Universidad De Cantabria

Childhood early life adverse events and neurocognitive deficits in first episode psychosis patients

Ariana Echave Guillén. Nursing Graduate from the University of the Basque Country. Student of the Master " Iniciación a la investigación en Salud Mental," from the University of Cantabria.

Director: Dr. Rosa Ayesa Arriola.

Department of Psychiatry, Marqués de Valdecilla University Hospital. IDIVAL.

School of Medicine. University of Cantabria, Santander, Spain.

Certificate of approval

The master´s thesis entitled "Childhood early life adverse events and neurocognitive deficits in first episode psychosis patients" conducted and submitted by Ariana Echave Guillén in partial fulfilment of the requirements for the degree of the Master "Iniciación a la Investigación en Salud Mental" of the College of Cantabria, has been examined and is recommended for acceptance and approval for Oral Examination.

Dr. Rosa Ayesa Arriola

Santander, 6 July 2016.

Declaration

I hereby declare that the project entitled "Childhood early life adverse events and neurocognitive deficits in first episode psychosis patients" submitted by me for the partial fulfilment for the Master "Iniciación a la Investigación en Salud Mental" under University of Cantabria, is my original work and has not been submitted earlier to any other University or Institution for the fulfilment of requirement for any course of study.

Ariana Echave

Santander, 6 July 2016.

Acknowledgement

The completion of the present study could not have been possible without the participation and assistance of so many people whose names may not all be enumerated. Their contributions are sincerely appreciated and gratefully acknowledged. Nevertheless, i would like to express my deep appreciation and indebtedness particulary to the following:

All PAFIP research team who helped with data collection, and specially acknowledge Dr. Rosa Ayesa.

I should also like to thank all patients and family members who participated in the study.

To all relatives, friends and others who in one way or another shared their support, either morally, financially and/or physically.

Thank You.

Index

Abstract

Neurocognitive impairments and a history of childhood adversity are highly prevalent in patients with schizophrenia. Childhood adversity has been associated with worse performance in working memory, information processing speed and executive function tasks. The pathophysiological substrate for this association remains unclear, particulary in first episode psychosis (FEP) patients. Therefore, the aim of the present study is to examine whether self-reported childhood adversity in FEP patients is linked to specific neurocognitive deficits. The potential impact of the cumulative effect of early life adverse events on this association was also examined. A total of 95 patients were recruited from the ongoing epidemiological and longitudinal program of first-episode of psychosis (PAFIP) conducted at the University "Hospital Marqués de Valdecilla", Spain. Information about early life adverse events was obtained using Childhood Traumatic Events Scale (CTES). Cognitive function was assessed through a comprehensive neuropsychological test battery. Childhood early life adverse events were significantly associated with reduced scores on Executive Function task (P=0.044). Patients who had experienced the combined effect of early life adverse events performed worse the Executive function (P=0.027) task, even after covarying for gender, age and years of education. Obtained results suggest that childhood trauma has a different effect on cognitive function in first-episode psychosis, and in particular, in those patients with a history of a variety of traumatic events. Nonetheless, the results of this study pose many questions and many issues for the development of neuropsychological models of schizophrenia. Therefore, future studies should clarify the psychological and biological mechanisms behind these subjects' sensitivity or vulnerability to the negative effect of childhood adverse events.

Key words: First episode psychosis; Childhood early life adverse events; Neurocognition; Neurocognitive deficits.

1. Introduction

Schizophrenia is one of the most complex and least understood psychiatric disorders. It is usually define as a ‘chronic and debilitating’ condition that may lead to a progressive functional decrease impacting social, affective and cognitive domains (Burton et al., 2016; Misiak et al., 2016). Little doubt remains regarding the significance of cognitive dysfunction as an endophenotype of schizophrenia. In addition to global cognitive deficits present in the disorder, specific cognitive domains including working memory, episodic memory and executive function are particularly affected (Aas et al., 2012). Furthermore, empirical evidence has consistently demonstrated stable enduring deficits in areas such as verbal learning and memory, executive functioning, attention, information processing speed and working memory (Fardig et al, 2016; Burton et al., 2016). Of note, most of the patients with schizophrenia function at a level at least one standard deviation below healthy comparison groups, even at the time of their first episode, suggesting that the cognitive decline may begin in childhood (Aas et al., 2012). Hence, exposure to childhood adversity has established as an important variable in understanding the neuropsychology of schizophrenia (Aas et al., 2012).

Recent investigations indicate that early social environments characterized by adversity, along with individual differences in susceptibility to such environments, increase the risk for lifelong chronic diseases, including psychiatric disorders (Schalinski & Teicher, 2015). Childhood adversity (CA) is common in the general population, but is particularly prevalent in individuals with psychosis (Schalinski & Teicher, 2015), playing an important role in approximately 30% of all mental illness worldwide (Van Dam, 2015). Besides, previous investigations have shown that history of CA have been observed in a large percentage of adults with severe and persistent mental

illness. In a recent review of the literature, Kilcommons and Morrison (2005) reported that 94% of psychiatric inpatients reported history of CA.

Childhood is thought to reflect a particularly sensitive developmental window for different brain regions (Schalinski & Teicher, 2015). Adversities during this sensitive period may induce structural, functional, and epigenetic changes in brain regions involved in different functions, such as cognition (Schalinski & Teicher, 2015). The brain regions most consistently reported to be affected are predominantly the frontal-temporal lobes and the hippocampus (Teicher & Samson, 2013). Moreover, recent research assessing neurobiological effects of CA has focused on regions of interest such as the hippocampus and amygdala. However, this approach does not allow the investigation of the effects of CA on the whole brain, especially on regions known to be affected by CA (eg, orbitofrontal cortex, nucleus accumbens, striatum, prefrontal cortex) (Van Dam, 2015). Literature showing adversity-related neurobiological attendants in different brain regions raises the important issue of whether these effects are specific to CA or instead are linked to other types of environmental deprivation, including psychiatric comorbidity associated with that kind of adversities (Van Dam, 2015).

A number of investigations have demonstrated associations between CA and poorer cognitive functioning in adulthood (Shannon et al., 2011). Although there is a growing literature interesting in early life adverse events as a potential factor for neurocognitive deficits in psychotic patients, the results remained inconsistent. In spite of recent progress in searching a link between childhood adverse events and neurocognitive function, it has been reviewed the findings of studies that have investigated the association between these two variables in patients with schizophrenic and schizoafective disorders. Table 1 gives an overview of the 8 examined studies, their

corresponding sample, aspect of childhood trauma mesured and tests used, and aspect of neurocognitive function mesured and tests used, as well as the key findings. Most samples consisted of first-episode psychosis patients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV or ICD-10. Only one sample explicitly comprised chronic schizophrenia patients. Notably, there was considerable variability in the aspect of CA and neurocognitive function mesured. Moreover, studies differed in the applied tests.

Few investigations have examined the relationship between adversity during childhood and neurocognitive functioning in schizophrenia spectrum disorders. In one early study on schizophrenic and schizoaffective disorders (Lysaker et al., 2001), self-reported sexual abuse was related to worse performance in working memory and information processing speed. By contrast, Schenkel et al. (2005), failured to find association between childhood adverse events and cognition in patients with schizophrenic and schizoafective disorder. In the only study on chronic schizophrenic disorder, sexual, physical and emotional abuse and neglect were associated with poorer working memory and episodic narrative memory (Shannon et al., 2011).

Studies on patients with first episode psychosis have provided inconsistent results. While not all studies have reported significant findings, others have reported correlations between early life adverse events and some neurocognitive domains. Whereas in four studies on first-episode psychosis (FEP) patients and matched controls, three found no correlation between history of physical, sexual and emotional abuse or neglect and loss of cognitive functions (Sideli et al., 2014; Aas et al., 2011; Aas et al., 2011), while the other one reported an correlation on different neurocognitive domains (Aas et al., 2012). The results obtained by Aas et al. (2012), suggest that physical, sexual and emotional abuse or neglect are correlate with worse neurocognitive function,

specially, with the following neurocognitive domains: working memory, perception and visuo spatial abilities. The remaining 3 studies (Sideli et al., 2014; Aas et al., 2011; Aas et al., 2011), did not find a link between early life adverse events and cognition dysfunction. These mixed findings suggest that further investigation is warranted.

Many of the reviewed studies suggest that FEP patients with a history of adverse events in childhood are significantly more likely to have worse impaired performance on neurocognitive tasks. Nevertheless, the relation between CA and neurocognition is not entirely clear. Therefore it has been carried out a study to test the association between childhood early life adverse events and neurocognition in a sample of FEP patients. It has been hypothesised that FEP patients with history of early life adverse events would be more cognitively impaired than patients who had not experienced that kind of events, particularly in working memory, executive function and information processing speed tasks. Moreover, it has been hypothesised that FEP patients who had been exposed to several types of varying events would have a stronger reduction in cognitive function across cognitive domains, in particular in working memory and executive function, as well as information processing speed compared with those who had only experienced 0-1 event.

2. Objective

The main purpose of the present study is to examine whether self-reported childhood early life adverse events are associated with specific neurocognitive deficits in a sample of FEP patients, in order to further understand the brain mechanism affected by both trauma and psychosis. Another goal of the present study is to examine the potential impact of the cumulative effect of early life adverse events on this association.

Table 1. Characteristics and key findings of the 8 included studies.

