Childhood adversities and Psychosis

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Childhood adversities and Psychosis:
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**Childhood adversities and Psychosis:
investigation of the potential
aetio-pathogenetic mechanisms**

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By

Giovanni Mansueto

Supervisor:

Prof. dr. Koen R.J. Schruers

Co-supervisors:

Prof. dr. Fiammetta Cosci, University of Florence, Florence, Italy

Prof. dr. Ruud van Winkel, KU Leuven, Leuven, Belgium

Assessment Committee:

Prof. dr. Philippe A.E.G. Delespaul (Chairman)

Prof. dr. Bart P.F. Rutten

Dr. Rikus Knegtering, Lentis Mental Health Institution, Groningen, Netherlands

Prof. dr. Richard Bruggeman, Universitair Medisch Centrum Groningen, Netherlands

Prof. dr. Thérèse A.M.J. van Amelsvoort

The research presented in this thesis was performed at the School for Mental Health & Neuroscience (MHeNS), department of Psychiatry & Psychology, Maastricht University, Maastricht, the Netherlands

*“Accadono cose che sono come domande. Passa un minuto,
oppure anni, e poi la vita risponde.”*

Alessandro Baricco

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Chapter 1

General Introduction

1.1 The spectrum of psychotic disorders

According to the Diagnostic and Statistical Manual of Mental Disorders (APA, 2013), the psychotic spectrum disorder is defined by the following categories: delusional disorder, brief psychotic disorder, schizophreniform disorder, schizophrenia, schizoaffective disorder, catatonia, schizotypal personality disorder, psychotic disorder due to substance/medication or medical condition, unspecified schizophrenia spectrum (APA, 2013; Heckers et al 2013; Van os, 2015). These categories represent different manifestations of the same syndrome and can be differentiated on the basis of the level of severity and persistence of the symptomatologic domains (i.e., delusions, hallucinations, disorganized thinking, abnormal motor behaviour, negative symptoms) (Heckers et al 2013; Van Os, 2015;). The lifetime prevalence of the spectrum of psychotic disorders has been estimated around 3.5% (Van Os, 2015).

Psychotic manifestations also vary during the longitudinal development of the psychotic disorder and different stages of schizophrenia have been proposed (Fava and Kellner, 1993; Lieberman et al 2001; McFarlane, 2009; Agius et al., 2010; McGorry et al., 2010; Cosci and Fava, 2013). In the 1993, Fava & Kellner suggested a prodromal phase, characterized by early symptoms (mainly affective and negative symptoms) with impaired functioning; a second stage is characterized by the acute psychotic episode; a third stage characterized by residual symptoms (e.g.: social withdrawal, blunted affect eccentric behaviour, mannerisms, diminished positive symptoms as odd thoughts, conceptual disorder) (Fava and Kellner 1993; Schennach et al 2014); a fourth stage represented by sub-chronic symptoms, that is symptoms lasting less than 2 years but more than 6 months; and a fifth stage with chronic symptoms (i.e., the illness lasts more than 2 years). Lieberman et al (2001) proposed a slightly different model adding the premorbid stage (e.g.: mild physical anomalies, poor motor coordination, mild cognitive impairments, social deficits) and integrating the residual and chronic phase at the same stage of the model. McFarlane (2009) theorized 4 stages: the premorbid state (slight indicators of disturbance of thinking and functioning); the prodrome stage (slight psychotic symptoms that did not meet the criteria for schizophrenia diagnoses); the first psychotic episode; the chronic illness (numerous relapses, significant disruption of functioning). Agius et al (2010) proposed a three-phase model: a period of high risk of development (characterized by the loss of grey matter and changes in cognition); the

first episode of illness and progressive cognitive decline; and the chronic phase (disruptions in neurodevelopment or neural plasticity). McGorry et al (2010) identified 8 stages: an increased risk of psychotic (or severe mood) disorder although there were no current symptoms (Stage 0); mild or nonspecific symptoms (Stage 1a); moderate sub-threshold symptoms (Stage 1b); the first episode of psychosis (or severe mood disorder mania or depression) (stage 2); an incomplete remission from the first episode (Stage 3a); recurrence or relapse of psychotic (or mood) disorder (Stage 3b); multiple relapses and objectively worsening in clinical extent and the impact of illness (Stage 3c); severe and persistent or unremitting illness (Stage 4).

Finally, a systematic review of the literature conducted by Cosci & Fava (2013) integrated the aforementioned models and suggested the following four stages of schizophrenia: a prodromal phase characterized by the presence of affective symptoms, mild psychotic symptoms and impaired functioning (Stage 1); the acute manifestation defined by the presence of severe positive and negative symptoms, affective symptoms and cognitive impairments (Stage 2); the residual phase with symptoms such as depression, trouble concentrating, trouble sleeping, being tense and nervous, restlessness and loss of interest, social withdrawal, blunted affect, eccentric behaviour, mannerisms, diminished positive symptoms (Stage 3); the chronic phase, with attenuated symptoms lasting for 6 months to 2 years or with persistent symptoms lasting more than 2 years (Stage 4).

1.1 Childhood adversities: definition and epidemiology

Childhood adversity is a broad term that denotes exposure to a range of unpleasant conditions, occurring before the age of 16, that exceeds one's ability to integrate the emotional experience and can affect the child's psychological development and own wellbeing throughout an individual's life (Reviere 1996; Bernstein et al 2003; Faravelli et al 2007; Pawlby et al 2017). The World Mental Health survey of 51,945 subjects conducted by Kessler et al (2010) estimated that, across all countries, around 60% of subjects were exposed to one childhood adversity while the prevalence of exposure to two or more adversities was around 40%. Early adversities tend to co-occur and persist over time, often in worsening cycles of disadvantage and vulnerability in which one difficulty leads to others (Morgan and Anderson, 2016). As shown by the Adverse Childhood Experience (ACE) study (Dong et al 2004), the exposure to one early adversity is associated with 2-18-fold increased risk of having additional early events. The co-occurrence of childhood adversities is clinically relevant since the negative short- and long-term influence of early adversities on behaviours, emotional, well-being, and health has repeatedly been shown to be cumulative (Dong et al 2004).

Childhood adversities are usually subtyped as follows: sexual/physical/emotional abuse, neglect, early parental loss (Bernstein et al 2003; Varese et al 2012). Sexual abuse is the involvement of a child or adolescent in sexual activity which cannot be understood, the person is unable to give consent to or is not developmentally prepared for it (WHO, 2002; Bernstein et al 2003). Physical abuse is an act of commission by a caregiver that causes actual physical harm or has the potential for harm (WHO, 1999). Emotional abuse includes acts that have an adverse effect on the emotional health of the individual, such as denigration, ridicule, threats, intimidation, discrimination, and rejection (WHO, 2002). Neglect concerns the failure of the caregiver to take care of the child's physical, emotional, and psychological needs (e.g., providing food, shelter, clothing, safety, health care, love and belonging) (WHO, 1999; Bernstein et al 2003). Finally, early parental loss events are represented by parental death or separation from one of the parents for six or more months (Faravelli et al 2001; Varese et al 2012). The literature emphasises the importance of taking into account the different subtypes of childhood adversities as they may have different impact on the mental health (Clausen and Crittenden, 1991; Blaauw et al 2002; Fisher et al 2010).

1.2 The relationship between childhood adversities and psychosis

In the last decade, substantial evidence has been accumulated to show that psychotic disorders are associated with a wide range of childhood adversities. Meta-analyses estimated that, regardless of the research design, the exposure to early adversities is associated with a 2-4-fold increased risk of psychosis (Morgan and Anderson, 2016). The strength of the association between early events and psychosis is highlighted by findings showing that this relationship persists beyond potential covariates as familial psychiatric history, psychiatric comorbidities, cannabis use, genetic risk, ethnicity, education level (Gibson et al 2016). Thus, early adversities might be in part independent from these variables.

Childhood adversities were found positively correlated with prodromal symptoms (Lataster et al 2006; Thompson et al 2009; Sommer et al 2010) and highly prevalent in subjects at ultra-high risk for psychosis (UHR) and in those with first episode of psychosis (FEP) (Mondelli et al 2010; Tommasi et al 2017) if compared to healthy controls (ranging from 42.7% to 60%) (Kraan et al 2015). In addition Trotta et al (2015) showed that the transition from UHR to FEP status might be more likely among subjects with early adversity than those not exposed. Within the staging models of schizophrenia (Cosci and Fava, 2013) these findings suggest that it is likely that childhood events are involved in the prodromal phase of schizophrenia influencing its progression to the acute manifestation (Figure 1).

The data evaluating the cumulative effect of early events suggested that experiencing more than one childhood adversities is associated with an increased risk for psychosis (Morgan and Anderson, 2016). Epidemiological studies showed that when the exposure to single childhood adversity was followed by re-victimisation to two or more adversities the odd ratio for psychosis increased from 2 to 7 (Shelvin et al 2007a; Shelvin et al 2007b; Shelvin et al 2011). Moreover, childhood adversities seem to have a “pathoplastic effect” on psychosis once the disorder is developed: greater is the severity of the symptoms, more persistent is the symptomatic course, and lower the functioning (Trotta et al 2015).

The literature also suggests a degree of partial specificity between different types of early adversities and psychosis (Bentall et al 2014). The transition from the UHR state to the FEP seems to be predicted by the experience of childhood sexual abuse but not by physical abuse, emotional abuse, or neglect (Trotta et al 2015). Childhood abuse or neglect lead to a 2 to 3-fold increased risk of psychosis while childhood loss does not influence such a risk (Varese et al 2012). Cutajar et al. (2010) found that while child sexual abuse involving penetration is associated with 2-3-fold increased risk of psychosis, abuse without penetration was not associated to it. Furthermore, childhood adversities with intention to harm were found to be a stronger predictor of psychotic experiences (Effect size: 2.12, $p < 0.001$) than adversities without intention to harm (Effect size: 1.14, $p = 0.04$) (Van Nierop et al 2014).

1.3 Possible pathways from childhood adversities to psychosis

Epidemiological studies showed that among psychotic patients around 58% had not been exposed to early adversities, and that among individuals exposed to childhood events only 62% of subjects presented psychosis (Matheson et al 2013). Moreover, since that the mean age at first presentation of schizophrenia spectrum was estimated to be around 31.3 ± 16.6 years (Bladwin et al 2005), psychotic symptoms seem to develop several year after the exposure to childhood adverse experiences. In addition, childhood adversities were also reported by around of 13% of healthy subjects (Matheson et al 2013).

These evidences suggest that childhood events seem neither sufficient nor necessary to explain the onset of psychosis (Morgan and Anderson, 2016). Thus, intervening factor mediating or moderating this relationship might be hypothesised (Beards and Fisher, 2014; Morgan and Anderson, 2016). In the framework of the socio-developmental (Morgan et al 2010; 2014) and traumagenic neurodevelopmental (Read et al 2014) models, the role of recent events, hypothalamic-pituitary-adrenal (HPA) axis, neurocognition, and social cognition have been explored as possible

underlying developmental trajectories from early adversities to psychosis. These possible third factors are here described in detail.

1.3.1 The role of recent life events

Recent life events are events that occur within 6–12 months before the onset of a psychiatric disorder (Brown and Birley, 1968). They may concern work, education, financial and legal problems, health, bereavement, migration, abuse, social and family relationships (Paykel et al 1971; Beards et al 2013). Meta-analysis estimated that, regardless of the research design, the exposure to recent life events is associated with a three fold increased risk of psychosis (Beards et al 2013). When compared to healthy controls, a higher rate of recent events was found in psychotic patients at FEP and in those with psychotic relapse (Brown and Birley 1968; Bebbington et al 1993; Phillips et al 2007; Beards et al 2013) but not among UHR patients (Krann et al 2015). The experience of recent life events seems did not predict the transition from UHR status to psychosis (Krann et al 2015). Within the staging perspective of schizophrenia (Cosci and Fava, 2013) it is likely that recent life events affect the progression from the acute phase to the residual or the chronic stage of schizophrenia, rather than, being associated to its prodrome phase (Figure 1).

Recent events and childhood adversities seem to be correlated (Korkeila et al 2010) since psychotic patients reporting stressful life events in adulthood were often exposed to childhood adversity (Morgan et al 2010; Bebbington et al 2011; Morgan et al 2014) and those who experienced early life events have almost a doubled risk to report social adversities in adulthood than those who did not (Bebbington et al 2011; Stilo et al 2012). In addition, childhood adverse experience might enhance the sensitivity to the psychotogenic effects of recent adversity (Lataster et al 2012). Bebbington et al (2011), using the data from the 2007 UK Adult Psychiatric Morbidity, showed that when childhood sexual abuse was followed by re-victimisation in adulthood, the odd ratio for psychosis increased from 3.49 to 17.65. Consistently with these findings, Lataster et al (2012) found that the effect size of the association between recent life events and psychotic symptoms is higher among those who had been exposed to early adversity (Effect Size: 2.98) than those who had not (Effect Size: 1.67). These findings support the socio-developmental hypothesis (Morgan et al 2010; Morgan et al 2014) according to which adverse experiences in childhood might lead to psychosis via further stressors in adulthood. Unfortunately, only one study examined this issue and showed that the relationship between childhood adverse experiences and psychosis was partially mediated by the exposure to adulthood adversities (Morgan et al 2014).

1.3.2 The role of the hypothalamic-pituitary-adrenal (HPA) axis

McEwen (2000) conceptualised the relationship between stress and the processes leading to disease based on allostasis, that is the ability of the organism to detect environmental (external) and physiological (internal) changes and to activate adaptive responses by which homeostasis is achieved through change. Three highly-integrated systems, e.g. the nervous, the immune, and endocrine systems, mediate allostatic processes promoting short-term adaptation in the face of environmental challenges (McEwen 1998; 2000; 2004). Chronic or repeated exposure to psychosocial stressors might lead to prolonged and sustained activation of the allostatic systems (allostatic load-overload) leading to detrimental physiological consequences (McEwen, 1998; 2000; 2004) as functional abnormalities in stress-sensitive regions of the nervous system (e.g., prefrontal cortex, amygdala, hippocampus) or an increase of inflammation levels in the immune system (Heim et al 2010; Danese and Mc Ewen 2012). In the endocrine system the repeated exposure to psychosocial stressors is associated with the increased corticotropin-releasing factor (CRH) levels and arginine vasopressin (AVP) levels, consistently with a chronic activation of the HPA axis (Danese and Mc Ewen 2012; Faravelli et al 2012). When the stress is persistent, the negative feedback system that serves to dampen the HPA axis activation is impaired inducing chronic cortisol release (Heim et al 2010, Faravelli et al 2012; Read et al 2014), which may provoke flatter circadian variation and heightened daily cortisol secretion (McEwen 2004; Heim et al 2010). The model was supported by the observation that a chronic activation of the HPA axis was found both in children and in adults who had been exposed to early adversities (Carlson and Earls 1997; Cicchetti and Rogosch, 2001; Danese and Mc Ewen, 2012; Heim et al 2010). In addition, a 30-year prospective follow-up study (Widom et al 2015) of a sample of abused and neglected children and their matched controls without early adversities, showed that abuse and neglect in childhood predicted allostatic load in adulthood (Effect size: 0.12, $p < 0.001$). Cross-sectional and longitudinal studies (Juster et al 2011; Rogosh et al 2011; Nugent et al 2015) suggested that higher levels of allostatic load, in both children and adults, were positively correlated with poor mental health as internalizing and externalizing symptoms, aggressive behaviour, thought disorders, depression, schizophrenia (Effect size ranging from 0.12 to 1.29, $p < 0.05$). According to these findings, it was assumed that allostatic load mediates the long-term effect of adverse childhood experiences in psychiatric disorders (Danese and McEwen, 2012) (e.g., the exposure to early adversities might lead to an increased vulnerability to psychiatric symptoms though and increasing levels of allostatic load).

In this framework, consistent with McEwen's studies (McEwen 1998; 2000; 2004; Danese and McEwen 2012), the traumagenic neurodevelopmental model (Read et al 2014) proposed that early

adversities might lead to psychosis via a dysregulation of the HPA axis. A chronic activation of the HPA axis has been found in schizophrenia patients (Bradely and Dinan 2010; Walker et al 2010; Nugent et al 2015) and there is evidence that either those with FEP and chronic psychotic patients experience periods of heightened cortisol secretion (Bradely and Dinan 2010). On the other hand, few studies (Braehler et al 2005; Mondelli et al 2010) evaluated the effect of childhood adversities on the HPA axis functioning in schizophrenia patients yielding mixed results. Braehler et al (2005) reported that schizophrenia patients who had experienced childhood events had lower cortisol in the first hour after waking compared with psychotic patients without early adversities. In contrast, Mondelli et al (2010) found a positive correlation between early adversity and higher cortisol awakening response when evaluating a sample of FEP patients with schizophrenia and schizophreniform disorder. No differences were found with regard to evening cortisol levels between psychotic patients with and without early adversities (Braehler et al 2005). Further studies to clarify the relationship between early event, HPA axis activation, and psychosis are needed.

1.3.3 The role of neurocognition

Neurocognition involves general information acquiring and processing functions as attention, vigilance, memory, processing speed, and executive function (Mehta et al 2013). From the early studies of Kraepelin (1919), neurocognitive impairments were considered a core feature of schizophrenia, estimating that psychotic patients performed between one and two standard deviations below controls in several neurocognitive domains (Antonova et al 2004; Reichenberg 2005; Van Os et al 2010;). Poor neurocognition negatively correlates with psychotic symptoms severity (De Gracia et al 2009). Thus, several hypotheses suggested that alterations in neurocognitive functioning might lead to psychosis have been formulated. Lower neurocognition might impair the ability to cope with stressful experiences, increasing the stress sensitivity which makes the individual more prone to psychosis (De Gracia et al 2009; Read et al 2014; Ruby et al 2014). In addition, impairment in episodic memory might affect the individuals' capacity to remember the specific details of their traumatic experiences, leading to an increased hypervigilance that might develop into psychotic symptom (Ruby et al 2014).

The literature suggests that childhood adverse experiences affect the neurocognitive development inducing impairments that might persist in adulthood (Heim et al 2010; Majer et al 2010; Read et al 2014). Early adversities induce a HPA dysregulation which, through the activity of glucocorticoid receptors, might diminish hippocampal neurogenesis leading to a neurocognitive decline (Read et al 2014). Early adversities could lead to poor neurocognition also as a result of developmental retardation due to under-nutrition and to the lack of stimuli (Majer et al 2010; Aas et al 2011).

However, although some evidences showed impairments on processing speed, memory, and executive functioning in psychotic patients exposed to childhood adversities (Read et al 2014), other studies did not confirm these findings (Sideli et al 2014). Thus, the neurodevelopmental hypothesis according to which neurocognition could be the mean by which early adversities increase the risk of psychosis (Reichemberg 2005; Read et al 2014) is not fully confirmed.

1.3.4 The role of social cognition

Social cognition refers to those processes which are related to emotion processing, social perception, mentalization, and attributional style/bias (Green et al 2015). Mentalization, or the Theory of Mind (ToM), concerns the ability to attribute mental states, such as thoughts, beliefs, and intentions to people, allowing an individual to explain, manipulate, and predict a behaviour (Fonagy et al 2002; Sprong et al 2007). Mentalization abilities develop during infancy and childhood on the basis of early attachment experiences, early social interactions, and actively seeking out social information (van Os and Rutten 2010; Jacobsen and Sahrp 2015). Such opportunities can be limited when childhood adversities (e.g., the lack of parent–child social interaction) occur and the child can learn poorly from social experiences, develop poor capacity to differ beliefs and mental states of others from his own (Colvert et al 2008; van Os and Rutten 2010). According to Sprog et al (2007), mentalization abilities in psychotic patients are more than one standard deviation below those of healthy controls. During the mentalizing task, a hyper-hypo neural activation in brain regions associated with ToM (e.g., bilateral temporo-parietal junction - TPJ, precuneus – PCC, medial prefrontal cortex - mPFC) was observed in psychotic patients suggesting a tendency to over attribute intention to others (“hypermentalizing”) or to infer the mental states of others more slowly than healthy subjects (Green et al 2015). Emerging data suggests that poor ToM in psychotic patients might be due to the experience of early adversities. A negative correlation between childhood adversity and ToM, as well as an increased activation of ToM brain regions (i.e., PCC, mPFC, and TPJ) in those exposed to early life events, has been found in schizophrenia and schizoaffective patients (Garcia et al 2016; Quidé et al 2017). Adverse childhood experiences might hinder the development of mentalization abilities, thus leading to psychosis.

1.4 From specific childhood adversities to specific psychotic symptoms

Despite the growing body of literature on the relationship between events and psychosis, etiopathogenic mechanisms linking childhood adversities to psychotic disorders are still not well known (Bentall et al 2014). It is argued that this might be due to the fact that the existing studies predominantly utilize the diagnostic categories of psychosis (Bentall et al 2014; Ajnakina et al

2016). Given that the phenomenology of psychosis can be better conceptualized by symptom dimensions (van Os et al 1999), the use of symptom profile to explore the association between early adversity and psychosis has been strongly recommended (Bentall et al 2014). Emerging data suggest that psychotic manifestations are unlikely to be a product of a single causal process, with different kinds of early adversity potentially increasing risk for different psychotic symptoms (Bentall et al 2014). The exposure to childhood abuse was found prevalently correlated to positive symptoms (Bentall et al 2014; van Dam et al 2015; Ajnakina et al 2016), whereas experiences of childhood neglect were most frequently associated to negative symptoms (Bentall et al 2014; Aas et al 2016; Gibson et al 2016).

It is possible that childhood abuse and neglect impact differently on the developmental trajectories to psychotic symptoms (Bentall et al 2014; Morgan and Anderson, 2016). Childhood abuse is assumed to be associated mainly with the dysregulated stress response system (Read et al 2014). Compared with psychotic patients without abuse, those exposed to it showed chronic activation of the HPA axis and higher stress sensitivity which were positively correlated with positive symptoms (Braehler et al 2005; Gracia et al 2009; Walker et al 2010; Bradely and Dinan 2010; Read et al 2014). Different pathways have been proposed for people with a history of neglect. Growing up under neglectful circumstances imply that child does not experience positive stimulating experience leading to poor neurocognition and social cognition, which are strongly correlated with negative symptoms (de Gracia et al 2009; Fett et al 2013; Ventura et al 2013).

Despite these findings suggest that specific pathway might link different early adversity to different psychotic symptoms, research aimed at identifying the underlying mechanisms between subtypes of childhood adversity and psychosis dimensions are still lacking. As recommend by some authors (Beards and Fisher 2014; Bentall et al 2014; Morgan and Anderson 2016), studies designed to evaluate early life experiences, specific symptoms and possible mediating psychological and biological variables, within the same sample of psychotic patients are worthwhile.

Figure 1. Childhood Adversities, Recent Life Events and the staging of Schizophrenia

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Chapter 2

Recent life events and psychosis: The role of childhood adversities

Giovanni Mansueto^{ab}

Carlo Faravelli^b

^a Maastricht University Medical Center, Dept. of Psychiatry & Psychology, School for Mental Health & Neuroscience, Maastricht, the Netherlands

^b Department of Health Sciences, University of Florence, Florence, Italy

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Abstract

Introduction

Life events are commonly reported to be related to psychosis. However, less attention has been given to the role that recent events play on psychosis, in relation to exposure to childhood adversity. The current study aimed to evaluate the relationship between recent events and psychosis, taking into account the role of early adversities.

Method

78 psychotic patients and 156 controls were enrolled. Childhood adversity was evaluated using a validated semi-structured interview and the Childhood Experience of Care and Abuse Questionnaire. Recent events were recorded using a semi-structured interview with a normative and contextual approach. The diagnosis of psychosis was made according to Jablenski's criteria. Chi-square, t-test, odds ratio, and binary logistic regression statistical analyses were performed.

Results

Psychotic patients reported an excess of recent events. The occurrence of more than one recent event increased the risk of psychosis; there was a cumulative effect between recent and childhood events on psychosis. Recent events were significantly related to psychosis, even in the absence of childhood adversity or when adjusted for it.

Conclusion

Our findings suggested that the effect of recent events on psychosis may be amplified by previous exposure to early adversity. Recent events alone, could be also linked to psychosis independently of childhood adversity.

1. Introduction

The relationship between stressful life events and psychosis is well established (Jung 1907; Bleuer 1911; Steinber and Durell 1968; Beck and Worthen 1972; Brown et al 1973; Varese et al 2012; Beards et al 2013; Gallagher et al 2013; Trotta et al 2015; Morgan and Gayer-Anderson 2016; Butjosa et al 2016). As assumed by the vulnerability-stress model, the threshold for triggering schizophrenia is influenced by the interaction between stressors and vulnerability factors (Zubin and Spring 1977). Minor stressors induce psychotic symptoms among those who are highly vulnerable, whereas major stressors might cause a similar reaction even in those with lower vulnerability (Ingram and Luxton 2005). Schizophrenia symptoms might develop whenever a threshold of stressors exceeds the individual's vulnerability (Zubin and Spring 1977; Van Winkel et al 2008). Starting from this basic perspective, several studies have enriched the vulnerability-stress model by integrating different paradigms of vulnerability, such as polygenetic liability (Walder et al 2014), hypothalamic-pituitary-adrenal axis activity (Pruessner et al 2017), personal resources (Pearlin et al., 1981; 2010; Katerndahl and Parchman 2002), cognitive functions (Ingram and Luxton 2005), and social support (Cheng et al 2016).

Recent life events are defined as events that occur shortly before the onset of a disorder, generally within 6–12 months prior to the onset (Brown and Birley 1968). A meta-analysis by Beards et al (2013) demonstrated that psychotic patients were three times more likely than controls to be exposed to a recent event, with a peak in the period prior to the onset of psychotic symptoms, or relapse or occurrence of sub- clinical experiences (Brown and Birley 1968; Bebbington et al 1993; Castine et al 1998; Phillips et al 2007). Other studies, however, failed to replicate these findings (Phillips et al 2007; Fallon 2008) or showed lower rates of recent events in patients with psychosis in comparison to controls Gureje and Adewunmi 1988; Horan et al 2005a; 2005b; Kraan et al 2015). In order to clarify the relationship between psychosis and illness it is customary to categorize life events as “independent” or “dependent,” where the former is not provoked by the subject (e.g., when it is due to an earthquake) while the latter is likely to be caused by the subject. Such a distinction may be ambiguous when using the normative approach (Paykel et al 1971), since in several cases the same type of event may be due to external circumstances (e.g., job loss due to an economic crisis), subject misbehavior (e.g., job loss due to absenteeism), or both. Moreover, the same occurrence may have a different meaning, emotional impact, and consequences depending on the context in which they happen. Hence, when the contextual approach was first proposed, during the early stages of life stress research, it was recommended that not only the event, but also the circumstances in which they occurred should be taken into account (Brown and Harris 1978).

