RESEARCH ARTICLE

Psychotic Experiences and Working Memory: A Population-Based Study Using Signal-Detection Analysis

Rodolfo Rossi1,2*, Stanley Zammit3,4, Katherine S. Button5, Marcus R. Munafò6,7, Glyn Lewis8, Anthony S. David2

1 Section of Psychiatry, University School of Medicine Federico II, Naples, Italy, 2 Section of Cognitive Neuropsychiatry, Institute of Psychiatry, Psychology and Neuroscience, King’s College, London, United Kingdom, 3 School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom, 4 Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, United Kingdom, 5 Department of Psychology, University of Bath, Bath, United Kingdom, 6 UK Centre for Tobacco and Alcohol Studies, School of Experimental Psychology, University of Bristol, Bristol, United Kingdom, 7 MRC Integrative Epidemiology Unit (IEU) at the University of Bristol, Bristol, United Kingdom, 8 Division of Psychiatry, University College London, London, United Kingdom

* rudy86.rossi@gmail.com

Abstract

Psychotic Experiences (PEs) during adolescence index increased risk for psychotic disorders and schizophrenia in adult life. Working memory (WM) deficits are a core feature of these disorders. Our objective was to examine the relationship between PEs and WM in a general population sample of young people in a case control study. 4744 individuals of age 17–18 from Bristol and surrounding areas (UK) were analyzed in a cross-sectional study nested within the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study. The dependent variable was PEs, assessed using the semi-structured Psychosis-Like Symptom Interview (PLIKSi). The independent variable was performance on a computerized numerical n-back working memory task. Signal-Detection Theory indices, including standardized hits rate, false alarms rate, discriminability index ($d'$) and response bias ($c$) from 2-Back and 3-Back tasks were calculated. 3576 and 3527 individuals had complete data for 2-Back and 3-Back respectively. Suspected/definite PEs prevalence was 7.9% (N = 374). Strongest evidence of association was seen between PEs and false alarms on the 2-Back, (odds ratio (OR) = 1.17 [95% confidence intervals (CI) 1.01, 1.35]) and 3-back (OR = 1.35 [1.18, 1.54]) and with c (OR = 1.59 [1.09, 2.34]), and lower $d'$ (OR = 0.76 [0.65, 0.89]), on the 3-Back. Adjustment for several potential confounders, including general IQ, drug exposure and different psycho-social factors, and subsequent multiple imputation of missing data did not materially alter the results. WM is impaired in young people with PEs in the general population. False alarms, rather than poor accuracy, are more closely related to PEs. Such impairment is consistent with different neuropsychological models of psychosis focusing on signal-to-noise discrimination, probabilistic reasoning and impaired reality monitoring as a basis of psychotic symptoms.
Introduction

Background

Psychotic Experiences (PEs) such as delusions and hallucinations are relatively common and not necessarily associated with a clinical condition in the general population. PEs estimated lifetime prevalence is about 2 to 3 times [1, 2] that of psychotic disorder (approximately 2.9% [3]). Estimates according to method of assessment, from 5% when assessed using semi-structured interview[4, 5] to 60% when using self-report measures[6]. PEs reach a prevalence peak during early adolescence subsiding to a plateau in early adulthood[1, 7–9], although the exact rate of persistence of PE is not known. PEs index increased risk for full-blown psychotic disorder and schizophrenia[10] although estimates of rate of conversion suggest that most individuals with PEs do not convert to a psychotic disorder[1]. PEs share some of the same underlying risk factors as psychotic disorders, including drug abuse, environmental stressors, neurodevelopmental factors and family history of psychiatric conditions[11, 12].

One well established association with psychotic disorders, including schizophrenia, is cognitive impairment, in particular of working memory. Working memory (WM) is a core cognitive function commonly found to be impaired across the schizophrenia spectrum and it represents a candidate endophenotype for schizophrenia [13–15]. In fact, WM deficits have been confirmed both before and after the first episode of the disorder[16–18]. Individuals with schizophrenia seem to follow specific deterioration trajectories in WM throughout their lives[17, 19, 20]. Furthermore, minor WM impairment is evident in first-degree relatives of people with schizophrenia and other individuals at familial-risk[21–23], suggesting a genetic contribution [24, 25]. Reduced WM capacity has also been found in those help-seeking individuals deemed to be at Ultra-High Risk (UHR)[26] or to have an At-Risk Mental State (ARMs) for psychosis, especially in those who convert to psychotic disorder[27–30]. Finally, a large body of work reports on the association of WM deficits with schizotypy with mixed results, possibly due to the heterogeneity of the instruments used [31].

The putative neuropsychological mechanisms by which WM deficits contribute to psychosis are debated. WM has been related to specific reasoning and neurocognitive anomalies, including source-monitoring or source-memory disturbances[32–34] and reasoning biases like jumping-to-conclusions (JTC)[35–37]. As a whole, psychotic phenomena are associated with a high rate of false memories and/or a failure to reject them[38, 39] culminating in impaired reality monitoring [40].