Studies	N	Diagnosis	Aspect of childhood trauma mesured and test used		Aspect of neurocognitive function mesured and tests used		Outcomes
Sideli et al. (2014)	134	First episode psychosis	- Physical abuse and sexual abuse	- The Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005)	(1) Vebal memory and intelligence (2) Visual learning and memory (3) Executive function and working memory (4) Attention, concetration and mental speed (5) Language (6) Premorbid and current IQ	(1) Logical memory task of the Wechsler Memory Scale- Third edition, WMS-III (Wechsler, 1997) (2) Visual reproduction task of the WMS-III (Wechsler, 1997) (3) Trail Making Test Part B (Reitan, 1958); Digit Span of the WAIS-III (Wechsler, 1997); Spatial span of the WSM-III (Wechsler, 1997) (4) Trail Making Test Part A (Reitan, 1958); Digit symbol of the WAIS-III (Wechsler, 1997) (5) Phonological and semantic fluency tasks (Yeudall et al., 1986) (6)The National Adult Reading Test (NART) (Nelson and Willison, 1991); five-subtest abreviates version of the Wechsler Adult Intelligence Scale -Third Edition, WAIS III (Wechsler, 1997)	No significant association was found
Aas et al. (2012)	83	First episode psychosis	- Physical abuse and sexual abuse	- The Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005)	(1) Learning and memory (verbal and visual) (2)Executive function and working memory (3) Attention, concentration and processing speed (4) Lenguage (5) Visual perception and organization (6)Verbal intelligence (7) Premorbid IQ	(1) Rey Auditory Verbal Learning Test (Spreen and Strauss, 1991); the visual reproduction subtest of the Wechsler Memory Scale- Revised (Wechsler, 1987) (2) Trail Making Test Part B (Spreen an Strauss, 1991); Letter-Number Span Test (Wechsler, 1987); Raven´s Colored Progressive Matrices Sets AB and B (Spreen and Strauss, 1991) (3) Train Making Test Part A (Wechsler, 1981): WAIS-R digit symbol subtest (Wechsler, 1981) (4) WAIS-R category fluency (semantic) and letter fluency (phonemic) tasks (5) Raven´s Colored Progressive Matrices Set A ; WAIS-R Block Design) (6)WAIS-R vocabulary and comprehension subtests (7) - The National Adult Reading Test (NART) (Nelson and Willison, 1991)	Significant correlation :executive function and working memory; attention and concentration; language and verbal intelligence

Studies	N	Diagnosis	Aspect of childhood trauma mesured and test used		Aspect of neurocognitive function mesured and tests used		Outcomes
Aas et al. (2012)	406	Schizophrenia and bipolar disorder	- Physical abuse, sexual abuse, emotional abuse, emotional neglect, physical neglect	-The Childhood trauma Questionnaire (CTQ) (Aas et al., 2012)	(1) Verbal memory (+ learning + recognition) (2) Working memory (3) Executive function (4) Perception and visuo-spatial abilities (5) Verbal abilities (6)General cognitive	(1) The Califonial Verbal Learning Test (CVLT) II (Delis etal., 2004) (2) Digit Span (Wecgsler, 1997) (3) Verbal fluency test and letter fluency tasks (Delis et al., 2004) (4) Block design task (Wechsler, 2007); matrix reasoning (Wechsler, 2007) (5) Similarities and vocabulary (Wechsler, 2007) (6) Full-scale IQ from the WASI (Wechsler, 2007)	Significant correlation: working memory, perception and visuo-spatial abilities
Aas et al. (2011)	138	First episode affective ando non-affective psychosis	- Emotional, physical and sexual abuse	- The Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005)	(1) Learning and memory (visual and verbal) (2) Executive function and working memory (3) Attention, concentration and mental speed (4) Language (5) Visuo construction /perceptual abilities (6) Verbal intelligence (7) Premorbid IQ	(1) Rey Auditory Verbal Learning Test (Spreeen, 1998); the visual reproduction subtest of the Wechsler Memory Scale-Revised (Wechsler, 1981) (2) Trail Making Test Part B (Spreen, 1998); Letter Number Span Test (Wechsler, 1981); Raven´s Colored Progressive Matrices Sets AB and B (Spreen, 1998) (3) Train Making Test Part A (Wechsler, 1981): WAIS-R digit symbol subtest (Wechsler, 1981) (4) WAIS-R category fluency (semantic) and letter fluency (phonemic) tasks (5) Raven´s Colored Progressive Matrices Set A ; WAIS-R Block Design (6) WAIS-R vocabulary and comprehension subtests (7) - The National Adult Reading Test (NART) (Nelson and Willison, 1991)	No significant association was found in schizophrenic patients
Aas et al. (2011)	30	First episode psychosis	- Physical and sexual abuse, separation and loss	- The Childhood Experiences of Care and Abuse Questionnaire (CECA.Q) (Bifulco et al., 2005)	(1) Verbal memory (2) Non verbal memory (3) Executive function and working memory (4) Processing speed (5) Perception and visuoespatial abilities (6) General knowledge (7) Premorbid IQ	(1) The Wechsler Memory Scale – Third edition (WMS-III) (Wechsler, 1997) (2) The Wechsler Memory Scale – Third edition (WMS-III) (Wechsler, 1997) (3) Trail B and the Spatial Working Memory (SWM) from the Cambridge Neuropsychological Test Automated Battery (Gau and Shang, 2010) (4) Digit Symbol Coding from the WAIS-III (Wechsler, 1997); Trail Making Test Part A. (5) the Block Design task (Wechsler, 1997); the Matrix Reasoning (Wechsler, 1997) (6) WAIS-III (Wechsler, 1997) (7) The National Adult Reading Test (NART) (Nelson and Willison, 1991)	No significant association was foun

Studies	N	Diagnosis	Aspect of childhood trauma mesured and test used		Aspect of neurocognitive function mesured and tests used		Outcomes
Shannon et al. (2011)	85	Chronic schizophrenia	-Physical abuse, sexual abuse, emotional abuse, emotional neglect, physical neglect	- Childhood trauma Questionnaire (CTQ) (Bersteins et al., 1998)	(1) Verbal memory (2) Premorbid IQ	(2) 3 subtest (logical memory, word list, letter-number sequencing)of Wechsler Memory Scale- Third edition (WMS-III) (2) The National Adult Reading Test (NART) (Nelson and Willison, 1991)	Significant correlation: working memory and episodic narrative memory.
Schenkel et al. (2005)	40	Schizophrenia or schizoaffective disorder	- Physical abuse , sexual abuse and neglect	- Interviews and reports from nursing, psychiatry, psycology and social work staff	(1) Verbal intelligence (2) Verbal processing speed and verbal inhibtion (3) Non-verbal problem-solving and sequencing skills (4) Verbal fluency and word generating ability (5) Learning and visual context processing	(1) The Shipley Institute of Living Scale Vocabulary subtest (Zachary, 1991) (2) The Hayling Sentence Completion Test (Burgess and Shallice, 1997) (3) The Brixton Spatial Anticipation Test (Burgess and Shallice, 1997) (4) Controlled Oral Word Association Test (COWAT) (Spreen and Benton, 1997) (5) The Contour Integration Test (Kovacs et al., 1999)	No significant association was found
Lysaker et al. (2001)	43	Schizophrenia or schizoaffective disorder	- Sexual abuse	- Childhood sexual abuse questionnaire	(1) Working memory (2) Verbal memory (3) Information processing speed (4) Premorbid IQ	(1) The Wisconsin Card Sorting Test (WCST) (Heaton et al. 1993); Letter-number Sequency (LNS) subtest of the WAIS-III (Wechslet, 1997) (2) The California Verbal Learning Test (CVLT)() (Delis et al., 1987) (3) TheDigit Symbol (DS) subtest of the WAIS-III (4) Vocabulary subtest of the WAIS-III	Significant correlation: working memory and information processing speed.

3. Material and methods

3.1. Study Design

Data for the present study were obtained from an ongoing epidemiological and longitudinal program of first-episode of psychosis (PAFIP) conducted at the University " Hospital Marqués de Valdecilla", Spain (Pelayo-Teran et al., 2008). Prior to international standards for research ethics, the program conduct written explanation to patients and informed consent form, as well as the conduct of the program were reviewed and approved by the regional institutional review boards. If any patient refused to give the consent or they requested withdrawal from the program, they were able to be immediately withdrawn from the program. A more detailed description of the programme has been previously reported (Pelayo-Teran et al., 2008).

3.2. Participants

The study comprised 95 patients (45 females and 50 males) recruited from the PAFIF, from 2011 to 2016. All subjects met the inclusion criteria for PAFIF: (a) be on ther range of age between 15-60; (b) live in the catchement area; (c) have experienced the first episode of psychosis; (d) not having been on treatment with antidepressant or have been treated but in a period of less than 6 weeks; (e) met DSM-IV criteria for brief psychotic disorder, schizophrenia, schizophreniform disorder, not otherwise specified psychosis or schizoaffective disorder. The exclusion criteria for the present study were as follows: have a history of (a) neurological disease; (b) head injury; (c) mental retardation (using DSM-IV criteria); (d) drug dependence (using DSM-IV criteria). Even, those patients who at six months evaluation (from the baseline visit) were diagnosed with the following diagnoses (using DSM-IV criteria), were excluded from the programm: schizoaffective disorder,

mental retardation or substance dependence (with the exception of nicotine dependence). Patients who accepted to participate and met these criteria, and their families, provided written informed consent to be included in the program. The informed conset was provided after detailed explanations of the study procedures had been given to them. Then, all patients were randomly assigned to three different pharmacological treatment: haloperidol, olanzapine or risperidone (for a detailed description see Crespo.Facorro et al., 2006; Pelayo-Teran et al., 2008).

Aside from the inclusion criteria from PAFIF, patients included in this study, had to have completed the Childhood Traumatic Events Scale (CTES) (Pennebaker & Susman, 1998). For the purpose of the study the data were colected from February 2011 to February 2016.

3.3. Clinical assessment and chart review

Clinical assessment was carried out by the same trained psychiatrist B.C.F., and clinical psychologists. A structured interview from DSM-IV (SCID) was conducted at 6 month on from the baseline visit, to confirmed the diagnoses. Current positive and negative symptoms were assessed using means from the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) and the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984). The SAPS and SANS scales were administered to generate dimensions of positive symptoms (hallucinations and delusions), disorganized symptoms (formal thought disorder, bizarre behavior and inappropriate affect) and negative symptoms (scores for alogia, affective flattening, apathy and anhedonia).

The duration of untreated psychosis (DUP) was defined as the time from the onset of the first psychotic symptom (corresponding to a score of 4 or higher on one of the SAPS items) to the

initiation of treatment with appropriate antipsychotic. The duration of untreated illness (DUI), however, was considered as the time from the onset of the first unspecific symptoms related to psychosis to initiation of appropiate antipsychotic treatment .

The age of onset of psychosis was defined as the age when the first psychotic symptoms (hallucinations, delusions, bizarre behavior, formal thought disorder, or inappropriate affect) which remained present most of the time, appeared. The Premorbid Adjustment Scale (Cannon-Spoor et al., 1982) was administered to participants and key relative (who knew the patient´s premorbid functioning) together in order to evaluate the premorbid functioning. Scores of this scale was focused mainly on social and academic domains of the first three stages of development (childhood and early and late adolescence) in order to evaluate the setting of early adjustment.