Although some studies have outlined that patients with psychosis experienced more independent events than controls (Brown and Birley 1968; Malla et al 1990; Bebbington et al 1993; Raune et al 2009), others reported higher rates of dependent events prior to the onset (Dohrenwend et al., 1987; Horan et al 2005b). Further, the literature suggests that individuals who experience stressful life events in adulthood might be also exposed to adversity during childhood (Korkeila et al 2010; Morgan et al 2014a; 2014b; Pos et al 2016). People can lead lives that are caught in a temporal proliferation of stressors, where one or more stressors repeatedly follow others through time (Pearlin 1981; 2010). However, only a few studies have explored the relationship between recent and childhood events within the psychotic disorder. Holtzman et al (2013) suggested that the sensitivity to recent event could be amplified by early exposure to stress. Lardinois et al (2011) highlighted that psychotic patients with childhood adversity were more sensitive to daily stressors than patients without history of trauma. Lataster et al (2012) found that the association between severe recent life stress and risk of psychosis was stronger among subjects who experienced childhood adversity. Moreover, Bebbington et al (2011) highlighted that sexual abuse combined with re-victimization in adulthood further increases the risk of probable psychotic disorder. These studies fit with the socio-development perspective (Morgan et al 2010; 2014a; 2014b), which suggests the synergic effect recent events and childhood adversity can have on the risk of developing a psychotic disorder. However, no studies have evaluated the association between recent events and psychosis, adjusting for childhood adversity (Beards et al 2013). Thus, it is still unclear whether recent events might contribute to psychosis regardless of exposure to childhood adversity. The current study aimed to replicate and extend previous research by exploring the relationship between recent life events and psychotic disorder, considering the role of childhood adversities. We hypothesized that there was: (a) an excess of events in the period preceding the onset/relapse of psychosis, and (b) a cumulative effect between recent events and childhood adversity on the psychotic disorder.

2. Method

This research is part of the Factors in Early Life, Diagnoses, and Symptoms, i.e., PSI-FIELDS project, which is an observational, multi-disciplinary, and transnosological study. All patients who were newly admitted to all psychiatric inpatient and outpatient facilities (public and private accredited) of Tuscany, which is a Central Italian Region that includes 10 Local Health Units and 3 University Hospitals, were studied. During a 2-month period, 409 consecutive unselected patients were recruited and evaluated within 1 week of admission. Among the entire cohort, patients with psychosis were selected according to the criteria outlined by Jablensky et al (1992), where the

patients had (a) at least one of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, or bizarre or grossly inappropriate behavior, or (b) two of the following symptoms that could not be explained by major depression: loss of interest, initiative, and drive; social withdrawal; episodic severe excitement; purposeless destructiveness; overwhelming fear; or marked self-neglect. A total of 78 patients met these criteria, and represented all cases admitted for psychosis in Tuscany over a 2-month period. For 4 patients, admission represented the onset of the psychosis, whereas for 74 patients, the psychiatric intervention was due to relapse or re-exacerbation of a previously developed disorder. The controls were drawn from a pool of 1.070 subjects who were representative of the general population living in the same area, and were randomly recruited from the lists of the Italian National Health System (INHS). The INHS covers the entire population and each citizen is assigned their own general practitioner (GP) in the geographic area where they live. Thus, the patient lists of GPs working in a given area correspond to the population living in that area. A random sample of 60 GPs was selected and 1.200 people were randomly drawn from their lists for the interview. In order to increase the collaboration of the people, the GPs were asked to introduce the interviewers. The interview was carried out at the GP's office or at the subjects' houses, depending on the preference on the interviewee, regardless of whether or not the subject had searched medical assistance. All 1.070 participants were interviewed and they underwent the same protocol as the psychiatric patients. According to a nested case-control 1:2 design (Torrey et al 2000; Byrne et al 2003), 156 participants were drawn from this pool to compose the control group. This procedure was adopted in order to increase the power of the study (Lewallen and Courtright 1998). The matching criteria were as follows: (a) age (± 5 years) (Agid et al., 1999), and (b) gender and educational level (± 2 years of school). The exclusion criteria for both patients and controls were as follows: (a) age > 75 years, and (b) a neurological and/or neurocognitive impairment.

The study was designed in strict accordance with the declaration of Helsinki of the World Medical Association as revised in 2008. The study protocol was approved by the local ethics committee and participants provided written informed consent.

2.1. Instruments

For both childhood and recent life events detection and evaluation followed two distinct paths. Firstly, the narration of events, their timing, the circumstances and the context in which they occurred and their consequences were recorded in detail by the interviewers using a semi-structured interview. Secondly, the reports were submitted to a couple of different evaluators, who did not

participate in the interview and were blind as to whether a given account referred to a patient or to a control subjects. These assessors assigned the events to their proper category.

2.1.1. Recent events

Life events were recorded using a semi-structured interview derived from Brown et al (1973), which was adapted to the Italian population (Faravelli and Ambonetti 1983). The semi-structured interview recorded the events of the prior year in detail, as well as the timing and the circumstances in which they occurred. On the basis of these accounts, a couple of assessors, who were blind to the patient or control status of the subjects, evaluated the following: a) whether a given event corresponded to any of the events listed in the Paykel et al (1971) scale; b) if it was considered severe (i.e., in the top 20 events of the Paykel list); and c) if the life event was “dependent” or “independent.” The scale of Paykel et al. is an instrument in which 61 life events, divided into 10 areas, are assigned a severity score that is derived from a calibration using the general population. Since each event is given a fixed score (e.g., Death of child = 19.33; Divorce = 15.93; Retirement = 9.33), this is a “normative approach”. The theoretical construct of independence derived from Brown (Brown et al 1973; Brown and Harris 1978) can be defined as follows: the event should be considered independent when it is unlikely to be a consequence or potential consequence of psychiatric illness and/or the subject's behavior. However, since this concept may be ambiguous in some circumstances (e.g., job loss could depend on a subject's misbehavior or be a consequence of economic crisis), it was decided to adopt what is called the “contextual approach” (Brown and Harris 1978). In this approach, the event, but also its circumstances and consequences are recorded in detail, so that external assessors can evaluate the weight and the correspondence of each event. This procedure, which has been widely used in the past, has proven reliable, with good agreement between raters. In the current study, Cohen's Kappa coefficient varied from 0.80 to 0.92.

For the purpose of this study, six main categories of recent events were also created: family conflicts, bereavement, loss of job/financial problems, health problems, and abuse (i.e., sexual and/or physical). According to the time period at which the event occurred, the following three time period groups were created: 0–4 months, 5–8 months, and 9–12 months prior to presentation.

2.1.2 Childhood Adversities

A structured interview was used to investigate childhood adversities (Faravelli et al 1986). All respondents were asked if they had experienced the following types of childhood adversities before the age of 15 years: death of mother, death of father, separation from mother (for 1 year or more), separation from father (for 1 year or more), divorce of parents, severe childhood disease, physical

abuse, and sexual abuse. Again, a couple of external assessors, who were not aware of the patient/control status of the reports, assigned the corresponding category to each event. The two assessors had good agreement with kappa values varying from 0.85 to 0.96 for different events. In addition, the Childhood Experience of Care and Abuse Questionnaire (CECA-Q; Bifulco et al 2005) was also administered. Childhood adversities were categorized as either the 'presence of a childhood loss event', when a parental death or separation (for 1 year or more) was reported, or the 'presence of an abuse event', when the CECA-Q or the interview demonstrated the occurrence of physical and/or sexual abuse. The presence of childhood neglect was based on the CECA-Q scores in the scales "Mother's Neglect" and "Father's Neglect"; scores on these subscales were dichotomized according to the cut-off point (i.e., ≥ 22 for Mother's neglect score and ≥ 24 for Father's neglect score) that was proposed by Bifulco et al (2005). The 'childhood neglect' variable was created by summing the dichotomous CECA-Q subscales scores, and recoding them as 0 (none) and 1 (presence of neglect by at least one parent).

2.1.3. Family history for mental disease and substance use

The protocol also included a form dedicated at exploring the family history in each of the following areas: psychopathology, substance use, psychiatric treatment, and suicide. These areas were separately explored for each parent, grandparent, sibling, and child. Since the interviewee was the only source of information, positive family history was only considered when the relative was reported to have been specially treated for their psychiatric disturbance.

2.2. Statistics

Chi-square test, Fisher's test, and Odds Ratio analyses were performed for categorical variables, while a Student's t-test was used for continuous variables. A binary logistic regression analysis, with the subjects' status as the dependent variable (i.e., controls vs. patients with psychosis) and the total number of recent events as the independent variable (i.e., no recent event, at least one recent event, or two or more recent events), was used to evaluate the presence of a cumulative effect of recent events. A simple contrast was used, which specified the first level (no recent event) as the reference category. All other categories of the predictor variable were compared with the reference category. This provided an estimate of the likelihood of psychosis for each number of recent events, compared with the recent event-free group. The same methodological approach was used to evaluate the presence of a cumulative effect between recent events and childhood adversity on psychosis. A binary logistic regression analysis, with the subjects' status as dependent variable (i.e., controls vs. patients with psychosis) and the total number of life events (i.e., no life events, only

childhood adversity, only recent events, or both childhood adversity and recent events) as the independent variable, was performed. A simple contrast was used to specify the first level (no life events) as the reference category. All other categories of the predictor variable were compared with the reference category, in order to estimate the likelihood of psychosis for each number of life events compared with the life event-free group. This analysis allowed us to evaluate if recent events could be associated with psychosis even in the absence of childhood adversity. The statistical methodology used in the current study to evaluate the occurrence of the cumulative effect of life events on psychosis was consistent with a previous publication by Shevlin et al (2008). Moreover, to evaluate the relationship between recent event and psychosis, adjusting for childhood adversity, a hierarchical logistic regression analysis was performed by entering the following: (a) childhood adversities (i.e., child abuse, child neglect, or child loss event) into step 1 and (b) recent events (i.e., family conflicts, loss of job/financial problem, bereavement, or health problems) into step 2. This model allowed us to evaluate the contribution of recent events, while controlling for childhood adversity, to explain changes in the variance of the dependent variable (i.e., the subjects' status: controls vs. patients with psychosis), after consecutively entering the variables above. All analyses were adjusted for age, gender, substance use, and family history for psychiatric diseases. Statistical analyses were performed using SPSS for Windows 20.0 (SPSS, IBM, 2011).

3. Results

The patient and control groups were comparable for age, gender, and educational level. Compared to control participants, patients with psychosis were more frequently single, and showed a higher rate of substance use and family history for psychiatric diseases. The most represented diagnostic categories in the patient cohort were non-affective psychosis, and bipolar, schizoaffective, and delusional disorders (Table 1).

3.1. Recent events and psychosis

Compared with control participants, patients with psychosis reported an excess of recent events, severe recent events and dependent recent events. Restricting the analyses to specific events, patients showed a higher rate of family conflicts (Table 2). The combination of various forms of recent events yielded a significant cumulative effect ($\chi^2 = 63.32$, $df = 6$, $p < 0.001$, Nagelkerke $R^2 = 0.32$). Compared with cases without a recent event, those with at least one recent event had a 2-fold increased risk of developing psychosis (odds ratio (OR) = 2.40, 95% confidence interval (CI)=1.23–4.68), while individuals with two or more recent events had an 11-fold increased risk of developing psychosis (OR=11.60, 95% CI=2.83–47.41). Recent events were significantly more

frequent in the 4 months preceding the interview ($\chi^2=29.96$, $df=1$, $p < 0.001$) (Fig. 1). The Paykel scale scores clearly distinguished patients from control participants, since the former showed higher scores (*mean $\pm$ standard deviation*= 19.43 ± 9.05 vs. 15.77 ± 7.06 , respectively; $t_{(df)} = -2.35(120)$; $p = 0.02$).

3.2. Recent events and childhood adversity in psychosis

The combination of recent event and childhood adversity yielded a significant cumulative effect ($\chi^2=73.59$, $df=7$, $p < 0.001$ Nagelkerke $R^2 = 0.37$). Compared with cases without either childhood adversity or a recent event, subjects with at least one childhood adversity event had a 5-fold increased risk of having psychosis (OR=5.27, 95% CI=1.55–17.92), while those with at least one recent event, and both childhood adversity and a recent event had more than a 8.5-fold (OR=8.82, 95% CI=2.70–28.79) and a 15-fold (OR=15.28, 95% CI=4.50–51.03) increased risk of having psychosis, respectively. The hierarchical logistic regression model showed that recent events were a significant predictor of psychosis, regardless of childhood adversities (Table 3).

4. Discussion

As previously reported (Nuechterlein et al 1994; Fallon 2008; 2009), an excess of recent stressful life events in the year prior to admission was found in patients with psychosis. Furthermore, our results are consistent with previous studies showing a peak in recent events in the 4 months prior to presentation, which suggest that proximal events may lead to a spike in the risk of development, re-exacerbation, or persistence of a psychotic disorder (Beards et al 2013; Morgan et al 2014b).

An excess of events can be a causal factor for psychosis, but it can also be the consequence of dysfunctional behavior due to psychosis. Thus, it is relevant to distinguish events into “independent” and “dependent.” Since such a distinction may be ambiguous when using the normative approach, the contextual approach was proposed (Brown and Harris 1978), where the detailed description of the event and their context is evaluated by assessors who are blinded to patient status. Using this approach, we found that the majority of events were almost entirely due to “dependent” events, i.e., those that are liable to be a consequence of the subject's behavior. Conversely, the events that were likely to be beyond personal control (i.e., independent events) failed to significantly distinguish between patients and controls, even when adjusted for age, gender, family history, and substance use. Since the patient cohort in this study was comprised almost exclusively of patients who had previous episodes of psychosis, it is possible that these patients already have altered behavior that increases the risk of encountering stressful events, which, in turn, worsens the psychotic condition. This result corroborated with previous evidence

(Lukoff et al 1984; Bebbington et al 1993) that suggests that patients with psychosis may have stress-prone lifestyles that predispose them to these life events. Moreover, we found a cumulative effect of recent events on psychosis, suggesting that continued exposure to stressors may amplify the risk of developing a psychotic disorder. Similarly, we also found a cumulative effect between childhood adversity and recent events. The association between recent events and psychosis was stronger among those who had experienced childhood adversity and the co-occurrence of recent events and childhood adversity increased the risk of developing psychosis. These findings are consistent with the socio-development perspective that exposure to a great number of social adversities predicts a greater risk of developing psychosis (Morgan et al 2008; Stilo et al 2013; Morgan et al 2014a; Stilo et al 2016). Our findings, however, also demonstrated a significant association between recent events and psychosis, regardless of exposure to early adversity, which suggests an effect of recent events per se. However, if this is a causative effect or merely the consequence of ill-behavior remains to be elicited.

Clinically, some implications for prevention and intervention should be considered. First, the systematic assessment, during clinical activity, of exposure to adversities during childhood (Read et al 2007) and/or adulthood might help identify high-risk subjects. Second, it is well known that patients with psychosis who are exposed to early or adulthood adversities might show an increased emotional reactivity to daily stress (Myin-Germeys and van Os 2007). Thus, treatment aimed at reducing sensitivity to stress in daily life, such as family intervention, self-relaxation, distraction techniques, and cognitive behavior therapy (CBT) should not be overlooked (Myin-Germeys and van Os 2007; Jaya et al 2016). Interventions aimed to promote protective factors toward stressors, as resiliency or support, should also be considered (Pearlin et al 1981; Pearlin et al 2010; Katerndahl and Parchman 2002; Cheng et al 2016). The effectiveness of multi-element psychosocial intervention including CBT, family treatment, and case management has been previously reported (Ruggeri et al 2015).

Some methodological considerations must be taken into account when interpreting the results of this study. Since the patient cohort in the current study was mainly comprised of those who had previously experienced psychotic episodes, the higher rate of events reported by patients might be an epiphenomenon of psychosis (Stilo et al 2016). However, it is worth noting that the excess of events occurred mainly in the 4 months preceding admission, highlighting that the higher risk of undergoing stressful events is not a stable characteristic of people with psychosis. It is questionable if the extra-events preceding admission were secondary to the return of symptoms or due to the occurrence of stressful events in subjects with limited coping abilities, which led to the onset of new episodes. The retrospective evaluation of early adversities could have also been affected by recall

bias (i.e., memory distortions, searching for meanings), although previous research suggests good reliability of the retrospective assessment of childhood adversity (Fisher et al 2009). Further, the clinical sample size was relatively small and the cross-sectional data limited the ability to formally test causality. Moreover, it is worth noting that stressors are not isolated occurrences but could also be interconnected each other, since the exposure to one stressor over time could lead to exposure to other secondary stressors (Pearlin et al 1981; Pearlin 2010). Thus, mediation and moderation analyses (Pearlin et al 1981; Pearlin 2010; Katerndahl and Parchman 2002; Morgan et al 2014a) are required to evaluate both main and indirect effects of childhood and recent events on psychosis. Unfortunately, the power of the current dataset does not allow further analyses. Finally, our clinical sample had a slight pre- valence of women. For this reason all analyses were adjusted for gender. It must be noted however, that: (a) recent literature tend to disconfirm the earlier notions that schizophrenia is more prevalent in men (Saha et al 2005; Perälä et al 2007; Abel et al 2010; Barajas et al 2015; Thara and Kamath 2015); (b) our recruitment focused on “psychosis” rather than schizophrenia.

The strengths of the current study include the following: (a) the clinical sample was representative of all the cases treated for psychosis in Tuscany, and (b) a wide range of recent events were evaluated. In conclusion, the current study confirmed that stressful life events could be involved in the etiology of psychosis. The effect of recent events on psychosis was amplified by exposure to childhood adversity. Moreover, recent events seem to be a risk factor for psychosis, independent of childhood adversity. According to neurodevelopmental (Read et al 2014), socio-developmental (Morgan et al 2010; 2014a; 2014b), and stress-process (Pearlin et al 1981; Pearlin 2010) models, further studies are required to identify the underlying pathways that might mediate or moderate the relationship between recent events and psychosis.

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Contributors

Giovanni Mansueto: wrote the first draft of the manuscript, managed the literature searches and analyses; Carlo Faravelli: designed the study, wrote the protocol, and supervised the entire process.

Conflict of interest: None

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Table 1. Socio-demographic table

		Psychotic <i>n</i> 78	Controls <i>n</i> 156	χ^2 /t (<i>df</i>)	p
Gender					
Female	n (%)	44 (56.4)	88 (56.4)	χ^2 =0.00 ₍₁₎	1.00
Male		34 (43.6)	68 (43.6)		
Age (years)	mean±SD	43.07±10.90	43.08±13.08	t= 0.007 ₍₂₃₂₎	0.99
Education (years)	mean±SD	11.14±3.49	11.42±3.57	t=0.57 ₍₂₃₂₎	0.56
Marital status (single)					
yes	n (%)	47 (60.3)	28 (17.9)	χ^2 =42.73 ₍₁₎	<0.001
no		31 (39.7)	128 (82.1)		
Recruitment area (Tuscany)	n (%)	78 (100)	156 (100)	-	
Family history for mental disease					
yes	n (%)	35 (44.9)	135 (86.5)	χ^2 = 45.43 ₍₁₎	<0.001
no		43 (55.1)	21 (13.5)		
Substance use					
yes	n (%)	43 (55.1)	64 (41)	χ^2 = 4.16 ₍₁₎	0.04
no		35 (44.9)	92 (59)		
Diagnosis	n (%)		-	-	-
non affective –psychosis		53 (67.9)			
delusional disorder		11 (14.1)			
schizoaffective		16 (20.5)			
bipolar		37 (47.4)			
Mean age first episode	mean±SD	25.38±12.15	-	-	-

Table 2. Prevalence of recent events: comparison between patients and controls

	Psychotic <i>n</i> 78 (%)	Controls <i>n</i> 156 (%)	$\chi^2_{(df)}$	<i>p</i>	ORa [95% CI]	ORb [95% CI]
At least one recent event	59 (75.6)	57 (36.5)	31.80 ₍₁₎	<0.001	5.39 [2.92-9.93]	3.98 [2.03-7.81]
Severe recent event	43 (55.1)	32 (20.5)	28.61 ₍₁₎	<0.001	4.76 [2.63-8.60]	3.74 [1.93-7.26]
Independent recent event	30 (38.5)	34 (21.8)	7.26 ₍₁₎	0.007	2.24 [1.23-4.06]	1.62 [0.82-3.20]
Dependent recent event	33 (42.3)	15 (9.6)	34.08 ₍₁₎	<0.001	6.89 [3.43-13.83]	6.67 [3.07-14.48]
Family Conflicts	24 (30.8)	11 (7.1)	22.99 ₍₁₎	<0.001	5.85 [2.68-12.76]	4.04 [1.71-9.55]
Loss of job/financial problem	12 (15.4)	9 (5.8)	5.88 ₍₁₎	0.01	2.97 [1.19-7.39]	1.82 [0.64-5.15]
Bereavement	21 (26.9)	21 (13.5)	6.39 ₍₁₎	0.01	2.36 [1.20-4.67]	1.65 [0.76-3.60]
Health problems	10 (6.4)	9 (11.5)	1.83 ₍₁₎	0.17	1.90 [0.74-4.89]	1.82 [0.61-5.38]
Recent Abuse	2 (2.6)	0	4.03 ₍₁₎	0.11c	-	-

Note a: unadjusted; b: adjusted for age; gender; family history for mental disease, substance use; c=fisher test.

Table 3. Hierarchical logistic regression: recent event and psychosis adjusted for childhood adversity

<i>Predictor</i>	R ²	ΔR ²	χ ²	df	B	S.E.	p	Exp (B) 95% CI
	Nagelkerke	Nagelkerke						
<i>Step 1</i>	0.28		53.47***	7				
Age					0.002	0.01	0.87	1.02 [0.97-1.02]
Gender					0.14	0.32	0.66	1.15 [0.60-2.19]
Family history for mental disease					2.01	0.34	<0.001	7.49 [3.85-14.58]
Substance use					0.36	0.32	0.26	1.44 [0.76-2.72]
Childhood Abuse					0.46	0.38	0.23	1.58 [0.74-3.38]
Childhood Neglect					0.88	0.40	0.02	2.42 [1.09-5.36]
Childhood Loss Event					0.33	0.41	0.42	1.39 [0.62-3.11]
<i>Step 2</i>	0.37	0.09	73.06***	11				
Age					-0.004	0.01	0.75	0.99 [0.96-1.02]
Gender					0.22	0.34	0.52	1.25 [0.63-2.47]
Family history for mental disease					1.53	0.37	<0.001	4.62 [2.23-9.58]
Substance use					0.42	0.34	0.21	1.53 [0.78-3.01]
Childhood Abuse					0.58	0.40	0.15	1.80 [0.80-4.01]
Childhood Neglect					1.12	0.43	0.01	3.06 [1.30-7.18]
Childhood Loss Event					0.30	0.42	0.46	1.36 [0.59-3.12]
Family Conflicts					1.63	0.46	<0.001	5.12 [2.07-12.69]
Loss job/financial problem					1.03	0.57	0.07	2.81 [0.91-8.71]
Bereavement					0.86	0.43	0.05	2.36 [0.99-5.59]
Health problems					0.94	0.58	0.11	2.57 [0.82-8.06]

Note = Independent variables insert into Step 1: Age, gender, family history for mental disease, substance use, Childhood Abuse, Childhood Neglect, Childhood Loss; Independent variables insert into Step 2: Family conflicts, Loss of job/financial problem, Bereavement, Health problems; Dependent variable: subjects' status (0=control; 1=psychotic patients). ***p<0.001

Figure 1. Time period at which recent events occurred and likelihood of psychotic experience. OR, adjusted odds ratio (adjusted for age, gender, substance use, family history for mental diseases).

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Chapter 3

Childhood Adversity, Cortisol Levels, and Psychosis: A Retrospective Investigation

Carlo Faravelli^a

Giovanni Mansueto^{ab}

Sara Palmieri^a

Carolina Lo Sauro^a

Francesco Rotella^a

Francesco Pietrini^a

Giulia Fioravanti^a

^a Department of Health Sciences, University of Florence, Florence, Italy

^b Maastricht University Medical Center, Dept. of Psychiatry & Psychology, School for Mental Health & Neuroscience, Maastricht, the Netherlands

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Abstract

Introduction

Although it has been proposed that the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may act as a possible pathway linking early life stress to psychosis, this relationship has not yet been fully confirmed. This study aimed to investigate the relationship between childhood adversity (CA), cortisol levels, and psychosis.

Method

Eighty-five patients with psychosis and 170 control subjects were enrolled in the study. CA was evaluated using the Florence Psychiatric Interview, and Childhood Experience of Care and Abuse Questionnaire. Positive symptoms (PS) were assessed using the Positive and Negative Syndrome Scale. Cortisol levels were evaluated in saliva samples.

Results

Patients experienced more CA and showed higher cortisol levels than controls. Patients with CA showed higher morning cortisol levels and more severe PS than those without CA. Patients with higher morning cortisol levels showed severe delusions.

Conclusion

These findings suggest that both CA and dysregulation of the HPA axis could be related to psychosis.

1. Introduction

The association between childhood adversity (CA) and psychosis has been well documented (Carr et al 2013; Hardy et al 2016; Isvoranu et al 2017; Jansen et al 2016; Morgan and Gayer-Anderson, 2016; Pos et al 2016; Trotta et al 2015; Varese et al 2012), although the relationship has not yet been fully confirmed (Bentall et al 2014; Varese et al 2012). Bentall et al (2014) suggested that patients with psychosis are 15.5 times more likely to have experienced childhood sexual abuse than those without any mental disorder. Subjects with a history of childhood abuse (sexual, physical, or emotional) seem to be particularly likely to report positive symptoms (PS) such as hallucinations, paranoid ideation, thought insertion, and claims of being able to read someone else's mind (Janssen et al 2004). Moreover, as reported by (Morgan et al 2007), loss events, such as permanent separation from or the death of one or both parents, produced a two-to threefold increased risk for psychosis. Furthermore, an unfavorable childhood environment, such as living in institutional care (Bebbington et al 2004) or a single-parent household (Wicks et al 2005), was also associated with adult psychosis. A meta-analysis by Varese et al (2012) confirmed that neglect and sexual, physical, and emotional abuse in childhood are related to an increased risk of psychosis; however, they failed to find a significant association between parental death and psychosis. In addition, CA may be related to specific aspects of psychotic disorders, such as higher global symptom severity and poorer functioning (Cotter et al 2015; Lysaker et al 2001; 2004; 2005; Morgan and Gayer-Anderson 2016; Read et al 2005; Üçok and Bıkmaz 2007; van Nierop et al 2015, 2016).

