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Mild depressive symptoms mediate the impact of childhood trauma on long-term functional outcome in early psychosis patients.

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Abstract

Introduction: The mechanism linking childhood trauma (CT) to the functional deficits observed in Early Psychosis (EP) patients is as yet unknown. We aim to examine the potential mediating effect of depressive symptoms in this well-established association.

Methods: 209 EP subjects aged 18-35 were assessed for functioning and psychopathology after 2, 6, 12, 18, 24, 30 and 36 months of treatment. Patients were classified into Early-Trauma if they had faced at least one experience of abuse (physical, sexual, or emotional) or neglect (physical or emotional) before age 12, and Late-Trauma if the exposure had occurred between ages 12 and 16. Diagnosis was based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). Psychopathology was assessed with the Positive and Negative Syndrome Scale and the Montgomery-Asberg Depression Rating Scale. Functioning was measured with the Global Assessment of Functioning (GAF) and the Social and Occupational Functioning Assessment Scale (SOFAS). Mediation analyses were performed in order to study whether the relationship between CT and functioning was mediated by depression.

Results: When compared with non-exposed patients, Early but not Late-Trauma patients showed lower levels of GAF and SOFAS scores over all the time points, excepting after the first assessment. After 30 and 36 months, the effect of Early-Trauma on functioning was completely mediated by depression. No mediating effect of positive or negative symptoms was highlighted at those time points.

Conclusion: Mild depressive symptoms mediated the impact of Early-Trauma on long-term functional outcome. Intensifying pharmacologic and/or psychotherapeutic treatment, focused on the depressive dimension, may help traumatised EP patients to improve their functioning.

Introduction

Functional impairment can be observed at all stages of psychotic disorders and remains a major challenge for treatment¹. Currently available medication have significant impact on positive symptoms, but improvement in this domain unfortunately do not correlate well with functional recovery²⁻⁴. Functional impairment is a broad term that covers activities of daily living, vocational activities, social relationships, and degree of independence; it is a key element of outcome in psychotic disorders which greatly impacts the burden of social disability^{5, 6}. We therefore need to develop a better understanding of the mechanisms contributing to these impairments, in order to improve current treatments. This remains one of the most difficult challenges for clinicians in this field⁷.

Recent research suggests that exposure to childhood trauma (CT) is a potential determinant of functional impairments in both chronic^{8, 9} and first episode of psychosis (FEP) patients^{10, 11}. Previous research has suggested that a better understanding of the psychological processes that link social adversity with functional impairments could provide new insights, with possible therapeutic implications¹². Along these lines, it has been recently suggested that so-called “ancillary symptoms”¹³ of psychosis (depression, anxiety, dissociation) might operate as mediators between social risk factors and psychotic symptoms, thus providing targets for psychological therapy in psychosis¹⁴⁻¹⁹. None of these studies, however, do comment on how social environmental risk factors lead to functional impairments in psychotic patients. Exploring potential mediators between CT and this important outcome may pave the way for helpful interventions in this domain.

Some studies in psychotic patients have linked CT to higher depressive symptoms^{20, 21}, full-blown depression²²⁻²⁴ and to a lack of response or remission in depression during psychotherapeutic and pharmacological treatments²⁵. On the other hand, literature has shown that patients suffering from schizophrenia with concurrent depressive symptoms have poorer long-term functional outcomes compared to non-depressed patients²⁶, and that depressive symptoms are indicator of poor prognosis regarding recovery and integration in the community²⁷. Connecting these findings with previous considerations highlighting the potential mediating role of “ancillary symptoms” in the psychotic processes¹³, we hypothesize that depressive symptoms may also operate as mediators between CT and functional deficits in patients suffering from psychosis.

A recently published paper by Palmier-Claus J. et al.,²⁸ explored this question in a sample of 44 patients. Its results suggest that childhood adversity acts on social functioning by increasing levels of depression, which is in line with our hypothesis. However, in addition to its limited sample size, this study was performed in a heterogeneous sample combining Ultra High Risk, FEP and chronic patients. Moreover, its cross-sectional and retrospective design did not enable exploration of the dynamic aspects of this interaction. These factors limit the conclusiveness of these promising results, which therefore need to be replicated in a larger, prospective and more homogeneous sample of EP patients.