To collect first-degree family history of psychotic illness, an interview (patient and closer family) was conducted. Informants were asked to approached information about each person in the family tree who had mental health disorders (disorders with psychotic symptoms such as schizophrenia or bipolar disorders), medication, psychotherapy, hospitalization or suicide (suicidal ideation and behavior, intent of attempt and lethality of attempt).

3.4. Childhood Traumatic Events Scale (CTES)

Data on early life adverse events (before the age of 17) were gathered using the Childhood Traumatic Events Scale (CTES) (Pennebaker & Susman, 1998). The CTES, was previously designed and reported by Pennebaker and Susman, who used the scale with a large sample of employees of a Texas corporation. This scale consist of brief survey of 6 early traumatic

experiences and ratings of the degree to which individuals confided the traumas. The items which are face valid included are as follow: death of a close family member or friend, sexual molestation, exposure to violence, illness or injury, major upheaval between parents (such as divorce or separation) and other major upheaval which could shape the life or personality of the examinees. To rate the degree of the trauma a 7 point scale, where 1 was “not at all traumatic”, 4 was “somewhat traumatic” and 7 was “extremely traumatic”, was assessed.

It were defined each of the six items for traumatic life items in childhood. The experience of a death was define as the loss of a relative or close friend before the age of 17. It was considered major upheaval between parents in the case there was divorce or separation of parents. Sexual abuse or molestation was considered to be unwanted or illegal sexual experiences (such as touching, attempted rape or involved sexual intercourse) prior to age 17 and was not limited to the immediate family. Physical abuse was defined as repeated exposure to physical violence before the age of 17. In order to be considered such as physical abuse, the incident had consisted of being hit with a stick or belt, or being punched or kicked. Mild forms of punishment such as being smacked or hit with a slipper were excluded. The remaining items (have been extremly ill or injured and have experienced other major upheaval) were registered if patients considered them as traumatic. It's worth mentioning that this questionnaire was read out to all participants, to improve the accuracy of the fixed category responses obtained.

3.5. Neurocognitive assessment and instruments

The majority of patients (n = 94) underwent neuropsichological assessment. A comprehensive neuropsychological battery was administered to patients by trained psychologists to

assess the following eight domains: (1) learning (verbal learning) and memory (delayed memory); (2) Information processing speed; (3) working memory; (4) executive function; (5) motor dexterity; (6) theory of mind; (7) attention; and (8) premorbid IQ.

Learning and memory

The Rey Auditory Verbal Test (RAVT) (Rey, 1964) and the Rey Complex Figure Test (Rey, 1941; Osterrieth, 1944) were administered to assess verbal learning and memory (delayed memory). The RAVT consist on give to the participants a list of 15 unrelated words repeated over five different trials. The subjects have to memorize and repeat the words. Then another list (different list) of unrelated 15 words are given, and participants have to repeat again the first list, and then after 30 minutes. In this study RAVL trial 5 and 7 scores were used to evaluate the verbal memory and delayed memory (after 30 minutes) (Rey, 1964). The Rey Complex Figure Test consist in presenting to the subjects an abstract linear shape and patients are instructed to make a copy, as accurate as possible. Three minutes after completion of the copy, participants will be asked to perform a reproduction of the figure. 20 minutes after the first copy, they will be request to replay the figure again (Rey, 1941; Osterrieth, 1944).

Information processing speed

WAIS-III Digit Symbol-Coding subtest (Salthouse, 1992; Brébion et al., 1998) and Trail Making Test Part A (Lezak, 1995), was given to participants as a mesure of information processing speed. Digit Symbol-Coding subtest consist in presenting to the participants a table with numbers from 1 to 9. Below each numbers there is a symbol that represent the number. Participants have to place under each number the corresponding symbol as shown in the table and as quickly as possible (time period of 120 sec) (Salthouse, 1992; Brébion et al., 1998). The Trail Making Test (TMT) is a

task that originally was included in the Army Individual Battery Test and it´s divide into two parts: TMT-Part A and TMT-Part B. TMT-Part A consists of 25 circles distributed over a sheet of paper and participants are asked to draw lines to connect the numbers in descendants order as fast as possible (Lezak, 1995).

Working memory

WAISS-III Digits subtest (Wechsler, 1999) was administered to assess the working memory. The test consist in two separate parts of aplication: digits forward and digits backwards. The task consist in presenting to the participants a digits sequences and then are asked to repeat the sequences forward and backwards (Wechsler, 1999). In this study digits backwards score were used to mesure working memory.

Executive function

The tower of London (Shallice, 1982), the Trail Making Test Part B (Lezak, 1995) and the Stroop Test (Golden, 1975) were administered to evaluate the executive function. The Tower of London (ToL), consist in presenting to the participants two tables (examiner and examinee tables) with three diferent coloured balls (red, green, blue) arranged on three pegs. Participants are asked to preplan mentally a sequence of movements, and then to execute the moves one by one in order to make the arrangement of balls identical to the opossing table (examiner table). This task has a maximum limit of 20 movements and a time period of 2 minutes for the completion of each design (Shallice, 1982). The Trail Making Test (TMT), is a task that originally was included in the Army Individual Battery Test and it´s divide into two parts: TMT-Part A and TMT-Part B. In TMT Part B, the circles include both, numbers and letters. Participant have to draw lines to connect the circles (as in Part A) in ascending order but with the added task of alterning between the number and letters

(number- letter) (Lezak, 1995). Finally, the Stroop test consist of three pages: a Word Page with color words printed in black ink; a Color Page with ‘X’s printed in diferent colours (red, blue or green); and a Color-Word Page with words printed in colours (red, blue or green). In the firt page, participants have to goes down each sheet reading words as quickly as possible. In the second page, the respondent are asked to named the ink colour as quickly as possible too. In the last page, they have to named the colour of the ink, not the word written. The test yields three scores based on the number of items completed on each of the three pages (Golden, 1975). In the present study Colour-Word test scores were used to evaluate de executive function.

Motor dexterity

The Gooved Pegboard Test (Lafayette Instrument Company) was utilized to evaluate the motor dexterity. This test consist of a table with twenty five holes with randomly positioned slots and pegs with a key along one side. The pegs must be rotated to insert them in the holes.The participants are asked to insert the pegs in each hole as quickly as possible. At first the participants have to put the pegs into the boards as fast as possible using only the dominant hand. If their dominant hand is the right hand, they have to fill the top row completely, from left side to right side and vice versa. Then, they will repeat the task using the other hand.

Theory of mind

Reading the mind (Eye Task) is a task from the Theory of Mind (Baron-Cohen, 2001). This test consist in a presentation on a computer screen, which shows 36 black and white photographs of the region of eyes. For each set of eyes, the participants have to choose between four adjetives, choosing the word which best describes what the person in the picture is feeling or thinking.

Attention

The Continuous Performance Test (CPT) computerized version (Conners, 1995) was administered to participants as a mesure of attention. The task is presented to the participants in a computer screen in which letters appear. The respondents are required to respond by pressing a key on the computer every time it appears the stimulus previously indicated (Conners, 1995).

Premorbid IQ

WAIS-III Vocabulary subtest (Wechsler, 1999) was apply in order to mesure de Premorbid IQ of the subjects. In this test a list of words of increasing difficulty are presented orally and the subjects have to define each word (Wechsler, 1999).

2.6. Statistical analysis

Initially participants were separated into 2 independent groups: patients who had not experienced any event listed in CTES and patients who had experienced them. Then, a new distribution was made according to the type of adverse event experienced. Lastly, another distribution was done: patients who had experienced 0-1 event listed in CTES and patients who had experienced more than 1 event. Statistical analyses addressed the following predictions: (1) In FEP patients, those who had experienced any event listed in CTES, the neurocognitive deficits will be increased in comparison with those who had not expereienced them. (2) Among patients, those who had experienced more than 1 events listed in CTES will perform worse the neurocognitive tasks.

Analyses were run using the Statistic Package for Social Science program (SPSS) version 19.0. The characteristics of the subjects will be described, showing the frequencies and percentages

of dichotomous and qualitative variables, and presenting mean±standard deviation (S.D.) of continuous variables, in the whole sample and divided by group (experimental and control groups). Both groups were compared according to socio-demographic, clinical and treatment characteristics and prevalence of the amount of early life adverse events, using parametric (t-tests) and none-Parametric (U of Mann Whitney) tests.

