THE RELEVANCE OF TRAUMATIC LIFE EVENTS IN SCHIZOPHRENIA SPECTRUM DISORDERS

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The central goal of this manuscript was to review literature about the interconnections of traumatic life events and symptoms of schizophrenia spectrum of the last 15 years. First of all, the stress-diathesis model and the traumagenic neurodevelopmental model are shortly presented. Psychological effects of traumas and specific psychotic symptoms in connection with traumatic events are discussed. The course of the disease in patients affected by previous traumas and possible mediating factors are also addressed. Studies of both clinical and community samples are cited. It was also our aim to review literature about the neurobiological and neurocognitive processes in people affected by schizophrenia and/or traumatic life events. The role of prefrontal and medial temporal regions are explored with a special emphasis on contextual memory and hippocampal functioning. Finally, the possible effects of exploring traumatic life events on the treatment of schizophrenia are discussed.

Keywords: *traumatic life events, schizophrenia spectrum disorder, neurobiology*

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Tanulmányunk célja az volt, hogy áttekintsük az elmúlt 15 évben megjelent, a traumatikus életesemények és a szkizofrénia tüneteinek összefüggéseit tárgyaló szakirodalmat. Először a stressz-diatézis modellt és a traumatogén idegfejlődési modellt mutatjuk be röviden. Ezt követően a traumatikus események pszichés hatásait tárgyaljuk, illetve az egyes pszichotikus tünetek traumatikus életeseményekkel való összefüggéseit tekintjük át. Kitekintünk arra, hogyan befolyásolják a megelőző traumák a betegség lefolyását, és elemezzük a lehetséges közvetítő tényezőket. Tanulmányunk célja volt továbbá a szkizofrénia és a súlyos traumatizáció hátterében feltárható neurobiológiai és neurokognitív folyamatokat bemutató szakirodalom áttekintése is. Tárgyaljuk a prefrontális és a mediotemporalis területek érintettségét, különös tekintettel a hippocampus működésére és a kontextuális emlékezetre. Tanulmányunkat annak a kérdésnek a megfontolásával zárjuk, hogy mennyiben járulhat hozzá a traumatikus életesemények feltárása a szkizofrénia kezelésének sikerességéhez.

Kulcsszavak: *traumatikus események, szkizofrénia spektrum zavar, neurobiológia*

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There is a long history of searching for the possible connections of certain negative life events to later psychopathology. In the case of a disease with such a firm genetic basis as schizophrenia, it is an especially interesting question to understand the possible role of life events. In the last 15 years there has been a growing interest in this subject, especially after the seminal article of *Honig* et al.[1] suggesting a connection between auditory hallucinations and the reactivation of previous trauma memories. After the year 2000 several cross-sectional and longitudinal studies were performed. Our aim in this paper is to review the connections of traumatic life events and schizophrenia spectrum disorders documented in the literature of the last 15 years.

Out of the several competing models of schizophrenia two are mentioned here. Walker and Diforio's diathesis-stress model[2] proposes that the genetic predisposition of schizophrenia means an increased vulnerability which takes the form of

heightened sensitivity to stress. In terms of this model, the predisposition to develop psychosis is genetically and biologically determined and stress only plays a role in precipitating symptoms that would sooner or later develop[3]. Read's[4] traumagenic neurodevelopmental model questions that biological factors always come first in developing a heightened sensitivity to stress. According to this model, if the trauma itself is severe or long lasting enough, it can determine the person's oversensitivity for later stressors, regardless if they have a predisposition for schizophrenia or not. The reason for this is that early traumatic states cause long lasting changes in the function of the HPA system and consequently the dopamine regulation.

Later reviews of literature[5–7] are more cautious about drawing causal conclusions and they stress that very few longitudinal studies have been published in support of the connections between early traumatic life events and later psychotic symptoms and recognizing possible confounders. This way, a reversed relationship is also possible: maybe children with predisposition to schizophrenia evoke abusive actions of the environment. A further limit is that the results published so far mainly come from studies on community samples and only partly from studies on psychiatric samples which are often very small and mixed[6].