Based on these elements we hypothesized, in a sample of 209 EP patients treated in a specialized program for 3 years, that severity of depressive symptoms would mediate the impact of CT on the functional level of patients at different time points of the follow-up. We have recently shown that only patients exposed to trauma before the age of 12

(and not later) show functional impairments during the three years of follow-up compared to non-exposed patients¹². According to these findings we also stratified patients according to their age at the time of exposure to the initial traumatic event.

Methods

Procedure and subjects

TIPP (Treatment and early Intervention in Psychosis Program), a specialized early psychosis program, was launched in 2004 at the Department of Psychiatry CHUV, in Lausanne, Switzerland^{29, 30}. Entry criteria to the program are: (I) age between 18 and 35; (II) residing in the catchment area (Lausanne and surroundings; population about 300 000); (III) meeting threshold criteria for psychosis, as defined by the 'Psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States (CAARMS³¹) scale. Patients are referred to other treatment programs if they have been taking antipsychotic medication for more than a total of 6 months, have psychosis related to intoxication or organic brain disease, or have an intelligence quotient below 70. In the TIPP program, each patient is followed up by a psychiatrist and a Case manager. The program offers an integrated bio-psycho-social treatment based on psychotherapy, psycho-education, family support, cognitive assessment and remediation (when needed), social support, assistance in finding employment, psychological interventions for cannabis use, and pharmacological treatment. The last is applied based on international guidelines and favors atypical antipsychotic. Any side effects due to medication are prospectively monitored³⁰.

A specially designed questionnaire is completed for all patients enrolled in the program by their case managers who have up to one hundred instances of contact with patients during the three years of treatment. It assesses demographic characteristics, past medical history, exposure to life events as well as symptoms and functioning. It is completed on the basis of information gathered with patients and their family over the first few weeks of treatment and can be updated during follow-up if new information emerges. Follow-up assessments, exploring various aspects of treatment and co-morbidities (such as the level of insight; the treatment adherence; the presence or absence of forensic history and substance use; intermittent exposure to trauma; suicide attempts and forensic events) as well as evolution of psychopathology and functional level, are conducted by a research psychologist (for psychopathology) and by case managers (for functional measures) after 2, 6, 12, 18, 24, 30 and 36 months of treatment.

The Research and Ethics Committee of the Faculty of Biology and Medicine of Lausanne University granted access to TIPP clinical data for research purposes. Therefore, every patient that takes part in TIPP automatically participates in this study, without exception. This is a prospective study based on the first 221 patients who had been enrolled in the program and who had been in treatment for 36 months.

Diagnostic Assessment

Diagnosis is the result of an expert consensus and is based on the following elements:

- (1) Diagnosis based on DSM-IV criteria³² reported by a treating psychiatrist in all medical documents and at the end of any hospitalization;
- (2) Longitudinal assessment by psychiatrist and clinical case manager over the 3 years of treatment. The consensus

diagnosis procedure is realized by a senior psychiatrist (LA & PB) and the senior psychologist (CF) in charge of scale-based assessment over the treatment period. They both review the entire file once after 18 months and again after 36 months (or at the end of treatment), and conduct a diagnostic process discussing any unclear issue with the clinical case manager. In this study we considered the diagnostic consensus conducted after 36 months. In case of changes between the 18- and the 36-month evaluation, the 36-month diagnosis was considered. In order to determine the overall rates of depression, we considered diagnosis of depression as a primary diagnosis of major depression with psychotic feature and/or as a co-morbidity.

Assessment of History of Past Trauma

Clinicians at TIPP are trained to conduct an extensive assessment of patients, including evaluation of exposure to traumatic life events. Case managers meet patients frequently over the treatment period, which provides the framework to establish a trusting relationship, where extensive knowledge of patients' history can be gathered. If patients agree, information can also be completed with family. In the case of inconsistency between the patient's and the family's report or in case of doubt regarding the exposure to trauma or the age at the time of exposure, patients were not included in the study¹².