A few studies have addressed the relationship between WM and PEs in the general population. For example, Korponay and colleagues[41] in the US found unexpectedly higher WM scores, assessed using the MATRICS Consensus Cognitive Battery (MCCB) in adult individuals experiencing positive sub-clinical psychotic symptoms defined using the Community Assessment of Psychic Experiences (CAPE) self-report questionnaire. However, concerns may be raised about the high mean age of this sample and its suitability to address the relationship between neurocognitive functioning and PE as a risk factor for psychosis, since such individuals may be resistant to transition to a psychotic disorder. An association between WM and PEs, again assessed using the CAPE, was also found in a large population study in Germany[42]. In this study WM was assessed using two tasks that do not permit signal detection analysis. A statistically robust correlation between WM capacity and PEs was detected, although its effect size was deemed small. Both studies addressed PEs using a self-report instrument, which may have overestimated the prevalence of PEs. In Ireland, a small interview-based study of PEs found no significant differences in WM capacity between adolescent cases and controls measured using the digit span task[43]. The same group also reported separately [44] a significant correlation...
between individuals with PEs and spatial WM. In the same cohort, a subsample of individuals with a prodromal syndrome showed a similar deficit in spatial WM tasks [45].

Objectives

Here we examine WM functioning using a version of the N-back task on the largest sample to date of around 4000 adolescents[5, 25, 46] within a signal-detection theory (SDT) framework. These participants came from a population-based birth cohort and were assessed using a psychologist administered semi-structured interview for PEs[5]. SDT describes the probabilistic processes of decision-making under conditions of uncertainty [47], and it is particularly useful for our purposes as it allows us to characterize features of WM functioning beyond simple WM capacity. Indeed, early uses of SDT revealed that hallucinatory proneness as well as hallucinatory experiences, are highly correlated with false recognitions, detected as ‘false alarms’ and a liberal response bias in an on-line SDT task (see below)[48].

We sought to test the overall hypothesis that there is continuity between PEs and psychotic disorders; hence WM anomalies should show an association with PEs despite the absence of clinical disorder. Our sample allowed us to test this association without the confounding effect of treatment, illness or help-seeking behaviour. We reasoned that if confirmed, this would enable us to better characterize which specific components in a WM task are related to the PEs-psychosis continuum.

Material and Methods

Sample

We examined data collected from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort[49]. ALSPAC is a population pre-birth cohort study of all the pregnancies in the Avon county, UK, with deliveries between 1 April 1991 and 31 December 1992[49, 50]. In total, 14,893 mothers enrolled, representing an estimated 85–90% of the eligible population. We selected cases from the “Focus on Teen 4” time-point, scheduled at age 17 (N = 5216) (for further details on data collected, see http://www.bristol.ac.uk/alspac/researchers/resources-available/). Of these, those who had completed either the interview for PEs or the N-Back task (see later) were selected. Participants provided written consent for data collection and analysis. Ethical approval was obtained from the ALSPAC Law and Ethics Committee and the local research ethics committees (http://www.bristol.ac.uk/alspac/researchers/data-access/ethics/). The research adheres to the tenets of the Declaration of Helsinki.

Measures

Psychotic Experiences. The presence of PEs was assessed using the semi-structured Psychosis-Like Symptom Interview (PLIKSi)[8]. The PLIKSi comprises an introductory set of questions to accustom the participant to probes for unusual experiences, followed by 11 “core” questions, based on, and rated according to guidelines for the WHO Schedules for Clinical Assessment in Neuropsychiatry version 2.0 (SCAN 2.0[51]).

PEs included hallucinations (visual and auditory), delusions (spied on, persecution, thoughts read, reference, control and grandiosity) and experiences of thought interference (broadcasting, insertion and withdrawal). Each PE was rated by the interviewer as “Absent”, “Suspected” or “Definitely Present”. Unclear or ambiguous responses were rated down. The PE was rated as “Definitely Present” only if a clear example was provided. In this study individuals were classed as having a PE if rated as having any “Suspected” or “Definite” PE, which was not attributed to sleep or fever. PLIKSi at age 12 showed good psychometric properties [5, 8].
**Working Memory.** WM was assessed using an N-Back task (for details see[25]). 3986 individuals had available N-Back data. Of these, 391 participants for the 2-Back and 341 for the 3-Back were excluded due to non-responsiveness to the task. Subjects were presented with a series of 0–9 numbers on a computer screen, each presented for 500ms with an inter-stimulus interval of 3000ms. Subjects were instructed to press button “1” if the number was the same as the number of N numbers before, “2” if it was different. Instructions provided to participants were neutral with respect to speed or accuracy. Two different blocks (2-Back and 3-Back) were administered, each of 48 trials. Four different parameters were automatically generated by the computer:

a. target identification accuracy (Hits), being the percentage of trials correctly identified as targets, b. non-target identification accuracy, being the percentage of trials correctly identified as non-targets, c. target identification median reaction time (Hits RT), d. non-target identification median reaction time (nonT RT).

**Signal Detection Theory (SDT)**
In a SDT-based task, subjects are required to detect the presence (or absence) of a target stimulus under conditions of relative uncertainty [47, 52]. According to SDT, on a given trial in which a target stimulus or noise can be alternatively presented, subjects respond according to the value that an inner unobserved decision variable achieves during each trial. If the decision variable exceeds a certain threshold, which is called criterion, the subject detects the target (i.e. responds "yes"); otherwise, the subject does not detect the target (i.e. responds "no")[53].