What is a traumatic event and how can it be connected to psychotic symptoms and disorders?

PSYCHOLOGICAL EFFECTS OF TRAUMATIC EVENTS

The main psychological effect of traumatic life events, that is such events where people feel their own or somebody else's life, health or integrity threatened[8], is the intense fear and helplessness. According to the broadly applied cognitive model of *Ehlers* and *Clark*[9], at the moment of the trauma the sensory impressions are not organized as a meaningful and logical whole, but the victim of the trauma switches to data-driven information processing. As a consequence, their memories become separate fragments which don't become a part of their narrative memory, even on the long term. These memory-fragments cannot be recalled intentionally; they can return independent of or against the person's will as flashback memories which is the most unpleasant symptom of post-traumatic stress disorder (PTSD). Flashback memories are from several aspects similar to hallucinations: they are intense visual and acoustic experiences in the absence of external stimuli accompanied by strong emotions and the feeling of reliving everything in the present[10, 11].

There has been an extensive research on the relationship between psychotic symptoms and early traumatic events, especially child physical and sexual abuse[12–17]and to a lesser extent physical and/or emotional neglect and bullying[18]. The way to determine and measure traumas has been relatively inconsistent and trauma concepts behind the hypotheses are often poorly defined[6].

THE INTERDEPENDENCE OF TRAUMATIC LIFE EVENTS AND PSYCHOTIC SYMPTOMS

Based on previous research on large community samples, life events and especially early traumas are positively connected to the development of psychotic symptoms, mainly the positive ones[15, 18, 19].

In a study of 182 psychiatric patients and geographically matched controls *Fisher* and colleagues[20] found that abuse, especially physical abuse committed by mothers before the age of 12 was three-fold in the history of people with psychotic symptoms compared to controls.

In accordance with previous cross-sectional research, in Lataster and colleagues'[21] 10-year follow-up of a community sample of 3021 teenagers and young adults, it was found that early adverse experiences enhanced sensitivity to stressors in later life which meant a greater risk of developing psychotic symptoms. The effects of age, gender, cannabis use and city life were controlled for.

In *Cutajar* and colleagues'[22] cohort study psychiatric symptoms of 2759 sexually abused children were followed up for more than 30 years. According to their results, people with a history of child sexual abuse used medical services 3.56 times more often than controls and the prevalence of several psychiatric disorders (posttraumatic stress disorder, anxiety, depression, eating disorders) was significantly greater in the abused group compared to controls.

Galletly and colleagues[23] in their 20-year follow-up of children surviving a natural disaster found that the number and types of other traumas and the support from family members affected more the development of psychotic symptoms later in life than the natural disaster itself.

Arsenault and colleagues[24] followed 2232 children and their families between the ages of five and 12. Children abused by adults or other children suffered significantly more often than non-abused peers from psychotic symptoms justified by a clinical test in this sample. While accidents had a week

and inconsistent correlation with symptoms later in life, abuse with the intent to hurt significantly increased the risk of later psychopathology, even after gender, socio-economical status and IQ were controlled for.

CONNECTIONS BETWEEN SPECIFIC PSYCHOTIC SYMPTOMS AND TRAUMATIC LIFE EVENTS

Based on several studies[25, 26], the association of traumatic life events seem to have a stronger association with positive than with negative symptoms. As regards to negative symptoms, no significant difference was found between abused and non-abused patient groups[27–30]. *Ross* and colleagues[25] and *Goff* and colleagues[26] found that negative symptoms were slightly less frequent in abused than non-abused patients. In contrast, *Vogel* and colleagues[31] in a sample of 25 patients with schizophrenia found an association of childhood traumas and negative symptoms. They assume negative symptoms to be defence mechanisms that help patients exclude distressing emotional and cognitive stimuli, similarly to avoidance in anxiety and post-traumatic stress disorder.