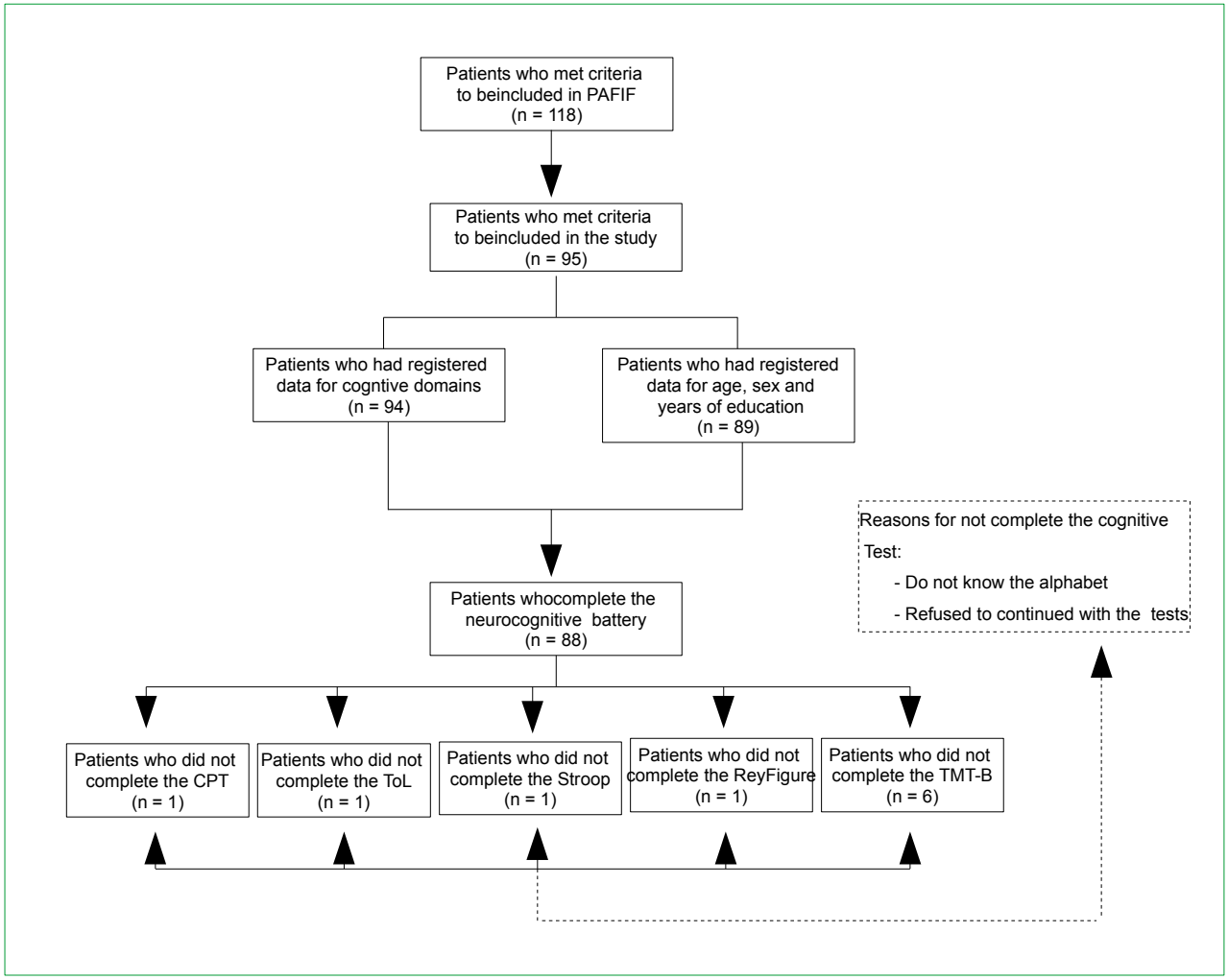
To test the first hypothesis, simple analysis were conducted using parametric and none-parametric tests. The differences between groups in dichotomous and qualitative variables were been analyzed using the chi-square test (e.g., gender) and quantitative variables using Student's t and the U of Mann-Whitney in case that variables do not follow a normal distribution (evaluated using the Kolmogorov- Smirnoff test). Additional analyzes were performed, dividing the participants by the type of traumatic event (i.e. patients who had experienced the dead of close family, patients who had experienced a major upheaval between parents, etc). Analyses of covariance (ANCOVA) were conducted to confirm the second hypothesis. ANCOVA was used to compare neurocognitive domains in subjects who had experienced 0 or 1 event listed in CTES versus those who had experienced more than 1 event, separately in two groups. Analyses were covaried for age, sex and years of education, as both groups differed on these variables. In spite of reduce the risk for type I error, Bonferroni correction for multiple testing was applied.

4. Results

4.1. Sample Description

The sample comprised 118 individuals. Ninety five (80.5%) out of the 118 individuals initially evaluated and included in the study, completed the Childhood Traumatic Events Scale (CTES). A further 23 people refused or were judged to be too distressed at the time to complete the CTES. Baseline cognitive information was totally available for 87 individuals that completed the CTES questionnaire. Due to the program is still running, not all participants had full information (Figure 1).

Figure 1. Flow chart.



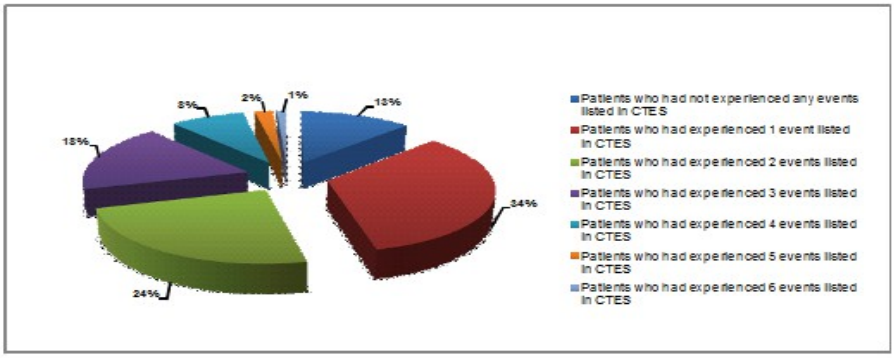
Of the 95 participants included in the study and had completed the CTES, 83 (87.4%) had childhood traumatic history of death (close family), major upheaval between parents, illnesses, other major upheaval, physical and/or sexual abuse (53% were males). The most common traumatic events reported were death of a family member or a close friend (66.27%) followed by major upheaval between parents and any other major upheaval. See Table 2 for rates, means, standard deviations and percentages.

Chart 2 . Early Life Adverse Events Categories

	N	Age		Sex	
		Mean	SD	Male (%)	Female (%)
Death of a family member or a close friend	55	11.84	3.980	31 (56.4)	24 (43.6)
Major upheaval between parents	34	9.94	4.776	16 (47.1)	18 (52.9)
Traumatic sexual situation	9	11.63	4.438	2 (22.2)	7 (77.8)
Repeated psychal abuse	17	11.25	4.282	10 (58.8)	7 (41.2)
Illness or injury	29	10.93	5.210	15 (51.7)	14 (48.3)
Any other major upheaval	33	11.69	4.314	12 (36.4)	21 (63.6)

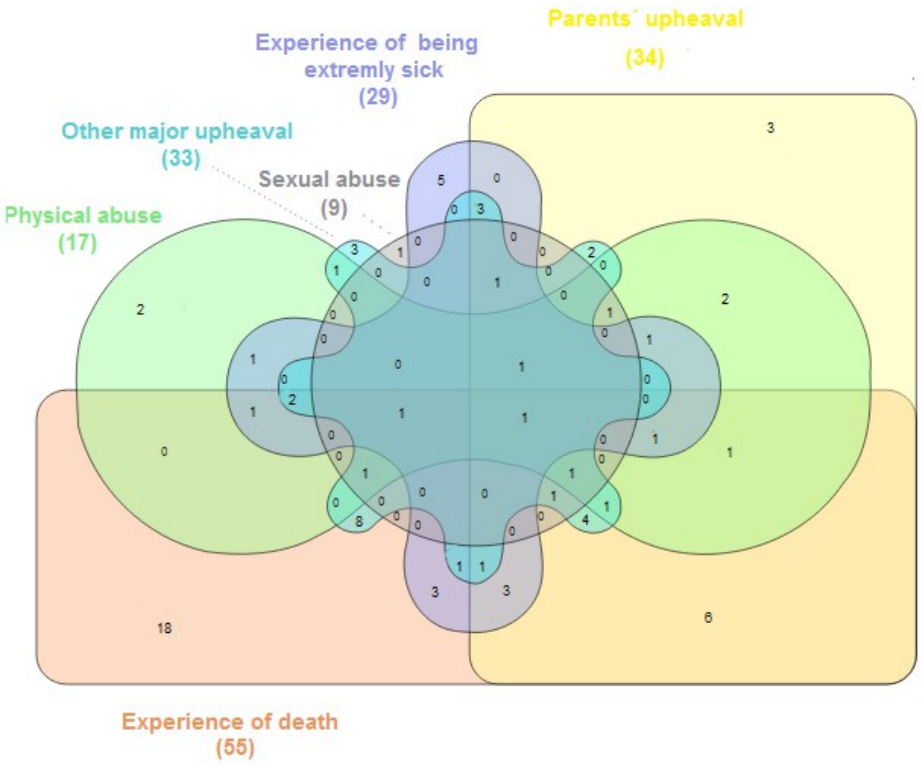
The resulting scores of CTES were skewed, as some individuals had not been exposed to traumatic event at all, while others had been exposed to several types of varying events. The numbers of participants who fell into each of the traumatic event categories was summarized in Figure 2.

Figure 2. The distribution of the events listed in CTES by the number of patients who reported having experienced them



There were some participants who had reported only one incident: death of close relative (n=18), physical abuse (n=2), sexual abuse (n=1), major upheaval between parents (n =3), illness (n=5), other major upheaval (n=3). However, most of the patients had reported more than one incident or event listed in CTES. The most common combinations are as follows (Figure 3): major upheaval between parents and death of close relative (n =6); major upheaval between parents and illness (n =2); illness and death of close relative (n =3); major upheaval between parents and other major upheaval (n =2); other major upheaval and death of close relative (n =8); illness and physical abuse (n =1); other major upheaval and physical abuse (n =1); major upheaval between parents, illness and death of close relative (n =3); major upheaval between parents, death of close of a close relative and other major upheaval (n =4); major upheaval between parents, illness and other major upheaval (n =3); other major upheaval, illness and death of close relative (n =1); major upheaval between parents, sexual abuse and physical abuse (n =1); major upheaval between parents, death of close relative and physical abuse (n =1); major upheaval between parents, illness and physical abuse (n =1); major upheaval between parents and death of close relative (n =1); illness, death of close relative and physical abuse (n =1); major upheaval between parents, death of close relative, sexual abuse and other major upheaval (n =1); major upheaval between parents, illness, sexual abuse and other major upheaval (n =1); major upheaval between parents, death of close relative, illness and other major upheaval (n =1); major upheaval between parents, death of close relative, illness and physical abuse (n =1); physical abuse, death of close relative, sexual abuse and other major upheaval (n =1); major upheaval between parents, death of close relative, physical abuse and other major upheaval (n =1); illness, death of close relative, physical abuse and other major upheaval (n =2); major upheaval between parents, death of a close relative, sexual abuse, physical abuse and other major upheaval (n =1); major upheaval between parents, illnesse, sexual abuse, physical abuse and other major upheaval (n =1). Only one participant had reported all traumatic events.

Figure 3. Venn diagram. The distribution of the events listed in CTES



4.2.Characteristics of the sample

The general demographics and clinical data of patients, are presented in Table 3. The case and control samples, both had a mixed gender (male 44 [53.0%] vs. 6 [50.0%]). Mean age was 30.55 years (range 15–60) in cases and 33.92 years in controls. There were no significant differences between groups in gender, age or education level (years). As expected, a significant difference between the groups was found on Brief psychotic disorder ($p = 0.021$). Those reporting childhood trauma had slightly lower percentage (8 [9.6%]) than those who did not report childhood trauma (4 [33.3%]). Neither in the case nor in the control group, were any of the above variables associated with childhood trauma. As it mentioned above, there were 23 individuals for whom baseline trauma data were not available, but these individuals were not significantly different on demographic or clinical characteristics compared with the 95 individuals included in the analysis.