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Case managers complete a table during the patients' three years of treatment, where exposure to traumatic life events can be recorded as follows: (1) Type of traumatic life event, rated as present or absent (sexual abuse, physical abuse, emotional and physical neglect, emotional abuse, among others...); (2) time of occurrence in relation

to psychosis stage (during the premorbid phase, during the prodrome or after onset of psychosis); (3) age at the time of first exposure to each one of the traumas that occurred and (4) single or repeated exposure to each one of the traumas that occurred. Considering that the clinicians who assessed exposure to life events did not rate the subjective perception of severity of the different forms of stressful events, patients were considered traumatized if they had been exposed to at least one experiences of abuse (physical, sexual, or emotional) or neglect (physical or emotional). The consideration was that such events would undoubtedly be considered as highly traumatizing by anyone, and have been shown to be associated with risk for psychosis and functional deficits in psychotic samples^{20, 33-35}. Sexual abuse refers to sexual molestation and/or rape. Physical abuse refers to physical attack or assault, or being repetitively beaten by parents, relatives or caregivers. Emotional abuse was defined as verbal assaults on a child's sense of worth or well-being or any humiliating or demeaning behavior directed toward a child by an adult or older person. Physical neglect was defined as the failure of caretakers to provide for a child's basic physical needs, including food, shelter, clothing, safety, and health care. Emotional neglect was defined as the failure of caretakers to meet children's basic emotional and psychological needs, including love, belonging, nurturance, and support³⁶.

Age at the time of first exposure was categorized as follows (1) Early-Trauma refers to exposure between birth and age 12, according to conventions applied elsewhere³⁷⁻⁴⁰, (2) Late-Trauma refers to exposure between ages 12 and 16. Patients who were exposed to trauma after age 16 were excluded from this study, according to other

studies⁴¹ suggesting that they may already have been in the prodromal phase of their first psychotic episode.

Level of Functioning

The level of functioning during follow-up was assessed with the Global Assessment of Functioning (GAF; APA, 1994³²) scale and the Social and Occupational Functioning Assessment Scale (SOFAS; APA, 1994³²). While the SOFAS only takes the social and occupational functioning into account, the GAF also includes the level of symptoms. The GAF scale is a one dimension scale rated from zero to 100 on the basis of anchor definitions: indeed, it provides a very global rating of mixing functional and symptomatic elements. For this reason, we have also conducted ratings on the basis of the SOFAS which is very similar to the GAF except that it does not include psychopathological elements in the definition of the various anchors. As such, these two dimensions were rated separately. The psychometric properties of these instruments have been attested^{42, 43}. All patients were assessed on the basis of the GAF and SOFAS scales at each time-point of the follow up (after 2, 6, 12, 18, 24, 30 and 36 months). Instead of relying on a categorical definition of functional recovery (which is dependent on one or several cut-off scores), these scale were taken as continuous variables when comparing the three groups of patients (Non-trauma, Early-Trauma and Late-Trauma).

Level of depressive, positive and negative psychotic symptoms.

Depressive, positive and negative symptoms were evaluated at each measurement occasion (after 2, 6, 12, 18, 24, 30 and 36 months of follow-up). Depressive symptoms were assessed using the total score of the Montgomery-Asberg Depression Rating

Scale (MADRS⁴⁴). The MADRS is a 10-item scale commonly used to measure the severity of depressive symptoms. The 10 MADRS items were selected for their ability to detect changes due to antidepressant treatment and their high correlations with overall change in depression. The level of positive and negative symptoms was assessed using the total score of the positive and negative components of the Positive and Negative Syndrome Scale (PANSS^{45, 46}). PANSS is a scale which is used to measure psychotic symptoms. It is composed of 30 items (1-7 severity scale) divided into 3 sections: the positive (7 items), the negative (7 items) and the general section (16 items).

Statistical analysis

Mediation analysis was performed in order to study whether the relationship between trauma and functioning was mediated by depressive symptoms. For each measurement occasion, a series of path analysis models were estimated with early/late trauma as two independent dummy variables and MADRS scores as the mediating variable. Because GAF and SOFAS scores were highly correlated ($<.90$) at each time point, the GAF and SOFAS scores were introduced simultaneously as the two dependent variables. These models allowed to determine whether significant indirect effects between trauma and functioning variables could be observed. Such indirect effect indicates the amount of mediation. Partial mediation is the situation in which the path between trauma and functioning (also called the direct effect) is reduced but still statistically significant when the mediator is introduced. Complete mediation describes the case where the path between trauma and functioning is no longer significant after the introduction of the mediating variable. To verify whether depressive symptoms only could mediate the relationship between trauma and functioning, positive and negative symptoms were also

considered as potential mediators in two series of alternate models. These path analysis models were estimated using maximum likelihood estimation and bootstrapped standard errors using the Mplus v7.4 software⁴⁷. All statistical tests were two-tailed and significance was determined at the .05 level. Considering indices of fit indicated perfect fit, we did not report these values.

