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

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**ABSTRACT**
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.

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.

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+.

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.

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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 (Morgan and Gaye-Anderson, 2016; Rössler et al., 2016; Varese et al., 2012), 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 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; Sidel 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 (Öök 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 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 cognitive 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 <10 years ago; (iv) were proficient in Dutch. Patients were excluded if their estimated level of intelligence was <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: 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 CT-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 exited 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:

- \(0 = \) no CT − no MP (CT−/MP−; \(n = 272\))
- \(1 = \) no CT − MP (CT−/MP+; \(n = 157\))
- \(2 = \) CT − no MP (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) (Nuechterlein and Dawson, 1984; Wohlberg and Kornetsky, 1973). 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) (Anders 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 (Aas et al., 2013; Pechtel and Pizzagalli, 2011) 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
Table 1
Baseline, 3-year follow-up, 6-year follow-up: descriptive analyses.

<table>
<thead>
<tr>
<th>Gender (male), n (%)</th>
<th>Baseline (n = 532)</th>
<th>3-year follow-up (n = 356)</th>
<th>6-year follow-up (n = 349)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>402 (76)</td>
<td>263 (74)</td>
<td>258 (74)</td>
</tr>
<tr>
<td>Age, mean (SD); range</td>
<td>27.61 (7.61); 15–56</td>
<td>31.13 (7.76); 18–56</td>
<td>34.46 (7.58); 21–63</td>
</tr>
<tr>
<td>Educational level, mean (SD); range</td>
<td>4.14 (0.78); 2–5</td>
<td>4.28 (0.72); 3–5</td>
<td>4.33 (0.72); 2–5</td>
</tr>
<tr>
<td>Childhood trauma, mean (SD); range</td>
<td>1.62 (0.51); 1–3.84</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Positive symptoms, mean (SD); range</td>
<td>1.81 (0.79); 1–5.28</td>
<td>1.52 (0.63); 1–4</td>
<td>1.67 (0.74); 1–4</td>
</tr>
<tr>
<td>Negative symptoms, mean (SD); range</td>
<td>1.89 (0.87); 1–5.42</td>
<td>1.61 (0.71); 1–5.57</td>
<td>1.66 (0.73); 1–4</td>
</tr>
<tr>
<td>General symptoms, mean (SD); range</td>
<td>1.69 (0.53); 1–3.68</td>
<td>1.47 (0.43); 1–3.5</td>
<td>1.48 (0.45); 1–3.31</td>
</tr>
<tr>
<td>Mania symptoms, mean (SD); range</td>
<td>0.08 (0.45); 0–4</td>
<td>0.06 (0.39); 0–4</td>
<td>0.11 (0.55); 0–5</td>
</tr>
<tr>
<td>Depressive symptoms, mean (SD); range</td>
<td>2.39 (1.48); 1–7</td>
<td>1.86 (1.16); 1–7</td>
<td>1.77 (1.12); 1–6</td>
</tr>
<tr>
<td>Anxiety symptoms, mean (SD); range</td>
<td>2.36 (1.29); 1–6</td>
<td>1.99 (1.13); 1–6</td>
<td>1.99 (1.12); 1–6</td>
</tr>
<tr>
<td>WLT immediate recall, mean (SD); range</td>
<td>23.22 (2.64); 7–40</td>
<td>25.32 (5.99); 9–40</td>
<td>24.68 (7.02); 5–43</td>
</tr>
<tr>
<td>WLT retention rate, mean (SD); range</td>
<td>0.77 (0.20); 0.09–1</td>
<td>0.78 (0.18); 0–1.2</td>
<td>0.78 (0.20); 0.22–2</td>
</tr>
<tr>
<td>WLT delayed recall, mean (SD); range</td>
<td>7.63 (2.85); 1–15</td>
<td>8.39 (2.88); 0–15</td>
<td>8.20 (3.07); 2–15</td>
</tr>
<tr>
<td>CPT-HQ reaction time, mean (SD); range</td>
<td>425.81 (83.55); 253.53–872.52</td>
<td>456.11 (85.19); 292.21–847.76</td>
<td>449.51 (78.31); 288.25–720.84</td>
</tr>
<tr>
<td>CPT-HQ accuracy, mean (SD); range</td>
<td>98.63 (3.71); 60–100</td>
<td>98.93 (3.15); 64.66–100</td>
<td>99.07 (2.79); 66–100</td>
</tr>
<tr>
<td>RST reaction time cost, mean (SD); range</td>
<td>227.11 (241.96); –744.6–1384.33</td>
<td>221.71 (231.34); –760.28–899.13</td>
<td>–</td>
</tr>
<tr>
<td>RST accuracy cost, mean (SD); range</td>
<td>0.18 (0.25; 0–0.44)</td>
<td>0.17 (0.24; 0–0.24)</td>
<td>–</td>
</tr>
<tr>
<td>IQ-WAIS, mean (SD); range</td>
<td>96.62 (16.28); 60–146</td>
<td>100.20 (16.27; 68–144</td>
<td>100.69 (17.25); 57–152</td>
</tr>
<tr>
<td>GAF symptoms, mean (SD); range</td>
<td>55.89 (16.61); 10–100</td>
<td>58.43 (16.79); 15–100</td>
<td>55.49 (16.46); 21–100</td>
</tr>
<tr>
<td>GAF functioning, mean (SD); range</td>
<td>55.60 (16.43); 1–100</td>
<td>60.55 (16.38); 25–100</td>
<td>58.12 (16.14); 21–100</td>
</tr>
<tr>
<td>Cannabis use, mean (SD); range</td>
<td>1.64 (1.34; 0–3</td>
<td>0.67 (1.31); 0–3</td>
<td>0.59 (1.08); 0–3</td>
</tr>
<tr>
<td>Antipsychotic use, n (%)</td>
<td>385 (72)</td>
<td>219 (61)</td>
<td>243 (70)</td>
</tr>
<tr>
<td>Medication use, n (%)</td>
<td>145 (27)</td>
<td>87 (24)</td>
<td>89 (25)</td>
</tr>
</tbody>
</table>

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 Psychopathology 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 (CAS). With one item (have you felt overly or abnormally excited or active) on a range 0–5 (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 (de-}
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.