Among the various performance indices derivable from SDT, we chose to analyse hits and false alarms (FA) separately, the discriminability index $d'$ as a global measure of performance, and response bias $c$, defined as the amount of certainty needed to make a decision on the response[54], or, given the same amount of uncertainty, the bias towards detecting (or rejecting) a stimulus as a target (a low value of $c$ means that less information is needed to detect the target).

Response bias $c$ can be conceptualized as an index of a liberal ($c<0$) vs cautious ($c>0$) or neutral ($c = 0$) decision-making strategy[55].

**SDT measures.** From the four raw scores, False Alarms (FA) were calculated as:

$$FA = 1 - \left( \text{non target identification accuracy} \right)$$

Standardized scores for Hits ($z$-Hits), FA ($z$-FA), Hits RT ($z$-Hits RT) and nonT RT ($z$-nonT RT) were calculated and included in the analysis.

Discriminability index $d'$ was calculated using the Stata syntax (adapted from[53]):

$$d' = \text{invnorm} (H) - \text{invnorm} (FA)$$

Response bias $c$ was calculated using the Stata syntax (adapted from[53]):

$$c = - \left( \text{invnorm} (Hits) \right) + \left( \text{invnorm} (FA) \right) / 2$$

**Confounders**
A number of potential socio-demographic confounders were selected a priori from the whole database, according to previously published papers from the same cohort. These were: ICD-10 diagnosis of depression, assessed using a computerized version of the Clinical Interview Schedule (CIS-R)[56, 57], bullying profile (bully/victim/bully and victim), standardized Total IQ measured at age 8 using an abbreviated form of the Wechsler Intelligence Scale for Children—III (WISC)(UK version)[58], Family Adversity Index (FAI) [59], cannabis abuse, assessed
using the Cannabis Abuse Screening Test (CAST) [60, 61] referring to the last 6 months before
the interview (coded as positive if CAST score was \( \geq 1 \), absent if subject had never tried canna-
bis before or if CAST score = 0), use of any hard drug during previous 3 months; Alcohol Use
Disorder Identification Test (AUDIT) scores; and gender.

Statistical Analysis
All statistical analyses were conducted using Stata v. 13 (StataCorp, College Station, Texas).
Frequencies for categorical variables, means and 95% Confidence Intervals (95% CIs) for con-
tinuous variable were calculated. A Wilcoxon signed-rank test for repeated measures was used
to compare the performance on the 2-Back vs. 3-Back. In a first wave of analyses, univariable
logistic regression was used to calculate unadjusted Odds Ratios (OR) and 95% CIs for PE out-
comes in relation to the different N-Back parameters.

In a second wave of analyses, a two-block nested multiple logistic regression was carried out
in order to separate the effect of confounding from missing data. In the first block, unadjusted
ORs were calculated for individual N-Back parameters on a sample restricted to those having
complete data for the confounders. In the second block, the aforementioned confounders were
introduced in the model on the same sample.

Missing data patterns were examined. Missing data were imputed using Multiple Imputation
by Chained Equation (MICE) methods using the –ice- command in Stata[62]. Imputation
was performed on the subsample initially selected for analysis (N = 4744).

Results
Sample
A total of N = 4744 (90.95%) individuals was selected for analysis, having attended the session
and having complete data for at least one of PLIKSi or N-Back. Of these, 56.5% [55.1, 57.9]
were female and 95.7% [95.1, 96.3] were of white ethnicity. The mean age of the sample was
17.78 years [17.77, 17.79], mean IQ was 107.3 [106.8, 107.8]. Details of other variables in the
sample are reported in Table 1.

PLIKSi
A total of 4718 cases had complete PLIKSi data. Of these, 7.9% [7.19, 8.73] (N = 374) had
reported at least one suspected or definite PE. Symptom-positive participants were 64.2%
[59.3, 69.0] female; 93.5% [90.8, 96.2] were of white ethnicity. Their mean IQ was 104.2 [102.4,
106.0], slightly lower than symptom-free individuals (107.6 [107.0, 108.1]). Detailed prevalence
for each of the single PLIKSi item is reported in the Table 2.

Working Memory
2-Back and 3-Back scores were available for 3595 and 3551 individuals, respectively. All perfor-
mance parameters differed between 2-back and 3-back procedures, with individuals having
lower Hits, and \( c \), and higher FA on the 3-back task. A detailed description of the individual
N-Back parameters is reported in Table 3.

Univariable Logistic Regression
In the crude model, of the 2-Back parameters investigated, higher z-FA rate was associated
with PEs (OR = 1.17 [1.01,1.35]). On the 3-Back task, higher z-FA rate (OR = 1.35 [1.18,1.54])
and \( c \) (OR = 1.59 [1.09,2.34]), and lower \( d' \) (OR = 0.76 [0.65,0.89]) were significantly associated
with PEs (Table 4).
In the nested logistic regression, the sample size dropped from N = 3576 to N = 1970 and from N = 3527 to N = 1947 for the 2-Back and 3-Back respectively, due to missing data. In the first unadjusted block, only the 3-Back z-FA and $d'$ showed an association with PEs, respectively: OR = 1.26 [1.03, 1.54] and 0.8 [0.64, 1.00]. No significant association between N-Back performance or response bias on the two N-Back tasks and PEs was found in the adjusted model (Table 4).