4.3. Early Life Adverse Events and Cognitive Impairments

To avoid unnecesary multiple testing, all cognitive data are presented as domains consisting of several individual subtests. Table 4 shows early life adverse events dichotomized into “patients with History of Childhood Traumatic Events (HCTE)” (defined as exposure to one of the following: the death of a family member or a close friend, a major upheaval between parents, a traumatic sexual situation, a repeated psychal abuse, an illnesses or any other major upheaval) or “patients without HCTE “. Patients with HCTE did not significantly differ from patients without it in any mesure of general cognitive function. By contrast, in HCTE patient sample, it has been found significantly negatively performance on the following domain: Executive Function (P=0.044). Nevertheless, when cases with HCTE were compared with controls (patients without HCTE), HCTE cases scored lower than controls in the majority of the task, with the exception of Social Cognition and Attention. Interstingly, patients with HCTE performed better on the social cognition and attention domains compared to the group without HCTE.

Then, it has been assessed childhood trauma distribution across the six adverse events categories (the death of a family member or a close friend, a major upheaval between parents, a traumatic sexual situation, a repeated psychal abuse, an illnesses or any other major upheaval) derived from CTES. The analysis of subtypes of early life adverse events, identified that patients with HCTE had lower scores on different neurocognitive tasks compared to controls. Cognition data for each categories are presented in Table 5, 6, 7, 8, 9 and 10. Patients with history of death of a family member or a close family showed a poor level of functioning on the following domain: Information Processing Speed (P=0.003). By contrast, those patients were more likely to perform significantly better the Delayed Memory task (P=0.006). A similar pattern was evident with regard

Table 3. Sociodemographic, clinical and treatment characteristic divided into patients with HCTE and patients without HCTE.

	Total (*n* = 95)	**Patients with HCTE (*n* = 83)**	**Patients withoout HCTE (*n* = 12)**	P_{value}
Male gender, n (%)	50 (52.6)	44 (53.0)	6 (50.0)	0.845
Age (years), mean (S.D.)	31.14 (10.41)	30.55 (10.3)	33.92 (10.57)	0.318
Education (years), mean (S.D.)	10.46 (3.31)	10.46 (3.09)	10.42 (4.62)	0.975
Pre-morbid IQ estimationa, mean (S.D.)	96.81 (12.40)	97.44 (12.77)	92.50 (8.66)	0.102
Family history of psychosis, n (%)	29 (30.5)	27 (32.5)	2 (16.7)	0.265
DUP , mean (S.D.)	7.21 (12.94)	6.4 (10.96)	12.32 (21.64)	0.371
DUI, mean (S.D.)	11.36 (16.87)	11.73 (17.64)	8.42 (8.98)	0.377
Age of psychosis onset (years), mean (S.D.)	29.87 (9.85)	29.36 (9.58)	33.05 (11.33)	0.304
Pre-morbid Adjustment Scale scoreb, mean (S.D.)				
Social functioning	1.18 (0.85)	1.19 (0.89)	1.09 (0.54)	0.608
Academic functioning	0.71 (1.19)	0.67 (1.11)	1.00 (1.59)	0.499
Diagnosis, n (%)				
Schizophrenia	28 (29.5)	24 (28.9)	4 (33.3)	0.754
Schizophreniform	42 (44.2)	38 (45.8)	4 (33.3)	0.417
Brief psychotic disorder	12 (12.6)	8 (9.6)	4 (33.3)	0.021*
Psychosis disorder NOS	12 (12.6)	12 (14.5)	0 (0.0)	0.159
Schizo-affective disorder	1 (1.1)	1 (1.2)	0 (0.0)	0.702
SANS at baseline, mean (S.D.)	5.54 (5.64)	5.36 (4.94)	6.75 (9.31)	0.622
SAPS at baseline, mean (S.D.)	14.40 (4.72)	14.41 (4.58)	14.33 (5.74)	0.963
BPRS at baseline, mean (S.D.)	64.99 (16.60)	65.41 (15.71)	62.17 (22.3)	0.635
Consumption of drugs, n (%)				
Cannabis	83 (87.4)	35 (42.2)	4 (33.3)	0.561
Amphetamines	8 (8.4)	8 (9.6)	0 (0.0)	0.261
BZD	0 (0.0)	0 (0.0)	0 (0.0)	-
Cocaine	16 (16.8)	15 (18.1)	1 (8.3)	0.399
Heroin	0 (0.0)	0 (0.0)	0 (0.0)	-
LSD	7 (7.4)	7 (8.4)	0 (0.0)	0.296

Table 4. Relationship between having experienced any event listed in CTES before the age of 17 and cognition in patients with FEP. Patients with CTEH Vs. patients without CTEH.

	Patients with CTEH (*n*=83)	**Patients without CTEH (*n*=12)**	**Statistical**	**P_{value}**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(82), 9.49 (2.554)	(12), 8.50 (1.732)	t	0.138
Verbal learning/memory				
RAVL Trial 5, (*n*) mean (S.D.)	(82), 7.70 (2.955)	(12), 8.08 (4.122)	t	0.212
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(82), 7.01 (2.921)	(12), 7.42 (2.466)	t	0.439
TMT-A (sec), (*n*) mean (S.D.)	(82), 49.91 (21.731)	(12), 42.33 (11.094)	t	0.137
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(81), 3.16 (2.813)	(12), 4.25 (1.815)	U	0.044*
ToL total move score, (*n*) mean (S.D.)	(81), 42.64 (18.376)	(12), 34.92 (18.223)	t	0.796
TMT-B (sec), (*n*) mean (S.D.)	(76), 108.18 (49.194)	(12), 88.92 (30.095)	U	0.200
Stroop color-word, (*n*) mean (S.D.)	(81), 33.77 (11.416)	(12), 33.27 (9.119)	t	0.860
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(82), 5.15 (1.626)	(12), 5.67 (1.670)	U	0.257
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(82), 7.54 (3.027)	(12), 8.08 (3.476)	t	0.668
Rey figure recall, (*n*) mean (S.D.)	(82), 17.1463 (6.74422)	(11), 14.5455 (4.63926)	t	0.139
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(82), 74.34 (27.111)	(12), 67.50 (10.185)	U	0.518
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(82), 20.01 (4.809)	(12), 19.33 (4.397)	t	0.347
Attention				
CPT total correct score, (*n*) mean (S.D.)	(81), 69.58 (13.379)	(12), 67.67 (20.268)	U	0.535

to patients with history of major upheaval between parents. Participant of these categorie scored significantly worse the Information Processing Speed (P=0.053) task. However, Delayed Memory task scores (P=0.055) were significantly better in patients with HCTE. In the same way, patients with history of a traumatic sexual experience performed significantly better the Delayed Memory (P=0.011) task. Otherwise, those patients who reported having experienced repeated psychal abuse scored significantly lower in Executive Function (P=0.012) task. Moreover, a significant association on Information Processing Speed domain (P=0.041) was found. Patients who experienced an illnesses or an injury before the age of 17, did not significantly differ from patients without HCTE in the majority of the cognitive domains. Of interest, these patients performed significantly better the Attention domain task (P=0.044). It was also observed that patients who reported other major upheaval had significantly poorer functioning on Executive Function (P=0.001) and Working Memory (P=0.043) domains.

It has been found strong evidence for the association between early life adverse events and poorer neurocognitive function, particulary on Information Processing Speed and Executive Function. Interestingly, Delayed Memory and Attention domains scores were positively better in the group of patients with HCTE. However, almost the entire sample reported having experienced more than 1 event listed in CTES. Therefore, the results previously shown are limited.

4.4. Several Types of Varying Events and Cognitive Impairments

Due to almost all participants had reported several types of varying events listed in CTES, a further analysis was carried out. Every individual could experience an adverse event in his childhood without this influence their cognitive development. Nonetheless, individuals who had

Table 5. Relationship between having experienced the death of a family member or a friend before the age of 17 and cognition in patients with FEP. Patients who had experienced the death of a close family or friend Vs. patients who had not experienced it

	Patients (*n* = 55) who had experienced the death of a very close friend or family	**Patients (*n* = 40) who had not experienced the death of a very close friend or family**	**Statistical**	***P*$_{value}$**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(54), 9.48 (2.718)	(40), 9.2 (2.139)	t	0.235
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(54), 7.8 (3.055)	(40), 7.35 (3.118)	t	0.491
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(54), 7.17 (2.718)	(40), 6.93 (3.067)	t	0.693
TMT-A (sec), (*n*) mean (S.D.)	(54), 44.74 (15.864)	(40), 54.63 (25.231)	t	0.033*
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(54), 3.37 (3.211)	(39), 3.21 (1.88)	U	0.7
ToL total move score, (*n*) mean (S.D.)	(54), 40.94 (19.199)	(39), 42.62 (17.54)	t	0.664
TMT-B (sec), (*n*) mean (S.D.)	(51), 104.33 (48.724)	(37), 107.24 (46.078)	U	0.621
Stroop color-word, (*n*) mean (S.D.)	(54), 34.48 (10.848)	(39), 33.44 (8.741)	t	0.609
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(54), 5.26 (1.673)	(40), 5.15 (1.594)	U	0.975
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(54), 9.48 (2.718)	(40), 9.2 (2.139)	t	0.235
Rey figure recall, (*n*) mean (S.D.)	(54), 18.3981 (6.59143)	(39), 14.6795 (5.95873)	t	0.006*
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(54), 70.06 (1.263)	(40), 78.08 (33.548)	U	0.193
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(54), 20 (4.093)	(40), 19.83 (5.551)	t	0.867
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(54), 71.57 (9.937)	(39), 66.23 (18.494)	U	0.403

Table 6. Relationship between having experienced a major upheaval between parents (divorce, separation, …) before the age of 17 and cognition in patients with FEP. Patients who had experienced a major upheaval between parents Vs. patients who had not experienced it.