However, in *Resnick* and colleagues'[29] study avoidance as a posttraumatic stress symptom was positively correlated with the positive symptoms of schizophrenia in male patients. *Kingdon* and *Turkington*[32] also stressed the association between traumatic life events and positive symptoms and regard traumatic psychosis as a subtype of schizophrenia with the following criteria: 1) the role of trauma in the development and the content of symptoms is justified, 2) frequent command hallucinations and criticising voices, somatic and visual hallucinations and persecutory delusions in connection with the traumas, 3) fluctuating depressive symptoms, suicide phantasies, drugs, 4) therapy resistance. In our pilot study of 25 hospitalised patients[33], trauma history was found to be more frequent in patients with predominantly positive symptoms.

The association between traumatic life events and *hallucination*s was found in several studies of psychotic patients[26, 28]. Sexual abuse before the age of 16 was found to be connected (in non-clinical samples too[14, 34]).

In clinical samples several results support the significant association between early traumas and *delusions* and/or hallucinations[26, 35, 36]. *Janssen* and colleagues[35] showed the association of traumatic events and the development of psychotic symptoms in a longitudinal setting, when possible confounders (gender, age, previous psychiatric disorder, drug abuse) were controlled for.

In a small group of youngsters with prodromal psychotic symptoms *Thompson* and colleagues[37] found that childhood abuse and symptom severity were positively connected, especially in the case of delusions of grandiosity. *Bentall* and colleagues[34] showed that growing up in official care and being abused were positively connected to developing paranoid delusions.

In an early study[38] positive correlation was found between child sexual abuse and *schizophrenic thought disorder*, but this finding has not been repeated since[39] *Read* and colleagues[28] found thought disorder to be more frequents in people with a history of child and adult sexual abuse.

TRAUMATIC LIFE EVENTS AND THE COURSE OF PSYCHOTIC DISORDERS

It appears that apart from symptom development the course and outcome of the psychotic disorder and consequently quality of life and mood are also affected by trauma history. *Lardinois* and colleagues[40] argue that early traumas increase sensitivity to stress in psychotic patients which means an acquired vulnerability independent of genetically based vulnerability to stressful life events. This is in accordance with Honig and colleagues'[1] results that hallucinations are often precipitated by the activation of a traumatic memory. An important implication can be the necessity to emphasize stress management in the treatment of schizophrenic patients.

At the same time, it is widely supported that there is more risk of substance abuse in psychotic patients with a history of childhood abuse[17], compared to non-abused controls with the same diagnosis. Psychotic patients who suffered early traumas in the past need treatment at an earlier age, are hospitalized more frequently and for a longer time, get more medication and suffer from more severe cognitive, autistic and depressive symptoms compared to controls[22, 39]. Traumatised patients with schizophrenia find their own quality of life worse and therefore are at a higher suicide risk[41]. *Read* and colleagues[42] found that child abuse was a better predictor of adult suicidal behaviour in a mixed outpatient sample than co-morbid depression.

At the same time, psychiatric intervention itself can be a trauma for a large number of patients with psychosis[43, 44].

WHY ARE PEOPLE WITH PSYCHOTIC DISORDERS ESPECIALLY AFFECTED BY TRAUMA HISTORY?

Several data suggest that the connection between early traumas and later psychopathology is general

and not specific to a certain disorder, for example, schizophrenia. Childhood abuse has been documented in patients with major depression, anxiety disorders or personality disorders[45]. Vogel and colleagues[31] for example found that various types of childhood abuse and the dissociation connected to them are in a close connection with positive symptoms, but this association was true for depressed patients too. However, there are several studies suggesting that early traumatic events are more common in patients with psychotic disorders than mood disorders or alcohol dependence. According to *Bebbington* and colleagues'[46] national survey in the United Kingdom, in the group of people with psychotic symptoms sexual abuse was threefold and domestic violence and bullying were twofold compared to people with so called neurotic symptoms. In *Friedman* and colleagues'[47] sample 78% of patients with schizophrenia, but 26% of patients with panic disorder, 30% of patients with anxiety disorders and 42% of patients with major depression suffered child sexual abuse. In a sample of Hungarian psychiatric patients *Judit Nagy*[48] found that the number of negative life events per person was the highest in the group of suicidal depressive patients in the last six months before the study, but regarding the last two years, this rate was the highest in the group of patients with schizophrenia. Unfortunately, the significance of these results is not known.