Table 1. Participant Characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Overall (Mean [95%CI] or Count (%))</th>
<th>Non-PEs (Mean [95%CI] or Count (%))</th>
<th>PEs (Mean [95%CI] or Count (%))</th>
<th>Effect Size (Cohen’s d or Cramer’s V)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Female)</strong></td>
<td>2681 (56.5%)</td>
<td>2425 (55.8%)</td>
<td>240 (64.2%)</td>
<td>-0.04</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>17.77 [17.76, 17.78]</td>
<td>17.77 [17.76, 17.78]</td>
<td>17.81 [17.77, 17.85]</td>
<td>-0.11</td>
</tr>
<tr>
<td><strong>Total IQ</strong></td>
<td>107.3 [106.80, 107.81]</td>
<td>107.54 [107.01, 108.07]</td>
<td>104.17 [102.30, 106.04]</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 2. Details of PLIKSi Items and their prevalence (count and proportion) in our sample.

<table>
<thead>
<tr>
<th>PLIKS Item</th>
<th>None</th>
<th>Suspect</th>
<th>Definite</th>
<th>Any (Suspect + Definitive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Auditory Hallucinations</td>
<td>4465 (94.66)</td>
<td>107 (2.27)</td>
<td>145 (3.07)</td>
<td>252 (5.34)</td>
</tr>
<tr>
<td>2. Visual Hallucinations</td>
<td>4516 (95.74)</td>
<td>88 (1.87)</td>
<td>112 (2.37)</td>
<td>200 (4.24)</td>
</tr>
<tr>
<td>3. Visual Illusions</td>
<td>4654 (98.66)</td>
<td>34 (0.72)</td>
<td>29 (0.61)</td>
<td>63 (1.33)</td>
</tr>
<tr>
<td>4. Delusions Of Being Spied On</td>
<td>4635 (98.24)</td>
<td>55 (1.17)</td>
<td>26 (0.55)</td>
<td>81 (1.72)</td>
</tr>
<tr>
<td>5. Delusions Of Persecution</td>
<td>4679 (99.17)</td>
<td>22 (0.47)</td>
<td>12 (0.25)</td>
<td>34 (0.72)</td>
</tr>
<tr>
<td>6. Delusions Of Thoughts Being Read</td>
<td>4700 (99.62)</td>
<td>12 (0.25)</td>
<td>6 (0.13)</td>
<td>18 (0.38)</td>
</tr>
<tr>
<td>7. Delusions Of Reference</td>
<td>4685 (99.32)</td>
<td>23 (0.49)</td>
<td>8 (0.17)</td>
<td>31 (0.66)</td>
</tr>
<tr>
<td>8. Delusions Of Control</td>
<td>4708 (99.79)</td>
<td>6 (0.13)</td>
<td>4 (0.08)</td>
<td>10 (0.21)</td>
</tr>
<tr>
<td>9. Delusions Of Grandiose Ability</td>
<td>4696 (99.53)</td>
<td>13 (0.28)</td>
<td>5 (0.11)</td>
<td>18 (0.39)</td>
</tr>
<tr>
<td>10. Thought Broadcasting</td>
<td>4677 (99.24)</td>
<td>28 (0.59)</td>
<td>8 (0.17)</td>
<td>36 (0.76)</td>
</tr>
<tr>
<td>11. Thought Insertion</td>
<td>4685 (99.41)</td>
<td>15 (0.32)</td>
<td>13 (0.28)</td>
<td>28 (0.6)</td>
</tr>
<tr>
<td>12. Thought Withdrawal</td>
<td>4708 (99.89)</td>
<td>4 (0.08)</td>
<td>1 (0.02)</td>
<td>5 (0.1)</td>
</tr>
</tbody>
</table>

Nested Regression

In the nested logistic regression, the sample size dropped from N = 3576 to N = 1970 and from N = 3527 to N = 1947 for the 2-Back and 3-Back respectively, due to missing data. In the first unadjusted block, only the 3-Back z-FA and $d'$ showed an association with PEs, respectively: OR = 1.26 [1.03, 1.54] and 0.8 [0.64, 1.00]. No significant association between N-Back performance or response bias on the two N-Back tasks and PEs was found in the adjusted model (Table 4).
After multiple imputation, our sample size was N = 4744. The results were similar to the univariable unadjusted model, suggesting that attrition may have affected standard errors in the adjusted models. In the 2-Back unadjusted model, z-FA and $d'$ were associated with PEs (respectively, OR = 1.17 [1.01, 1.34] and OR = 0.89 [0.79, 0.99]). In the 3-Back unadjusted model z-FA (OR = 1.36 [1.20, 1.55]), $d'$ (OR = 0.74 [0.64, 0.86]), and response bias $c$ (OR = 0.64 [0.43, 0.93]) showed a significant association with PEs. In the adjusted imputed model, only on the 3-Back, z-FA (OR = 1.25 [1.08, 1.44]) and $d'$ (OR = 0.82 [0.69, 0.96]) showed an association with PEs (Table 5).