It has also been proposed that the relationship between early life stress (ELS) and psychosis can be explained by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the subsequent alterations in the dopaminergic and serotonergic systems (Morgan and Gayer-Anderson 2016; Read et al 2005; 2014; Ruby et al 2014; Walker and Diforio 1997). It is assumed that the heightened sensitivity to stress found in people with psychotic disorders may originate from the neurodevelopmental changes in the brain (including hyperactivity of the HPA axis) caused by traumatic events during the early developmental years (Morgan and Gayer-Anderson 2016; Read et al 2014).

Studies aimed at exploring the relationships among CA, the HPA axis, and psychosis have produced mixed results. Braehler et al (2005) found HPA axis dysregulation, most notably lower diurnal cortisol levels, in patients with schizophrenia exposed to CA (sexual and/or emotional abuse). In contrast, Mondelli et al (2010) found that childhood sexual abuse was associated with an increased cortisol awakening response in a sample of patients with first-episode psychosis. No differences were found in the evening cortisol levels among the subjects who reported CA (Braehler et al 2005; Mondelli et al 2010). The association between cortisol secretion and PS is also

controversial, with it being reported in some studies (Murri et al 2012; Keshavan et al 1989; Rybakowski et al 1990; Walder et al 2000; Faravelli et al 2010; Walker et al 2013) but not others (Bradley and Dinan 2010).

Given the inconsistency of these findings, we attempted to investigate the relationship between CA, cortisol levels, and psychosis in this study. We hypothesized that a) patients with psychosis would be more likely to report CA; b) patients with psychosis would show increased cortisol secretion; c) exposure to CA would be related to increased cortisol secretion; and d) patients who experienced CA would have more severe PS. As a corollary, we also hypothesized that the presence of PS could be related to higher cortisol levels.

2. Method

This study is part of the Factors in Early Life, Diagnoses, and Symptoms project, an observational, multidisciplinary, and transnosological study. All patients newly admitted to psychiatric facilities (public and private) in Tuscany, a region of central Italy that includes 10 local health units and three university hospitals, were studied. During a 2-month period, 409 patients were recruited to the study and evaluated within 1 week of admission. Patients with psychosis were selected according to the criteria set out by Jablensky et al (1992). This includes having a) at least one of the following symptoms: hallucinations, delusions, a qualitative speech disorder, a qualitative psychomotor disorder, and bizarre or grossly inappropriate behavior; or b) two of the following symptoms: loss of interest, initiative, and drive, social withdrawal, episodic severe excitement, purposeless destructiveness, overwhelming fear, or marked self-neglect.

Subjects who met any of the following criteria were excluded from the study: age more than 75 years; neurological and/or neurocognitive impairment; presence of disorders that might compromise the ability to provide informed consent; pregnant or breast-feeding; substance abuse and/or addiction; on going treatments or medications (i.e., corticosteroids, L-DOPA [L-3,4 dihydroxyphenylalanine], phenytoin, metyrapone, ketoconazole, lithium, and opioids); habits (i.e., shift workers, habitual smokers, and caffeine), medical conditions known to alter HPA axis functioning (i.e., Cushing's disease, Addison's disease, obesity, thyroid dysfunctions, chronic infections, and others); hospitalized patients, owing to the relationship between hospitalization and the cortisol response (Copolov et al 1989).

Eighty-five patients were included in the study after assessment of the above criteria. There was a slight preponderance of female patients (52%), with the age ranging between 18 and 71 years, and 42% of patients were not working (unemployed or with a pension). Moreover, 5% of the patients were experiencing their first episode of psychosis, 39% met the Diagnostic and Statistical Manual

of Mental Disorders, 4th Edition, diagnosis of schizophrenia or schizophreniform disorder, 19% had a schizoaffective disorder, and 13% had a delusional disorder. All cases featured symptoms that were at an acute stage.

It was possible to match (for age, sex, and education) a control group of 170 subjects, drawn from a pool of 1070 subjects, according to a case-control 1:2 procedure. The study protocol was approved by the local ethics committee, and all participants provided a written informed consent.

2.1 Instruments

2.1.1 Symptom Measurement

Psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale, which has shown good reliability and validity (Kay et al 1987).

2.1.2 Childhood adversity

The presence of CA was investigated using the Childhood Experience of Care and Abuse Questionnaire (CECA-Q; Bifulco et al 2005) and a structured interview for early trauma included in the Florence Psychiatric Interview (FPI; Faravelli et al 2001). Respondents were asked if they had experienced the following types of adversity before the age of 15 years: death of mother, death of father, separation from mother, separation from father, divorce of parents, severe childhood disease, physical abuse, or sexual abuse. The presence of CA was evaluated using the following categories:

- loss events: whenever a death or separation (for 1 year or more) from parents was reported;
- sexual or physical abuse events: when the CECA-Q or the interview revealed the presence of physical and/or sexual abuse;
- neglect: based on the CECA-Q scores in the scales “mother's neglect” and “father's neglect,” according to the cutoff proposed by Bifulco et al (2005) (≥ 22 for mother's neglect score and ≥ 24 for father's neglect score; example of CECA-Q items: she/he made me feel unwanted; she/he was very critical of me).

In the context of the CECA-Q responses, we did not consider events that were reported after the age of 15 years. Life events were evaluated by experts who were not involved in the interview and who were blind to the patient or control status of the subjects.

2.1.3 Cortisol Levels

The measurement of salivary cortisol is seen as a reliable tool for investigating HPA axis activity (Kiess et al 1995; Kirschbaum and Hellhammer 1989; Walder et al 2000). Furthermore, salivary,

urinary, and plasma measures of cortisol are both highly interrelated and comparable in terms of their sensitivity as measures of stress reactivity (Bassett et al 1987; Shipley et al 1992; Walder et al 2000; Weinstein et al 1999). Since saliva sampling is relatively non invasive, it is considered to be a preferable method for repeated assessments (Baum and Grunberg 1995). Saliva samples were collected for cortisol analyses 30 and 60 minutes after the subject woke up and at 8:00 p.m. The data produced from these samples might indicate whether differences in cortisol are sustained over time while also detecting differences in cortisol secretion at different times of the day, indicating disruption to normal circadian rhythms (Bradley and Dinan 2010). The highest of the two diurnal measurements was used as the morning value. Saliva was collected in a device using a cotton swab that was chewed by the subjects for 2 minute and then inserted into a double-chamber plastic tube. The saliva samples were refrigerated at 4°C (for a maximum of 10 hours) and subsequently stored at -20°C. Salivary cortisol levels were analyzed using an immunoassay (Elecsys, Roche, Switzerland) (Chiu et al 2003). All assays were conducted by personnel blind to the diagnostic status or group, and all preliminary laboratory tests to evaluate recovery rate, sensitivity, and reproducibility were satisfactory. Before the saliva collection, all subjects were instructed not to smoke or consume alcohol or caffeine.

2.2 Statistics

Chi-square or Fisher's tests, odds ratio (OR) tests, and t tests were used for comparisons between the two groups, and a one-way analysis of variance (ANOVA) using a Bonferroni post hoc analysis was performed to compare cortisol levels in the subgroups. A binary logistic regression analysis with the subjects' status as the dependent variable (control subjects versus patients with psychosis) and the total number of CA events as the independent variable was used to evaluate the presence of a cumulative effect of CA. A simple contrast was used, specifying the first level (no CA) as the reference category. All other categories of predictor variables were compared with the reference category. This provided an estimate of the likelihood of psychosis for the number of CA events experienced compared with the CA-free group. The statistical analyses were performed using SPSS for Windows 20.0 (IBM; Statistics IS 2011).

3. Results

Although all subjects underwent the same protocol, it was not possible to analyze salivary cortisol in 31 patients and 68 control subjects. This was because some subjects either failed to return the swab or they returned a non-analyzable sample. No differences in terms of age, sex, education, prevalence of CA, or clinical variables (for patients) were found between the subjects for whom we

did or did not have salivary cortisol levels. Data for 54 patients and 102 control subjects were, therefore, analyzable.

Although the case-control 1:2 procedure was not met, results for patients and control subjects were comparable in terms of sex (women: 44.4% vs. 48%, $\chi^2 = 0.18$, $df = 1$, $p = 0.67$), age (43.74 ± 10.51 years vs. 43.46 ± 12.24 years, $t(df) = -0.14(154)$, $p = 0.89$), and educational level (mean education years: 11.54 ± 3.58 years vs. 11.62 ± 3.42 years, $t(df) = 0.13(154)$, $p = 0.89$). Compared with subjects in the control group, patients were found to be more frequently single (61.1% vs. 16.7%, $\chi^2 = 32.02$, $df = 1$, $p < 0.001$) and unemployed and/or retired (46.3% vs. 7.8%, $\chi^2 = 31.30$, $df = 1$, $p < 0.001$).

3.1 Childhood adversity and Psychosis

Compared with control subjects, patients with psychosis showed a higher prevalence of CA (Table 1). Various forms of CA yielded a significant cumulative effect ($\chi^2 = 6.06$, $df = 2$, $p = 0.04$, R^2 Cox and Snell = 0.03). Compared with the patients who had not experienced CA, subjects who experienced one CA event were over one and a half times more likely to have psychosis (OR, 1.62; 95% confidence interval [CI], 0.79–3.30), whereas individuals who experienced two or more CA events were nearly four times more likely to have psychosis (OR, 4.13; 95% CI, 1.22–13.89).

3.2 Cortisol Levels and Psychosis

Compared with control subjects, patients with psychosis showed higher levels of both morning cortisol (mean $\pm$ SD_{patients} 15.45 ± 15.01 nmol/L vs. mean $\pm$ SD_{control} 10.52 ± 6.89 nmol/L, $t(df) = -2.80(154)$, $p = 0.01$) and evening cortisol (mean $\pm$ SD_{patients} 4.66 ± 5.08 nmol/L vs. mean $\pm$ SD_{control} 2.24 ± 2.35 nmol/L, $t(df) = -4.05(154)$, $p \leq 0.001$).

3.3 Childhood adversity and Salivary Cortisol

A one-way ANOVA with Bonferroni post hoc correction showed that patients who experienced at least one CA event had higher morning cortisol levels (mean $\pm$ SD, 19.36 ± 18.61 nmol/L) than any other group ($F(df) = 6.15(155)$; $p < 0.05$). Patients who had not experienced any CA events (mean $\pm$ SD, 10.56 ± 6.15 nmol/L; Bonferroni $p = 0.01$), control subjects who had experienced CA (mean $\pm$ SD, 9.98 ± 6.70 nmol/L; Bonferroni $p = 0.001$), and control subjects who had not experienced CA (mean $\pm$ SD, 10.87 ± 7.04 nmol/L; Bonferroni $p = 0.001$) had comparable morning cortisol levels (Bonferroni $p = 1.00$) (Fig. 1). Moreover, a one-way ANOVA ($F(df) = 7.72(155)$; $p < 0.05$) showed that patients who had experienced at least one CA event had higher evening cortisol levels (mean $\pm$ SD, 5.29 ± 5.88 nmol/L) than both control subjects who had experienced CA (mean $\pm$ SD, $2.89 \pm$

3.15 nmol/L; Bonferroni $p = 0.03$) and control subjects who had not experienced CA (mean $\pm$ SD, 1.83 ± 1.54 nmol/L; Bonferroni $p < 0.001$). No significant difference was found in evening cortisol levels (mean $\pm$ SD, 3.87 ± 3.82 nmol/L; Bonferroni $p = 0.85$) among patients who had or had not experienced CA. No significant differences were found with regard to evening cortisol levels between patients who had not experienced CA and control subjects who had experienced CA (Bonferroni $p = 1.00$), and between patients who had not experienced CA and control subjects who had not experienced CA (Bonferroni $p = 0.10$). Controls who had or had not experienced CA showed comparable evening cortisol levels (Bonferroni $p = 0.82$) (Fig. 1).

3.4 Childhood adversity, Salivary Cortisol, and Positive Symptoms

Patients with psychosis who had experienced CA showed an increased severity of PS than those who had not experienced CA (mean $\pm$ SD, 26.27 ± 7.30 vs. 20.62 ± 7.65 , $t_{(df)} = -2.76_{(52)}$, $p = 0.01$). Patients with psychosis with higher morning cortisol levels (based on a cut-off of the average + 1SD morning cortisol level of patients who had not experienced CA) showed more severe delusions (mean $\pm$ SD, 5.18 ± 1.79 vs. 3.92 ± 2.48 , $t_{(df)} = -1.84_{(52)}$, $p = 0.04$) than subjects with lower morning cortisol levels.

4. Discussion

The results from the current study support the hypothesis that exposure to traumatic childhood events and increased cortisol secretion are associated with psychosis and the severity of PS, whereas the relationship between CA and cortisol levels seems more complex than expected. According to previous studies (Bentall et al 2014; Morgan and Gayer-Anderson 2016; Varese et al 2012), patients with psychosis showed a higher rate of CA. Moreover, experiencing more than one early adversity event may further increase the risk for psychosis, supporting previous evidence regarding the cumulative effects of CA on psychosis (Morgan and Gayer-Anderson 2016; Varese et al 2012; Wickham and Bentall 2016).

Although our findings support several earlier studies confirming the involvement of cortisol dysregulation in the etiology of psychosis (Girshkin et al 2014; Read et al 2014; Morgan and Gayer-Anderson 2016), it is unclear whether increased cortisol secretion is due mostly to CA exposure or to the presence of a psychotic condition. In contrast, an increase in morning cortisol levels seems to be related to both the exposure to CA and the presence of a psychotic condition. Indeed, our findings only showed higher levels of morning cortisol in patients who had experienced CA rather than in patients who had not experienced CA or in control subjects (who had or had not experienced CA). These findings support the notion that the cortisol awakening response might act

as a dynamic index of HPA axis reactivity that is affected by psychological factors, such as stressful life events and the clinical symptoms of psychosis (Bradley and Dinan 2010; Fries et al 2009; Murri et al 2012). The causative effects of evening cortisol levels seem to be less clear. In fact, although we found higher levels of evening cortisol in patients who had experienced CA compared with control subjects (who had or had not experienced CA), no differences were found among patients who had or had not experienced CA. Thus, it is still unclear whether the increase in levels of evening cortisol is a by-product of exposure to ELS or the severity of psychotic disease. Our data do not allow for further speculation.

However, the literature is of little help here because the times at which cortisol is measured have not been standardized (Bradley and Dinan 2010; Braehler et al 2005; Mondelli et al 2010). Moreover, previous studies have yielded mixed results. For instance, Braehler et al (2005) reported a negative association between CA and morning cortisol levels; in contrast, Mondelli et al (2010) found a positive correlation between CA and morning cortisol levels, whereas no association was found between CA and evening cortisol levels (Mondelli et al 2010).

Our results also confirmed that CA is associated with an increased severity of PS, which is consistent with previous findings (Cotter et al 2015; Lysaker et al 2001; 2004; 2005; Morgan and Gayer-Anderson 2016; Read et al 2005; Üçok and Bıkmaz 2007; van Nierop et al 2016). Therefore, it might be considered that CAs influence the form and severity of the disease once it has developed (Birnbaum 1923; Furukawa et al 1998).

Finally, our findings support earlier studies that have shown a relationship between cortisol secretion and PS (Murri et al 2012; Read et al 2014; Ruby et al 2014). It is worth noting that PS may represent a “pseudostressor” that can be emotionally intense (Dinan 2004). As a result, the perception of these symptoms, whether they are stressful, may influence cortisol levels (Bradley and Dinan 2010). It should also be noted that the increased release of glucocorticoids produces hyperactivity of the dopaminergic system, which in turn is associated with PS (Ruby et al 2014).

Some methodological issues should be considered when interpreting the results of this study.

1) The evaluation of CA is notoriously problematic. Retrospective assessment is highly susceptible to recall bias, in terms of both memory distortion and the search for meaning. Prospective evaluations such as those conducted in the Dunedin (Poulton et al 2015) and Munich (Lataster et al 2012) studies offer the advantage of evaluating stressful events at the moment of their occurrence, thus eliminating any bias due to memory or the consequences of the event. Apart from the enormously increased difficulties of using this approach, such as the cost and time involved, it nevertheless does not yield totally satisfactory results, because events that are difficult to express, communicate, and understand for a child (such as child abuse) often remain confined to the inner

experiences of the individual. Forensic psychiatry and psychology adopt specific procedures to examine such cases. Retrospective assessment might therefore be an acceptable compromise, because some events (e.g., death or separation of/from parents) may be reliably reported even after decades, whereas other events are difficult to detect, even in the present moment. Although it has been reported that retrospective assessment of childhood abuse is often reliable (Fisher et al 2009), the evaluation of CA is still caught between the Scylla of loss of reliability and the Charybdis of loss of sensitivity, as reported three decades ago (Faravelli et al 1986).

- 2) The clinical sample size is relatively small.
- 3) Socioeconomic and housing contexts were not evaluated, even though disruptions in both can lead to CA and psychosis.
- 4) The cross-sectional data limit our ability to formally test for causality.

5. Conclusion

Similar to other studies that have addressed this particular topic (Morgan and Gayler-Anderson 2016 Read et al 2014), the current study confirms that experiencing adverse events during childhood and abnormal HPA axis functioning are associated with psychosis, although the relationship between CA and cortisol levels requires further investigation. Early experiences of CA and the stressful experiences associated with psychotic symptoms can affect cortisol levels. The dysregulation of the HPA system that often follows early trauma is well known; however, increased cortisol levels could be an effect of reaching an acute stage of psychosis, as exposure to CA determines greater severity, which in turn might be responsible for higher cortisol levels. In addition, excessive amounts of CA could be a product of social disadvantage, for example, poverty, which is associated with psychosis. Furthermore, it has been repeatedly reported that different genotypes may condition the outcome of exposure to CA (Caspi et al 2002; 2003). Finally, inheritance might also explain both CA and HPA axis malfunctioning: a parent with psychosis may increase the risk of both biological vulnerability and of being exposed to life stress.

Unfortunately, disentangling such a complex relationship is beyond the scope of the present study and must be addressed in the future. However, our results underline the importance of evaluating childhood trauma during the clinical assessment of patients with psychosis. This finding will help facilitate meaningful formulations and treatment plans (Read et al 2007).

Conflict of Interest: none

Table 1. Prevalence of Childhood Adversity (evaluated by FPI and CECA-Q): comparison between patients with psychosis and controls

	Psychotic (n = 54) n(%)	Controls (n = 102) n(%)	p	OR	[95% CI]
At least one CA	30 (55.6)	40 (39.2)	0.05	1.93	0.99-3.77
Physical abuse	13 (24.1)	16 (15.7)	0.20	1.70	0.75-3.87
Sexual abuse	9 (16.7)	0	<0.001a	-	-
Loss of mother	9 (16.7)	5 (4.9)	0.02a	3.88	1.23-12.24
Loss of father	6 (11.1)	16 (15.7)	0.43	.67	0.24-1.83
Mother Neglect	10 (18.5)	7 (6.9)	0.03	3.08	1.10-8.64
Father Neglect	5 (9.3)	4 (3.9)	0.27a	2.50	0.64-9.72

Note. CA=Childhood adversity; a: Fisher exact test.

Figure 1. Mean ($\pm$ Standard Deviation) salivary cortisol levels (nmol/L) in patients with psychosis and control subjects with and without CA. $\bullet$ — $\bullet$ Morning cortisol levels (nmol/L). Significant differences were found between: (a) psychotic with CA and psychotic without CA, $p = 0.01$; (b) psychotic with CA and control with CA, $p = 0.001$; (c) psychotic with CA and control without CA, $p = 0.001$. $\blacklozenge$ — $\blacklozenge$ Evening cortisol levels (nmol/L). Significant differences were found between: (a) psychotic with CA and control without CA, $p \leq 0.001$; (b) psychotic with CA and control with CA, $p = 0.03$.

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Chapter 4

The role of cognitive functioning in the relationship between childhood trauma and a mixed phenotype of affective-anxious-psychotic symptoms in psychotic disorders.

Giovanni Mansueto^a, Martine van Nierop^b, Koen Schruers^c, GROUP Investigators, Berhooz Z. Alizadeh^d, Agna A. Bartels-Velthuis^d, Nico J. van Beveren^{e,f}, Richard Bruggeman^d, Wiepke Cahn^g, Lieuwe de Haan^h, Philippe Delespaul^c, Carin J. Meijer^h, Inez Myin-Germeys^b, Rene S. Kahn^g, Frederike Schirmbeck^h, Claudia J.P. Simons^{ci}, Neeltje E.M. van Haren^g, Jim van Os^{e,j}, Ruud van Winkel^k

^aDepartment of Health Sciences, University of Florence, Florence, Italy

^bKU Leuven, Department of Neuroscience, Research Group Psychiatry, Center for Contextual Psychiatry, Leuven, Belgium

^cMaastricht University Medical Center, Dept. of Psychiatry & Psychology, School for Mental Health & Neuroscience, Maastricht, The Netherlands

^dUniversity of Groningen, University Medical Center Groningen, University Center for Psychiatry, Groningen, The Netherlands

^eAntes Center for Mental Health Care, Rotterdam, The Netherlands

^fErasmus MC, Dept. of Psychiatry, Dept. Of Neuroscience, Rotterdam, The Netherlands

^gUniversity Medical Centre Utrecht, Dept. Of Psychiatry, Brain Centre Rudolf Magnus, Utrecht, The Netherlands

^hAcademic Medical Centre, University of Amsterdam, Dept. Of Psychiatry, Amsterdam, The Netherlands

ⁱGGzE, Institute for Mental Health Care Eindhoven and De Kempen, Eindhoven, The Netherlands

^jKing's College London, King's Health Partners, Dept. Of Psychosis Studies, Institute of Psychiatry, London, United Kingdom

^kKU Leuven, University Psychiatric Center KU Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium

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Abstract

Introduction

Cognitive impairments in patients with psychotic disorder have been associated with poor functioning and increased symptom severity. Furthermore, childhood trauma (CT) exposure has been associated with worse cognitive functioning as well as co-occurrence of affective-anxious-psychosis symptoms or a ‘mixed phenotype of psychopathology’ (MP), which in turn is associated with greater symptom severity, and poor functioning. This study aims to evaluate if cognition could be associated with CT/MP.

Method

532 patients with non-affective psychotic patients were assessed on CT, symptom profile, cognition, functioning, and symptom severity at baseline and 3 and 6-year follow-up. Four subgroups were made according to trauma exposure (CT⁻ or CT⁺) and presence of a mixed phenotype (MP⁻ or MP⁺): CT⁻/MP⁻ (n = 272), CT⁻/MP⁺ (n = 157), CT⁺/MP⁻ (n = 49), and CT⁺/MP⁺ (n = 54). Mixed-effects multilevel regression, linear regression, and Tobit analyses were performed.

Results

Patients with both CT and MP showed lower verbal learning and memory than CT⁻/MP⁺ individuals ($p < 0.001$). No other significant differences were found among the 4 subgroups. No cognitive decline was found at follow-up, neither in the CT⁺/MP⁻ nor in CT⁻/MP⁻ group. Lower cognition was not associated with increased symptom severity or poor functioning at follow-up, neither in the CT⁺/MP⁻ nor in CT⁻/MP⁻ group.

Conclusion

Although cognitive impairments and CT may be related to clinical or functional features of psychotic disorder, and cognitive functioning could be affected by CT exposure, cognition does not discriminate subgroups of patients stratified by CT exposure and MP.

1. Introduction

Cognitive impairments are considered core features in psychotic disorder (PD), suggesting neurocognition as an endophenotypic marker of psychosis (Aas et al 2013; Mehta et al 2013; Rajji et al 2014; Reichenberg 2005). Cognitive dysfunctions occur across several domains such as executive functioning, episodic and working memory, attention, language, explicit learning, and motor processing (Antonova et al 2004). Generally, PD patients show a cognitive ability between 1.5 and 2 standard deviations below that of a sample of matched healthy controls (Antonova et al 2004). Similarly, it has been shown that relatives of PD patients exhibit cognitive impairments that are milder than, yet similar to, those seen in patients (Reichenberg 2005). Moreover, neuropsychological impairments are associated with lower general functioning in first episode psychosis (FEP) as well as in chronic psychosis (Rajji et al 2014). Follow-up studies of 2–10 years (Malla et al 2002; Smith et al 2002; Stirling et al 2003; Tandberg et al 2011) have linked attention, executive function, and memory with both work performance and social functioning. Furthermore, there is some evidence linking cognitive impairment with psychotic symptom severity (de Gracia Dominguez et al 2009).

It has also been shown that psychotic patients who have experienced childhood trauma (CT), an environmental risk factor for psychosis (Varese et al 2012; Morgan and Gayer-Anderson 2016; Rössler et al 2016), score lower on a range of cognitive domains than those without CT (Aas et al 2013). Cross-sectional studies on psychotic spectrum disorder found lower processing speed, and working and episodic memory deficits in patients with CT compared to patients without CT, after adjusting for premorbid intelligent quotient (IQ) (Lysaker et al 2001) and depressive symptoms (Shannon et al 2011). Schenkel et al (2005) found some evidence of an association between childhood abuse and impairment in visual-perceptual organization (Schenkel et al 2005). Furthermore, in a sample of 406 patients with PD or bipolar disorder, CT was related with lower working memory and executive functioning, although these associations seemed to be driven by IQ reductions (Aas et al 2012a). Analogous findings have been found in case-control studies on FEP patients, where CT was associated with deficits in language, verbal intelligence, executive functioning, and working memory (Aas et al 2011a; 2012b), although other studies did not replicate these results (Aas et al 2011b; Sideli et al 2014). Furthermore, a recent study of individuals with ultra-high risk (UHR) for psychosis highlighted worse attention, interference inhibition, working memory, and cognitive flexibility, in subjects exposed to childhood physical abuse (Üçok et al 2015).

Recent studies have also shown that PD patients with a history of CT, compared with their non-exposed counterparts, display a phenotype composed of an admixture of affective, anxious, and

psychotic symptoms, rather than of any of these symptom clusters in isolation (Van Nierop et al 2015). A follow-up study showed that the co-occurrence of CT and this mixed phenotype of affective, anxious, and psychotic symptoms (CT/MP) is associated with clinically and functionally meaningful differences within PD patients (Van Nierop et al 2016). Psychotic patients with CT/MP had worse quality of life, lower educational levels, greater symptom severity, and higher prevalence of drug disorder, than patients without CT, patients without a mixed phenotype, or without both (Van Nierop et al 2016). This subgroup of psychotic patients with CT/MP, given their poor functional outcome, may be more resistant to treatment (Van Nierop et al 2016). However, the relationship between CT, MP and diminished general functioning is still unclear.