### 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.

### 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).

<table>
<thead>
<tr>
<th>Group comparison B coefficients indicate</th>
<th>CT−/MP+ (n = 157) vs. CT−/MP− (n = 272)</th>
<th>CT+/MP− (n = 49) vs. CT−/MP− (n = 272)</th>
<th>CT+/MP+ (n = 54) vs. CT−/MP− (n = 272)</th>
<th>CT+/MP+ (n = 54) vs. CT−/MP+ (n = 49)</th>
<th>CT+/MP+ (n = 54) vs. CT−/MP+ (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal learning and memory</td>
<td>WLT immediate recall</td>
<td>0.63 (−0.12–1.38) (0.10)</td>
<td>−0.13 (−1.39–1.13) (0.84)</td>
<td>−1.12 (−2.47–0.24) (0.11)</td>
<td>−0.98 (−2.51–0.53) (0.20)</td>
</tr>
<tr>
<td></td>
<td>WLT retention rate</td>
<td>0.02 (−0.01–0.04) (0.16)</td>
<td>−0.02 (−0.06–0.02) (0.39)</td>
<td>−0.04 (−0.09–0.001) (0.05)</td>
<td>−0.02 (−0.08–0.02) (0.34)</td>
</tr>
<tr>
<td></td>
<td>WLT delayed recall</td>
<td>0.44 (0.09–0.80) (0.01)</td>
<td>−0.02 (−0.62–0.57) (0.92)</td>
<td>−0.71 (−1.35 to −0.07) (0.03)</td>
<td>−0.68 (−1.39–0.02) (0.06)</td>
</tr>
<tr>
<td>Attention and vigilance</td>
<td>CPT-HQ reaction time</td>
<td>−7.20 (−18.35–3.94) (0.20)</td>
<td>0.05 (−19.66–19.78) (0.99)</td>
<td>−3.67 (−24.61–17.26) (0.73)</td>
<td>−3.73 (−27.42–19.95) (0.76)</td>
</tr>
<tr>
<td></td>
<td>CPT-HQ accuracy</td>
<td>−0.22 (−0.99–0.55) (0.57)</td>
<td>−0.53 (−1.92–0.85) (0.45)</td>
<td>−0.03 (−1.07–1.01) (0.95)</td>
<td>0.50 (−1.15–2.16) (0.55)</td>
</tr>
<tr>
<td>Reasoning and problem solving/working memory</td>
<td>RST reaction time cost</td>
<td>−1.36 (−41.52–44.64) (0.94)</td>
<td>−5.21 (−67.80–57.37) (0.87)</td>
<td>−10.09 (−75.94–55.74) (0.76)</td>
<td>−8.88 (−87.78–78.01) (0.91)</td>
</tr>
<tr>
<td></td>
<td>RST accuracy cost</td>
<td>0.003 (−0.04–0.04) (0.90)</td>
<td>−0.03 (−0.09–0.04) (0.43)</td>
<td>0.07 (0.006–0.14) (0.03)</td>
<td>0.09 (0.01–0.18) (0.02)</td>
</tr>
</tbody>
</table>

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.
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 (Killore 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, although 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; Killore et al., 2009; Nieuwenstein et al., 2001), and between cognition and comorbid symptoms in PD on the other hand (Duke et al., 2010; Fan et al., 2008; Goodman et al., 2007; Hermesh et al., 2003; Kerss and Berenbaum, 2002; Potvin et al., 2012; Rapp et al., 2012; Ralevski et al., 2012; Yuel 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 (de Gracia Dominguez et al., 2009; Myin-Germeys and van Os, 2007). 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 (Kerss and Berenbaum, 2002; Potvin et al., 2012; Rapp et al., 2012; Wong and Miller, 2015), while others showed worse cognitive functioning (Fan et al., 2008; Goodman et al., 2007; Yuel et al., 2012), and some did not find any difference (Duke et al., 2010; Ralevski et al., 2012; Hermesh et al., 2003). 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 assessed. 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 (Burgess, 2000; Burgess et al., 2006; Chaytor and Schmitter-Edgecombe, 2003; Damasio, 1995; Lamberts et al., 2010; Larri 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 (Fish et al., 2011).

In conclusion, although cognition and CT have been related to psychosis (Aas et al., 2013; de Gracia Dominguez et al., 2009; Varese et al., 2012), 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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Contributors
Giovanni Mansueto: wrote the first draft of the manuscript, managed the literature searches and analyses; Martine van Nierop: drafted and revised both analyses and manuscript; both Ruud van Winkel and Koen Schruers: revised the manuscript; GROUP Investigators: designed the study, wrote the protocol, and revised the manuscript.

Conflict of interest
None.

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References