Discussion

This study clarifies evidence of impaired WM performance in individuals with PEs in a general population birth cohort. Our findings replicate and extend previous studies[41, 63]. Compared to those studies, we report on a larger sample size, and we used an interview-based assessment

### Table 3: Mean, 95% CI and Range of performance on 2-Back and 3-Back.

<table>
<thead>
<tr>
<th></th>
<th>2-Back (N = 3595)</th>
<th></th>
<th></th>
<th>3-Back (N = 3551)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Mean 95% CI</td>
<td>Range</td>
<td>Mean</td>
<td>Mean 95% CI</td>
<td>Range</td>
</tr>
<tr>
<td>Hits</td>
<td>0.71</td>
<td>[0.71, 0.72]</td>
<td>0.13, 0.94</td>
<td>0.56</td>
<td>[0.55, 0.57]</td>
<td>0.13, 0.94</td>
</tr>
<tr>
<td>FA</td>
<td>0.21</td>
<td>[0.20, 0.21]</td>
<td>0.01, 0.97</td>
<td>0.22</td>
<td>[0.21, 0.22]</td>
<td>0.01, 0.97</td>
</tr>
<tr>
<td>Hits RT</td>
<td>702.84</td>
<td>[695.11, 710.57]</td>
<td>139.50, 2002.50</td>
<td>737.12</td>
<td>[727.20, 747.04]</td>
<td>74.5, 2410</td>
</tr>
<tr>
<td>nonT RT</td>
<td>671.91</td>
<td>[664.92, 678.89]</td>
<td>6.50, 1858.50</td>
<td>696.94</td>
<td>[688.27, 705.61]</td>
<td>32, 2278</td>
</tr>
<tr>
<td>$d'$</td>
<td>1.73</td>
<td>[1.69, 1.77]</td>
<td>-3.01, 3.79</td>
<td>1.12</td>
<td>[1.08, 1.15]</td>
<td>-2.77, 3.79</td>
</tr>
<tr>
<td>$c$</td>
<td>0.19</td>
<td>[0.17, 0.21]</td>
<td>-1.70, 1.50</td>
<td>0.37</td>
<td>[0.35, 0.38]</td>
<td>-1.53, 1.70</td>
</tr>
</tbody>
</table>

*a negative values of c signify liberal bias, whereas positive values signify conservative bias.

doi:10.1371/journal.pone.0153148.t003

### Table 4: Unadjusted and adjusted Odds Ratios, p value, and 95% CI of individual N-Back parameters for participants with PEs versus those without PEs.

<table>
<thead>
<tr>
<th>N-Back Parameters</th>
<th>OR</th>
<th>p</th>
<th>95%CI</th>
<th>OR</th>
<th>p</th>
<th>95%CI</th>
<th>OR</th>
<th>p</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>z-Hits</td>
<td>0.94</td>
<td>0.445</td>
<td>[0.80,1.10]</td>
<td>0.93</td>
<td>0.549</td>
<td>[0.74,1.17]</td>
<td>0.96</td>
<td>0.738</td>
<td>[0.76,1.22]</td>
</tr>
<tr>
<td>z-False Alarms</td>
<td>1.17</td>
<td>0.032</td>
<td>[1.01,1.35]</td>
<td>1.05</td>
<td>0.687</td>
<td>[0.84,1.31]</td>
<td>0.95</td>
<td>0.706</td>
<td>[0.74,1.22]</td>
</tr>
<tr>
<td>$d'$</td>
<td>0.90</td>
<td>0.084</td>
<td>[0.80,1.01]</td>
<td>0.96</td>
<td>0.694</td>
<td>[0.81,1.15]</td>
<td>1.03</td>
<td>0.753</td>
<td>[0.85,1.25]</td>
</tr>
<tr>
<td>$c$</td>
<td>0.79</td>
<td>0.173</td>
<td>[0.56,1.11]</td>
<td>1.08</td>
<td>0.786</td>
<td>[0.63,1.82]</td>
<td>1.25</td>
<td>0.423</td>
<td>[0.73,2.14]</td>
</tr>
<tr>
<td>z-Hits RT</td>
<td>1.01</td>
<td>0.871</td>
<td>[0.86,1.19]</td>
<td>1.01</td>
<td>0.939</td>
<td>[0.80,1.28]</td>
<td>1.00</td>
<td>0.984</td>
<td>[0.79,1.26]</td>
</tr>
<tr>
<td>z-nonT RT</td>
<td>1.03</td>
<td>0.693</td>
<td>[0.88,1.21]</td>
<td>1.08</td>
<td>0.515</td>
<td>[0.86,1.35]</td>
<td>1.10</td>
<td>0.431</td>
<td>[0.87,1.38]</td>
</tr>
<tr>
<td></td>
<td>3-Back, Unadjusted (N = 3527)</td>
<td>3-Back block 1 (N = 1947)</td>
<td>3-Back, adjusted* (N = 1947)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>z-Hits</td>
<td>0.91</td>
<td>0.227</td>
<td>[0.77,1.06]</td>
<td>0.90</td>
<td>0.350</td>
<td>[0.71,1.13]</td>
<td>0.92</td>
<td>0.494</td>
<td>[0.73,1.17]</td>
</tr>
<tr>
<td>z-False Alarms</td>
<td>1.35</td>
<td>0.001</td>
<td>[1.18,1.54]</td>
<td>1.26</td>
<td>0.023</td>
<td>[1.03,1.54]</td>
<td>1.19</td>
<td>0.106</td>
<td>[0.96,1.48]</td>
</tr>
<tr>
<td>$d'$</td>
<td>0.76</td>
<td>0.001</td>
<td>[0.65,0.89]</td>
<td>0.80</td>
<td>0.049</td>
<td>[0.64,1.00]</td>
<td>0.84</td>
<td>0.150</td>
<td>[0.67,1.06]</td>
</tr>
<tr>
<td>$c$</td>
<td>0.63</td>
<td>0.017</td>
<td>[0.43,0.92]</td>
<td>0.75</td>
<td>0.322</td>
<td>[0.43,1.32]</td>
<td>0.84</td>
<td>0.528</td>
<td>[0.48,1.46]</td>
</tr>
<tr>
<td>z-Hits RT</td>
<td>0.87</td>
<td>0.127</td>
<td>[0.74,1.04]</td>
<td>0.85</td>
<td>0.197</td>
<td>[0.66,1.09]</td>
<td>0.89</td>
<td>0.391</td>
<td>[0.69,1.16]</td>
</tr>
<tr>
<td>z-nonT RT</td>
<td>0.94</td>
<td>0.466</td>
<td>[0.80,1.11]</td>
<td>0.90</td>
<td>0.381</td>
<td>[0.71,1.14]</td>
<td>0.93</td>
<td>0.580</td>
<td>[0.73,1.19]</td>
</tr>
</tbody>
</table>