Results

Patient sample

Of the first 221 patients consecutively admitted to TIPP between 2004 and 2012 and for which data was available at the time of the study, 12 patients were excluded for the following reasons: (I) Age at exposure to trauma was not available, or there was a doubt about the exactly age (n=2); (II) First exposure to trauma occurred during their prodromal phase (n=4), after psychosis onset (n=3) or after age 16 (n=3); (III). Therefore, analysis was carried out on the data of 209 patients.

Rates of Trauma, demographic characteristics

The diagnostic breakdown, the baseline and demographic characteristics of the sample, the treatment adherence, the program commitment and the number of hospitalizations are described in Table 1. Among the 209 patients, 72 (34.4% of total patients) had a history of Trauma. Within the Trauma group, 52 (72.2% of exposed patients) had been exposed before age 12 (Early-Trauma) and 20 (27.8% of exposed patients) between age 12 and 16 (Late-Trauma). There were no differences in terms of diagnostic distribution, demographic and baseline characteristics, neither between exposed and

non exposed patients, nor between those exposed early and late. There were only 43 (20.6%) patients with a diagnosis of depression in the entire sample. Among the Non-Trauma patients, 22 (16.1% of this group) had a diagnosis of depression; among the Early-Trauma patients, 17 (32.7% of this group) had a diagnosis of depression; and among the Late-Trauma patients only 4 (20.0% of this group) had a diagnosis of depression.

Effect of Early and Late trauma on the level of functioning of patients during follow-up

At the 2 months time-point, Early and Late-Trauma were not significantly related to functioning as assessed by the GAF (Early-Trauma: $B = -3.412$, $p = .205$; Late-Trauma: $B = -2.010$, $p = .542$). Early-Trauma was related to the SOFAS (Early-Trauma: $B = -5.126$, $p = .044$) but not Late-Trauma ($B = -1.011$, $p = .754$). Most importantly, at all the other time points, as illustrated in figure 1 (left for GAF scores and right for SOFAS scores), Early-Trauma was significantly related to functioning, while this was not the case for Late-Trauma.

Mediating effects of depressive symptoms on the link between trauma and the level of functioning of patients during follow-up

As there was no effect of Early or Late-Trauma on the level of functioning (GAF) after 2 months, accordingly, no mediating effect from depressive symptoms could be expected. For the SOFAS, there was no mediating role of depressive symptoms between Early-Trauma and functioning. After 6 months of follow-up, the effect of Early-trauma was only partially mediated by depressive symptoms (Figure 1a and 1b). Although there was a

significant indirect effect of depressive symptoms between Early-Trauma and functioning assessed by the GAF ($B = -3.678, p = .031$), the direct effect of Early-Trauma was still significant ($B = -5.209, p = .039$). The same pattern of results could be observed when functioning was assessed by the SOFAS (Figure 1b; Indirect effect: $B = -3.448, p = .027$; Direct Effect: $B = -5.885, p = .014$). For the 12 months, 18 months and 24 month's time-points, depressive symptoms did not play any mediating role between trauma and functioning. After 30 (Figure 2) and 36 months (Figure 3) of follow-up, the effect of Early-trauma on functioning was completely mediated by depressive symptoms. There was a significant indirect effect between Early-Trauma and functioning measured by the GAF after 30 months (Indirect effect: $B = -4.542, p = .015$) and 36 months; Indirect effect: $B = -5.785, p = .003$). The direct effect of Early-trauma was not significant anymore indicating that the overall effect of Early-Trauma could completely be accounted for by depressive symptoms. Results when functioning was measured with the SOFAS were exactly the same after 30 months (Indirect effect: $B = -4.398, p = .014$) and 36 months ($B = -5.127, p = .004$).