	Patients (*n* = 34) who had experience a major upheaval between parents	**Patients (*n* = 61) who haad not experienced a major upheaval between parents**	**Statistical**	***P*$_{value}$**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(33), 9.76 (2.362)	(61), 9.16 (2.538)	t	0.286
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(33), 8.39 (2.680)	(61), 7.18 (3.027)	t	0.055*
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(33), 7.52 (2.959)	(61), 6.82 (2.796)	t	0.272
TMT-A (sec), (*n*) mean (S.D.)	(33), 44 (14.213)	(61), 51.62 (23.346)	t	0.053*
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(33), 3.18 (1.811)	(60), 3.37 (3.124)	U	0.798
ToL total move score, (*n*) mean (S.D.)	(33), 44 (18.470)	(60), 40.35 (18.454)	t	0.365
TMT-B (sec), (*n*) mean (S.D.)	(31), 102.10 (49.367)	(57), 107.44 (46.604)	U	0.328
Stroop color-word, (*n*) mean (S.D.)	(33), 35.09 (10.153)	(60), 33.47 (9.924))	t	0.460
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(33), 5.33 (1.534)	(61), 5.15 (1.692)	U	0.522
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(33), 8.39 (2.680)	(61), 7.18 (3.207)	t	0.055*
Rey figure recall, (*n*) mean (S.D.)	(33), 18.4394 (7.01088)	(60), 15.9583 (6.19068)	t	0.094
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(33), 67.94 (13.754)	(61), 76.46 (29.877))	U	0.136
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(33), 20.45 (4.957)	(61), 19.64 (4.637)	t	0.439
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(33), 70.42 (11.568)	(60), 68.73 (15.695)	U	0.910

Table 7. Relationship between having experienced a traumatic sexual situation before the age of 17 and cognition in patients with FEP. Patients who had experienced a traumatic sexual event Vs. patients who had not experienced it

	Patients (*n* = 9) who had experienced a traumatic sexual situation	**Patients (*n* = 86) who had not experienced a traumatic sexual situation**	**Statistical**	P_{value}
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(9), 9.89 (2.759)	(85), 9.31 (2.459)	t	0.557
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(9), 9.78 (2.167)	(85), 7.38 (3.074)	t	0.011*
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(9), 7.44 (3.504)	(85), 7.02 (2.803)	t	0.735
TMT-A (sec), (*n*) mean (S.D.)	(9), 49.56 (12.401)	(85), 48.88 (21.596)	t	0.889
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(8), 2.63 (1.847)	(85), 3.36 (2.790)	U	0.516
ToL total move score, (*n*) mean (S.D.)	(8), 52.88 (21.983)	(85), 40.59 (17.863)	t	0.164
TMT-B (sec), (*n*) mean (S.D.)	(8), 120.88 (44.176)	(80), 104.03 (47.679)	U	0.201
Stroop color-word, (*n*) mean (S.D.)	(8), 35.88 (7.882)	(85), 33.87 (10.178)	t	0.520
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(9), 5.22 (1.787)	(85), 5.21 (1.626)	U	0.995
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(9), 9.78 (2.167)	(85), 7.38 (3.074)	t	0.011*
Rey figure recall, (*n*) mean (S.D.)	(9), 15.6667 (6.92369)	(84), 16.9643 (6.55642)	t	0.603
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(9), 77.89 (35.268)	(85), 73 (24.645)	U	0.639
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(9), 18.67 (4.583)	(85), 20.06 (4.764)	t	0.408
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(8),72 (6.969)	(85), 69.08 (14.830)	U	0.923

Table 8. Relationship between having been victim of violence (child abuse, mugged or assaulted – other than sexual) before the age of 17 and cognition in patients with FEP. Patients who had been victim of violence Vs. patients who had not.

	Patients (*n* = 17) who had been victim of violence	**Patients (*n* = 78) who had not been victim of violence**	**Statistical**	***P*** $_{value}$
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(17), 8.47 (2.809)	(77), 9.56 (2.376)	t	0.152
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(17), 7.65 (3.161)	(77), 7.60 (3.075)	t	0.954
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(17), 5.76 (2.725)	(77), 7.35 (2.823)	t	0.041*
TMT-A (sec), (*n*) mean (S.D.)	(17), 59.29 (31.664)	(77), 46.66 (17.071)	t	0.128
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(17), 2.47 (2.067)	(76), 3.49 (2.826)	U	0.107
ToL total move score, (*n*) mean (S.D.)	(17), 53.88 (21.074)	(76), 38.91 (16.761)	t	0.012*
TMT-B (sec), (*n*) mean (S.D.)	(17), 127.12 (58.129)	(71), 100.39 (43.335)	U	0.081*
Stroop color-word, (*n*) mean (S.D.)	(17), 30.71 (10.769)	(76), 34.79 (9.715)	t	0.164
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(17), 4.88 (1.576)	(77), 5.29 (1.645)	U	0.401
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(17), 7.65 (3.161)	(77), 7.60 (3.075)	t	0.954
Rey figure recall, (*n*) mean (S.D.)	(17), 15.8824 (5.75144)	(76), 17.0526 (6.74691)	t	0.470
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(17), 82.71 (46.450)	(77), 71.43 (18.091)	U	0.648
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(17), 20.65 (5.798)	(77), 19.77 (4.504)	t	0.563
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(17), 66.88 (16.874)	(76), 69.88 (13.758)	U	0.123

Table 9. Relationship between having been extremly ill or injured before the age of 17 and cognition in patients with FEP. Patients who had been extremly ill or injured Vs. patients who had not.

	Patients (*n* = 29) who had been extremly ill or injured	**Patients (*n* = 66) who had not been extremly ill or injured**	**Statistical**	***P*$_{value}$**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(29), 9.10 (2.870)	(65), 9.48 (2.299)	t	0.504
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(29), 7.79 (3.256)	(65), 7.52 (3.011)	t	0.706
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(29), 6.59 (3.018)	(65), 7.28 (2.781)	t	0.299
TMT-A (sec), (*n*) mean (S.D.)	(29), 51.59 (18.768)	(65), 47.77 (21.743)	t	0.390
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(29), 3.17 (2.139)	(64), 3.36 (2.962)	U	0.973
ToL total move score, (*n*) mean (S.D.)	(29), 43.90 (19.458)	(64), 40.63 (18.029)	t	0.446
TMT-B (sec), (*n*) mean (S.D.)	(28), 113.18 (58.081)	(60), 102 (41.548)	U	0.638
Stroop color-word, (*n*) mean (S.D.)	(29), 34.76 (10.270)	(64), 33.72 (9.913)	t	0.649
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(29), 5.55 (1.882)	(65), 5.06 (1.499)	U	0.243
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(29), 7.79 (3.256)	(65), 7.52 (3.011)	t	0.706
Rey figure recall, (*n*) mean (S.D.)	(29), 16.3103 (7.00180)	(64), 17.0781 (6.40016)	t	0.617
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(29), 70.72 (13.255)	(65), 74.69 (29.562)	U	0.902
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(29), 20.31 (4.489)	(65), 19.75 (4.873)	t	0.591
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(29), 67.93 (12.595)	(64), 69.97 (15.093)	U	0.044*

Table 10. Relationship between having experienced any other major upheaval that could shape their life or personality before the age of 17 and cognition in patients with FEP. Patients who had experienced any other major upheaval Vs. patients who had not experienced it

	Patients (*n* = 33) who experience any other major upheaval that could shape their life or personality significantly	**Patients (*n* = 62) who not experience any other major upheaval that could shape their life or personality significantly**	**Statistical**	**P**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(33), 9.88 (2.913)	(59), 9.15 (2.180)	t	0.217
Verbal learning/memory				
RAVL Trial 7, (*n*) mean (S.D.)	(33), 7.82 (2.755)	(59), 7.61 (3.232)	t	0.745
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(33), 6.70 (2.687)	(59), 7.34 (2.916)	t	0.290
TMT-A (sec), (*n*) mean (S.D.)	(33), 49.97 (13.282)	(59), 47.24 (23.376)	t	0.477
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(33), 3.12 (2.043)	(58), 3.48 (3.056)	U	0.790
ToL total move score, (*n*) mean (S.D.)	(33), 44.45 (19.807)	(58), 39.74 (17.716)	t	0.262
TMT-B (sec), (*n*) mean (S.D.)	(32), 125.03 (47.868)	(56), 94.43 (43.738)	U	0.001*
Stroop color-word, (*n*) mean (S.D.)	(33), 32.39 (9.608)	(58), 35.22 (10.208)	t	0.191
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(33), 4.81 (1.372)	(59), 5.51 (1.675)	U	0.043*
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(33), 7.82 (2.755)	(59), 7.61 (3.232)	t	0.745
Rey figure recall, (*n*) mean (S.D.)	(33), 16.8485 (6.69945)	(58), 17.1552 (6.41285)	t	0.83
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(33), 70.94 (15.584)	(59), 74.36 (30.128)	U	0.945
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(33), 20.82 (4.341)	(59), 19.56 (4.825)	t	0.204
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(33), 69.21 (11.997)	(58), 70.45 (14.682)	U	0.285

experienced 2 or more events before the age of 17, are more likely to present cognitive impairments. Therefore, it was hypothesized that the FEP patients who had been exposed to 2 or more events listed in CTES, would have stronger deficits on neurocognitive function across cognitive domains compared with those who had only experienced 0-1 event. Consequently, to examine the potential cumulative impact of early life adverse events, it has been created a simple index by summing the number of events reported (range 0–6). For the analyses, it has been combined those with two or more events (n=50 [52.63%]) into a single category. The other category was composed of those individuals who had experienced 0 or 1 event. Between group analyses, conducted using ANCOVA and covariying for gender, age and years of education, revealed significant group differences on Executive Function (P=0.027), suggesting that those who reported more than 1 adverse event in childhood scored worse on these tasks. Surprisingly, patients who had experienced the combined effect of early life adverse events, performed better the Social Cognition task (P=0.05) -Theory of mind- than those who had experienced the sum of these individual effects. In doing this, it has been found very strong evidence of a linear relationship between number of events and poorer cognitive functioning, a pattern suggestive of a cumulative impact (Figura 4). Means, standard deviations, percentages and significant values are displayed in Table 11.

Figure 4. Comparison of FEP patients and healthy volunteers on cognitive domains.