*a adjusted for: ICD-10 Diagnosis of depression, Bullying profile, Total IQ at age 8, Family Adversity Index, cannabis abuse, Hard Drugs use, Gender

b Negative values of c signify liberal bias, whereas positive values signify conservative bias.

doi:10.1371/journal.pone.0153148.t004

Multiple imputation

After multiple imputation, our sample size was N = 4744. The results were similar to the univariable unadjusted model, suggesting that attrition may have affected standard errors in the adjusted models. In the 2-Back unadjusted model, z-FA and $d'$ were associated with PEs (respectively, OR = 1.17 [1.01, 1.34] and OR = 0.89 [0.79, 0.99]). In the 3-Back unadjusted model z-FA (OR = 1.36 [1.20, 1.55]), $d'$ (OR = 0.74 [0.64, 0.86]), and response bias $c$ (OR = 0.64 [0.43, 0.93]) showed a significant association with PEs. In the adjusted imputed model, only on the 3-Back, z-FA (OR = 1.25 [1.08, 1.44]) and $d'$ (OR = 0.82 [0.69, 0.96]) showed an association with PEs (Table 5).
method for PEs. Furthermore, we used SDT to obtain a fine-grained profiling of WM unlike previous studies that, for example, used the MATRICS Consensus Cognitive Battery[64] to assess global cognitive functioning[41].

Our data show that poor performance on the 3-Back paradigm was more strongly associated with PEs than was the 2-Back, suggesting that the WM deficit emerges in a PE-positive population only at higher WM loads. This could be related to the narrower WM span demonstrated in psychotic disorders and schizophrenia[65–67], although the same association is hitherto less established with PE [41–45]. In our sample, the association of impaired WM with PEs was only partially confounded by general intelligence, as shown in the multiple imputation analysis. Moreover, the loss of association between WM and PEs after adjusting for potential confounders may be due, at least in part, to the drop in sample size, as highlighted in the nested block 1 model. Hence, we judge the overall confounding effect to be relatively small, although not null.

In our study, false alarms showed the strongest association with PEs, suggesting that the performance on this task is being dragged down by poor accuracy in rejecting non-targets rather than poor accuracy in detecting targets. This result, together with a liberal response bias, is consistent with findings of an association between increased false recognitions and psychotic phenomena. For example, a similar SDT profile, with diminished discriminability and a liberal response bias, has been found to be associated with positive schizotypy in two studies [68, 69]. In a recent study, individuals with schizophrenia displayed a similar SDT pattern in two similar tasks with higher rates of false alarms and diminished d’ compared to controls [70]. Moreover, auditory hallucinations were found to be associated with visual memory errors [71], false recognition of auditory signals [48, 72] and words [73]. Taken together, these findings suggest that liberal response bias and diminished discriminability are general non-mnemonic characteristics underlying impaired reality-testing and positive psychotic phenomena.

A liberal response bias (lower value of c) could be viewed as an impulsive style of responding [74]. This would imply a correlation between reaction time and response bias. In our study, neither speed nor accuracy was favoured in the task instructions. However, we carried out a post-hoc correlation analysis (Table 6) and found a negative correlation between reaction time and z-hits RT for the 3-Back task.