It is worth noting that after three years of follow-up, Non-Trauma patients scored on average 8.14 points ($SD = 6.41$) to the MADRS scale which corresponds to mild depression levels (7 to 19 points; ⁴⁸). Early-Trauma patients scored on average 5.08 points higher ($p = .003$) and Late-Trauma patients scored 3.90 points higher ($p = .162$) than Non-trauma patients which also falls into the mild depression category. Earlier in the follow-up (2 months) Non-Trauma patients scored on average 14.19 ($SD = 9.04$) while Early-Trauma patients scored 5.56 points higher ($p = .009$) and Late-Trauma patients scored 3.31points higher ($p = .304$). After 18 months Non-Trauma patients

scored on average 11.79 (SD = 9.18) while Early-Trauma patients scored 1.97 points higher ($p = .340$) and Late-Trauma patients 0.61 points higher ($p = .844$). In other words, overall depressive symptom levels were low and decreasing over time.

Mediating effects of positive and negative symptoms on the link between trauma and the level of functioning

Positive and negative symptoms measured with the PANSS were next considered as potential mediators in order to verify whether depression only could mediate the relationship between trauma and functioning. As illustrated in Figure 1, positive symptoms had a total mediating effect at 24 months of follow-up for GAF and SOFAS. For all others time-points (2, 6, 12, 18, 30 & 36 months), impact of trauma on functional outcome was mediated neither by positive nor by negative symptoms.

Discussion

The current study demonstrates, in a sample of EP patients, that poorer functional levels at 30 and 36 months in patients exposed to CT when compared to of non exposed patients, is completely mediated by the severity of depressive symptoms. Long-term effects of Early-Trauma on functioning was not accounted for by positive and/or negative symptomatology at those time points. This reveals an important mediating role of depression in this association at the end of the treatment period. Our study also shows that the mediating role of depressive symptoms exists only in patients exposed to CT before the age of 12; this is understandable, considering that patients

exposed to trauma at a later age, as previously shown¹², have a better outcome at 30 and 36 months and do not display lower functional level than non exposed patients.

The mediating role of depressive symptoms between early adversity and the onset and persistence of psychotic experiences has been highlighted recently in different studies^{13, 16, 17, 49}. However, to our knowledge, Palmier-Claus J. et al., study²⁸ and ours are the only two studies addressing the potential mediating role of depression on the link between early adversity and the functional outcomes in EP patients. Our results confirm findings reported by Palmier-Claus J. et al.,²⁸ in a larger, more homogeneous sample of EP patients followed-up in a prospective setting.

These results have important therapeutic implications and open new avenues for future research. They suggest that mild depressive symptoms, even if they are below the diagnostic threshold for depression, may be a useful target to aim at with pharmacological and/or psychotherapeutic treatment in patients exposed to severe trauma, particularly in those exposed prior to the age of 12. They also suggest that psychotherapy focusing on the negative perceptions of self, anxiety, insomnia and depressive mood - symptoms that are part of the depressive syndrome - may also help patients to improve some of their social and vocational difficulties. In addition, in future prospective studies it would be very interesting to stratify patients according to the time at exposure to trauma, and examine whether depressive symptoms, (but also some other possible factors such as anxiety, dissociation, insomnia...) may mediate the link between trauma and positive symptoms. In addition, if our results are confirmed, it would be important to try and develop interventions and explore in the frame of a

randomized controlled trial, if the treatment of sub-threshold depression would improve outcome in such patients.

Primary diagnosis of depression with psychotic features was rare in our sample (2.4%), and an additional 18.2% of patients displayed co-morbid depression. However, using depressive symptoms based on the MADRS's score as a continuous variable, we could show that sub-diagnostic depressive symptoms were determinant regarding outcome. This provides additional support to the utility of a dimensional approach of psychiatric disorders⁵⁰⁻⁵² and highlights the importance of exploring sub-diagnostic non-psychotic symptom in EP patients.

Our data showed in addition that while positive symptoms mediated the link between trauma and functional level, they did so only at the 24-months follow-up. This limited impact of positive psychotic symptoms is in line with Palmier-Claus J. et al.,²⁸ who did not find any mediating effect of paranoia between childhood adversity and social functioning. This observation may explain why treatments aimed mainly at the resolution of positive symptoms are not sufficient to improve patients' functioning level^{2, 3, 7} and again highlights the importance of addressing other potential mediators¹³ such as attachment styles^{53, 54} or social cognition⁵⁵. Besides these elements, the fact that we only found this significant mediating effect of positive symptoms at one time point is intriguing and needs to be further explored in future studies.