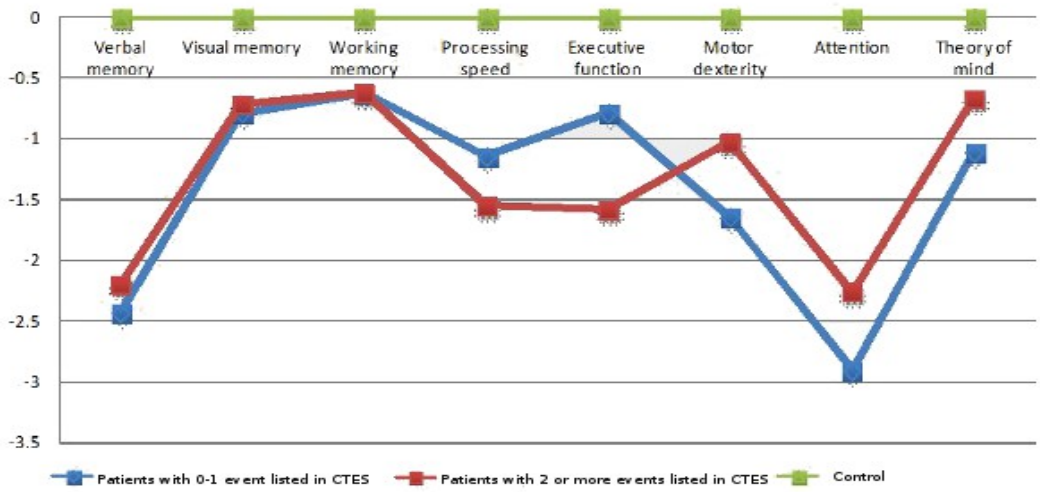


Table 11. Relationship between having experienced different events listed in CTES before the age of 17 and cognition in patients with FEP. Patients who had not experienced or had experienced one of the events listed in CTES Vs. patients who had experienced more than 1 event listed in CTES.

	Patients (*n*=44) who had experienced 0-1 events listed in CTES	**Patients (*n*=50) who had experienced more than 1 events listed in CTES**	**F**	***P*$_{value}$**
Cognitive domains				
Premorbid IQ				
WAIS-III vocabulary raw score, (*n*) mean (S.D.)	(43), 9.16 (2.29)	(45), 9.56 (2.61)	1.496	0.225
Verbal learning/memory				
RAVL Trial 5, (*n*) mean (S.D.)	(43), 10.21 (2.69)	(45), 10.27 (2.39)	0.004	0.953
Information processing speed				
WAIS-III digit symbol raw score, (*n*) mean (S.D.)	(43), 7.51 (2.96)	(45), 6.53 (2.63)	2.229	0.139
TMT-A (sec), (*n*) mean (S.D.)	(43), 50.49 (2.96)	(45), 48.24 (2.63)	0.078	0.781
Executive function				
ToL total correct score, (*n*) mean (S.D.)	(42), 3.43 (3.41)	(45), 3.27 (1.96)	0.014	0.905
ToL total move score, (*n*) mean (S.D.)	(42), 39.00 (17.04)	(45), 42.98 (18.96)	0.916	0.341
TMT-B (sec), (*n*) mean (S.D.)	(39), 96.49 (42.33)	(43), 111.79 (45.74)	5.049	0.027*
Stroop color-word, (*n*) mean (S.D.)	(42), 34.33 (10.08)	(45), 33.00 (9.98)	1.449	0.232
Working memory				
WAIS-III digits backward raw score, (*n*) mean (S.D.)	(43), 5.21 (1.60)	(45), 5.18 (1.68)	0.047	0.829
Delayed memory				
RAVL Trial 7, (*n*) mean (S.D.)	(43), 7.21 (3.43)	(45), 7.62 (2.66)	0.095	0.758
Rey figure recall, (*n*) mean (S.D.)	(42), 16.33 (6.44)	(45), 17.29 (6.84)	0.053	0.818
Motor dexterity				
Gooved pegboard dominant hand (sec), (*n*) mean (S.D.)	(43), 76.93 (34.48)	(45), 70.71 (14.99)	0.026	0.872
Theory of mind				
Eye task total correct, (*n*) mean (S.D.)	(43), 18.95 (5.15)	(45), 21.24 (4.07)	3.942	0.050*
Attention				
CPT discrimination subscore, (*n*) mean (S.D.)	(42), 67.86 (18.08)	(45), 70.20 (10.69)	0.156	0.694

Univariate analysis of variance with age, gender and education as covariates

*$p < 0.05$

5. Discussion

This study is a modest contribution to the ongoing discussions about the association between early life adverse events and cognitive impairments in FEP patients. In agreement with previous studies, patients with a history of early life adverse events in our sample, showed significant cognitive deficits compared to patients without it, in particular on Information Processing Speed and Executive Function. Equally, in line with the second hypothesis, it has been found that compared to non-exposed patients group, those exposed to a variety of early life adverse events before the age of 17, displayed poorer cognitive impairments, especially on Executive Functioning. Indeed, FEP patients who had experienced the combined effect of varying adverse events performed better the Social Cognition task, than those who had experienced the sum of these individual effects. Therefore, it can be suggested that obtained results add to a growing literature which supports the relationship between childhood trauma exposure and the development of cognitive dysfunction in psychotic patients.

A number of clinical implications arising from the present findings merit discussion. Several studies has examined the exposure to early life adverse events in psychotic patients (e.g., exposure to severe marital conflict, severe chronic illness, the death of a close relative, etc.) finding an association with poorer cognitive domains task performance (De Bellis et al., 2014; Aas et al., 2012; Aas et al., 2012; Shannon et al., 2011; Lysaker et al., 2001). Truthfully, its known that early life adverse events are related to diverse cognitive deficits observed in schizophrenia patients. Although the mechanisms behind this association is not fully understood, there are a number of important theoretical implications addressed to explain them. Firstly, it has been proposed that childhood trauma could lead to cognitive decline as results of developmental retardation due to lack of stimuli or malnutrition (Aas et al., 2011). Besides, certain forms of maltreatment as physical

abuse (when the head get involved) may cause direct injury to the brain. Other forms of maltreatment that do not cause frank neurological injury (e.g., sexual abuse or molestation, psychological violence) have also been associated with cognitive developmental deficits, giving to hypothesize that childhood adversity involves cognitive outcomes through stress pathways. Clearly, extreme stress has been associated with enduring changes in the secretion and processing of numerous neurotransmitters and hormones. These responses could be relates to different altered neural structure and functioning, especially if the adverse events occurs in early stages of development, when the brain is undergoing its most rapid phase of growth, organization and differentiation (Enlow et al., 2012). Another proposed hypothesis is the traumagenic neurodevelopmental model of schizophrenia (Read et al., 2001), which is heavily based on the similarities between the effects of early life adverse events on the developing brain, as well as the biological abnormalities found in people diagnosed with schizophrenia. Severe stress, like childhood trauma, affects both structure and function of brain areas important for cognition, such as hippocampus, prefrontal lobe and/or amygdala (Aas et al., 2012; McCrory et al., 2011). Amygdala reduction volume has also been linked to childhood adverse events. An alternative explanation mechanism for the relationship between amygdala volume, adverse events and cognitive impairment could be the amygdala vulnerability to early and severe stress. This vulnerability could lead to an atypical development of limbic circuitry, reflecting in structural and functional alterations of this area (Aas et al., 2012). Furthermore, the abnormal functioning of the hypothalamic-pituitary adrenal axis (HPA axis) response has been reported in patients with schizophrenia. Childhood trauma influences the main stress response system, over activating the hypothalamus–pituitary–adrenal (HPA) axis, which in turn may affect medial temporal volumes and cognitive function (De Bellis et al., 2014). That can be responsible for the worse performance on information processing speed found in patients with psychosis.

Noteworthy, it has been found differences between participants who had experienced one type of childhood maltreatment and those who had experienced two or more types on Executive functioning. Participants with two or more types of childhood adverse events were significantly more impaired on the executive function task than participants with zero or one type of childhood maltreatment. Every individual can experience an adverse event in his childhood without this influence their cognitive development. Instead, individuals who had experienced 2 or more events before the age of 17, are more likely to present cognitive impairments. These results, therefore, highlight that specific domains of cognitive functioning may be more sensitive to the number of times childhood adverse events occurs, as meaningful factors in the development of the mental disorders. In addition, it might be that some of the effects of childhood maltreatment are cumulative and become more evident in adulthood, and/or after illness onset. The chronicity of the disorder could be essential to reveal the effects of childhood trauma in patients with a schizophrenia spectrum diagnosis. The cumulative effect of the early trauma with the repeated adult stress, eventually makes the effect on cognition evident (Aas et al., 2011).

Unexpectedly, the opposite effect was found for Social cognition and Attention domains.This findings suggests that schizophrenia participants with history of childhood adverse events show significantly greater scores in Theory of Mind and Attention tasks, than those without maltreatment history. As previous literature has linked, severe forms of childhood adversity, affects the way children process social and emotional information (Germine et al., 2015). Domains of social cognition may be particularly vulnerable to the effects of adverse childhood environments, resulting in impaired empathy. Such impairments may differ depending on the level of maltreatment: moderate maltreatment was linked to emotional blunting and impaired cognitive empathy, whereas severe maltreatment was associated with emotional overarousal and diminished

cognitive insight (Mahy et al., 2014; Germine et al., 2015). This emotional overarousal may explain the disparity of the obtained results. Otherwise, a possible explanation for greater scores on Attention task may be the development of hypervigilance behaviours. It is worth noting the relationship between early life adverse events and Post Traumatic Syndrome Disorder (PTSD) symptoms (intrusive thoughts, avoidance, dissociation and hyperarousal) (De Bellis et al., 2014). In mistreated children with PTSD, has been observed a reduction in total brain volume, with a smaller corpus callosum, a higher volume of cerebrospinal fluid in the lateral ventricles and larger prefrontal cortical areas (De Bellis et al., 2014). Such structural and functional changes may explain the development of behaviors of hypervigilance and widespread defensiveness.