<table>
<thead>
<tr>
<th>N-Back Parameters</th>
<th>OR 2-Back unadjusted MICE (N = 4744)</th>
<th>p 2-Back unadjusted MICE (N = 4744)</th>
<th>95% CI 2-Back unadjusted MICE (N = 4744)</th>
<th>OR 2-Back adjusteda MICE (N = 4744)</th>
<th>p 2-Back adjusteda MICE (N = 4744)</th>
<th>95% CI 2-Back adjusteda MICE (N = 4744)</th>
</tr>
</thead>
<tbody>
<tr>
<td>z-Hits</td>
<td>0.92</td>
<td>0.292</td>
<td>[0.78, 1.08]</td>
<td>1.00</td>
<td>0.965</td>
<td>[0.84, 1.19]</td>
</tr>
<tr>
<td>z-FALSE Alarms</td>
<td>1.17</td>
<td>0.034</td>
<td>[1.01, 1.34]</td>
<td>1.03</td>
<td>0.721</td>
<td>[0.88, 1.21]</td>
</tr>
<tr>
<td>d’</td>
<td>0.89</td>
<td>0.040</td>
<td>[0.79, 0.99]</td>
<td>0.99</td>
<td>0.841</td>
<td>[0.87, 1.13]</td>
</tr>
<tr>
<td>c^b</td>
<td>0.82</td>
<td>0.317</td>
<td>[0.56, 1.22]</td>
<td>0.96</td>
<td>0.852</td>
<td>[0.66, 1.42]</td>
</tr>
<tr>
<td>z-Hits RT</td>
<td>1.00</td>
<td>0.987</td>
<td>[0.83, 1.20]</td>
<td>1.03</td>
<td>0.755</td>
<td>[0.85, 1.24]</td>
</tr>
<tr>
<td>z-nonT RT</td>
<td>1.04</td>
<td>0.633</td>
<td>[0.88, 1.23]</td>
<td>1.08</td>
<td>0.360</td>
<td>[0.91, 1.29]</td>
</tr>
</tbody>
</table>

Table 5. Unadjusted and adjusted Odds Ratios, p value, and 95% CI of individual N-Back parameters for participants with PEs—Multiple Imputation.

*adjusted for: ICD-9 Diagnosis of depression, Bullying profile, Total IQ at age 8, Family Adversity Index, cannabis abuse, Hard Drugs use, Gender

Negative values of c signify liberal bias, whereas positive values signify conservative bias.

doi:10.1371/journal.pone.0153148.t005
and false alarms (ie., faster response, more false alarms) and a positive correlation with hits, for the 3–back task. While this might suggest impulsivity, there was no correlation between c and reaction time. Experimental manipulation of speed and accuracy may shed light on this issue and relevance to the formation of PEs [75] in future studies.

Theoretical implications

Our SDT-based dissection of WM impairment is consistent with other neuropsychological models of psychosis. The relevance of poor accuracy in rejecting non-targets in PEs, rather than inhibiting the response, is confirmed by studies on auditory hallucinations. According to the SDT-based framework, hallucinations can be conceptualized as false alarm-equivalents, in the sense that the absence of a stimulus elicits a response as if that stimulus was actually present [76]. In fact, it has indeed been found that auditory hallucinations are related to poor discriminability and liberal response bias [77, 78]. The response bias, in turn, could be influenced by aberrantly hypervigilant attentional systems, affecting the rate of false alarms [79, 80]. The importance of attentional systems has been addressed by Cohen and colleagues [81–83] using the Continuous Performance Test (CPT). Our results are in line with theirs, in terms of SDT. However, attention based SDT-models focus on the processing of present stimuli or on lower loads of WM. We are assuming that both mnemonic and online representations of stimuli are governed by similar processes, hence similar response biases to those shown on WM tasks but based on ongoing perceptual inputs could lead to judgment errors and possibly PEs.

Our finding of a liberal response bias and a high rate of false alarms associated with PEs is consistent with neurocognitive models of psychosis involving bias in data gathering, including the Jumping-To-Conclusions (JTC) model of delusions [84–86]. This reasoning bias has also been revealed in individuals at risk for psychosis [85, 87] and in delusion-prone individuals [88, 89], suggesting that data-gathering may be impaired before the onset of full-blown psychosis. Moreover, an association between JTC and WM has been reported [35–37, 85] although this has not been addressed in terms of SDT.

A unifying model that puts together data gathering, sensory processing and SDT, that could eventually explain the role of WM deficits in producing PEs is derived from computational

<table>
<thead>
<tr>
<th>Table 6. N-Back indices Pearson Correlations.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>z-Hits</td>
</tr>
<tr>
<td>z-False Alarms</td>
</tr>
<tr>
<td>z-Hits RT</td>
</tr>
<tr>
<td>z-nonT RT</td>
</tr>
<tr>
<td>c</td>
</tr>
<tr>
<td>d</td>
</tr>
<tr>
<td>* p&lt;0.05, ** p&lt;0.01, *** p&lt;0.001</td>
</tr>
</tbody>
</table>

and false alarms (ie., faster response, more false alarms) and a positive correlation with hits, for the 3–back task. While this might suggest impulsivity, there was no correlation between c and reaction time. Experimental manipulation of speed and accuracy may shed light on this issue and relevance to the formation of PEs [75] in future studies.