It is important to mention that the mediating effect of depressive symptoms between CT and functional outcome was only found in patients exposed to trauma before the age of 12, which provide additional evidence for a differential impact of trauma according to

age at the time of exposure^{40, 56}. This may be linked to the neuro-developmental stage of patients at the time of exposure to trauma which may be linked to different degree of brain vulnerability⁵⁷⁻⁶¹. Taking this into account, and stratifying patients cohorts according to age of exposure to stress may be important in future research in order to better understand the link between trauma and patient's outcome.

The absence of a mediating effect of depressive symptoms before the 30th month time point in traumatised patients may be linked to the progressive development of insight over time in our sample⁶². As mentioned by others⁶³⁻⁶⁶, the development of insight often goes along with the emergence of depressive affects, which may in turn impact functional levels. It is therefore critical to explore this process in patients and to offer support and psychological approaches that promote integration of the episode along with psycho-education, in order to prevent self stigmatisation and pessimism.

Our study has various limitations. Firstly, exposure to CT was assessed retrospectively, which may be particularly problematic for patients suffering from psychosis due to recall bias⁶⁷. However, exposure to trauma was assessed on the basis of information obtained from patients and their families in the context of a 3-year therapeutic relationship⁶⁸. This reduces the risk of recall bias existing in other forms of self-report or cross-sectional research interviews⁶⁹. Secondly, we did not explore some aspects of trauma exposure, such as repetition, length of exposure or the nature of the perpetrator, variables that have all been shown to modulate the impact of trauma on later outcomes^{40, 70} and that may have played a role in our results. Thirdly, the mediation models being cross-sectional, they assume that functioning is mediated by mood, while mood could actually also be mediated by functioning. While this may suggest reciprocal interactions between

depressive symptoms and functioning, it is worth noting that when depressive symptoms and functioning were to permutated in the mediation models, we did not observe a complete mediation of the effect of early trauma on depressive symptoms. Finally, the fact that patients have received specialized comprehensive treatment may have influenced the results, possibly reducing the size of the difference between groups.

Despite these limitations, this study shows that the persistence of the impact of trauma on functional outcome in patients who were exposed to trauma in early childhood is completely determined by depressive symptoms. This suggests not only that clinicians should explore this dimension very carefully in such patients but also that even at sub-diagnostic levels these symptoms may have a significant impact on functional recovery. If confirmed, these results may pave the way for the development of specific interventions that may contribute to improve this aspect of outcome, which so far has resisted to most of the approaches which can be offered to these patients.

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Figure Legends

Table 1. *Demographic and baseline factors related to Early or Late exposure to sexual, physical and/or emotional abuse and/or emotional and physical neglect (Trauma).*

Fig.1. *Level of functioning measured with the Global Assessment of Functioning Scale (GAF; left) and the Social and Occupational Assessment of functioning Scale (SOFAS; right) with assessments after 2, 6, 12, 18, 24, 30 and 36 months of treatment.*

Footnote (Fig.1). At the 2 months time point there were no differences in terms of Global Assessment of Functioning (GAF) and the Social and Occupational Assessment Scale (SOFAS) scores between Early nor Late Trauma patients, and No trauma patients. At the 6, 12, 18, 24, 30 and 36 time points, Early Trauma patients showed lower levels of GAF score, while this was not the case for Late Trauma patients. (*1): At the 6 months time point a partial mediation of depressive symptoms between Early trauma and GAF scores was observed. (*2) : At the 24 months time point a total mediation of positive symptoms between Early trauma and GAF scores was observed. At the 30 (*3) and 36 (*4) months time points a total mediation of depressive symptoms between Early trauma and GAF scores was observed.

Fig.2. *Analyses showing the mediating effect of depressive symptoms between trauma and functional outcomes after 30 months of follow-up.*

Footnote (Fig.2). * $p < .05$, ** $p < .01$; MADRS: Montgomery Asberg Depression Rating Scale; GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Assessment Scale.

Fig.3. Analyses showing the mediating effect of depressive symptoms between trauma and functional outcomes after 36 months of follow-up.

Footnote (Fig.3). * $p < .05$, ** $p < .01$; MADRS: Montgomery Asberg Depression Rating Scale; GAF: Global Assessment of Functioning; SOFAS: Social and Occupational Assessment Scale.