TRAUMA AND PSYCHOSIS: POSSIBLE MEDIATING FACTORS

Several studies have been looking for the factors that mediate the development of psychotic disorders after previous traumas. The role of dissociation has been recognised in precipitating psychotic (especially positive) symptoms[18, 49, 50]. According to Vogel and colleagues'[51] results, high dissociation was associated mainly with child physical neglect.

Campbell and Morrison[18], Read and colleagues[28] and *Kilcommons* and *Morrison*[50] argue that apart from dissociation negative thoughts about the self were also associated with psychotic symptoms, especially hallucinations in the victims of previous abuse.

Based on studies of psychiatric samples, the mediating role of post-traumatic stress and comorbid depression were also emphasised in the development of psychotic symptoms[30, 52]. *Lysaker* and *LaRocco*[30] found that such post-traumatic symptoms as intrusion and avoidance had a significant association with delusions, whereas hallucinations were correlated with irritability and the severity of post-traumatic stress symptoms. However, no such connection was found in the case of psychotic thought disorder and negative symptoms. Based on their results, similarities of PTSD and psychotic symptomatology were emphasized.

The idea of the similarity between these two disorders was previously described in the review by Morrison and colleagues[11]. They argue that flashback memories and hallucinations, avoidance, flattened emotion in PTSD and negative psychotic symptoms are analogous phenomena, so that these two disorders may be regarded as parts of the same spectrum. This idea is supported by research data that veterans and adults who previously had been victims of child sexual abuse score the highest on schizophrenia scale of MMPI[53, 54].

Questions for further research could be the factors determining the specific form of later psychiatric disorders and also the role specific elements of the traumatic experience play in the development of psychopathology.

Neurocognitive and neurobiological processes as possible determinants of the relationship between traumatic experiences and psychotic symptoms in schizophrenia

DISTURBANCES OF CONTEXT-DRIVEN DATA-PROCESSING AND CONTEXTUAL MEMORY

Working memory and attention or the central executive system are usually disturbed in schizophrenia[55, 56] and the cause of this deficit is related to the dysfunction of prefrontal cortex. Decreased activity of this brain region has been demonstrated in several studies using mental imaging[57]. However, there is evidence that although the impairment of this region is a major characteristic of schizophrenia, cannot be specifically attributed to this illness[55].

Dysfunction of context-driven data-processing and contextual memory has also been widely demonstrated and several studies suggest this medial temporal lobe impairment to be primary deficit in schizophrenia which is independent of impaired executive functions[55].

The precondition of context-driven data processing is the complex mental representation of a certain set of stimuli or a certain event and all its surroundings. Detailed and elaborated memories do not only facilitate voluntary retrieval of memory contents, but also enhance security of remembering. Based on research data, it seems that patients with schizophrenia can only partly capture and represent a complex set of stimuli and do not encode

all the important details of an episode[55]. It is well documented that patients with schizophrenia, even if they remember a certain stimulus, they cannot at all or can only partly recall its environment and to solve a task they do not use all the contextual information[58–61].This means that in certain tasks they perform worse than healthy controls but in those tasks where data-driven information-processing is an advantage, they outperform healthy controls[62]. The deficit of context-driven data processing in patients with schizophrenia has been demonstrated by using visual[55, 58], verbal[63] and cognitive (eg. Wisconsin Card Sorting Test)[64] tasks.

Based on several results, problems of context-driven data-processing seems to be specific of schizophrenia, in comparison to healthy controls and patients with depression as well[65–67]. The latter group mainly had problems with retrieval of memories. At the same time, deficits of context-driven processing were documented in high schizotypes of community samples[68, 69]. However, *Kéri* (2008)[70], based on their own and others' results, argues that deficits of certain visual tasks are more specific to schizophrenia, compared to depression than tasks using the medial temporal cortex.