Theoretical implications

Our SDT-based dissection of WM impairment is consistent with other neuropsychological models of psychosis. The relevance of poor accuracy in rejecting non-targets in PEs, rather than inhibiting the response, is confirmed by studies on auditory hallucinations. According to the SDT-based framework, hallucinations can be conceptualized as false alarm-equivalents, in the sense that the absence of a stimulus elicits a response as if that stimulus was actually present [76]. In fact, it has indeed been found that auditory hallucinations are related to poor discriminability and liberal response bias [77, 78]. The response bias, in turn, could be influenced by aberrantly hypervigilant attentional systems, affecting the rate of false alarms [79, 80]. The importance of attentional systems has been addressed by Cohen and colleagues [81–83] using the Continuous Performance Test (CPT). Our results are in line with theirs, in terms of SDT. However, attention based SDT-models focus on the processing of present stimuli or on lower loads of WM. We are assuming that both mnemonic and online representations of stimuli are governed by similar processes, hence similar response biases to those shown on WM tasks but based on ongoing perceptual inputs could lead to judgment errors and possibly PEs.

Our finding of a liberal response bias and a high rate of false alarms associated with PEs is consistent with neurocognitive models of psychosis involving bias in data gathering, including the Jumping-To-Conclusions (JTC) model of delusions [84–86]. This reasoning bias has also been revealed in individuals at risk for psychosis [85, 87] and in delusion-prone individuals [88, 89], suggesting that data-gathering may be impaired before the onset of full-blown psychosis. Moreover, an association between JTC and WM has been reported [35–37, 85] although this has not been addressed in terms of SDT.

A unifying model that puts together data gathering, sensory processing and SDT, that could eventually explain the role of WM deficits in producing PEs is derived from computational
neurosciences[90–92]. In computational terms, high “cognitive noise” is associated with reduced precision of high-level representations, and with increased relevance and strength of new sensory evidence, eventually leading to psychotic symptoms[91]. Computational models of WM have suggested that the net effect of the putative dopaminergic perturbation occurring in the dorsolateral prefrontal cortex (dlPFC) results in increased “cognitive noise” and impaired gating[93, 94], causing defective stimulus discriminability[95]. Moreover, dopaminergic perturbations in dlPFC produce a persistent state of “WM activation” that, together with impaired gating functions, results in higher error-rates[93]. These mechanisms foster false identification of the present sensory (bottom-up) stimulus as matching the preceding (top-down) one, resulting in a false alarm response.

Finally, the tendency of over-responding in the face of uncertainty, expressed by a liberal response bias, could be explained by the Bayesian concept of precision[90] and metacognitive strength of “prior belief”. In this case, the subject would attribute excessive precision, or is too confident in his mental representations, regardless of the degree of uncertainty associated with them[91, 96]. Such over-confidence may underlie reasoning biases such as JTC[97]. Testing such models would benefit from manipulation of reward/punishment as well as speed/accuracy trade offs[98].

Strengths and limitations
Our project replicates several previous findings. Although the subject of this report has been extensively addressed before, to date no other work has reported on such sample size. Moreover, no other work in this field has used such a comprehensive SDT approach, detailing some of the psycho-mathematical features of reality processing in subjects with PEs.

One major limitation of our study is the narrow focus on WM, and on N-back. The N-Back task explores, by its nature, only some aspects of the neural mechanism (i.e. encoding and updating) underlying WM as a whole. However, the use of n-back allowed us to dissect some of the non-purely mnemonic aspects involved in performing a WM task, which may have implications for other similar tasks. Indeed, our results are largely consistent with results of Continuous Performance Tasks, of which the n-back is a variation, on the psychosis continuum. Assessing the WM profile in the context of a wider cognitive screening could have helped establish the mutual relationship between different cognitive domains.

A second limitation of ALSPAC is the extent of attrition with under-representation of lower socio-economic groups and ethnic minorities [5] and consequent potential selection bias. However, we used multiple imputation of missing data to help address attrition bias.

The present study has several strengths.
Firstly, as noted, this study is based on a considerably larger sample than any previous study. Secondly, we focused on a non-clinical sample. A large body of work has confirmed WM deficits in clinical populations of ARMS, UHR or FEP [16, 28, 99]. Such clinical samples may be subject to selection bias towards help-seeking and perhaps poor coping strategies. Studying PEs in the general population reduces selection bias based on clinical severity and the effects of medication. Thirdly, PEs were assessed with a semi-structured interview derived from widely-used diagnostic interviews, rather than relying on self-report measures. Fourthly, our study includes a wealth of other demographic and clinical data, allowing us to adjust for potential confounders and better interpret the results.

Conclusion
In conclusion, this study confirms and extends prior reports of cognitive impairments in individuals with PEs. Our approach using SDT suggests critical connections between different
underpinnings of psychosis, including reasoning biases and probabilistic reasoning, and WM functioning.

Acknowledgments
We are extremely grateful to all the families who took part in this study and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. This research was funded by MRC grant n° G0901885”.

Author Contributions
Conceived and designed the experiments: MM SZ GL ASD. Analyzed the data: RR. Contributed reagents/materials/analysis tools: RR SZ KB MM GL ASD. Wrote the paper: RR SZ KB MM GL ASD.

References


70. Nuechterlein KH, Green MF, Calkins ME, Greenwood TA, Gur RE, Gur RC, et al. Attention/Vigilance in schizophrenia: performance results from a large multi-site study of the Consortium on the Genetics of