The current study aims to evaluate if cognition could be related with CT/MP, as well as with lower general functioning. It could be hypothesized that cognition may discriminate psychotic patients subdivided by CT and MP, and that diminished cognitive functioning may be associated with increased symptom severity and poor daily functioning. In order to test these hypotheses, we will examine cognitive functioning (i.e. verbal learning, memory, attention, and working memory) in a sample of non-affective PD patients, stratified by CT history and a mixed psychopathology phenotype. We expect that: (a) psychotic patients with both CT and MP compared with those without CT or without MP, or without both, may show lower cognitive functioning, and (b) poor cognition may predict a diminished general functioning.

2. Methods

This research is part of the 6-year longitudinal observational study called the “Genetic Risk and Outcome of Psychosis Project (GROUP)” (Korver et al 2012). The GROUP study has enrolled a sample of patients with a diagnosis of non-affective PD, their unaffected siblings, parents, and controls. For the purpose of this study we have only used the patient sample. Patients were recruited from 5 university hospitals in the Netherlands and Belgium (Groningen, Amsterdam, Maastricht, Utrecht, and Leuven) and their affiliated mental healthcare institutions. Patients were eligible for inclusion if they: (i) were aged 16–65; (ii) met the Diagnostic and statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for non-affective PD (APA, 2000); (iii) had first contact with mental health care b10 years ago; (iv) were proficient in Dutch. Patients were excluded if their estimated level of intelligence was b 70.

In Amsterdam, Maastricht, Utrecht, and Leuven patients were assessed with Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al 1992), and in Groningen with the Schedules for Clinical Assessment in Neuropsychiatry (SCAN 2.1; Wing et al 1990). As this study used symptom data from the CASH we have only included participants from the Amsterdam,

Maastricht, Utrecht, and Leuven sites (n = 532). The GROUP study included three measurements: at baseline, at 3-year follow-up, and 6-year follow-up.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and by local review boards of each participating institute. The study was designed in strict accordance with the declaration of Helsinki of the World Medical Association as revised in 2008. All subjects gave written informed consent in accordance with the committee's guidelines.

2.1. Measures

2.1.1. Childhood trauma

CT was assessed with the Dutch version of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al 2003), a 25-item self-report questionnaire rated on a scale of 1 (never true) to 5 (very often true). The CTQ-SF measures physical abuse, physical neglect, sexual abuse, emotional abuse, and emotional neglect. A total CT score was obtained by calculating the average of all 25 items.

2.1.2. Symptoms

Present state depression, anxiety, and psychotic symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS; Kay et al 1987). The PANSS is a 30-item interview consisting of three subscales on a range from 1 (absent) to 7 (very severe): the positive scale (e.g. delusion/hallucinations), negative scale (e.g. blunted affect, difficulty in abstract thinking) and a general psychopathology scale (e.g. depression, feeling of guilt). Depression and anxiety were assessed with one item each (depression: have you felt sad, down or depressed; anxiety: worried, nervous, restless or panicked).

Present state mania was assessed with the CASH (Andreasen et al 1992). The CASH includes the 34-item Scale for the Assessment of Positive Symptoms (SAPS; Andreasen 1984) and the 21-item Scale for Assessment of Negative Symptoms (SANS; Andreasen 1989) both on a range from 0 (no) to 5 (severe). Mania was assessed with one item (have you felt overly or abnormally excited or active). All symptoms were assessed at all three measurements.

2.1.3. Definition of subgroups

Following previous studies (Van Nierop et al 2015; 2016) a total score of the CTQ-SF (Bernstein et al 2003) was dichotomized to 0 (low CT; n = 429; "CT-") and 1 (high CT; n = 103; "CT+") using the 80th percentile of the total childhood trauma score. The psychosis, depressive, anxiety scores of the PANSS (Kay et al 1987), were dichotomized to 0 (score 1) and 1 (score of 2 or above). Similarly, the mania item's score, from the CASH (Andreasen et al 1992), was dichotomized to 0

(score 0) and 1 (score of 1 or above). According with previous studies (Van Nierop et al 2015, 2016) a dichotomous variable called “mixed phenotype of psychopathology (MP)” was created:

- 0 = no or minimal symptom clustering “MP–” (e.g. no symptoms, isolated symptoms only, or combinations of two symptom clusters; n = 211)
- 1 = symptom clustering “MP+” (e.g. combination of at least three symptom clusters; n = 321).

Following previous work (Van Nierop et al 2015; 2016), CT and a MP were combined to generate one categorical variable, called “Childhood trauma-mixed symptom profile (CT/MP)”, describing four groups:

- 0=noCT–noMP(CT–/MP–;n=272);
- 1=noCT–MP(CT–/MP+;n=157);
- 2=CT–noMP(CT+/MP–;n=49);
- 3=CT–MP(CT+/MP+;n=54).

2.1.4. Cognitive functioning

At all three measurements, verbal learning and memory was assessed with the Word Learning Task (WLT) (Brand and Jolles 1985). Outcome measures were immediate recall (number of words recalled over the three 15-word trials), retention rate (delayed free recall after 20 min divided by the maximum score of immediate recall trials 1–3), and delayed recall (number of correctly remembered words). Lower scores of all WLT subscales reflected worse performance. At each measurement, attention and vigilance was assessed using a Continuous Performance Test (CPT-HQ) (Wohlberg and Kornetsky 1973; Nuechterlein and Dawson 1984). Outcome measures were reaction time (reaction time for correct detections) and accuracy (proportion of correct detections). Higher scores of reaction time and lower scores of accuracy reflected worse performance. Reasoning/problem solving and working memory were evaluated with the Response Shifting Task (RST) (Bilder et al 1992). Outcome variables were reaction time cost (reaction time in the reversal condition minus reaction time in the imitation condition) and accuracy cost (proportion correct in the imitation condition minus proportion correct in the reversal condition). Higher scores reflected worse performance. Reasoning/problem solving and working memory was evaluated at baseline and 3 year follow-up. At each measurement, general cognitive abilities and achievement, expressed as a single intelligence quotient (IQ) score, were assessed using four subtests of the Wechsler Adult Intelligence Scale 3rd (WAIS-III) (Wechsler 1997): Digit Symbol-Coding, Information, Arithmetic and Block Design.

2.1.5. General functioning, cannabis use and medication use

General functioning was assessed using the Global Assessment of Functioning scale (GAF), ranging from 0 to 100 (higher score indicating better functioning) (APA 2000). This scale defined a symptom score (GAF-S) and functioning score (GAF-F), reflecting the severity of symptoms and the level of daily functioning. Cannabis frequency of use, during the lifetime period of heaviest use, was assessed with the Composite International Diagnostic Interview (CIDI 2.1) (Andrews and Peters, 1998) on a scale of 1 (less than weekly) to 3 (daily). Antipsychotic and other medication use (anti-depressant, mood stabilizer, anti-cholinergic, benzodiazepine, anxiolytic, medication against components of the metabolic syndrome) was assessed by clinical interview. General functioning, cannabis use and medication use were assessed at all three measurements.

2.2 Analyses

All analyses were performed in STATA, version 13, including age and gender as a priori confounders. Separate analyses were performed for each cognitive variable. Sample attrition was evaluated using t-test and Chi-square test respectively for continuous and dichotomous variables.

2.2.1. Cognition and CT/MP

In order to evaluate the relationship between cognition and CT/MP, mixed-effects multilevel regression analyses (MIXED command in STATA) were performed, using CT/MP as the independent variable and cognitive functioning as dependent. Both baseline and the two follow-up measurements of cognitive functioning were used, thus an extra level was added to account for clustering within subjects. Comparative effects sizes were obtained performing post-hoc analyses using the LINCOM command. These analyses allow us to evaluate whether significant differences on cognitive functioning may occur among patients stratified for CT and MP.

In order to evaluate if CT/MP may affect the progression of cognition, mixed-effects multilevel regression (MIXED command in STATA) analysis was performed, evaluating interaction effects between CT/MP and measurement (baseline, 1st follow-up, 2nd follow-up) on cognitive functioning. Since both baseline and follow-up measurements of cognitive functioning were used, an extra level was added to account for clustering within subjects.

In accordance with earlier studies (Pechtel and Pizzagalli 2011; Aas et al 2013) these analyses were repeated including IQ, cannabis use, and medication use as potential confounders. Adjustment for multiple testing was carried out using Bonferroni correction. Given the number of tests performed (5 CT/MP group contrasts * 7 cognitive tests = 35 tests), we acquired a conservative significance level of $p = 0.001$.

The CPT-HQ accuracy score was skewed. Log transformation (Altman et al 1983) did not improve the normality of distribution, thus the CPT-HQ accuracy score was analysed using the TOBIT command in STATA (Breen 1996). Tobit regression models allow for the estimation of the relationship between one or more predictors and the outcomes of interest when there is either left and/or right censoring in the outcome variable (Altman et al 1983; Breen 1996). The model coefficients indicate how unit changes in the predictor variables are related to changes on a latent continuum, which is only observed in censored form via the outcome variable.

2.2.2. Cognition and general functioning

Linear regression analyses (REGRESS command in STATA) were performed to evaluate the relationship between cognitive functioning at baseline and GAF score at 6-year follow-up, co-varying for the GAF score at baseline, in both groups CT –/MP – and CT +/MP –.

Adjustment for multiple testing was carried out using Bonferroni correction. Given the number of tests performed (2 CT/MP groups * 7 cognitive tests * 2 GAF scores = 28 tests), we acquired a conservative significance level of $p = 0.002$.

3. Results

3.1. Sample and attrition

A total of 532 subjects participated at the baseline measurement, 356 subjects participated at the three-year follow-up (2nd measurement) and 349 were interviewed at the six-year follow-up (3rd measurement) (Table 1). At baseline, 11 of the 532 subjects did not participate on the cognitive measures. Participants without data on cognition did not significantly differ from subjects available for the cognition measures in term of gender, age, educational level, CT, psychopathology, cannabis use, and medication use.

Subjects lost to follow-up at the 2nd measurement did not significantly differ from subjects who were available for 3-year follow-up in terms of age, gender, CT, cannabis use, medication use, mania, negative symptoms, IQ, cognition, and GAF score at baseline. Subjects who did not participate on the 2nd measurement reported lower educational levels ($\text{mean}_{\text{no follow-up}} 3.90$ vs $\text{mean}_{\text{follow-up}} 4.18$, $t = -2.89$, $p = 0.004$) more depressive symptoms ($\text{mean}_{\text{no follow-up}} 2.72$ vs $\text{mean}_{\text{follow-up}} 2.34$, $t = 2.004$, $p = 0.04$), more anxiety ($\text{mean}_{\text{no follow-up}} 2.65$ vs $\text{mean}_{\text{follow-up}} 2.32$, $t = 2.02$, $p = 0.04$), and more positive symptoms ($\text{mean}_{\text{no follow-up}} 1.99$ vs $\text{mean}_{\text{follow-up}} 1.78$, $t = 2.06$, $p = 0.03$) at baseline.

Subjects who did not participate on the 3rd measurement did not significantly differ from subjects who were available for 6-year follow-up in terms of age, gender, cannabis use, medication use,

psychopathology, retention rate, and GAF score at baseline. Subjects lost to 3rd measurement showed lower educational levels ($\text{mean}_{\text{no follow-up}} 3.92$ vs $\text{mean}_{\text{follow-up}} 4.25$, $t = -4.54$, $p < 0.001$), lower IQ ($\text{mean}_{\text{no follow-up}} 93.51$ vs $\text{mean}_{\text{follow-up}} 98.14$, $t = -3.06$, $p = 0.002$), more CT ($\text{mean}_{\text{no follow-up}} 1.71$ vs $\text{mean}_{\text{follow-up}} 1.57$, $t = 2.82$, $p = 0.005$), worse delayed recall ($\text{mean}_{\text{no follow-up}} 7.11$ vs $\text{mean}_{\text{follow-up}} 7.89$, $t = -2.93$, $p = 0.003$), and worse immediate recall ($\text{mean}_{\text{no follow-up}} 22.04$ vs $\text{mean}_{\text{follow-up}} 23.81$, $t = -3.06$, $p = 0.002$) at baseline.

There was some evidence for an association (at $p < 0.05$) between CT and verbal learning (WLT immediate recall: $B = -1.22$, $p = 0.01$, $95\%CI = -2.15$ to -0.029 ; WLT retention rate: $B = -0.04$, $p = 0.003$, $95\%CI = -0.06$ to -0.01 ; WLT delayed recall: $B = -0.62$, $p = 0.004$, $95\%CI = -1.03$ to -0.19). No association was observed with CPT-HQ reaction time ($B = 1.65$, $p = 0.78$, $95\%CI = -10.20$ – 13.51) or working memory (RST reaction time cost: $B = -19.99$, $p = 0.20$, $95\%CI = -50.67$ – 10.68 ; RST accuracy cost: $B = 0.01$, $p = 0.56$, $95\%CI = -0.02$ – 0.04). The association between CT and CPT-HQ accuracy was marginally significant at $p < 0.05$ ($B = -0.92$, $p = 0.02$, $95\%CI = -1.69$ to -0.16).

3.2. Cognitive functioning, CT/MP and general functioning

Before adjusting for IQ, cannabis use, and medication use, none of the cognition measures reached significance at the adjusted conservative significance level, when contrasting the different subgroups (Table 2). However, adjusting for these covariates revealed that patients with both CT history and mixed phenotype of psychopathology displayed significantly lower verbal learning and memory (WLT delayed recall) than patients with a mixed phenotype but without CT (Table 3). No other contrasts were found when comparing the four subgroups. Similarly, no significant (at $p < 0.001$) cognitive decline was found at follow-up, in the CT +/MP – group nor in the CT –/MP – group. When assessing the general daily functioning and symptoms' severity (GAF), none of the cognition measures was associated with a change in functioning at follow-up in either the CT +/MP – or the CT –/MP – group.

4. Discussion

The present study found no clear evidence for differences in cognitive functioning or progression of cognition, when contrasting groups based on CT exposure and symptom phenotype. We did find that in PD patients with a MP, CT exposure was associated with worse delayed recall. No evidence was found that cognitive deficits at baseline were associated with disability or symptom severity at follow-up.

The finding of worse delayed recall in individuals with CT/MP is consistent with a previous study

that highlighted worse performance in delayed memory tasks in PD patients with CT than in those without CT exposure (Shannon et al 2011). As CT may affect amygdala volume (Heim et al 2010; Read et al 2014), and left amygdala volume could be related with delayed verbal recall performance (Killgore et al 2009), the difference found in the current study among patients with MP may in part due to underlying neurobiological differences. It is not clear why CT would be related with lower delayed recall only in the subgroup of patients with MP, and it is not clear whether lower scores on delayed recall are due mostly to CT exposure rather than the interaction between CT and MP. Furthermore, the comparison of subgroups of patients, stratified for CT/MP, on cognition was based on cross-sectional data. Moreover, neither cognitive decline nor associations between poor cognition and lower functioning were found at follow-up. Therefore, although all associations were in the expected direction, our hypotheses that lower cognition could be associated with CT/MP, and that it may lead to poor functioning are not supported by the data at hand. Since we did not find significant differences on cognitive functioning among subgroups of patients stratified for CT/MP, a mediator role of cognition in the relationship between CT and MP is unlikely. The lack of association between CT/MP and cognition may in part be explained by the unclear relationship between cognition and psychotic symptoms on the one hand (de Gracia Dominguez et al 2009; Killgore et al 2009; Nieuwenstein et al 2001), and between cognition and comorbid symptoms in PD on the other hand (Kerns and Berenbaum 2002; Hermesh et al 2003; Goodman et al 2007; Fan et al 2008; Duke et al 2010; Yücel et al 2012; Potvin et al 2012; Rapp et al 2012; Ralevski et al 2012; Wong and Miller 2015). While neurocognitive impairment is mostly related with negative/disorganized dimensions (de Gracia Dominguez et al 2009), development of positive and depressive symptoms is more likely based on changes in stress sensitivity (Myin-Germeys and van Os 2007; de Gracia Dominguez et al 2009;). The results could suggest that stress sensitivity, rather than neurocognition, may be related to symptom comorbidity. On the other hand, however, studies comparing PD patients with and without comorbid disorders have yielded mixed findings: some studies found better cognitive functioning in those with comorbid disorders (Kerns and Berenbaum, 2002; Potvin et al 2012 Rapp et al 2012; Wong and Miller 2015), while others showed worse cognitive functioning (Goodman et al 2007; Fan et al., 2008; Yücel et al., 2012), and some did not find any difference (Hermesh et al 2003; Duke et al 2010; Ralevski et al 2012). Therefore it seems that role of cognitive functioning in the relationship between CT and psychosis is still unclear; large-scale prospective studies may be required to disentangle this complicated relationship. Several methodological issues should be considered. Firstly, the lack of significant findings may be due to a lack of power of the analyses because of the small sample size of each subgroup. On the other hand, the follow-up nature of the study allowed us to assess associations between cognition

and disease outcome, and a wide range of cognitive domains was evaluated. Secondly, although we incorporated several measures of cognition, the possibility remains that these measures did not reflect actual daily cognitive functioning within these patients. Some researchers have argued that standard cognitive batteries are insufficient to measure real world functioning, and a more ecological approach is needed (Damasio 1995; Burgess 2000; Chaytor and Schmitter-Edgecombe 2003; Burgess et al 2006; Lamberts et al 2010; Larøi et al 2010). Finally, CT was assessed by subjective retrospective report, thus recall bias may have influenced these results, although research suggest good reliability of retrospective assessment of CT (Fisher et al 2011).

In conclusion, although cognition and CT have been related to psychosis (de Gracia Dominguez et al 2009; Varese et al 2012; Aas et al 2013), and cognitive functioning could be affected by CT exposure (Aas et al 2013), cognition does not differentiate between subgroups of patients stratified by CT exposure and mixed phenotype.

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Table 1 Baseline, 3-year follow-up, 6-year follow-up: descriptive analyses

	Baseline (n = 532)	3-year follow-up (n = 356)	6-year follow-up (n = 349)
Gender (male), n (%)	402 (76)	263 (74)	258 (74)
Age, mean (SD); range	27.61 (7.61); 15-56	31.13 (7.76); 18-56	34.46 (7.58); 21-63
Educational level ^A , mean (SD); range	4.14 (0.78); 2-5	4.28 (0.72); 3-5	4.33 (0.72); 2-5
Childhood Trauma ^B , mean (SD); range	1.62 (0.51); 1-3.84	n.a.	n.a.
Positive symptoms ^C , mean (SD); range	1.81 (0.79); 1-5.28	1.52 (0.63); 1-4	1.67 (0.74); 1-4.85
Negative symptoms ^C , mean (SD); range	1.89 (0.87); 1-5.42	1.61 (0.71); 1-5.57	1.66 (0.73); 1-4
General symptoms ^C , mean (SD); range	1.69 (0.53); 1-3.68	1.47 (0.43); 1-3.5	1.48 (0.45); 1-3.31
Mania symptoms ^D , mean (SD); range	0.08 (0.45); 0-4	0.06 (0.39); 0-4	0.11 (0.55); 0-5
Depressive symptoms ^E , mean (SD); range	2.39 (1.48); 1-7	1.86 (1.16); 1-7	1.77 (1.12); 1-6
Anxiety symptoms ^F , mean (SD); range	2.36 (1.29); 1-6	1.99 (1.13); 1-6	1.99 (1.12); 1-6
WLT immediate recall ^G , mean (SD); range	23.22 (6.24); 7-40	25.32 (5.99); 9-40	24.68 (7.02); 5-43
WLT retention rate ^G , mean (SD); range	0.77 (0.20); 0.09-1.5	0.78 (0.18); 0-1.2	0.78 (0.20); 0.22-2
WLT delayed recall ^G , mean (SD); range	7.63 (2.89); 1-15	8.39 (2.88); 0-15	8.20 (3.07); 2-15
CPT-HQ reaction time ^H , mean (SD); range	425.81 (83.55); 253.53-872.52	456.11 (85.19); 292.21-847.76	449.51 (78.31) 288.25-720.84
CPT-HQ accuracy ^H , mean (SD); range	98.63 (3.71); 60-100	98.93 (3.15); 64.66-100	99.07 (2.79); 66-100
RST reaction time cost ^I , mean (SD); range	227.11 (241.96); -744.6-1384.33	221.71 (213.34); -760.28-899.13	-
RST accuracy cost ^I , mean (SD); range	0.18 (0.25); -0.44-1	0.17 (0.24); -0.24-1	-
IQ-WAIS ^L , mean (SD); range	96.62 (16.28); 60-146	100.20 (16.27); 68-144	100.69 (17.25); 57-152
GAF symptoms ^M , mean (SD); range	55.89 (16.61); 10-100	58.43 (16.79); 15-100	55.49 (16.46); 21-100
GAF functioning ^M , mean (SD); range	55.60 (16.43); 1-100	60.55 (16.38); 25-100	58.12 (16.14); 21-100
Cannabis use ^N , mean (SD); range	1.64 (1.34); 0-3	0.67 (1.13); 0-3	0.59 (1.08); 0-3
Antipsychotic use ^O , n (%)	385 (72)	219 (61)	243 (70)
Medication use ^O , n (%)	145 (27)	87 (24)	89 (25)

^A Educational Level: 0 (no education), 1(primary school), 2-3(secondary school), 4-5 (high school), 6 (lower vocational), 7 (higher vocational), 8 (university) ^B Childhood Trauma measured with the Childhood Trauma Questionnaire scale (CTQ-SF). A total trauma score was obtained by calculating the average of all 25 items (physical, sexual and emotional abuse, and physical and emotional neglect) each ranging 1(never true)-5(very often true) ^C Severity of present state (past two weeks) of positive symptoms, negative symptoms and general psychopathology were measured respectively with subscales of the Positive and Negative Syndrome Scale (PANSS). Positive scale (range 1-7) Negative Scale (range 1-7) General Psychopathology Scale (range 1-7) ^D Severity of present state (past month) of mania assessed with the Comprehensive Assessment of Symptoms and History (CASH), with one item (have you felt overly or abnormally excited or active) on a range 0 (no) - 5 (severe) ^E Severity of present state (past two weeks) of depression assessed with the PANSS, with one item (have you felt sad, down or depressed) on a range 1 (absent) - 7 (extreme) ^F Severity of present state (past two weeks) of anxiety assessed with the PANSS, with one item (have you felt worried, nervous, restless or panicked) on a range 1 (absent) - 7 (extreme) ^G Verbal learning and memory assessed with subscales of Word Learning Task (WLT): Immediate recall (number of words recalled over the three 15-word trials), retention rate (delayed free recall after 20 min divided by the maximum score of immediate recall trials 1-3) and delayed recall (number of correctly remembered words) ^H Attention and vigilance assessed with subscales of Continuous Performance Test (CPT-HQ): reaction time (reaction time for correct detections) and accuracy (proportion of correct detections) ^I Reasoning/problem solving and working memory assessed with subscales of the Response Shifting Task (RST): reaction time cost (reaction time in the reversal condition minus reaction time in the imitation condition) and accuracy cost (proportion correct in the imitation condition minus proportion correct in the reversal condition) ^L Intelligence quotient (IQ) measured with the Wechsler Adult Intelligence Scale 3rd (WAIS-III) on a range 1-145 ^M Functioning in terms of symptoms severity and disability was measured with the Global Assessment of Functioning scale (GAF), on a range 0-100 ^N Cannabis use assessed with the Composite International Diagnostic Interview (CIDI) 2.1 ^O Antipsychotic and other medication use (anti-depressant, mood stabilizer, anti-cholinergic, benzodiazepine, anxiolytic, medication against components of the metabolic syndrome) assessed by clinical interview

Table 2 Association between childhood trauma and mixed phenotype of psychopathology with neurocognitive functioning in patients with non-affective psychotic disorder. (Adjusted for age and gender) (1st-2nd-3rd measurement)

Group comparison	CT-/MP+ (n=157) vs. CT-/MP- (n=272)	CT+/MP- (n=49) vs. CT-/MP- (n=272)	CT+/MP+ (n=54) vs. CT-/MP- (n=272)	CT+/MP+ (n=54) vs. CT+/MP- (n=49)	CT+/MP+ (n=54) vs. CT-/MP+ (n=157)
	Association of mixed phenotype of psychopathology with neurocognitive functions in patients without trauma history	Association of trauma with neurocognitive functions in patients without mixed phenotype of psychopathology	Association of trauma and mixed phenotype of psychopathology with neurocognitive functions (vs. absence of both)	Association of mixed phenotype of psychopathology with neurocognitive functions in patient with trauma	Association of trauma with neurocognitive functions in patients with mixed phenotype of psychopathology
B coefficients indicate	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value
WLT immediate recall	0.26 (-0.52-1.05) (0.51)	-0.54 (-2.03-0.94) (0.47)	-1.45 (-3.02-0.11) (0.07)	-0.90 (-2.53-0.72) (0.27)	-1.71 (-3.35- -0.06) (0.04)
WLT retention rate	0.02 (-0.01-0.04) (0.26)	-0.02 (-0.06-0.02) (0.33)	-0.04 (-0.09-0.002) (0.06)	-0.02 (-0.08-0.03) (0.41)	-0.06 (-0.11- -0.01) (0.02)
Verbal learning and memory	0.29 (-0.07-0.65) (0.12)	-0.16 (-0.87-0.50) (0.62)	-0.78 (-1.49- -0.07) (0.03)	-0.61 (-1.36- 0.13) (0.11)	-1.07 (-1.81- -0.32) (0.005)
Attention and vigilance	CPT-HQ reaction time -8.54 (-18.58-1.48) (0.09)	-1.97 (-20.58-16.63) (0.83)	-3.49 (-23.47-16.48) (0.73)	-1.51 (-22.32-19.29) (0.88)	5.05 (-15.89-26.01) (0.63)
	CPT-HQ accuracy -0.47 (-1.30-0.36) (0.27)	-0.51 (-1.78-0.75) (0.43)	0.001 (-0.99-0.99) (0.99)	0.51 (-0.89-1.92) (0.47)	0.47 (-0.73-1.67) (0.44)
Reasoning and problem solving/working memory	RST reaction time cost -9.46 (-48.56-29.64) (0.63)	-22.11 (-78.47-34.25) (0.44)	2.41 (-59.02-63.86) (0.93)	24.52 (-51.21-100.27) (0.63)	11.87 (-53.85-77.60) (0.72)
	RST accuracy cost 0.02 (-0.01-0.06) (0.23)	-0.05 (-0.11-0.01) (0.11)	0.07 (0.006-0.14) (0.03)	0.12 (0.04-0.20) (0.002)	0.04 (-0.02-0.12) (0.17)

Bonferroni correction p value=0.001

CI: confidence interval; CT: childhood trauma; MP: mixed phenotype of psychopathology; RST was evaluated at the 1st and 2nd measurements only.