THE ROLE OF HIPPOCAMPUS AND AMYGDALA AND THEIR CO-OPERATION WITH THE PREFRONTAL CORTEX

The role of hippocampus is central in long-term memory and as a consequence, in contextual memory[55], however, the volume reduction of hippocampus and amygdale in patients with schizophrenia is well-documented[55, 71, 72.]. *Hoy* and colleagues[73] found in the MR-study of a small group of first psychotic episode patients that childhood traumatic experiences measured by self-report questionnaires were significant predictors of amygdale and hippocampus volume reduction.

Based on their study of patients with first episode psychosis *Aas* and colleagues[72] argued that amygdale volume reduction (compared to controls) plays a mediating role between childhood traumatic life events and the cognitive deficits typical of psychotic disorders, while age, gender, race and level of education were controlled for. They assumed that volume reduction of the hippocampus followed at a later stage of the illness and emphasized the importance of further research exploring the co-operation of hippocampus, amygdale and prefrontal cortex. *Grace*[57] pointed out that stress-induced deterioration of amygdale and hippocampus is likely to be mediated by dysfunction of the prefrontal cortex which is unable to fulfil the proper control of stress responses. This way, stressors have a long term negative effect on the brain, leading to the over-activity of amygdale and hippocampus and consequently the over-activity of the dopamine system and a psychotic state. According to others, the combined dysfunction of hippocampus and the prefrontal cortex may be assumed in the background of psychosis[74].

DYSREGULATION OF HPA-AXIS AND THE DOPAMINE SYSTEM

In Walker and Diforio's[2] stress-diathesis model stress-induced over-activity of HPA axis is emphasized. Originally, ventral hippocampus is responsible for the regulation of HPA axis, but in reaction to the long-lasting over-activity of HPA axis and presence of stress hormones it is also over-activated, finally deteriorates and its volume decreases[75].

The HPA over-activation decreases neuronal plasticity and immune response of the organism. High levels of stress increase adrenergic activity responsible for the stress response[76].

At the same time, because of its pivotal role in the regulation of the dopamine system with the over-activation of the hippocampus the dysregulation of dopamine activity follows. When this happens the organism cannot selectively react with increasing dopamine level to dangerous or especially rewarding or with decreasing dopamine level to harmless or not so rewarding environmental stimuli. Over-activity of the ventral hippocampus results an increase of dopamine response even to such stimuli that would normally be neglected[77]. This altered functioning might explain hallucinations and delusions in schizophrenia[78].

Walker and Diforio pointed out that in adults suffering from schizophrenia stress-induced HPA dysregulation, the increased density of dopamine receptors and the increased emission of dopamine are all typical phenomena[2, 3]. At the same time, Read and colleagues[4] argue that the dysregulation of dopamine system typical of schizophrenia have been documented in abused children also.

Taken all together, it looks like, the dysregulation of HPA axis and cortisol secretion in early years can become permanent for adulthood and it may contribute to the increased vulnerability to certain mental disorders[9, 39].

Conclusions

It is very likely that a pathway may exist between environmental adversities and psychotic symptoms that lead through hormonal and neural and consequently neuro-cognitive changes, even though a lot more longitudinal studies and studies of clinical

samples are needed. Finally, two important questions must be addressed that often come to mind when discussing traumatic life events of people with schizophrenia spectrum.

The first question is the credibility of patients' reports about their traumatic events. It has been documented repeatedly, that reports of psychiatric patients about the abuse they had suffered are reliable[28, 80], stable in time and independent of psychotic symptom severity[81] and they usually under-report and not over-report abusive experiences[82].

The second question is the relevance of traumatic life events in relation to the psychiatric treatment. As it has been discussed above, the course of the disease seems to be heavily affected by traumatic experiences of the patients. At the same time, trauma history may determine how much patients trust their therapists and according to *Lysaker* and colleagues'[83] study there is a difference between abused and non-abused patients even after psychotic symptom severity was controlled for, although therapists did not notice it at all.

It would be too long to discuss effectiveness of different types of psychotherapy in patients with schizophrenia and trauma history in this paper. However, there seems to be a consensus that not all patients need and want psychotherapy but exploring and understanding the relationship between life events and symptoms previously hard to understand may have a therapeutic effect in itself[35].

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