascade (MAPKII, PKA, PKC, MAPK and their various isoforms). Subsequent to correction for multiple comparisons, a variation in the gene encoding PKC alpha (*PRKCA* rs4790904 A allele) was found to be

significantly associated with enhanced memory and differential brain activation for negative information in a healthy Swiss sample. Moreover, this effect was mirrored by a higher PTSD risk for A-allele carriers in survivors of the Rwandan genocide (de Quervain et al. 2012). This study illustrates how a memory-centered approach can inform genetic association studies on PTSD and could inspire future studies to focus on the molecular mechanisms of fear memory stabilization.

Quo Vadis, Patho-Genetics?

The discovery of epigenetic mechanisms (i.e. DNA methylations and histone modifications) which regulate the transcription of the DNA without changing its structure (Zhang & Meaney 2010), have received broad scientific attention. The finding that the second, epigenetic code is shaped by environmental experiences is promising for a deeper understanding of the bio-molecular underpinnings of PTSD, a disorder that requires environmental stress exposure to manifest. At the same time, these new findings challenge the traditional assumptions of genetic association studies, because the polymorphisms under investigation might be epigenetically silenced in some individuals of the study population and hence do not exert any behavioral effects (Charney 2012). Consequently, the association between genotype and phenotype is much more complex than initially thought. Therefore, a mere focus on genetic associations in PTSD research provides only a partial picture, and the joint investigation of genetic variations, environmental factors and associated epigenetic modifications is necessary to obtain valid conclusions for the biological factors involved in PTSD etiology.

In spite of this clear rationale, the practical application for PTSD research is not that straight forward. Initial studies investigated methylation levels in PTSD clients as opposed to controls (cf. Domschke, in this issue). However, these studies have been confined to the investigation of peripheral cells. Since epigenetic regulation is tissue-specific, we cannot draw valid conclusions about the corresponding methylation patterns in the brain. Hence, the question how epigenetic modifications contribute to the formation of pathological fear memories has yet to be answered. Animal research, as well as advancements in the methodologies of human epigenetic studies, will help to gain further insights. In the future, the joint investigation of genetic and epigenetic risk and resilience factors might finally lead to an improved sense of the underlying bio-molecular pathways of the development of pathological fear memories in PTSD.

Acknowledgements: None.

Conflict of interest : None to declare.

References

1. Brewin CR: *What is it that a neurobiological model of PTSD must explain?* *Prog Brain Res* 2008; 167:217-28.
2. Brewin CR: *The nature and significance of memory disturbance in posttraumatic stress disorder.* *Annu Rev Clin Psychol* 2011; 7:203-27.
3. Charney E: *Behavior Genetics and Post Genomics.* *Behav Brain Sci* 2012, In Press.
4. Elbert T, Schauer M: *Burnt into memory.* *Nature* 2002; 419(6910):883.
5. Johnson LR, McGuire J, Lazarus R, Palmer AA: *Pavlovian fear memory circuits and phenotype models of PTSD.* *Neuropharmacology* 2012; 62; 638-646.
6. Kolassa IT, Elbert T: *Structural and Functional Neuroplasticity in Relation to Traumatic Stress.* *Curr Dir Psychol Sci* 2007; 16:321-325.
7. Kolassa IT, Ertl V, Eckart C, Glöckner F, Kolassa S, Papassotiropoulos A, de Quervain DJF, et al.: *Association study of trauma load and SLC6A4 promoter polymorphism in posttraumatic stress disorder: evidence from survivors of the Rwandan genocide.* *J Clin Psychiatry* 2010b; 71:543-547.
8. Kolassa IT, Ertl V, Eckart C, Kolassa S, Onyut LP, Elbert T: *Spontaneous remission from PTSD depends on the number of traumatic event types experienced.* *Psychological Trauma: Theory, Research, Practice, and Policy* 2010b; 2:169-174.
9. Kolassa IT, Kolassa S, Ertl V, Papassotiropoulos A, De Quervain DJF: *The risk of posttraumatic stress disorder after trauma depends on traumatic load and the catechol-o-methyltransferase Val(158)Met polymorphism.* *Biol Psychiatry* 2010c; 67:304-8.
10. Pape HC, Pare D: *Plastic synaptic networks of the amygdala for the acquisition, expression, and extinction of conditioned fear.* *Physiol Rev* 2010; 90:419-63.
11. Rockstroh B, Elbert T: *Traces of fear in the neural web--magnetoencephalographic responding to arousing pictorial stimuli.* *Int J Psychophysiol* 2010; 78:14-9.
12. Rodrigues SM, LeDoux JE, Sapolsky RM: *The influence of stress hormones on fear circuitry.* *Annu Rev Neurosci* 2009; 32:289-313.
13. Zhang TY, Meaney MJ: *Epigenetics and the environmental regulation of the genome and its function.* *Annu Rev Psychol* 2010; 61:439-66, C1-3.
14. de Quervain DJF, Kolassa IT, Ackermann S, Aerni A, Boesiger P, Demougin P, Elbert T, et al.: *PKC alpha is genetically linked to memory capacity in healthy subjects and to risk for posttraumatic stress disorder in genocide survivors.* *Proc Natl Acad Sci U S A* 2012; 109:8746-51.

Sarah Wilker & Iris-Tatjana Kolassa

*Clinical & Biological Psychology, Institute of Psychology & Education
University of Ulm, Albert-Einstein Allee 47, 89069 Ulm, Germany*