Indeed, in the current study it was not possible to disentangle the association between history of early life adverse events and deficits on tasks of working memory, learning or/and memory. Differences on mentioned tasks would have been expected due to recent theories suggesting that childhood adverse events may serve to exacerbate the appearance of cognitive deficits in schizophrenia patients. Of note, evidence for this theory comes from recent findings indicating more impaired neurocognitive functioning in people with schizophrenia with history of childhood traumatic events, specially related to working memory (Aas et al., 2011; Shannon et al., 2011; Lysakert et al., 2001). One possible explanation for the disparity between obtained findings and most of the previous studies, may be attributable to different characteristics of the samples or different assessment of trauma and cognitive functions. Additionally, the lack of significant findings on working memory, learning and/or memory tasks, may have been a result of insufficient sensitivity of the neuropsychological tests, as well as the insufficient power to detect differences between the two schizophrenia groups. Utilizing larger samples and a more comprehensive battery of neuropsychological tests is clearly an area for further research to focus on.

This study has several limitations which should be mentioned. Firstly, sample size is not very big, which might have led to false positive or negative results due to outliers. Therefore, replication of obtained findings in larger samples is necessary. Secondly, data on childhood adverse events were obtained retrospectively with the inherent weakness of retrospective reporting designs.This relates, not only to the natural process of forgetting, but also more specifically to the possibility that those with psychosis may have particular memory disfunction, or may exaggerate adverse early life events in an attempt to understand their illness. Furthermore, there may be another barriers, including concerns about offending or distressing, fear of vicarious traumatization and fear of inducing false memories. This accentuates the need for mandatory training for mental health professionals in the routine assessment of trauma. However, the use of validated psychometric instruments would increase the validity of self-reported data. Thirdly, although it has been decreased the number of multiple statistical comparisons by grouping, individual neuropsychological tests into domains, the chance for type 1 errors is still present. Additionally, the present study has also focused on a sample of patients with first-episode psychosis, thus reducing the effects of the disorder on recall compared with previous studies that have predominantly relied on samples of patients with chronic disorder. Lastly, it has not been consider the effect of adulthood trauma and life stress that might mediate the relationship between childhood adversity and cognitive dysfunction.

In summary, it has been demostrated a relationship between childhood early life adverse events and impaired cognitive function in FEP patients. However, further prospective researches are needed to dissect the direction of the effects, as well as to better examine the interaction between cognitive disfunctions and early life adversity in psychotic patients.

6. Conclusion

In conclusion, the present study supports previous data suggesting that childhood early life a adverse events are related to an impairment in general cognitive functioning. Obtained results suggest that childhood trauma has a different effect on cognitive function in first-episode psychosis, and in particular, in our sample, in those patients with history of a variety of events. Nonetheless, the results of this study pose many questions and many issues for the development of neuropsychological models of schizophrenia. The results highligth the implication of childhood adversity as a significant variable in neuropsychological research into this disorder. Therefore, future studies should clarify the psychological and biological mechanisms behind these subjects' sensitivity or vulnerability to the negative effect of childhood adverse events.

7. References

Aas, M., Dazzan, P., Fisher, H. L., Morgan, C., Morgan, K., Reichenberg, A., et al. (2011). Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. *Schizophrenia Research, 129*(1), 12-19.

Aas, M., Dazzan, P., Mondelli, V., Toulopoulou, T., Reichenberg, A., Di Forti, M., et al. (2011). Abnormal cortisol awakening response predicts worse cognitive function in patients with first-episode psychosis. *Psychological Medicine, 41*(3), 463-476.

Aas, M., Steen, N. E., Agartz, I., Aminoff, S. R., Lorentzen, S., Sundet, K., et al. (2012). Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning? *Psychiatry Research, 198*(3), 495-500.

Aas, M, Navari, S, Gibbs, A, Mondelli, V, Fisher, H. L., Morgan, C, et al. (2012). Is there a link between childhood trauma, cognition, and amygdala and hippocampus volume in first-episode psychosis? *Schizophrenia Research, 137*, 73-79.

Andreasen, N. C. (1983). Scale for the assessment of negative symptoms (SANS). University of Iowa, Iowa City.

Andreasen, N. C. (1984). Scale for the assessment of positive symptoms (SAPS). University of Iowa, Iowa City.

Baron-Cohen, B., Wheelwright, S., Hill, J., Raste, Y., Plumb, I. (2001). The "Reading the Mind in

the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *J Child Psychol Psychiatry, 42(2):241-51.*

Burton, C. Z., Harvey, P. D., Patterson, T. L., & Twamley, E. W. (2016). Neurocognitive insight and objective cognitive functioning in schizophrenia. *Schizophrenia Research, 171*(1-3), 131-136.

Brebion, G., Amador, X., Smith, M.J., Gorman, J.M. (1998). Memory impairment and schizophrenia: the role of processing speed. *Schizophr. Res. 30, 31-39.*

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J. (1982). Measurement of Premorbid Adjustment in Chronic Schizophrenia. *Schizophr Bull., 8(3):470–484.*

Conners, C. K. (1995). Conners´ Continuous Performance Test. *Multi-Health Systems, Inc. Canada.*

Crespo-Facorro, B., Perez-Iglesias, R., Ramirez-Bonilla, M., Martinez-Garcia, O., Llorca, J., Luis Vazquez-Barquero, J. (2006) A practical clinical trial comparing haloperidol, risperidone, and olanzapine for the acute treatment of first-episode nonaffective psychosis. *J Clin Psychiatry, 67(10):1511–21.*

De Bellis, M. D., & Zisk, A. (2014). The biological effects of childhood trauma. *Child and Adolescent Psychiatric Clinics of North America, 23(2), 185-222, vii.*

Enlow, M. B., Egeland, B., Blood, E. A., Wright, R. O., & Wright, R. J. (2012). Interpersonal trauma exposure and cognitive development in children to age 8 years: A longitudinal study. *Journal of Epidemiology and Community Health, 66(11), 1005-1010.*

Fardig, R., Fredriksson, A., Lewander, T., Melin, L., & Mueser, K. T. (2016). Neurocognitive functioning and outcome of the illness management and recovery program for clients with schizophrenia and schizoaffective disorder. *Nordic Journal of Psychiatry, 70*(6), 430-435.

Germine, L., Dunn, E. C., McLaughlin, K. A., & Smoller, J. W. (2015). Childhood adversity is associated with adult theory of mind and social affiliation, but not face processing. *PloS One, 10(6), e0129612.*

Golden, C. J. (1975). A group form of the Stroop color and word test. *Journal of Personality Assessment, 39, 386-388.*

Kilcommons, A. M., & Morrison, A. P. (2005). Relationships between trauma and psychosis: An exploration of cognitive and dissociative factors. *Acta Psychiatrica Scandinavica, 112(5), 351-359.*

Lezak, M. (1995). Neuropsychological assessment (3rd ed.). *Oxford: Oxford University Press*.

Lysaker, P. H., Meyer, P., Evans, J. D., & Marks, K. A. (2001). Neurocognitive and symptom correlates of self-reported childhood sexual abuse in schizophrenia spectrum disorders. *Annals of Clinical Psychiatry : Official Journal of the American Academy of Clinical*

Psychiatrists, 13(2), 89-92.

Mahy, C. E., Vetter, N., Kuhn-Popp, N., Locher, C., Krautschuk, S., & Kliegel, M. (2014). The influence of inhibitory processes on affective theory of mind in young and old adults. *Neuropsychology, Development, and Cognition.Section B, Aging, Neuropsychology and Cognition, 21(2), 129-145.*

Misiak, B., Moustafa, A. A., Kiejna, A., & Frydecka, D. (2016). Childhood traumatic events and types of auditory verbal hallucinations in first-episode schizophrenia patients. *Comprehensive Psychiatry, 66*, 17-22.

McCrory, E., De Brito, S. A., & Viding, E. (2011). The impact of childhood maltreatment: A review of neurobiological and genetic factors. *Frontiers in Psychiatry, 2, 48.*

Osterrieth, P. A. (1944). Le test de copie d'une figure complex: Contribution à l'étude de la perception et de la memoir. *Archives de Psychologie, 30, 286–356.*

Pelayo-Teran, J.M., Perez-Iglesias, R., Ramirez-Bonilla, M., Gonzalez-Blanch, C., Martinez-Garcia, O., Pardo-Garcia, G., et al. (2008). Epidemiolo- gical factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the clinical programme on early phases of psychosis. *Early Interv. Psychiatry, 2, 178–187.*

Pennebaker, J. W., & Susman, J. R. (1988). Disclosure of traumas and psychosomatic processes. *Social Science & Medicine (1982), 26*(3), 327-332.

Read, J., Agar, K., Barker-Collo, S., et al (2001). Assessing suicidality in adults: integrating childhood trauma as a major risk factor. *Professional Psychology: Research and Practice, 32, 367 -372.*

Rey, A. (1941). L'examen psychologique dans les cas d'encephalopathie traumatique. *Archives de Psychologie, 28, 21.*

Rey, A. (1964). L'examen clinique en psychologie. *Paris: Presses Universitaires de France.*

Salthouse, T. A. (1992). Mechanisms of age–cognition relations in adulthood. *Hillsdale, N.J.: Erlbaum.*

Sideli, L., Fisher, H. L., Russo, M., Murray, R. M., Stilo, S. A., Wiffen, B. D., et al. (2014). Failure to find association between childhood abuse and cognition in first-episode psychosis patients. *European Psychiatry : The Journal of the Association of European Psychiatrists, 29*(1), 32-35.

Schalinski, I., & Teicher, M. H. (2015). Type and timing of childhood maltreatment and severity of shutdown dissociation in patients with schizophrenia spectrum disorder. *PloS One, 10*(5), e0127151.

Schenkel, L. S., Spaulding, W. D., DiLillo, D., & Silverstein, S. M. (2005). Histories of childhood maltreatment in schizophrenia: Relationships with premorbid functioning, symptomatology, and cognitive deficits. *Schizophrenia Research, 76*(2-3), 273-286.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London B, 298, 199-209.*

Shannon, C., Douse, K., McCusker, C., Feeney, L., Barrett, S., & Mulholland, C. (2011). The association between childhood trauma and memory functioning in schizophrenia. *Schizophrenia Bulletin, 37(3), 531-537.*

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *Am J Psychiatr, 170(10)*:1114-33.

Van Dam, N. T., Rando, K., Potenza, M. N., Tuit, K., & Sinha, R. (2014). Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry, 71*(8), 917-925.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence. *The Psychological Corporation: Harcourt Brace & Company. New York, NY.*