Table 3 Association between childhood trauma and mixed phenotype of psychopathology with neurocognitive functioning in patients with non-affective psychotic disorder. (Adjusted for age, gender, IQ, cannabis use, antipsychotic and other medication use) (1st-2nd-3rd measurement)

Group comparison	CT-/MP+ (n=157) vs. CT-/MP- (n=272)	CT+/MP- (n=49) vs. CT-/MP- (n=272)	CT+/MP+ (n=54) vs. CT-/MP- (n=272)	CT+/MP+ (n=54) vs. CT-/MP- (n=49)	CT+/MP+ (n=54) vs. CT-/MP+ (n=157)
	Association of mixed phenotype of psychopathology with neurocognitive functions in patients without trauma history	Association of trauma with neurocognitive functions in patients without mixed phenotype of psychopathology	Association of trauma and mixed phenotype of psychopathology with neurocognitive functions (vs. absence of both)	Association of mixed phenotype with psychopathology with neurocognitive functions in patient with trauma	Association of trauma with neurocognitive functions in patients with mixed phenotype of psychopathology
B coefficients indicate	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value	B (95% CI) p-value
Verbal learning and memory					
WLT immediate recall	0.63 (-0.12-1.38) (0.10)	-0.13 (-1.39-1.13) (0.84)	-1.12 (-2.47-0.24) (0.11)	-0.98 (-2.51-0.53) (0.20)	-1.75 (-3.18- -0.31) (0.02)
WLT retention rate	0.02 (-0.01-0.04) (0.16)	-0.02 (-0.06-0.02) (0.39)	-0.04 (-0.09-0.001) (0.05)	-0.02 (-0.08-0.02) (0.34)	-0.06 (-0.12- -0.02) (0.01)
WLT delayed recall	0.44 (0.09-0.80) (0.01)	-0.02 (-0.62-0.57) (0.92)	-0.71 (-1.35- -0.07) (0.03)	-0.68 (-1.39-0.02) (0.06)	-1.15 (-1.83- -0.48) (0.001)
Attention and vigilance					
CPT-HQ reaction time	-7.20 (-18.35-3.94) (0.20)	0.05 (-19.66-19.78) (0.99)	-3.67 (-24.61-17.26) (0.73)	-3.73 (-27.42-19.95) (0.76)	3.52 (-18.47-25.53) (0.75)
CPT-HQ accuracy	-0.22 (-0.99-0.55) (0.57)	-0.53 (-1.92-0.85) (0.45)	-0.03 (-1.07-1.01) (0.95)	0.50 (-1.15-2.16) (0.55)	0.18 (-1.01-1.38) (0.76)
Reasoning and problem solving/working memory					
RST reaction time cost	1.56 (-41.52-44.64) (0.94)	-5.21 (-67.80-57.37) (0.87)	-10.09 (-75.94-55.74) (0.76)	-4.88 (-87.78-78.01) (0.91)	-11.66 (-82.07-58.75) (0.74)
RST accuracy cost	0.003 (-0.04-0.04) (0.90)	-0.03 (-0.09-0.04) (0.43)	0.07 (0.006-0.14) (0.03)	0.09 (0.01-0.18) (0.02)	0.07 (-0.001-0.14) (0.05)

Significant result on the basis of Bonferroni correction (p=0.001) is marked in bold.

CI: confidence interval; CT: childhood trauma; MP: mixed phenotype of psychopathology; RST was evaluated at the 1st and 2nd measurements only.

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Chapter 5

Childhood adversities and psychotic symptoms: the potential mediating or moderating role of neuro or social cognition

Giovanni Mansueto^{AB}, Koen Schruers^A, Fiammetta Cosci^B, Jim van Os^{ACD}, GROUP Investigators[§]

^A Maastricht University Medical Center, Dept. of Psychiatry & Psychology, School for Mental Health & Neuroscience, Maastricht, the Netherlands

^B Department of Health Sciences, University of Florence, Florence, Italy

^C Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands

^D King's College London, King's Health Partners, Dept. of Psychosis Studies, Institute of Psychiatry, London, United Kingdom

^E University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Groningen, the Netherlands

^F KU Leuven, Dept. of Neuroscience, research group Psychiatry, Center for Contextual Psychiatry, Leuven, Belgium

^G Antes Center for Mental Health Care, Rotterdam, the Netherlands

^H Erasmus MC, Dept of Psychiatry, Dept. of Neuroscience, Rotterdam, the Netherlands

^I University Medical Centre Utrecht, Dept. of Psychiatry, Brain Centre Rudolf Magnus, Utrecht, the Netherlands

^J Academic Medical Centre, University of Amsterdam, Dept. of Psychiatry, Amsterdam, the Netherlands

[§]The GROUP Investigators are: Behrooz Z. Alizadeh^E, Agna A. Bartels-Velthuis^E, Nico J. van Beveren^{GH}, Richard Bruggeman^E, Wiepke Cahn^I, Lieuwe de Haan^J, Philippe Delespaul^A, Carin J. Meijer^J, Inez Myin-Germeys^F, Rene S. Kahn^I, Frederike Schirmbeck^J, Claudia J.P. Simons^{AC}, Neeltje E.M. van Haren^I, Ruud van Winkel^F

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Abstract

Introduction

Childhood abuse and neglect are risk factors for psychotic symptoms. Early adversities might lead to poor neuro/social cognitive functioning, which in turn is associated to psychosis. This study aimed to explore the mediating and moderating role of neuro/social cognition in the relationship between childhood abuse, neglect, and psychotic symptoms.

Method

1.119 patients with a psychotic disorder were enrolled. Childhood adversities were evaluated with the Dutch version of the Childhood Trauma Questionnaire. Psychotic symptoms were assessed via the Positive and Negative Syndrome Scale. Verbal learning-memory, attention-vigilance, working memory, information processing speed, reasoning-problem solving were evaluated as measures of neurocognition using the Word Learning Task, the Continuous Performance Test, the Wechsler Adult Intelligence Scale 3rd. Mentalization were evaluated as a measure of social cognition using the Hinting Task. Correlation, mediation, moderation, and 95% Bias Corrected and accelerated (BCaCI) bootstrapped analyses were performed.

Results

Within male patients with a psychotic disorder, attention and vigilance mediated the association between childhood neglect and negative symptoms (Indirect effect: .18, BCaCI: .03-.54), disorganization (Indirect effect: .26, BCaCI: .05-.61), excitement (Indirect effect: .07, BCaCI: .004-.23); mentalizing abilities mediated the association between childhood neglect and negative symptoms (Indirect effect: .21, BCaCI: .02-.51), excitement (Indirect effect: .07, BCaCI: .01-.20) disorganization (Indirect effect: .29, BCaCI: .02-.64); working memory mediated the association between childhood abuse and disorganization (Indirect Effect: .28, BCaCI: .05-.57), excitement (Indirect Effect: .08, BCaCI: .01-.20), emotional distress (Indirect Effect: .10, BCaCI: .01-.27).

Conclusion

Within male patients with a psychotic disorder, neurocognition and mentalization might be involved in the association between childhood abuse, neglect, and psychotic symptoms.

1. Introduction

The association between childhood adversities and psychosis is well known (Varese et al 2012a; Trotta et al 2015; Mansueto and Faravelli 2017) with some evidence (Beards and Fisher 2014; Bentall et al 2014; Morgan and Anderson 2016) that specific subtypes of childhood adversities may predict later development of psychosis. Childhood abuse and childhood neglect may lead to a 2- to 3-fold increased risk of psychosis while childhood loss events may not (Varese et al 2012a; Shevlin et al 2015; Trausalen et al 2015; Ajnakina et al 2016). Childhood adversities with intention to harm seem to be a stronger predictor of psychotic experiences than childhood adversities without intention to harm (Van Nierop et al 2014). Furthermore, childhood physical abuse increases the vulnerability to psychosis (Fisher et al 2010) as does sexual abuse involving penetration (Cutajar et al 2010).

It has been suggested that specific kinds of childhood adversities may lead to specific psychotic manifestations. The exposure to childhood abuse was found to be a strong predictor of positive symptoms (Lisaker et al 2001; Heins et al 2011; Gallagher and Jones 2013; Bentall et al 2014; Sitko et al 2014; Chae et al 2015; Schalinski et al 2015; Shevlin et al 2015; van Dam et al 2015; Aas et al 2016; Ajnakina et al 2016; Cristóbal-Narváez et al 2016) while results on disorganization, excitement, and emotional distress are mixed (Chae et al 2015; Schalinski et al 2015; Aas et al 2016). Experiences of childhood neglect have been associated with paranoia and negative symptoms (Vogel et al 2011; Gallagher and Jones 2013; Bentall et al 2014; Sitko et al 2014; van Dam et al 2015; Cristóbal-Narváez et al 2016; Gibson et al 2016) as well as with disorganization, excitement, and emotional distress (Chae et al 2015; Schalinski et al 2015; Aas et al 2016).

Neurocognition (which involves attention, memory, processing speed, and executive functions) (de Gracia et al 2009) and social cognition (which involves perception, encoding, storage and regulation of information about people as well as the ability to think about and imagine mental states) (Fonagy et al 2002; Green et al 2015) have been hypothesised as an aetiological mechanism underlying the association between childhood adversities and psychosis (Garcia et al 2016; Morgan and Anderson, 2016; Schalinski et al 2017). Childhood adversities may induce a hypothalamic-pituitary-adrenal axis dysregulation that, through glucocorticoid receptors, diminishes hippocampal neurogenesis leading to altered neurocognition (Read et al 2014). The exposure to childhood adversities may also cause deprivation of early social interactions, cognitive biases such as ‘jumping to conclusions’ and disrupted attachment, which in turn may affect the development of social cognitive abilities (Gibson et al 2016; Jacobsen et al 2015; Van Os et al 2010). Childhood adversity contributes to functional alterations of brain regions such as the temporoparietal junction (TPJ), the posterior cingulate cortex (PCC), and dorsomedial prefrontal cortex (dmPFC), which are essential for effective mental state inference (Quidé et al 2017). Neurocognitive impairments were

found in patients with psychotic disorder with a history of childhood abuse (Lisaker et al 2001; Üçok et al 2015) and poorer social cognition was observed in those exposed to childhood neglect if compared to those not exposed to childhood adversities (Garcia et al 2016). In turn, impairments in neurocognition and social cognition were strongly associated with disorganization and negative symptoms, and were weakly associated with positive symptoms (de Gracia et al 2009; Fett et al 2013; Ventura et al 2013).

Guided by these findings, we hypothesised that exposure to childhood abuse or childhood neglect may predict poor functioning in the area of neurocognition or social cognition, which in turn may predispose to psychotic symptoms. Thus, we explored whether neurocognition and social cognition mediate or moderate the association between childhood abuse/childhood neglect and psychotic symptoms.

2. Methods

The present research is part of a 6-year longitudinal observational study called the ‘Genetic Risk and Outcome of Psychosis Project (GROUP)’ (Korver et al 2012). The GROUP study includes a sample of patients with a diagnosis of non-affective psychotic disorder, their unaffected siblings, their unaffected parents, and healthy controls. The current analyses focus on the patients only. Patients were recruited from five university hospitals in the Netherlands and Belgium (i.e., Groningen, Amsterdam, Maastricht, Utrecht, Leuven) and their affiliated mental healthcare institutions. Patients were eligible for inclusion if they: (i) were aged 16-65 years; (ii) met the Diagnostic and Statistical Manual of mental Disorders Fourth Edition (DSM-IV) (APA 2000) criteria for non-affective psychotic disorder; (iii) had their first contact with mental health care for psychosis less than 10 years before; and (iv) were proficient in Dutch.

The GROUP study included three assessments: baseline, 3-year follow-up, and 6-year follow-up. The present analyses are based on the baseline assessment (n=1,119 patients).

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and by the local review boards of each participating institute. All subjects provided written informed consent.

2.1 Measures

Childhood adversities were assessed via the Dutch version of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al 2003), a 25-item retrospective self-report questionnaire rating on a Likert scale ranging from 1 (never true) to 5 (very often true) with good internal consistency, reliability, and validity (Thombs et al 2009). The CTQ-SF measures physical abuse, physical neglect, sexual abuse, emotional abuse, and emotional neglect, all occurring before the age

of 17 years.

Since the literature suggests that the phenomenology of psychosis can be adequately reduced to symptom dimensions (Ajnakina et al 2016; Costello 1992; van Os et al 1999), we focused on psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1987). This is a 30-item interview-based scale rated on a 7-point Likert scale with good internal reliability and validity (Peralta and Cuesta 1994).

Neurocognition encompassed the domains of verbal learning and memory, attention and vigilance, working memory, information processing speed, and reasoning and problem solving. Verbal learning and memory were assessed by means of the Word Learning Task (WLT) (Brand and Jolles 1985). Outcome measures were immediate recall (i.e., number of words recalled over the three 15-word trials), retention rate (i.e., delayed free recall after 20 min divided by the maximum score of immediate recall trials 1-3). Lower scores of these outcomes variables reflect worse performance.

Attention and vigilance was assessed with the Continuous Performance Test (CPT-HQ) (Wohlberg and Kornetsky 1973; Nuechterlein and Dawson 1984), presenting a series of 300 white letters (on a laptop computer-controlled video monitor) at a rate of one per second in a randomized sequence. Subjects were instructed to press the space bar each time that the letter H was preceded by the letter Q (van Ommen et al 2016). The CPT has shown good reliability and validity (Cornblatt and Keilp 1994). Accuracy (i.e., proportion of correct detections) was used as outcome measure; lower scores meant worse performance.

General cognitive abilities and achievement (i.e., IQ) were estimated with four subtests of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (Blyler et al 2000; Wechsler 1997). Working memory was assessed using the WAIS-III subtest Arithmetic; information processing speed was evaluated using the WAIS-III subtest Digit Symbol-Coding; reasoning and problem solving was assessed using the subtest WAIS-III Block Design; and the WAIS-III Information subtest was used as a measure of acquired knowledge.

Mentalizing abilities or Theory of Mind (ToM) was evaluated as a measure of social cognition (van Os et al 2010; Fett et al 2011; Green et al 2015) using the Hinting Task (HT) (Corcoran et al 1995; Fett et al 2011) which assesses subjects' ability to infer real intentions behind indirect speech utterances. It comprises ten short passages presenting an interaction between two characters that ends with one of the characters dropping a hint. The subject is asked what the character really meant. Correctly identified hints were scored 2; in case of an incorrect response, a more obvious hint was added and the subsequent correct response was scored 1; incorrect responses were scored 0. The outcome measure was the sum of the scores of the ten items (range 0–20). The HT has shown good validity (Corcoran and Frith 2003).

Frequency of cannabis use, during the lifetime period of heaviest use, was assessed with the short

version of the Composite International Diagnostic Interview (CIDI) (Andrews and Peters 1998; World Health Organization 1990) on a scale of 1 (less than weekly) to 3 (daily), using the Substance Abuse Module section L. Acceptability and reliability of the questions were found to be high (Cottler et al 1989).

2.2 Statistic analyses

Some studies (Alemany et al 2011; van Dam et al 2015; Killian et al 2017) considered abuse and neglect as separate childhood trauma dimensions showing a degree of specificity between these two types of early adversities and psychotic symptoms. To make present results comparable with previous studies (Alemany et al 2011; Killian et al 2017; van Dam et al 2015), we grouped CTQ scores creating an abuse score (e.g. the sum of sexual abuse, physical abuse, emotional abuse scores) and a neglect score (e.g. the sum of physical neglect, and emotional neglect scores).

In order to discriminate patients with childhood adversity from those without childhood adversity, both childhood neglect and childhood abuse scores were dichotomized into high trauma and low trauma. We used as cut-off the 80th percentile of trauma scores as in previous studies (Heins et al 2011; van Dam et al 2015; van Nierop et al 2015) since having grouped CTQ scores to create a childhood abuse score and a neglect score, we could not use the cut-offs proposed by other authors (e.g., by Bernstein et al 2003).

The five-factor of the PANSS including positive symptoms, negative symptoms, disorganization, excitement, and emotional distress, was used (van der Gaag et al 2006ab). This model may reflect the complex reality of schizophrenia and comorbid symptoms (Korver et al 2012) and represents the dimensional structure of the PANSS (van der Gaag et al 2006ab; Wallwork et al 2012) better than the original 3-factor model (Kay et al 1987).

The Kolmogorov-Smirnov test was used to test normality of data (Ali and Bhaskar 2016). Given that the data were not normally distributed, the non-parametric Mann-Whitney U test was performed to compare rank means of continuous variables. Chi-square tests were conducted to compare proportions. Analyses were performed with SPSS, version 21 (SPSS Inc).

The possible mediating and moderating roles of neurocognition and social cognition in the association between childhood neglect, childhood abuse, and psychotic symptoms were estimated according to Baron & Kenny's criteria (1986). Mediation analyses allowed to evaluate whether neurocognition or social cognition represent the intermediary process through which childhood adversities lead to psychotic symptoms. Moderation analyses allowed to evaluate whether neurocognition or social cognition influence the strength of the relation between childhood adversities and psychosis.

A correlation analysis was used to ensure that independent variables (IV) (i.e., childhood neglect or childhood abuse), dependent variables (DV) (i.e., psychotic symptoms), and hypothesized mediator (M)/moderator (MR) (i.e., neurocognition or social cognition) were associated (Baron and Kenny 1986). Mediation models were tested when independent variables IV, DV, and M were associated; moderation models were tested when both IV and MR were significantly associated with the DV (Baron and Kenny 1986). Mediation analyses and moderation analyses were performed using the Hayes PROCESS macro model 4 and the Hayes PROCESS macro model 1, respectively (Preacher and Hayes 2004; Hayes 2013).

To test the mediation models, three regression equations were run to verify the following conditions: (a) IV affects M; (b) IV affects DV; (c) M affects DV (Baron and Kenny 1986). Fully mediating associations were considered when the association between IV and DV was not statistically significant after controlling for the effect of M; partial mediation was considered when, controlling for M, the direct effect of IV on DV was significant (Baron and Kenny 1986). A bootstrapping procedure with $n = 5,000$ bootstrap re-samples was used to assess indirect effects (Efron and Tibshirani 1998; Kenny, 1998; MacKinnon, 2002; Preacher and Hayes 2004). An indirect effect was considered significant if the 95% Bias Corrected and accelerated bootstrapped confidence interval (BCa CI) excluded zero.

Before testing the moderation models, both IV and MR were mean-centred (Shieh 2011; Dawson 2014) to mitigate the potential threat of multicollinearity between IV and the constructed cross-product term, thus facilitating the interpretation of the interaction effects (Shieh 2011). To test moderation models, three regression equations were run and the following conditions verified: (a) IV affects DV; (b) MR affects DV; (c) the interaction effect between IV and MR affects DV (Baron and Kenny, 1986).

Mediation and moderation models were adjusted for the covariates age, sex, and lifetime cannabis use as *a priori* potential cofounders (van Os et al 2002; Bäckman et al 2006; Fisher et al 2009; van Os et al 2010; Pechtel and Pizzagalli 2011; Han et al 2012; Sánchez et al 2013; Morgan et al 2014; Green et al 2015; Itting et al 2015).

Sex differences in cognition, clinical symptoms, and impact of early adversities, as well as a possible association between duration of psychotic illness, age, and cognitive functioning have been observed in previous studies (Bilder et al 2000; Daba et al 2002; Üçok et al 2015; Ventura et al 2015; Mendrek et al 2016). Thus the analyses of correlation, mediation, and moderation between childhood adversities, cognitive functioning and psychotic symptoms were run separately for men and women as well as for subgroups of patients on the basis of the duration of illness (recent onset vs non recent onset of psychotic disorder; recent onset was considered in the last 24 months) and age. According to Nakane et al (1992), we considered the following 5 age groups: 15-19 years

(n=90); 20-24 (n=207); 25-29 (n=205); 30-34 (n=116); 35-39 (n=72); 40-44 (n=57) 45-49 (n=14); 50-54 (n=3); 55-60 (n=3). Given the lower number of subjects with ≥ 45 years, we excluded them from the analyses.

Release 5.0 of the GROUP database was used for the present study. The two-sided significance level was set at $p < .05$.

3. Results

3.1 Sample attrition

Of the 1.119 patients enrolled at baseline, 757 had data on childhood adversities. Around 30% of the subjects did not or could not answer the childhood trauma questionnaire. Comparing those who completed the childhood trauma questionnaire with those who did not, we found in the latter group: lower educational level (mean ranks no childhood adversity data vs childhood adversity: 501.90 vs 567.54; $p = .001$); more severe symptoms: positive symptoms (mean ranks no childhood adversity data vs childhood adversity: 547.70 vs 495; $p = .009$), negative symptoms (mean ranks no childhood adversity data vs childhood adversity: 548.81 vs 471.15; $p \leq .001$), disorganization (mean ranks no childhood adversity data vs childhood adversity: 590.75 vs 470.07; $p \leq .001$), excitement (mean ranks no childhood adversity data vs childhood adversity: 589.49 vs 496.25; $p \leq .001$), and emotional distress (mean ranks no childhood adversity data vs childhood adversity: 556.66 vs 497.45; $p = .003$); lower score on neurocognitive tasks and social cognition: immediate recall (mean ranks no childhood adversity data vs childhood adversity: 489.42 vs 536.16; $p = .02$), attention (mean ranks no childhood adversity data vs childhood adversity: 441.47 vs 507.59; $p \leq .001$), processing speed (mean ranks no childhood adversity data vs childhood adversity: 486.97 vs 543.32; $p = .005$), acquired knowledge (mean ranks no childhood adversity data vs childhood adversity: 481.15 vs 547.20; $p = .001$), working memory (mean ranks no childhood adversity data vs childhood adversity: 494.64 vs 39.09; $p = .02$), reasoning-problem solving (mean ranks no childhood adversity data vs childhood adversity: 476.56 vs 547.84; $p \leq .001$) and mentalizing abilities (mean ranks no childhood adversity data vs childhood adversity: 462.35 vs 540.54; $p \leq .001$). For the other analyses only participants with data on childhood adversity were included. For more details on descriptive analyses please see Table 1.

3.2 Childhood neglect

Patients with childhood neglect, compared with those without childhood neglect, showed more severe positive symptoms, disorganization, excitement, emotional distress, and lower scores on retention rate, and attention (Table 2). Childhood neglect was positively associated with psychotic symptoms and negatively associated with immediate recall, attention and vigilance, as

well as with mentalizing abilities (Table 3). Both neurocognitive functions and mentalizing abilities were negatively associated with psychotic symptoms (Table 3).

Mediation models showed that lower immediate recall partially mediated the association between childhood neglect and disorganization (adjusted R-squared = .07, $p \leq .001$; Total Effect: 1.20, BCa 95% CI: .46 - 1.94; Indirect effect: .13, BCa 95% CI: .006 - .30) (Table 4). Moreover, mentalizing abilities partially mediated the association between childhood neglect and negative symptoms (adjusted R-squared = .07, $p \leq .001$; Total Effect: 1.01, BCa 95% CI: .27-.75; Indirect effect: .17, BCa 95% CI: .02-.40); childhood neglect and disorganization (adjusted R-squared = .11; $p \leq .001$; Total Effect: 1.29, BCa 95% CI: .46-1.95; Indirect effect: .23, BCa 95% CI: .03-.49); and childhood neglect and excitement (adjusted R-squared = .055, $p \leq .001$; Total Effect: .76, BCa 95% CI: .32-1.21; Indirect effect: .05, BCa 95% CI: .009-.14) (Table 4; Figure 1). Childhood neglect was not significantly associated with attention-vigilance, when adjusted for covariates (Table 4). Thus, mediation models between childhood neglect, attention-vigilance, and psychotic symptoms were not examined.

Moderation models showed that neither neurocognitive domains nor mentalizing abilities moderated the association between childhood neglect and psychotic symptoms (Table 5).

3.3 Childhood abuse

Patients with psychotic disorder with childhood abuse showed more severe psychotic symptoms than those without childhood abuse, while no statistically significant differences were found for neurocognition and social cognition (Table 2). Childhood abuse was positively associated with all psychotic dimensions except for negative symptoms and was negatively associated with working memory (Table 3). Adjusting for age, sex, and lifetime cannabis use, the association between childhood abuse and working memory was no longer significant ($B = -.57$, $SE = .38$, $p = .10$, BCa 95% CI: -.10 - .11). Since the independent variable (i.e., childhood abuse) did not predict the hypothesized mediator variable (i.e., working memory) (Baron and Kenny, 1986), mediation models between childhood abuse, working memory, and psychotic symptoms were not run.

Moderation analyses showed that neither neurocognitive domains nor mentalizing abilities moderated the association between childhood abuse and psychotic symptoms (Table 6).

3.4 Mentalization and neurocognition

A positive association between mentalization and neurocognition scores was found. Mentalizing abilities were positively correlated with verbal learning and memory, attention and vigilance, working memory, processing speed, reasoning, and problem solving abilities (Table 3).

3.5 Association between childhood adversities, cognitive functioning, and psychotic symptoms in male and female

3.5.1 Male psychotic patients

Childhood neglect was positively associated with all psychotic symptoms, and negatively associated with immediate recall, attention and vigilance, working memory and mentalizing abilities; both neurocognitive functions and mentalizing abilities were negatively associated with psychotic symptoms (Table 7).

Attention and vigilance partially mediated the association between childhood neglect and negative symptoms (adjusted R-squared = .05, $p \leq .001$; Total Effect: 1.22, BCa 95% CI: .29-2.14; Indirect effect: .18, BCa 95% CI: .03-.54), disorganization (adjusted R-squared = .06, $p \leq .001$; Total Effect: 1.21, BCa 95% CI: .24-2.19; Indirect effect: .26, BCa 95% CI: .05-.61) and excitement (adjusted R-squared = .04, $p = .001$; Total Effect: .88, BCa 95% CI: .32-1.44; Indirect effect: .07, BCa 95% CI: .004-.23) (Table 8). Mentalizing abilities: (a) partially mediated the association between childhood neglect and negative symptoms (adjusted R-squared = .06, $p < .001$; Total Effect: 1.29, BCa 95% CI: .39-2.18; Indirect effect: .21, BCa 95% CI: .02-.51); excitement (adjusted R-squared = .04, $p < .001$; Total Effect: .86, BCa 95% CI: .31-1.41; Indirect effect: .07, BCa 95% CI: .01-.20); (b) fully mediated the association between childhood neglect and disorganization (adjusted R-squared = .09, $p < .001$; Total Effect: 1.10, BCa 95% CI: .18-2.02; Indirect effect: .29, BCa 95% CI: .02-.64) (Table 10) (Table 8). When adjusted for covariates (e.g., age, cannabis), childhood neglect was not significantly associated with working memory ($B = -.38$, $p = .10$, BCa 95% CI = -.84-.08) nor with immediate recall ($B = -.88$, $p = .05$, BCa 95% CI = -1.74-.002), thus, the mediating role of working memory and immediate recall were not examined. Neither neurocognition nor social cognition moderated the association between childhood neglect and psychotic symptoms (Table 9).

Childhood abuse was positively associated with all psychotic dimensions, except negative symptoms; and negatively associated with attention and vigilance, working memory (Table 8). Attention and vigilance did not mediate the association between childhood abuse and disorganization (Indirect effect: .32, BCa 95% CI: -.07 - 1.16), excitement (Indirect Effect: .07, BCa 95% CI: -.02 - .40) (Table 10). Working memory partially mediated the association between childhood abuse and disorganization (adjusted R-squared = .12; Total Effect: 3.34, BCa 95% CI: 2.19-4.49; Indirect Effect: .28, BCa 95% CI: .05-.57), excitement (adjusted R-squared = .09; Total Effect: 2.36, BCa 95% CI: 1.68-3.05; Indirect Effect: .08, BCa: .01-.20), emotional distress (adjusted R-squared = .11; Total Effect: 3.47, BCa: 2.47-4.48; Indirect Effect: .10, BCa 95% CI: .01-.27) (Table 10). Neither neurocognition nor social cognition moderated the association between childhood abuse and psychotic symptoms (Table 11).

3.5.2 Female psychotic patients

Childhood adversity was correlated with psychotic symptoms, but not with neurocognition or mentalization (Table 12). Thus, the mediating role of neurocognition and ToM in the association between childhood neglect, childhood abuse, and psychotic symptoms was not tested. Given that both neurocognition and mentalization were negatively associated only with disorganization, we tested its possible mediating role. Moderation analyses showed that neither neurocognition nor mentalization moderated the association between childhood neglect, abuse, and disorganization (Table 13).

3.6 Association between childhood adversities, cognitive functioning and psychotic symptoms according to the duration of psychotic disorder

Within subjects with recent onset of psychotic disorders (i.e., < 24 months) neither neurocognition nor ToM correlated with psychotic symptoms (p-value range from .10 to .78), thus, the mediating or moderating role of cognitive functioning was not examined.

Within psychotic patients with late psychotic onset (≥ 24 months), neurocognitive scores were correlated with childhood abuse and psychotic symptoms (at $p < .01$). Adjusting the analyses for age, gender, and cannabis, problem solving ($B = -.02$, 95%CI = $-.03$ – $-.002$, $p = .03$) moderated the relationship between childhood abuse ($B = 3.18$, 95%CI = 2.32 – 4.05 , $p < .001$) and emotional distress ($B_{\text{childhood abuse} \times \text{problem solving}} = .03$, 95%CI = $.001$ – $.06$, $p = .04$) (Adjusted r-square = .13, $p < .001$).

3.7 Association between childhood adversities, cognitive functioning and psychotic symptoms according to the age of subjects adjusted of covariates (e.g. age, gender, cannabis and duration of the illness)

Within subjects aged 15-19 years: (a) processing speed ($B = -.51$, 95%CI = $-.93$ – $-.09$, $p = .01$) moderated the relationship between childhood abuse ($B = 3.91$, 95%CI = 1.10 – 6.72 , $p = .01$) and positive symptoms ($B_{\text{childhood abuse} \times \text{processing speed}} = -.82$, 95%CI = -1.59 – $-.05$, $p = .03$, adjusted r-square = .35, $p < .001$); (b) problem solving ($B = -.38$, 95%CI = $-.67$ – $-.09$, $p = .01$) moderated the association between childhood abuse ($B = 3.47$, 95%CI = 1.89 – 5.05 , $p < .001$) and excitement ($B_{\text{childhood abuse} \times \text{problem solving}} = -.55$, 95%CI = -1.08 – $-.02$, $p = .04$, adjusted r-square = .29, $p < .001$).

Within subjects aged 20-24 years, attention and vigilance ($B = -.82$, 95%CI = -1.51 – $-.13$, $p = .01$) moderated the association between childhood neglect ($B = 2.37$, 95%CI = $.58$ – 4.16 , $p = .01$) and disorganization ($B_{\text{childhood neglect} \times \text{attention and vigilance}} = -1.43$, 95%CI = -2.83 – $-.02$, $p = .04$, adjusted r-square = .16, $p < .001$).

Within subjects aged 25-29 years: (a) immediate recall fully mediated the association between

childhood neglect and disorganization: the path direct coefficient was significant ($B = 1.90$, $95\%CI = .37-3.44$, $p = .01$); childhood neglect predicted immediate recall ($B = -1.46$, $95\%CI = -2.77--.16$, $p = .02$); immediate recall ($B = -.24$, $95\%CI = -.43--.09$, $p = .002$) fully mediated the relationships between childhood neglect and disorganization ($B = 1.52$, $95\%CI = -.003-.3.04$, $p = .05$; adjusted $R^2 = .11$; $p = .002$; Total Effect: 1.90 , $BCa\ 95\% CI: .37-3.44$; Indirect Effect: $.38$, $BCa\ 95\% CI: .06-.99$).

No significant correlations were found between childhood adversities and cognitive functions, as well as between cognition and psychotic symptoms in those aged 35 and over. For this reason, mediation and moderation analyses were not tested.

4. Discussion

The present findings suggest that neurocognition and mentalization might be involved in the relationship between childhood adversities and psychotic symptoms, in particular in males.

Within male patients with a psychotic disorder, lower mentalization, attention and vigilance seem to mediate the association between childhood neglect and negative symptoms, disorganization and excitement, while poor working memory appears to have a mediating role between childhood abuse and disorganization, excitement, and emotional distress. This finding supports previous findings suggesting that early experience of abuse or neglect might negatively impact the development of neurocognitive functions and mentalizing abilities, which may subsequently lead to psychotic symptoms (Covert et al 2008; Read et al 2014; Jacobsen et al 2015; Garcia et al 2016) (Fig. 2). Our results suggest that the intervening role of neurocognition or ToM in the association between childhood adversities and positive symptoms seems to be not likely, thus, different pathways as for example dissociation (Varese et al 2012b) or affective dysregulation (Isvoranu et al 2017) might link early stress with positive symptoms. Within female psychotic patients, cognition seems not be involved in the association between childhood adversities and psychosis, consistently with studies in FEP and UHR samples showing a significant correlation between early adversities and cognitive impairments only in males (Aas et al 2011; Üçok et al 2015). These findings might in part be explained by sex differences on cognitive functioning in schizophrenia, which showed impairments on neurocognition and mentalization abilities most often in males than in females (Ochoa et al 2012; Barajas et al 2015; Mendrek et al 2016). Within females, the association between early adversities and psychotic dimensions can be explained by mechanisms (Misiak et al 2017) such as dissociation (Read et al 2001). Our findings are not consistent with some studies (Sideli et al 2014; Mansueto et al 2017; Palmier et al 2017). This discrepancy may be due to methodological features since neither specific type of childhood adversities nor sex differences were explored (Sideli et al 2014; Mansueto et al 2017; Palmier et al 2017).

We found that the association between cognitive impairments and psychotic symptoms is significant within subjects with later onset of psychosis, but not among those with recent onset of illness. Previous studies suggested that the association between cognitive impairments and psychosis might be weaker during early onset of illness than thereafter (Bilder et al 2000; Daban et al 2002; Ventura et al 2015), assuming that illness progression could change the relationship between psychotic symptoms and cognitive impairment (Daban et al 2002). It is possible that acute psychotic symptoms may be influenced by factors other than cognitive deficits (Ventura et al 2015) and that the association between cognitive impairments and psychosis dimensions might arise after acute episode effects have resolved (Daban et al 2002; Ventura et al 2015). Probably, in the association between childhood adversities and psychotic symptoms, cognitive impairments might influence mostly the severity and maintenance of psychotic symptoms rather than their onset. Furthermore, we observed that the association between early adversities, cognition, and psychosis is significant within younger subjects (e.g. 15-29 years old) than in those aged 30 or over. These findings might be explained by age differences in the clinical presentation of psychosis according to which psychotic symptoms might be less severe in older patients than in the younger ones (Schultz et al 1997; Folsom et al 2006).

Finally, we found that childhood abuse and childhood neglect were associated with more severe psychotic symptoms. This result is consistent with Heins et al. (2011) as well as with the literature according to which patients with psychotic disorder with a history of childhood adversities, compared to those not exposed to childhood adversities, have greater severity of psychopathology and longer persistence of symptoms (Cotter et al 2015; Trotta et al 2015; van Nierop et al 2016; Faravelli et al 2017). This means that childhood adversities may have a ‘pathoplastic effect’ once the disorder is developed (Birnbaum 1923; Furukawa et al 1998). These findings may enrich the debate about the use of a stratified medicine approach (Kapur et al 2012) in psychiatric research and in clinical practice.

Several methodological limitations should be considered. Although we assessed a broad range of neurocognitive functions, the assessments may not reflect the daily cognitive functioning of the patients; standard cognitive batteries may be insufficient to measure real-world functioning and a more ecological approach might be warranted (Damasio 1995; Burgess 2000; Chaytor and Schmitter 2003; Burgess et al 2006; Lamberts et al 2010). Recent findings showed that other aspects of social cognition, such as emotion recognition (Bilgi et al 2017; Kilian et al 2017), might be involved in the association between childhood adversities and psychosis. Unfortunately, we did not investigate these further aspects; future studies are warranted. Moreover, although we assessed psychotic symptoms according to the classification proposed by van der Gaag et al (2006ab), we did not focus on specific positive symptoms. Future investigations are warranted to explore the role

of cognition in the relationship between early adversities and specific positive symptoms. Another limitation of our study is the large attrition rate (~30%). Patients with more severe impairments did not or could not answer the childhood trauma questionnaire. Thus, the present results should be interpreted with caution and generalized only to patients with mild or moderate psychosis. Moreover, childhood adversities were assessed using subjective retrospective report, thus recall may have influenced the results, although the research suggests a good reliability of retrospective childhood adversity assessment procedures (Fisher et al 2011). Another limitation is that this is a cross-sectional study; correlational data allow evaluation of the association between early adversity, cognition, and psychosis, without causal inferences. On the basis of the literature (Read et al 2014), the present findings allow to hypothesize that childhood adversity, cognitive, and psychotic domains correlate. Longitudinal studies (Berthelot et al 2015) are warranted. We aim at using the follow-up data collected in the framework of the GROUP database to extend the present findings. Strengths of the current study are: (a) the large sample size; (b) the focus on childhood neglect and abuse rather than the broader concept of childhood adversity, thus reducing interpretative biases; (c) the assessment of psychotic dimensions consistently with a ‘symptoms approach’ which, according to some authors, is preferable to operational diagnostic criteria (van Os et al 1999; Costello 1992; Ajnakina et al 2016).

In conclusion, neurocognition and ToM might be involved in the association between childhood adversities and psychosis, although mostly within males. From a clinical point of view, some recommendations may be formulated. The possible mediating role of neurocognition and mentalizing abilities between childhood adversities and psychosis suggests that cognition may act as a protective factor mitigating the effect of childhood neglect and abuse on the persistence of psychotic symptoms, as reported earlier (Bartels-Velthuis et al 2011). Thus, treatment aimed to improve neurocognitive and mentalizing abilities should be considered in male patients with a psychotic disorder with a history of childhood neglect and/or abuse. Future research should clarify the potential pathways linking childhood adversities to psychotic symptoms within females and in patients with a recent onset of psychotic disorder.

Table 1 Descriptive analysis (n=757)

Variables		n(%)
	Gender (male)	568 (75%)
	Age	Mean (SD); range
	Educational level	27.66 (7.60); 15 - 60
		4(2.04); 0 - 8
CTQ	Childhood Neglect	1.86 (.63); 1 - 4.19
	Childhood Abuse	1.43 (.52); 1 - 3.73
PANSS	Positive symptoms	13.62 (6.58); 2 - 41
	Negative symptoms	14.19 (6.19); 3 - 39
	Disorganization	16.16 (6.29); 10 - 44
	Excitement	11.70 (3.89); 8 - 38
	Emotional distress	15.49 (5.63); 8 - 35
WLT	Immediate recall	23.28 (6.05); 7 - 41
	Retention rate	.77 (.20); .01 - 1.50
	Acquired knowledge	17.12 (5.48); 1 - 28
	Working memory	12.48 (4.77); 2 - 22
	Reasoning and problem solving	41.64 (16.7); 0 - 68
	Processing speed	66.18 (15.84); 13 - 120
CPT-HQ	Attention and vigilance	98.65 (3.85); 60 - 100
HT	Mentalizing abilities	17.71 (2.73); 3 - 20
CIDI	Cannabis use	.64 (.88); 0-3

CTQ: Childhood Trauma Questionnaire; PANSS: Positive and Negative Syndrome Scale; WLT: Word Learning Task; WAIS-III: Wechsler Adult Intelligence Scale III; CPT-HQ: Continuous Performance Test HQ (accuracy); HT: Hinting Task; CIDI: Composite International Diagnostic Interview 2.1

Table 2 Comparison between patients with childhood adversity and patients without childhood adversity on cognition and psychotic symptoms. Mann-Whitney U test for independent samples

		No Childhood Neglect (n =560)	Childhood Neglect (n =168)		No Childhood Abuse (n =574)	Childhood Abuse (n =153)	
		mean	mean	p	mean	mean	p
WLT	Immediate recall	370.44	342.91	.13	364.64	361.60	.87
	Retention rate	373.13	325.78	.01	364.41	352.94	.54
CTP-HQ	Attention/vigilance	341.19	298.71	.01	326.88	349.22	.21
	World knowledge	368.70	357.17	.53	363.05	376.95	.46
WAIS-III	Working memory	367.65	356.29	.53	372.20	338.10	.07
	Reasoning and problem solving	368.65	353	.39	343.20	370.89	.14
	Processing speed	369.17	349.04	.27	363.98	366.42	.89
HT	Mentalizing abilities	361.09	362.85	.92	360.38	365.76	.77
PANSS	Positive	340.86	407.32	<.001	338.25	421.83	<.001
	Negative	346.29	366.67	.25	354.16	339.38	.42
	Disorganization	339.18	394.46	.002	342.07	388.61	.01
	Excitement	350.34	396.63	.01	350.65	398.80	.01
	Emotional distress	342.94	410.45	<.001	337.46	435.93	<.001

WLT: Word Learning Task; CPT-HQ: Subscale of Continuous Performance Test (accuracy);
WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task; PANSS: Positive and Negative
Syndrome Scale.

Table 3 Bivariate Pearson Correlations between childhood neglect, childhood abuse, neurocognition, mentalizing abilities, and psychotic symptoms

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)	<i>r</i> (<i>p</i>)
CTQ															
1. Childhood Neglect	1	.55***	-.07*	-.06	-.08*	-.01	-.02	-.06	-.03	-.07*	.14***	.08**	.12***	.12***	.16***
2. Childhood Abuse		1	-.02	-.04	-.06	-.01	-.01	-.09**	-.06	.04	.25***	.02	.25***	.23***	.26***
WLT															
3. Immediate recall			1	.26***	.23***	.14***	.36***	.38***	.32***	.24**	-.04	-.16***	-.19***	-.08*	-.03
4. Retention rate				1	.06	.22***	.18***	.15**	.14***	.15**	.01	-.01	-.07*	-.04	-.01
CTP-HQ															
5. Attention and Vigilance					1	.17***	.18***	.22***	.21***	.13**	-.04	-.15***	-.23***	-.11**	-.02
6. Processing speed						1	.37***	.41***	.39***	.34***	-.10**	-.18***	-.26***	-.09*	-.10**
WAIS-III															
7. World knowledge							1	.65***	.49***	.34***	-.03	-.08*	-.19***	-.05	-.04
8. Working memory								1	.50***	.30***	-.09*	-.15***	-.27***	-.10**	-.10**
9. Reasoning problem-solving									1	.19***	-.09*	-.08*	-.16***	-.07*	-.07
HT										1	-.09**	-.22***	-.29***	-.13***	-.05
PANSS															
11. Positive symptoms												1	.34***	.64***	.65***
12. Negative symptoms													1	.53***	.55***
13. Disorganization														1	.65***
14. Excitement															1
15. Emotional distress															1

CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task; PANSS: Positive and Negative Syndrome Scale.
p*<.05; *p*<.01; ****p*<.001

Figure 1 A partial mediating role of mentalizing abilities in the relationship between childhood neglect and psychotic symptoms adjusting for age, gender, cannabis use

Table 4 Mediating effect of neurocognitive domains and mentalizing abilities in the association between childhood neglect and psychotic symptoms, adjusted for age, gender, cannabis. Mediation analyses according to Baron and Kenny criteria (1986) and Bootstrapping

	Step 1			Step 2			Step 3						
	Cognitive function (DV); Childhood Neglect (IV)			Positive Symptoms (DV); Childhood Neglect (IV)			Positive Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a						
HT	Mentalizing abilities	B	SE	p	95%BCa	B	SE	p	95%BCa	B	SE	p	95%BCa

IV=independent variable; DV= dependent variable; M=mediator. BCa = 95% Bias Corrected and Accelerated bootstrapped confidence interval. Significant mediation models (IV affect the M; IV affect the DV; M affect the DV) are evidenced in bold. Fully mediation: controlling for M, the direct effect of IV on DV was not significant; Partial mediation: after controlling for M, the direct effect of IV on DV is significant (Baron and Kenny, 1986). WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); HT: Hinting Task.

Table 5 Moderating effect of neurocognitive domains and mentalizing capacity in the association between childhood neglect and psychotic symptoms, adjusted for age, gender, cannabis use. Moderation analyses according to Baron and Kenny's criteria (1986)

IV	MR	Interaction between IV-MR	Positive Symptoms		Negative Symptoms		Disorganization		Excitement		Emotional distress	
			B [95%CI]	p	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p
CTQ	Childhood neglect				.91[.17-1.63]	.01	1.08[.35-1.81]	.003	.73[.29-1.18]	.001		
WLT	Immediate recall	Nc	Nc	Nc	-.15[-.22--.07]	.0001	-.17[-.25-.10]	<.001	-.04[-.08-.004]	.07	Nc	Nc
	Interaction				-.003[-.12-.11]	.95	1.08[-.16-.06]	.39	-	-		
CTQ	Childhood neglect				.95[.21-1.69]	.01						
WLT	Retention rate	Nc	Nc	Nc	-1.40[-3.72-.92]	.23	Nc	Nc	Nc	Nc	Nc	Nc
	Interaction				-1.46[-5.29-2.36]	.45						
CTQ	Childhood neglect				.89[.16-1.62]	.01	1.04[.33-1.76]	.004	.75[.30-1.21]	.001	1.48[.82-2.15]	<.001
WLT	Processing speed	-			-.18[-.28--.08]	.0002	-.31[-.41--.21]	<.001	-.09[-.15--.03]	.002	-.11[-.20-.03]	.008
	Interaction	-			-.05[-.21-.09]	.47	-.03[-.18-.12]	.69	.75[-.09-.10]	.94	.03[-.10-.17]	.64
CTQ	Childhood neglect				.99[.26-1.71]	.007	1.23[.51-1.95]	.0008	.82[.36-1.27]	.000	1.57[.91-2.24]	<.001
WALS-III	Working memory				-.07[-.10--.04]	<.001	-.09[-.12--.06]	<.001	-.02[-.03--0005.]	.04 ⁴	-.03[-.06-.01]	.01
	Interaction				.02[-.02-.06]	.39	.005[-.04-.05]	.83	.002[-.03-.03]	.88	.01[-.02-.05]	.45
CTQ	Childhood neglect				1.002[.27-1.73]	.007	1.17[.44-1.89]	.001	.80[.34-1.25]	.005	1.53[.86-2.19]	<.001
WALS-III	Reasoning-problem solving	-			-.03[-.6--006]	.01	-.06[-.09--.04]	<.001	-.02[-.4-.01]	.003	-.02[-.05-.001]	.04
	Interaction				-.02[-.06-.02]	.32	.003[-.04-.04]	.88	-.007[-.03-.02]	.61	.005[-.03-.04]	.78
CTQ	Childhood neglect				.95[.22-1.68]	.01	1.09[.37-1.81]	.003	.78[.32-1.23]	.005		
WALS-III	Acquired knowledge	-			-.12[-.20--.03]	.008	-.24[-.33-.16]	<.001	-.05[-.10-.001]	.04	Nc	Nc
	Interaction	-			-.06[-.19-.06]	.34	-.02[-.16-.10]	.65	.002 [-.08-.08]	.94		
CTQ	Childhood neglect				.88[.12-1.64]	.02	1.03[.25-1.79]	.008	.75[.29-1.21]	.001		
CPT-HQ	Attention and vigilance	Nc	Nc	Nc	-.24[-.37--.12]	.001	-.39[-.51-.26]	<.001	-.12[-.19--.03]	.003	Nc	Nc
	Interaction				.07[-.11-.27]	.42	.18[-.01-.37]	.06	.10[-.01-.22]	.08		
CTQ	Childhood neglect				.84[.12-1.57]	.02	.97[.25-1.69]	.008	.71[.26-1.15]	.001	1.51[.84-2.18]	<.001
HT	Mentalizing abilities	-			-.42[-.59--.25]	<.001	-.61[-.78-.44]	<.001	-.13[-.23--.02]	.01	-.05[-.21-.10]	.49
	Interaction	-			-.19[-.44-.06]	.13	-.03 [-.28-.21]	.77	-.10[-.25-.05]	.19	-	-

IV=independent variable; DV= dependent variable; MR=moderator; nc: no significant correlation between variables. To test moderation models both IV and MR must be correlated with DV (Baron and Kenny, 1986), thus moderation analyses were not run among variables that were not significantly correlated each other. Moderation models were considered significant whether IV affects DV; MR affects DV; the interaction effect between IV and MR affects DV (Baron and Kenny, 1986). CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task.

Table 6 Moderating effect of neurocognitive domains and mentalizing capacity in the association between childhood abuse and psychotic symptoms, adjusted for age, gender, cannabis. Moderation analyses according to Baron and Kenny's criteria (1986)

	IV	Positive Symptoms		Disorganization		Excitement		Emotional distress	
		MR	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p	B [95%CI]
CTQ	Childhood Abuse	Interaction between IV-MR	Nc	Nc	2.52 [1.62-3.41]	<.001	1.78 [1.25-2.31]	<.001	
					-0.17 [-.25 - .10]	<.001	-.03 [-.08-.005]	.08	Nc
WLT	Immediate recall	Interaction			-.08 [-.22-.05]	.25	.04 [-.04-.12]	.31	
CTQ	Childhood Abuse	Retention rate	Nc	Nc	2.61 [1.71-3.52]	<.001			
					-1.78 [-4.06-.50]	.12	Nc	Nc	Nc
WLT	Interaction				-1.89 [-6.57-2.79]	.42			
CTQ	Childhood Abuse	Working memory	3.56 [2.62-4.49]	<.001	2.55 [1.65-3.45]	<.001	1.97 [1.42-2.53]	<.001	3.12 [2.30-3.94]
					-.08 [-.18-.01]	.09	-.08 [-.14- .03]	.004	-.11 [-.19- .02]
WAIS-III	Interaction		-.01 [-.22-.19]	.87	-.02 [-.21-.17]	.84	.06 [-.06-.18]	.36	.08 [-.09-.26]
CTQ	Childhood Abuse	Processing speed	3.58 [2.68-4.49]	<.001	2.65 [1.78-3.52]	<.001	1.96 [1.42-2.50]	<.001	3.11 [2.31-3.91]
					-.02 [-.05-.002]	.07	-.02 [-.03-.001]	.07	-.03 [-.05 - -.004]
WAIS-III	Interaction		-.002 [-.06-.06]	.95	-.04 [-.09-.02]	.28	.01 [-.03-.05]	.59	.03 [-.02-.09]
CTQ	Childhood Abuse	Reasoning and problem solving	3.58 [2.68-4.49]	<.001	2.74 [1.85-3.64]	<.001	1.94 [1.39-2.48]	<.001	3.04 [2.23-3.85]
					-.04 [-.06- .01]	.008	-.02 [-.03 - .01]	.006	-.02 [-.04-.001]
WAIS-III	Interaction		-.009 [-.06-.04]	.71	.02 [-.02-.07]	.31	.001 [-.03-.03]	.96	-.005 [-.05-.04]
CTQ	Childhood Abuse	Acquired knowledge	3.63 [2.72-4.53]	<.001	2.82 [1.95-3.69]	<.001	1.98 [1.44-2.52]	<.001	
					-.09 [-.17- .004]	.04	-.06 [-.11- .01]	.01	
WAIS-III	Interaction		-.10 [-.27 - .07]	.25	.03 [-.13- .19]	.70	.01 [-.09- .10]	.90	
CTQ	Childhood Abuse	Attention and vigilance	Nc	Nc	2.45 [1.49-3.40]	<.001	1.78 [1.23-2.34]	<.001	
					-.36 [-.48 - .23]	<.001	-.09 [-.16- .02]	.01	
CTP-HQ	Interaction				.05 [-.08-.18]	.43	.01 [-.06-.09]	.73	
CTQ	Childhood Abuse	Mentalizing abilities	3.65 [2.74-4.56]	<.001	2.78 [1.91-3.40]	<.001	1.82 [1.29-2.35]	<.001	
					-.16 [-.34-.002]	.05	-.16 [-.26- .06]	.001	
HT	Interaction		-.02 [-.38-.33]	.89	.009 [-.33-.34]	.95	-.03 [-.24- .17]	.75	

IV=independent variable; DV= dependent variable; MR=moderator; nc: no significant correlation between variables. To test moderation models both IV and MR must be correlated with DV (Baron and Kenny, 1986), thus moderation analyses were not run among variables that were not significantly correlated each other. Moderation models were considered significant whether IV affects DV; MR affects DV; the interaction effect between IV and MR affects DV (Baron and Kenny, 1986). CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task.

Table 7 Bivariate Pearson Correlations between childhood neglect, childhood abuse, neurocognition, mentalizing abilities, and psychotic symptoms within male patients with a psychotic disorder (n=568)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>
1.Childhood Neglect	1														
2.Childhood Abuse		1													
CTQ			1												
3. Immediate recall				1											
WLT					1										
4.Retention rate						1									
CTP-HQ							1								
5.Attention and Vigilance								1							
6.Processing speed									1						
W/ALS-III										1					
7.World knowledge											1				
8.Working memory												1			
9.Reasoning problem-solving													1		
HT														1	
10.Mentalizing abilities															1
11.Positive symptoms															
PANSS															
12.Negative symptoms															
13.Disorganization															
14.Excitement															
15.Emotional distress															

CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); W/ALS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task; PANSS: Positive and Negative Syndrome Scale. *p<.05; **p<.01; ***p<.001

Table 8 Mediating effect of neurocognitive domains and mentalizing abilities in the association between childhood neglect and psychotic symptoms, adjusted for age, cannabis within male patients with a psychotic disorder. Mediation analyses according to Baron and Kenny criteria (1986) and Bootstrapping

	Step 1				Step 2				Step 3								
	Cognitive function (DV); Childhood Neglect (IV)				Positive Symptoms (DV); Childhood Neglect (IV)				Positive Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a								
	B	SE	p	95%BCa	B	SE	p	95%BCa CI	B	SE	p	95%BCa CI					
HINTS	Mentalization	-46	.20	.02	-87- -.05	1.50	.47	.001	.56-2.44	a. 1.42	.48	.003	.47-2.36	b. -1.17	.10	.09	-.37- -.02
HINTS	Mentalization	-47	.20	.02	-89- -.06	Negative Symptoms (DV); Childhood Neglect (IV)				Negative Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						1.29	.45	.004	.39-2.18	a. 1.07	.45	.01	.19-1.96	b. -.44	.09	<.001	-.63- -.25
CPT-HQ	Attention and vigilance	-73	.31	.02	-1.36- -.11	Disorganization Symptoms (DV); Childhood Neglect (IV)				Disorganization Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						1.10	.47	.01	.18-2.01	a. .81	.45	.07	-.08-1.70	b. -.62	.09	<.001	-.88- -.43
HINTS	Mentalization	-47	.21	.02	-88- -.05	Excitement (DV); Childhood Neglect (IV)				Excitement (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						1.10	.47	.01	.18-2.01	a. .81	.45	.07	-.08-1.70	b. -.62	.09	<.001	-.88- -.43
CPT-HQ	Attention and vigilance	-74	.32	.01	-1.38- -.12	Disorganization Symptoms (DV); Childhood Neglect (IV)				Disorganization Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						1.21	.49	.01	.24-2.19	a. .95	.48	.05	-.002-1.91	b. -.34	.07	.001	-.48- -.21
HINTS	Mentalization	-48	.20	.01	-89- -.08	Excitement (DV); Childhood Neglect (IV)				Excitement (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						.86	.27	.002	.31-1.14	a. .78	.27	.005	.23-1.33	b. -.15	.05	.01	-.2- -.04
CPT-HQ	Attention and vigilance	-74	.31	.01	-1.35- -.12	Disorganization Symptoms (DV); Childhood Neglect (IV)				Disorganization Symptoms (DV); cognition (M)b; Childhood Neglect (IV)a							
						B	SE	p	95%BCa CI	B	SE	p	95%BCa CI				
						.88	.28	.002	.32-1.44	a. .81	.28	.004	.25-1.37	b. -.09	.04	.02	-.17- -.01

CPT-HQ: Continuous Performance Test-HQ (accuracy); HINTS: Hinting Task.

Table 9 Moderating effect of neurocognitive domains and mentalizing capacity in the association between childhood neglect and psychotic symptoms, adjusted for age, cannabis use within male patients with a psychotic disorder. Moderation analyses according to Baron and Kenny's criteria (1986)

	IV MR	Positive Symptoms		Negative Symptoms		Disorganization		Excitement		Emotional distress	
	Interaction between IV-MR	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p
CTQ WLT	Childhood neglect Immediate recall Interaction	Nc	Nc	1.17 [.27-2.06] -.13 [-.22--.04] -.06 [-.21-.07]	.01 .003 .35	.96 [.04-1.87] -.14 [-.24-.05] -.11 [-.25-.03]	.03 .002 .13	Nc	Nc	Nc	Nc
CTQ WAIS-III	Childhood neglect Processing speed Interaction	1.38 [.42-2.33] -.18 [-.35--.005] -.09 [-.39-.20]	.004 .04 .54	1.13 [.23-2.03] -.14 [-.21-.02] -	.01 .08 .	.98 [.07-1.89] -.32 [-.49--.15] -.06 [-.35-.22]	.03 .002 .66	Nc	Nc	Nc	Nc
CTQ WAIS-III	Childhood neglect Working memory Interaction	1.38 [.43-2.33] -.17 [-.35-.004] -.23 [-.52-.05]	.004 .05 .11	1.10 [.21-2.004] -.24 [-.41--.07] -.06 [-.34-.20]	.01 .04 .61	.91 [.01-1.80] -.47 [-.64--.30] -.12 [-.39-.14]	.04 <.001 .35	.81 [.24-1.37] -.14 [-.25-.04] .03 [-.13-.20]	.005 .01 .69	1.45 [.64-2.26] -.19 [-.34-.04] -.09 [-.34-.14]	.005 .01 .43
CTQ WAIS-III	Childhood neglect Reasoning-problem solving Interaction	1.37 [.42-2.33] -.02 [-.04--.001] -.02 [-.06-.008]	.04 .005 .77	1.12 [.22-2.02] -.03 [-.05--.01] -.006 [-.03-.03]	.01 .001 .72	.97 [.07-1.87] -.06 [-.08--.04] -.002 [-.03-.03]	.03 <.001 .91	.85 [.28-1.42] -.01 [-.02--.002] -.002 [-.01--.02]	.03 .02 .81	1.52 [.70-2.34] -.02 [-.04--.002] -.01 [-.04-.01]	.001 . .34
CTQ WAIS-III	Childhood neglect Acquired knowledge Interaction	Nc	Nc	1.16 [.26-2.05] -.16 [-.35-.01] -.14 [-.43-.13]	.01 .07 .31	-.42 [-.61--.24] .95 [.05-1.85] -.05 [-.33-.22]	<.001 .03 .70	Nc	Nc	Nc	Nc
CTQ CPT-HQ	Childhood neglect Attention and vigilance Interaction	Nc	Nc	1.05 [.14-1.97] -.27 [-.42--.12] -.09 [-.12--.31]	.02 .001 .39	.99 [.04-1.95] -.41 [-.56-.25] -.20 [-.02-.42]	.04 <.001 .07	.83 [.27-1.40] -.12 [-.21--.03] -.11 [-.01-.24]	.003 .005 .09	Nc	Nc
CTQ HT	Childhood neglect Mentalizing abilities Interaction	1.40 [.46-2.35] -.14 [-.35-.05] -	.003 .15 .	1.06 [.17-1.94] -.41 [-.60--.22] -.21 [-.47-.07]	.02 <.001 .15	.80 [-.08-1.69] -.60 [-.79-.41] -.10 [-.37-.17]	.07 <.001 .47	.77 [.22-1.32] -.14 [-.26--.02] -.08 [-.26--.08]	.005 .01 .32	Nc	Nc

IV=independent variable; DV= dependent variable; MR=moderator; nc: no significant correlation between variables. To test moderation models both IV and MR must be correlated with DV (Baron and Kenny, 1986), thus moderation analyses were not run among variables that were not significantly correlated each other. Moderation models were considered significant whether IV affects DV; MR affects DV; the interaction effect between IV and MR affects DV (Baron and Kenny, 1986). CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task.

Table 10 Mediating effect of neurocognitive domains in the association between childhood abuse and psychotic symptoms, adjusted for age, cannabis within male patients with a psychotic disorder. Mediation analyses according to Baron and Kenny criteria (1986) and Bootstrapping

	Step 1				Step 2				Step 3				
	Cognitive function (DV); Childhood Abuse (IV)				Positive Symptoms (DV); Childhood Abuse (IV)				Positive Symptoms (DV); cognition (M)b; Childhood Abuse (IV)a				
WAIS-III	Working Memory	B	SE	p	95%BCa	B	SE	p	95%BCa CI	B	SE	p	95%BCa CI
		-62	.29	.03	-1.21 - -.04	4.15	.58	<.001	3 - 5.30	a. 4.06	.58	<.001	2.90-5.22
CPT-HQ	Attention and vigilance	Disorganization Symptoms (DV); Childhood Abuse (IV)											
		B	SE	P	95%BCa CI	B	SE	P	95%BCa CI	B	SE	P	95%BCa CI
WAIS-III	Working memory	-63	.30	.03	-1.23 - -.04	3.34	.58	<.001	2.19-4.49	a.3.05	.57	<.001	1.93 - 4.17
		Excitement (DV); Childhood Abuse (IV)											
CPT-HQ	Attention and vigilance	-91	.39	.01	-1.71--.18	2.03	.34	<.001	1.34 - 2.71	a. 1.95	.34	<.001	1.26-2.63
		Excitement (DV); cognition (M)b; Childhood Abuse (IV)a											
WAIS-III	Working memory	-65	.29	.02	-1.24- -.07	2.36	.35	<.001	1.68-3.05	a. 2.28	.35	<.001	1.59-2.97
		Emotional Distress (DV); Childhood Abuse (IV)											
WAIS-III	Working Memory	-61	.30	.04	-1.20- -.009	3.47	.51	<.001	2.47-4.48	a. 3.37	.51	<.001	2.36-4.38
		Emotional Distress (DV); cognition(M)b; Childhood Abuse (IV)a											

CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III

Table 11 Moderating effect of neurocognitive domains and mentalizing capacity in the association between childhood abuse and psychotic symptoms, adjusted for age, cannabis use within male patients with a psychotic disorder. Moderation analyses according to Baron and Kenny's criteria (1986)

	IV	Positive Symptoms		Disorganization		Excitement		Emotional distress	
		MR	Interaction between IV-MR	B [95%CI]	p	B [95%CI]	p	B [95%CI]	p
CTQ WLT	Childhood abuse Immediate recall Interaction	Nc	Nc	3.02 [1.85-4.2] -14 [-23- -.05] -11 [-29-.08]	<.001 .002 .27	Nc	Nc	Nc	Nc
CTQ WAIS-III	Childhood abuse Processing speed Interaction	4.15 [2.96-5.35] -16 [-.33-.01] -	<.001 .06	3.35 [2.17-4.53] -30 [-47-.13] -18 [-15-.52]	<.001 .003 .28	Nc	Nc	Nc	Nc
CTQ WAIS-III	Childhood abuse Working memory Interaction	3.90 [2.69-5.11] -14 [-.31-.02] -18 [-.58-.21]	<.001 .09 .36	2.94 [1.77-4.11] -45 [-61-.28] -12 [-.50-.25]	<.001 <.001 .52	2.43 [1.71-3.15] -12 [-.22-.02] -17 [-.06-.41]	<.001 .02 .16	3.38 [2.33-4.44] -16 [-.31-.02] -01 [-.33-.35]	<.001 .02 .94
CTQ WAIS-III	Childhood abuse Reasoning-problem solving Interaction	4.06 [2.87-5.24] -02 [-.04--.001] -003 [-.04-.04]	<.001 .03 .89	3.17 [2.02-4.32] -06 [-.08-.04] -01 [-.03-.05]	<.001 <.001 .68	2.50 [1.79-3.21] -01 [-.02-.001] .02 [-.0003-.05]	<.001 .03 .05	3.46 [2.42-4.50] -02 [-.03-.003] .007 [-.06-.07]	<.001 .02 .88
CTQ WAIS-III	Childhood abuse Acquired knowledge Interaction	Nc	Nc	3.32 [2.19-4.45] -44 [-.62-.26] -02 [-.34-.40]	<.001 <.001 .88	Nc	Nc	Nc	Nc
CTQ CPT-HQ	Childhood abuse Attention and vigilance Interaction	Nc	Nc	3.01 [1.79-4.23] -35 [-.49-.21] -07 [-.07-.21]	<.001 <.001 .32	1.98 [1.28-2.68] -09 [-.17--.003] -01 [-.06-.10]	<.001 .04 .67	Nc	Nc
CTQ HT	Childhood abuse Mentalizing abilities Interaction	4.12 [2.96-5.28] -20 [-.40-.02] -21 [-.63-.22]	<.001 .03 .34	3.36 [2.23-4.48] -64 [-.82-.46] -05 [-.46-.34]	<.001 <.001 .77	2.12 [1.43-2.80] -17 [-.29-.06] -05 [-.07-.02]	<.001 .002 .67	Nc	Nc

IV=independent variable; DV= dependent variable; MR=moderator; nc: no significant correlation between variables. To test moderation models both IV and MR must be correlated with DV (Baron and Kenny, 1986), thus moderation analyses were not run among variables that were not significantly correlated each other. Moderation models were considered significant whether IV affects DV; MR affects DV; the interaction effect between IV and MR affects DV (Baron and Kenny, 1986). CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task.

Table 12 Bivariate Pearson Correlations between childhood neglect, childhood abuse, neurocognition, mentalizing abilities, and psychotic symptoms within female patients with a psychotic disorder (n=189)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>	<i>r(p)</i>
CTQ	1	.64***	1	.64***	1	.64***	1	.64***	1	.64***	1	.64***	1	.64***	1
	1.Childhood Neglect	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress
WLT	1	-.04	1	-.02	.04	.12	.03	.005	.05	-.02	.14	.01	.15*	.08	.16*
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	-.02	1	-.01	.07	.03	.07	-.04	.003	.01	.26**	.05	.17*	.21**	.26***
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.31***	1	.25**	.34***	.47***	.42***	.54***	.32***	-.12	-.19*	-.31**	-.13	-.06	-.005
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	.09	1	.16*	.22**	.15*	.21**	.26***	.05	-.07	-.11	-.11	-.08	-.005	
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.14	1	.15	.19**	.14	.23**	.02	-.04	-.04	-.21**	-.06	-.04		
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	.56***	1	.52***	.79***	.34***	-.09	-.11	-.19*	-.14	-.05				
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.64***	1	.64***	.84***	.41***	.001	-.12	-.25**	-.12	-.04				
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	.82***	1	.82***	.33***	-.04	-.13	-.25**	-.08	-.08	-.08				
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.42***	1	.42***	-.06	-.14	-.30***	-.13	-.08						
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	-.02	1	-.18*	-.25**	-.07	.01								
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.37***	1	.37***	.59***	.62***	.71***								
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	.52***	1	.52***	.61***	.42***	.49***								
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.63***	1	.63***	.49***										
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
CTP-HQ	1	.49***	1	.49***											
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	
WLT	1	.49***	1	.49***											
	2.Childhood Abuse	3.Immediate recall	4.Retention rate	5.Attention and Vigilance	6.Processing speed	7.World knowledge	8.Working memory	9.Reasoning problem-solving	10.Mentalizing abilities	11.Positive symptoms	12.Negative symptoms	13.Disorganization	14.Excitement	15.Emotional distress	

CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task; PANSS: Positive and Negative Syndrome Scale. *p<.05; **p<.01; ***p<.001

Table 13 Moderating effect of neurocognitive domains and mentalizing capacity in the association between childhood neglect, childhood abuse and disorganization, adjusted for age, cannabis use within female patients with a psychotic disorder. Moderation analyses according to Baron and Kenny's criteria (1986)

IV			Disorganization		Disorganization	
MR						
Interaction between IV-MR			B [95%CI]	p		p
CTQ	Childhood neglect	1.41 [.28-2.55]	.01	Childhood abuse	1.67 [.40-2.95]	.01
WLT	Immediate recall	-.26 [-.38--.14]	<.001	Immediate recall	-.26 [-.38--.14]	<.001
	Interaction	-.10 [-.07-.29]	.25	Interaction	.05 [-.14-.24]	.59
CTQ	Childhood neglect	1.88 [.71-3.04]	.001	Childhood abuse	1.96 [.66-3.25]	.03
WAIS-III	Processing speed	-.36 [-.59--.13]	.02	Processing speed	-.32 [-.55--.09]	.005
	Interaction	.14 [-.18-.47]	.38	Interaction	-.03 [-.33-.40]	.84
CTQ	Childhood neglect	1.57 [.41-2.73]	.01	Childhood abuse	1.86 [.57-3.15]	.004
WAIS-III	Working memory	-.43 [-.68-.17]	.001	Working memory	-.43 [-.68--.17]	.001
	Interaction	-.11 [-.30-.52]	.59	Interaction	-.08 [-.35-.53]	.69
CTQ	Childhood neglect	1.75 [.62-2.88]	.002	Childhood abuse	1.98 [.73-3.25]	.002
WAIS-III	Reasoning-problem solving	-.06 [-.08--.03]	<.001	Reasoning-problem solving	-.05 [-.08--.03]	<.001
	Interaction	-.01 [-.02-.05]	.51	Interaction	-.005 [-.04-.05]	.83
CTQ	Childhood neglect	1.57 [.43-2.71]	.01	Childhood abuse	2.02 [.75-3.30]	.02
WAIS-III	Acquired knowledge	-.42 [-.66-.18]	.001	Acquired knowledge	-.44 [-.68--.20]	.003
	Interaction	-.19 [-.20-.58]	.33	Interaction	-.22 [-.23-.68]	.33
CTQ	Childhood neglect	1.15 [-.12-2.42]	.07	Childhood abuse	1.59 [.13-3.06]	.03
CPT-HQ	Attention and vigilance	-		Attention and vigilance	-.53 [-.91--.15]	.01
	Interaction	-		Interaction	-.38 [-1.32-.56]	.42
CTQ	Childhood neglect	1.36 [-.19-2.54]	.02	Childhood abuse	1.78 [.47-3.09]	.01
HT	Mentalizing abilities	-.63 [-1.01--.27]	.001	Mentalizing abilities	-.58 [-.94--.21]	.002
	Interaction	-.33 [-.26-.93]	.27	Interaction	-.47 [-.16-1.11]	.14

IV=independent variable; DV=dependent variable; MR=moderator; nc: no significant correlation between variables. To test moderation models both IV and MR must be correlated with DV (Baron and Kenny, 1986), thus moderation analyses were not run among variables that were not significantly correlated each other. Moderation models were considered significant whether IV affects DV; MR affects DV; the interaction effect between IV and MR affects DV (Baron and Kenny, 1986). CTQ: childhood trauma questionnaire; WLT: Word Learning Task; CPT-HQ: Continuous Performance Test-HQ (accuracy); WAIS-III: Wechsler Adult Intelligence Scale III; HT: Hinting Task.

Figure 2 A mediating role of neurocognition and mentalizing abilities in the relationship between childhood adversities and psychotic symptoms adjusting for age and cannabis use within male patients with a psychotic disorder

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Chapter 6

Parasomnias and Childhood Adversity in an Adult Psychiatric Population

Giovanni Mansueto^a, Sara Palmieri^a, Carlo Faravelli^a

^aDepartment of Health Sciences, University of Florence, Florence, Italy

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Abstract

Introduction

A wide evidence suggest that sleep disorders and psychopathology could be related each other, as well as, that childhood adversities (CAs) may be associated with both. However, the relationship between CA and sleep disorders in psychiatric patients is still unclear. This study aims to explore the hypothesis that CA could be associated with sleep impairments in a sample of psychiatric patients.

Method

351 psychiatric patients and 177 controls draw from the general population were recruited. Sleep symptoms were assessed by FPI. CAs were evaluated by FPI and CECA-Q. Chi-square, Fisher's test, Odds Ratios, Binary Logistic Regression were performed.

Results: Patients with childhood sexual abuse (CSA) showed higher rate of nightmares, bruxism, somnambulism and pavor nocturns than those without CSA. Cases with negligence of father or mother reported higher rate of terminal insomnia and nightmares than patients without neglect. Controls with childhood physical abuse (CPA) showed higher rate of pavor nocturns.

Conclusion

CA could be related with sleep impairments in adulthood, moreover, seems to be a specific relationship between childhood sexual abuse and parasomnia. The association CAs-parasomnia seems to be more relevant among psychiatric cases than in the general population.

1. Introduction

Descriptive and cross-sectional studies provide a robust evidence of a possible connection between sleep disturbances and psychopathology, showing an excess of sleep impairments in a wide array of psychiatric disorders as well as a psychiatric comorbidity among patients with insomnia and parasomnia (Harvey et al 1996; Moring and Ware 1996; Manfredini et al 2004; Manfredini et al 2005; Szelenberger et al 2005; Lam et al 2008; Carra et al 2012; Alves et al 2013; Swart et al 2013). Current evidence suggests that childhood adversities (CAs) might be linked with both psychopathology and sleep disorders (Carr et al 2013; Kajeepeta et al 2015; Verdolini et al 2015;). CAs are commonly defined as life events that may occur during childhood and/or adolescence, such as childhood abuse (emotional, physical, or sexual), neglect, and loss event (parental loss and/or divorce) (Carr et al 2013).

Substantial evidence from both cross-sectional and prospective studies indicates that childhood abuse and neglect are strongly associated with the development, persistence, and severity of adult psychopathology such as anxiety, PTSD (Carr et al 2013; Verdolini et al 2015), depression (Infurna et al 2016), psychosis (Varese et al 2012), eating disorder, and personality disorder (Carr et al 2013). On the other hand, controversial findings have been reported about the role of early loss events (Varese et al 2012; Carr et al 2013; Infurna et al 2016).

Although a recent review by Kajeepeta et al (2015) suggested that sleep problems could be related with exposure to adversity during childhood, the relationship between CAs and sleep disorders in psychiatric patients remains still unclear. Indeed, we do not own a very robust amount of data confirming the role of early stress on sleep problems in psychiatric patients, as only two studies (Schafer and Bade 2013; Faravelli et al 2014) have extensively evaluated this possible association. In this regard, Schafer & Bade (2013) showed that high stress load in childhood was associated with prolonged sleep onset latency, decreased sleep efficiency and increased number of body movements during sleep. Faravelli et al (2014) showed that childhood abuse (physical and/or sexual) seems to increase by nearly 3 times the risk of recurrent nightmares.

Moreover, the research has largely focused on the relationship between CAs and insomnia (Kajeepeta et al 2015), in part neglecting the role of parasomnia. Parasomnia is defined as an arousal disorder, characterized by unusual behaviours during sleep, such as nightmares, bruxism, sleep terrors, and somnambulism (Morin and Ware, 1996). CAs seem to be associated with both nightmare and bruxism (Messer 1992; Agargun et al 2003; Duval et al 2013; Faravelli et al 2014; Molina et al 2015), while on the basis of our knowledge, any study has evaluated the relationship between CAs and experience of pavor and somnambulism in adulthood yet. In order to provide additional evidences to previous studies (Messer 1992; Agargun et al 2003; Duval et al 2013; Schafer and Bade 2013; Faravelli et al 2014; Kajeepeta et al 2015; Molina et al 2015) the current

research aims: (a) to evaluate the relationship between CA and sleep impairments in a representative sample of psychiatric patients, exploring the hypothesis that CAs could be associated with a cluster of sleep impairments; (b) to explore the association between CA and sleep disorders also in a control group of subjects drawn from a general population, in order to evaluate if the relationship CA-sleep disorders is present only in the psychiatric patients.

2. Method

This research is part of the PSI-FIELDS (Factors in Early Life, Diagnoses, and Symptoms) project, an observational, multidisciplinary, and trans-nosological study. During a two-month period it was possible to contact and interview 351 consecutive patients admitted, within one week of the interview, to all the psychiatric in-and outpatient facilities of Tuscany.

Exclusion criteria were: age >75 years, neurological and/or neurocognitive impairment, disorders that might compromise the ability to give informed consent, pregnant or breast-feeding, substance abuse and/or addiction. A group of 177 people randomly drawn from the general population living in the same catchment area and matched with the psychiatric cases for age, gender and education made up the controls. The study protocol was approved by the local ethics committee and participants provided written informed consent.

2.1 Measure

DSM-IV diagnoses were made using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al 1995). Sleep impairments, insomnia and parasomnia symptoms were assessed by the Florence Psychiatric Interview (FPI) (Faravelli et al 2001). Each symptom is scored on a 5-point severity scale (0=absent, 1=dubious, 2=mild, 3=moderate and 4=severe). A score of at least 2 was considered for a symptom to be present. Sleep disorders were assessed referring to the last month. The FPI (Faravelli et al 2001), a semi structured interview for evaluating the psychopathology in the community, is basically made up of the items from several well established rating scale combined in a single instrument. 121 symptoms are systematically explored, independent of the subject's diagnosis. As the interview uses a typically bottom up method, diagnoses may be obtained by specific algorithms: the correspondence with the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al 1995) is almost complete (Faravelli et al 2001). Moreover, sociodemographic information, life events, treatments received are also recorded. The FPI has shown good reliability (Faravelli et al 2001).

The presence of childhood adversity was investigated by means of the Childhood Experience of Care and Abuse Questionnaire (CECA- Q) (Bifulco et al 2005) and through a structured interview for early trauma included in the FPI (Faravelli et al 2001). CA was evaluated as follows: (a) presence of loss events whenever a death or separation (for 1 year or more) from parents was

reported; (b) presence of sexual or physical abuse events when the CECA-Q or the interview revealed the presence of physical and/or sexual abuse; (c) presence of neglect was based on the CECA-Q scores in the scales “Mother’s Neglect” and “Father’s Neglect” using the proposed cut-off (Bifulco et al 2005). Insofar as the CECA-Q responses were concerned, we did not consider events that occurred after the age of 15. Life events were evaluated by experts who were not involved in the interview and who were blind to the patient or control status of the subjects.

According to previous studies (Faravelli et al 2010; 2014), we have avoided using operational diagnoses due their high rate of comorbidity and lack of specificity. The lack of diagnostic specificity seems to be common in psychiatry, indeed, having one single diagnosis is unusual in psychiatry with the comorbidity being the rule, rather than the exception (Kessler et al 2005). Furthermore, it has been shown that early adversities seem to influence differentially specific symptom profiles rather than specific diagnoses (Faravelli et al 2014).

It is conceivable that CAs might produce sleep symptom patterns that range transdiagnostically. Thus, we have assessed the relationship between CAs and sleep impairments in a representative sample of psychiatric patients according to a transnosographic perspective.

2.2. Statistic analyses

Chi-square (Fisher’s test when needed) and Odds Ratios were performed. Moreover, as childhood adversities were not independent of each other, we adopted the stepwise forward conditional method of binary logistic regression for controlling the multicollinearity.

Thus, binary logistic regression analyses, with each sleep symptoms (absence vs presence), as dependent variable, and CAs (sexual abuse, physical abuse, loss of mother, loss of father, mother neglect, father neglect) as independent variables were performed. Separate binary logistic regression analyses were performed for each sleep symptoms.

The statistical analyses were performed using SPSS for Windows 20.0 (IBM 2011).

3. Results

Patients and controls resulted comparable for gender (females: 64.1% vs 61%, $\chi^2=0.48$, $df=1$, $p=0.48$) age (44.03 ± 13.22 vs 42.48 ± 12.82 , $t(df)=-1.28$ (526), $p=0.19$) and educational level (mean education years: 11.23 ± 4.02 vs 11.53 ± 3.57 $t(df)=0.83$ (526), $p=0.40$).

Patients were more frequently single than those in the control group (54.4% vs 19.2%, $\chi^2=59.64$, $df=1$, $p<0.001$).

As regards the clinical sample the most represented diagnostic category was the major depression ($n=139$; female: 74.1%), followed by panic disorder ($n=113$; female: 69.9%), psychosis ($n=87$; female: 52.9%), bipolar disorder ($n=71$; female: 56.3%), obsessive-compulsive disorder ($n=71$;

female: 62%), eating disorder (n=57; female: 73.7%) and social phobia (n=53; female: 64.2%). No significant associations were found between drug use-treatments received and sleep impairments.

3.1 CA and sleep impairments in adult psychiatric population

Cases with childhood sexual abuse (CSA) compared with those without CSA were characterized by an excess of nightmare (20.1% vs 12.2%, $\chi^2=4.13$, df=1, p=0.04), somnambulism (42.9% vs 14.5%, $\chi^2=8.15$, df=1, fisher exact test p=0.01) bruxism (23.4% vs 13.5%, $\chi^2=4.43$, df=1, p=0.03) and pavor nocturnus (23.6% vs 13.6%, $\chi^2=4.32$, df=1, p=0.03).

Moreover, compared with cases without neglect, patients with early experience of father neglect showed a higher prevalence of nightmares (12.3% vs 6.1%, $\chi^2=4.18$, df=1, p=0.04), while cases with mother neglect showed a higher rate of terminal insomnia (13.3% vs 22.6%, $\chi^2=5.01$, df=1, p=0.02).

Binary logistic regression analyses, adjusted for CAs co-occurrence, confirmed that: sexual abuse was associated with somnambulism ($\beta=1.48$, p=0.008, OR=4.41, 95% CI=1.46-13.25), bruxism ($\beta=0.67$, p=0.03, OR=1.95, 95% CI=1.03-3.67), and pavor nocturnus ($\beta=0.67$, p=0.04, OR=1.96; 95% CI=1.03-3.72); father neglect was associated with nightmares ($\beta=0.77$; p=0.04, OR=2.17, 95% CI=1.01-4.62); mother neglect was associated with terminal insomnia ($\beta=0.64$, p=0.02, OR=1.89, 95% CI=1.07-3.33).

Dividing patients according to their DSM-IV diagnoses, similar patterns of results were found across different diagnostic categories: the association between CA and sleep impairments is not diagnosis-specific (Table 1).

3.2 CA and sleep impairments in adult controls drawn from the general population

Subjects with childhood physical abuse (CPA) showed higher rate of pavor nocturnus (40% vs 11.4%, $\chi^2=6.83$, df=1, p value Fisher's exact test=0.02, OR=5.2, 95% CI=1.34-20.07) than those without CPA. None other significant associations were found between CAs and sleep impairments in control group.

4. Discussion

The current study highlighted that among adult psychiatric patients CSA was associated with nightmares, bruxism, pavor and somnambulism, as well as, that father and mother neglect were related with nightmares and terminal insomnia respectively. On the other hand, no significant association was found between childhood loss events and sleep impairments. Moreover, among subjects drawn from the general population, except for the association CPA-pavor, none significant

relationships were found between CAs and sleep impairments.

Our findings are consistent with previous studies showing that nightmares are significantly associated with both child abuse and neglect (Agargun et al 2003; Duval et al 2013; Faravelli et al 2014). Dreaming is considered as being a relevant process for emotional adaptation to emotionally salient and traumatic events (Agargun et al 2003; Stickgold 2008; Duval et al 2013). It might be that disturbed dreaming may arise and persist when dreaming fails to accomplish its putative function of emotional regulation during sleep (Duval et al 2013). Furthermore, as suggested by Duval et al (2013), the exposure to stressful events in traumatized individuals, implies an increased risk of activation of memories and schemas related to CA, with nightmares possibly resulting from this mental activity. Our study may support previous evidence (Messer 1992; Molina et al 2015) about the association between CSA and bruxism. Furthermore, the experience of CSA seems to increase the risk of pavor and somnambulism in adulthood. Unfortunately, no data from the literature evaluated the role of CA on pavor and/or sleep walking in adulthood, thus comparisons on this issue are not possible.

Moreover, we found that insomnia might be related with mother neglect, but we could not prove its association with child abuse as reported by previous studies (Kajeepeta et al 2015). This result is only apparently inconsistent with the literature (Kajeepeta et al 2015), since previous studies were conducted on patients with primary insomnia (Bader et al 2007) and alcohol- dependent patients (Zhabenko et al 2012), while we focused on a sample of merely psychiatric patients. It is therefore conceivable that the clinical nature of our sample contributed to this contradictory finding. Finally, in agreement with Agargun et al (2003), our results highlight that childhood loss events seem not to be associated with sleep impairments in adulthood.

Summing up, our findings suggest that could be a specific relationship between CSA and parasomnia, since no other form of CA appears to be strongly related with it, and no other sleep problems seem to be related with CSA. Thus, the relationship between CA and sleep impairments in adult psychiatric patients seems to be specific according to the type of CA and pattern of sleep symptoms. The underlying mechanism linking CA to sleep disorders in adulthood is still unclear. On the one hand the increased corticotropin-releasing hormone (CRH) and the hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, induced by CA, may act as a pathway to sleep disorders in adulthood (Kajeepeta et al 2015). Furthermore, from a social perspective it could be argued that children exposed to CA, grow up in disorganized families and thus never learn good sleeping habits: this has a negative impact on sleep pattern that can persist into adulthood (Kajeepeta et al 2015).

Moreover it should be considered that the relationship between CA and sleep disorders could be biased by current psychopathology, since CA may induce psychiatric diseases that in turn could be

related to sleep disorders. Indeed, our findings showed that the relationship CA- sleep disorders seems more relevant in psychiatric patients rather than in a control group of subjects drawn from the general population. Further investigation of the underlying pathways linking CA to sleep diseases will be an important issue for subsequent research.

Some methodological issues should be considered when interpreting the results of this study: (a) CAs were assessed by subjective retrospective reports, thus recall bias (memory distortions, search for meanings) may have influenced these results, although research suggests good reliability of retrospective assessment of CA (Fisher et al 2009); (b) CA and sleep symptoms are based on subjective data therefore they should be overestimated; (c) the cross-sectional data precludes conclusions regarding causal relationships; (d) since that our research did not primarily plan to assess sleep disorders, the sleep symptoms were evaluated only by the FPI rather than by specific instruments focused on sleep parameters. Strengths of the study were: (a) a large sample size; (b) a wide range of CA were evaluated.

5. Conclusion

CA may be related with sleep problems in adulthood, but probably it exists a specific relationship between CSA and parasomnia. Moreover the effect of CAs on sleep impairments in adulthood seems more specific in the psychiatric population rather than in the general population. However, the cross-sectional design of this study does not allow us to make further speculation on this issue, thus longitudinal studies will be necessary to confirm the findings of the present study, as well as to clarify the underlying pathways on the relationship between CA, psychopathology, and sleep impairments in adulthood. On the clinical ground, in order to facilitate meaningful formulations and treatment plans, the assessment of CA should not be overlooked in anamnesis and treatment of sleep impairments.

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Table 1 Association of childhood adversity and sleep impairments in adult psychiatric cases (n=351). CA=childhood adversity; a=adjusted for age and gender. Significant findings are marked in bold.

	Initial insomnia	Middle insomnia	Terminal Insomnia	Somnambulism	Nightmares	Bruxism	Pavor nocturnus	Altered sleep–wake cycles	
% Cases with CA	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	ORa [95% CI]	
At least one CA	53.80%	0.91 [0.58-1.41]	1.22 [0.79-1.88]	1.43 [0.94-2.18]	2.20 [0.67-7.17]	1.26 [0.82-1.93]	1.10 [0.66-1.84]	1.56 [0.91-2.65]	1.42 [0.89-2.27]
Physical abuse	23.40%	1.17 [0.69-1.99]	1.30 [0.77-2.19]	1.52 [0.92-2.52]	0.89 [0.24-3.72]	1.56[0.95-2.57]	1.20 [0.67-2.14]	1.34 [0.74-2.42]	1.11 [0.65-1.90]
Sexual abuse	15.70%	1.34 [0.71-2.51]	1.17 [0.64-2.13]	1.28 [0.71-2.29]	4.40 [1.46-13.25]	1.81 [1.01-3.24]	1.95 [1.03-3.67]	1.96 [1.03-3.72]	1.16 [0.63-2.16]
Loss of mother	13.40%	1.14 [0.59-2.20]	1.35 [0.69-2.57]	1.23 [0.66-2.29]	1.08 [0.23-4.99]	0.76 [0.40-1.44]	0.82 [0.37-1.78]	1.05 [0.49-2.23]	1.11 [0.57-2.15]
Loss of father	18.20%	0.92 [0.52-1.62]	1.06 [0.57-1.76]	1.08 [0.63-1.87]	1.84 [0.56-6.08]	0.91 [0.53-1.59]	1.11 [0.58-2.11]	1.37 [0.72-2.59]	1.65 [0.94-2.91]
Mother Neglect	18.20%	1.73 [0.93-3.20]	1.68 [0.93-3.05]	1.89 [1.07-3.33]	1.84 [0.56-6.06]	1.16 [0.67-1.98]	1.23 [0.65-2.32]	1.10 [0.57-2.13]	1.28 [0.72-2.28]
Father Neglect	8.80%	1.31 [0.58-2.95]	1.52 [0.68-3.42]	1.25 [0.59-2.62]	0.78 [0.10-6.22]	2.17 [1.01-4.62]	1.79 [0.80-4.01]	1.14 [0.47-2.77]	0.95 [0.42-2.14]

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Chapter 7

General discussion

Although the aetiological role of childhood adversities in patients with psychotic spectrum disorder has been established (Morgan and Anderson, 2016), the etiopathogenic mechanisms linking early adverse experiences to psychotic disorders are still not well known (Bentall et al 2014; Morgan and Anderson 2016). Within the socio-developmental (Morgan et al 2014), neurodevelopmental (Read et al 2014), and social-cognitive perspective (van Os and Rutten 2010; Green et al 2015; Jacobsen and Sahrp 2015), environmental factors such as recent life events, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and cognitive functioning have been assumed as underlying pathways from early adversities to psychosis. The first aim of this thesis is devoted to test these hypotheses.

The second chapter explores the role of recent life events in the association between childhood adversity and psychosis. Compared to controls recruited from the general population, patients with psychosis reported higher rates of recent life events with a peak in the 4 months prior to the onset or relapse of psychosis. Those with childhood and recent events showed a greater risk of psychosis (OR=15.28, 95% CI=4.50–51.03) than those who was exposed only to childhood adversity (OR=5.27, 95% CI=1.55–17.92) or recent events (OR=8.82, 95% CI=2.70–28.79). The effect of early adversities on psychosis seems to be amplified by subsequent exposure to recent stressful events as well as to the sensitivity to daily stress which appears to be increased by childhood adverse experiences. These results support the socio-development perspective (Morgan et al 2010; Morgan et al 2014) according to which recent events could be considered as an aetiological pathway from childhood adversity to psychosis.

The third chapter explores the role of the HPA axis in the relationship between early events and psychosis. Findings confirmed previous evidences (Bradely and Dinan 2010; Walker et al 2010; Nugent et al 2015) reporting a chronic activation of HPA axis (e.g. increased levels of morning and evening cortisol secretion) in schizophrenia patients than in controls. Morning cortisol secretion seems to be involved in the association between childhood adversity and psychosis given that higher levels of cortisol were found in patients who were exposed to early events rather than in those who had not been exposed or in controls (i.e., with no experience of childhood adversity). The role of evening cortisol is still ambiguous because higher levels were reported by patients exposed to early adversity while no differences were found with psychotic patients who had or had not experienced childhood adversity. Thus, whether an increase of evening cortisol levels is a by-product of exposure to early events or the severity of psychotic disease is still unclear.

Chapter four and five provide evidence that the exposure to early adversities is correlated with lower scores on neurocognitive domains such as verbal learning, attention, and working memory, within a sample of patients with non-affective psychotic disorder. In this sample, the exposure to early adversities was also found negatively correlated to psychosis.

The results proposed in chapters three, four and five give support to the neurodevelopmental hypothesis according to which early adversities might induce a HPA-axis dysregulation which, through the activity of glucocorticoid receptors and a decreased hippocampal neurogenesis, might induce neurocognitive decline leading to psychosis (Read et al 2014). Findings from chapter five give also support to the hypothesis that early adverse experiences might hinder the development of mentalization abilities leading to psychosis (van Os and Rutten 2010; Jacobsen and Sahrp 2015; Garcia et al 2016): lower mentalization was found to mediate the relationship between childhood adversities and psychosis.

Finally, chapter six shows higher rates of sleep impairments in psychiatry patients who have been exposed to childhood abuse or neglect than in those not exposed. These findings, together with those presented in chapters three and five, suggest more severe symptom in psychotic patients with childhood events than in those without it and confirm that early adversities may have a “pathoplastic effect” once the disorder is developed. To be noted that these results were found in two independent sample of patients with psychosis disorder (chapter three and five).

Considering that research exploring the relationship between subtypes of childhood adversity and psychosis is still lacking (Bentall et al 2014; Morgan and Anderson 2016), the second aim of this thesis was devoted to investigate this issue. Findings proposed in chapter three and five give support for specificity of the association between different forms of childhood events and psychosis. While childhood sexual abuse, mother’s neglect, loss of mother lead to a 2 to 3-fold increased risk of psychosis, childhood physical abuse, father’s neglect and loss of father seem does not influence such a risk; negative symptoms were found to be positively correlated with childhood neglect but not with childhood abuse. In addition, findings presented in the chapter three and five suggested that childhood adversities might impact differently on the developmental trajectories to psychotic symptoms. HPA axis dysregulation might be mostly involved in the association between childhood adversities and positive symptoms while impairments on cognitive functioning seems to be a pathway through which early events lead to negative symptoms, disorganization, excitement, and emotional distress.

As showed in chapter three, more severe positive symptoms were reported in psychotic patients with early adversity and higher morning cortisol than in those without childhood events and lower morning cortisol. By contrast, chapter five showed that neither neurocognition nor mentalization mediate the association between childhood adversity and positive symptoms. Poor mentalization,

attention and vigilance mediate the relationship between childhood neglect and negative symptoms, disorganization, excitement; lower working memory mediates the association between childhood abuse and disorganization, excitement, emotional distress. In addition, findings presented in chapter five suggested that the mediating role of cognitive impairments between childhood adversities and psychosis is statistically significant within males and in those with late onset of disease but not in females or in those with recent onset of psychosis. It is plausible that underlying pathways from early events to psychosis might be different in males and in females as well as that the cognitive impairments is mostly associated with the persistence of psychosis rather than its onset.

Some methodological considerations should be taken into account when interpreting the results of the present thesis. Childhood adversities were assessed using subjective retrospective report, thus recall may have influenced the results, although the research suggests a good reliability of retrospective childhood adversity assessment procedures (Fisher et al 2011; Simpson et al 2018). We did not enrol patients with first episode of psychosis (FEP); thus, whether recent events, HPA-axis dysregulation, and cognitive impairments influence mostly the severity and persistence of psychosis or its onset it is still unclear. Another limitation is the cross-sectional design that allow the evaluation of the association between early adversity, recent events, HPA-axis, cognition, and psychosis, without causal inferences. Thus, the results are in need to be replicated in longitudinal studies including FEP and chronic patients.

Strengths of the current thesis are: (a) the assessment of different subtypes of early events evaluating both their independent and cumulative effects, as recommended by literature (Dong et al 2004); (b) the assessment of psychotic dimensions consistently with a “symptoms approach” which according to some authors is preferable to operational diagnostic criteria (Costello 1992; van Os et al 1999; Ajnakina et al 2016).

In accordance with the diathesis-stress (Zubin and Spring 1977) and the biopsychosocial (Fava and Sonino 2008), perspectives this thesis point out that childhood adversities might lead to psychosis via and/or interact with other factors which might include recent events and/or HPA axis dysregulation and/or cognitive functioning (Figure 1). Childhood adversities might impact differently on the developmental trajectories to psychotic symptoms (Figure 2).

Figure 1. Underlying developmental trajectories from childhood adversities to psychosis

Figure 2. Underlying developmental pathways between childhood adversities to psychotic symptoms

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Summary and concluding remarks

The present thesis focuses on the relationship between childhood adversity and psychosis. The studies here proposed suggest that childhood adversities might lead to psychosis via and/or interact with recent events and/or HPA-axis dysregulation and/or cognitive functioning. Findings are also consistent with the hypothesis that different types of childhood might impact differently on psychosis.

Chapter one provides a general introduction about the relationship between early events and psychosis.

Chapter two provides support to the socio-developmental perspective showing that the impact of early adversities on the risk of onset or persistence of psychosis might be amplified by subsequent exposure to recent events.

In chapters three, four and five the role of the HPA axis dysregulation and neurocognitive functioning were evaluated on the basis neurodevelopmental perspective. Chapter three suggested that HPA-axis dysregulation could be involved in the relationship between early adversity and psychosis given that higher morning cortisol secretion was found in patients with early events than in those without or in controls. However, whether variations on evening cortisol levels are related to the exposure to early events or to the severity of psychotic disease is still unclear. Chapters four and five showed that childhood adversities might lead to psychosis by impairments on neurocognitive domains. In chapter five, the role of social cognition was also evaluated and evidences suggested that the relationship between childhood adversity and psychosis might be mediated by impairments in mentalization abilities.

Findings presented in chapters three, five and six also suggested that childhood adversity might have a “pathoplastic effect” once the disorder is developed since more severe symptoms were found in patients with early events than in those who had not been exposed to them. In addition, results proposed in chapters three and five emphasises the importance of taking into account the different subtypes of childhood adversities as they may have different impact on psychosis. If compared with subjects without early events, while the exposure to childhood sexual abuse, mother’s neglect/loss was associated with a risk almost doubled to be psychotic patients than controls, childhood physical abuse and father’s neglect/loss seem not to influence such a risk; negative symptoms were found positively correlated with childhood neglect but not with childhood abuse. Furthermore, findings presented in chapters three and five underlined that childhood adversities might impact differently on the developmental trajectories to psychotic symptoms. HPA-axis dysregulation seems to be mostly involved in the association between childhood adversities and positive symptoms while

cognitive impairments might be a pathway linking early events to negative symptoms, disorganization, excitement, and emotional distress.

Finally, chapter seven provides a general discussion.

Valorisation

The present thesis suggests that: (a) psychotic patients with childhood adversity might showed worse clinical outcomes (e.g., more severe symptoms; cognitive impairments; HPA-axis dysregulation; higher sensitivity to stress) than those who were not exposed; (b) the impact of childhood adversity on psychosis seems also influenced by factors such as recent life events, HPA-axis dysregulation, cognitive functioning.

From a clinical point of view these findings might have implications in terms of assessment and treatment. The differences observed between patients with psychosis with early adversity and those without in terms of clinical outcomes may enrich the debate on the clinical validity and reliability of current diagnostic systems (Cosci and Fava 2013; First et al 2018; Maj 2018).

According to the customary clinical taxonomy in psychiatry, within the psychotic spectrum disorder, patients might be classified across different diagnostic categories resulting from the presence of a certain number of symptoms (APA 2013; Heckers et al 2013; Van Os 2015). However, it should be noted that, the clinical assessment of psychotic patients exclusively reliance on diagnostic criteria might impoverishes the clinical process given that: (a) patients with and without childhood adversities, even though clinically different, might be classified under the same diagnostic category; (b) although psychotic patients with early adversity due to their poor outcome might be more resistant to treatment (Hassan and De Luca 2015; van Nierop et al 2016), any variables that might demarcate prognostic and therapeutic differences, as life events and/or severity of illness, are not taken into account.

This underscore the need for a more complete assessment of patients with psychotic disorder, which expand the narrow range of information based on the customary nosography by including the evaluation of childhood adversities and clinical outcomes related to them (e.g. pattern of symptom; severity of symptoms). The clinimetric approach (Feinstein 1982; Fava et al 2012ab) and the stratified medicine perspective (Kapur et al 2012; van Winkel 2015) have been proposed as strategies to improve the clinical assessment beyond the current traditional nosography approach.

Clinimetrics' is the term introduced by Feinstein in the early 1980s to indicate a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include types, severity and sequence of symptoms, rate of progression in illness (staging); severity of comorbidity, life events, and many other aspects of daily life, such as well-being and distress (Feinstein 1982; Fava et al 2012ab).

The stratified medicine perspective presupposes to focus on clinically meaningful differences between clinical populations through the identification of valid markers (Kapur et al 2012). This approach allows to target specific subgroups of patients in terms of personalised

prevention, treatment and lifestyle interventions (van Winkel 2015). According to previous studies (van Winkel 2015) this thesis suggested that childhood adversities might be a suitable environmental marker to distinguish clinical significant subgroups within patients with psychotic disorder.

In addition, the present findings suggest that the cognitive functioning and the sensitivity to stress might act as a protective buffer against the impact of childhood adversity on the persistence and severity of psychotic symptoms. Thus, treatment aimed to improve neurocognitive and mentalizing abilities (Bartels-Velthuis et al 2011; Weijers et al 2016) and/or reducing sensitivity to stress in daily life (Myin-Germeys and van Os 2007; Jaya et al 2016) could be considered in psychotic patients who were exposed to childhood adversities.

Furthermore, this thesis underlines that the impact of early adversity on the risk of onset or persistence of psychosis might be amplified by the exposure to adulthood stressful events. This provides additional awareness on the detrimental effects of social disadvantages on mental health (Morgan et al 2010; Morgan et al 2014) which may increase efforts for primary prevention.

From the scientific perspective, this thesis adds to the body of the literature stressing the importance of childhood adverse experiences in the development of psychosis filling a gap (Bentall et al 2014; Ajnakina et al 2016). Indeed, most of the existing studies aimed at identifying the pathway between childhood adversity and psychosis focused on diagnostic categories rather than on symptoms dimensions (van Os et al. 1999; Bentall et al 2014; Ajnakina et al 2016) and studied childhood life events as a whole rather than different kinds of early adversity which are known to potentially increase risk for different psychotic symptoms (Bentall et al 2014).

Finally, the present findings suggest that sex differences and duration of illness should be taken into account in the investigation of the pathways linking early adversity to psychosis. These pathways could be different for males and females as well as for first onset psychosis and persistent psychosis. Future research should address these topics.

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Propositions

- 1) Childhood adversities are necessary but not sufficient condition to explain the onset of psychosis: recent events and/or HPA-axis dysregulation and/or cognitive functioning impairments are underlying developmental trajectories from early adversities to psychosis.
- 2) The underlying pathways linking childhood adversities to psychosis are different for men and women.
- 3) Childhood adversities have a cumulative effect on psychosis.
- 4) Childhood adversities have a “pathoplastic effect” on psychosis.
- 5) Different types of childhood adversities impact differently on the developmental trajectories to psychotic symptoms.
- 6) Childhood adversities are a suitable environmental marker to distinguish clinically significant subgroups within patients with psychotic disorder.
- 7) Exclusive reliance on diagnostic criteria will impoverished the clinical process: patients with and without childhood adversities, although they share the same diagnostic category, are clinically different.
- 8) Comprehensive assessment of childhood adversities and clinical outcomes related to them is a necessary part in the assessment of psychotic spectrum disorder.
- 9) Specialised centres to treat psychotic spectrum disorder would derive benefit from expertise in the field of psychological interventions addressed to childhood adversities.
- 10) Treatment aimed to improve neurocognitive and mentalizing abilities and/or reducing sensitivity to stress in daily life should be considered in psychotic patients who have been exposed to childhood adversities.
- 11) There is nothing more deceptive than an obvious fact (Arthur Conan Doyle).

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Curriculum Vitae

Giovanni Mansueto was born on November 22nd 1984 in Putignano (Bari, Italy). He completed the high school in 2003 and graduated as a Clinical Psychologist at the Faculty of Psychology of the University of Florence (Italy) on February 28th 2012 with an experimental thesis entitled “*Prodromes of mental illness. Are they diagnosis-specific?*”.

In 2012-2014 he had been involved as research assistant at the Department of Psychology of the University of Florence on a project investigating the relationship between childhood adversity and psychopathology, and at the Department of Pathological Addictions of the National Italian Health System on a project investigating the role of cognition in addictive behaviours.

He frequented the Institute of Psychiatry at the campus of Kortenberg of the University Psychiatric Center Katholieke Universiteit Leuven (Belgium) from July to September 2015. In 2016 he was appointed as PhD student at Maastricht University, Department of Psychiatry and Psychology, School of Mental Health and Neuroscience. During his PhD path, he was involved in projects such as the Factors in Early Life, Diagnoses, and Symptoms (PSI-FIELDS) and the Genetic risk and Outcome of Psychosis (GROUP). From 2017 he has been appointed as volunteer research at the Department of Health Sciences of the University of Florence.

He graduated as Cognitive Behavioural Psychotherapist on December 15th 2017 at the Cognitive Psychotherapy School and Research Institute Studi Cognitivi of Milano (Italy).

He had the degree of the International Master in Affective and Neuroscience, joint title delivered by the University of Maastricht and the University of Florence, on July 4th 2018 with a dissertation entitled “Childhood adversity and Psychosis: the role of Neurocognition”.

The research studies included in the present PhD thesis were presented at the 5th and 6th Schizophrenia International Research Society (SIRS) (Florence, Italy), at the 2nd International College of Psychosomatic Medicine Workgroup on Psychosomatic Research and Practice (Paris, France), and at the 8th International Cognitive Analytic Therapy Conference (ICATA) (Ferrara, Italy) as poster or oral presentations. He received a Travel Award at SIRS 2016. He is a member of the International College of Psychosomatic Medicine (ICPM).

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