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Duration of untreated psychosis and neurocognitive functioning in first-episode psychosis: a systematic review and meta-analysis

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Abstract

Background. Previous reviews suggest there is minimal evidence for an association between duration of untreated psychosis (DUP) and neurocognition. This is based on tallied findings of studies with small samples and neurocognition viewed as a single construct. We aimed to conduct a systematic review and meta-analysis examining the association between DUP and individual neurocognitive domains and tests in first-episode psychosis (FEP).

Method. MOOSE and PRISMA guidelines were followed. Forty-three studies involving 4647 FEP patients were included. For studies providing correlations between DUP and neurocognition, 12 separate meta-analyses were performed based on neurocognitive domains/indices. The influence of demographic/clinical variables was tested using weighted linear meta-regression analyses.

Results. The relationship between DUP and most neurocognitive domains/indices was not significant. Longer DUP was associated with a larger cognitive deterioration index, i.e. current minus premorbid intellectual functioning ($N = 4$; mean ES −0.213, 95% confidence interval (CI) (−0.344 to −0.074), $p = 0.003$). Findings were homogeneous, with no evidence of publication bias or significant influence from moderators. For studies providing mean and standard deviations for neurocognitive measures and DUP, 20 meta-regressions were performed on individual neurocognitive tests. One significant finding emerged showing that longer DUP was associated with fewer Wisconsin Card Sorting Test-perseverative errors (mean ES −0.031, 95% CI (−0.048 to −0.013), $p < 0.001$). Exploratory meta-regressions in studies with mean DUP <360 days showed longer DUP was significantly associated with poorer performance on Trail Making Test A and B and higher Full-Scale IQ.

Conclusion. There may not be a generalised association between DUP and neurocognition, however, specific cognitive functions may be associated with longer DUP or delayed help-seeking.

Introduction

Large neurocognitive impairments encompassing multiple domains are apparent from the first episode of psychosis (Mesholam-Gately *et al.* 2009) and to a lesser extent in ultra-high-risk or clinical high-risk populations (Fusar-Poli *et al.* 2012), particularly in individuals who later develop full-threshold psychotic disorder (Fusar-Poli *et al.* 2012; Meier *et al.* 2014). Neurocognitive deficits following first-episode psychosis (FEP) have shown relative stability (Bozikas & Andreou, 2011; Rund *et al.* 2016), suggesting that neurocognitive deterioration occurs prior to psychotic disorder (Zipursky *et al.* 2013), offering a window of opportunity for early intervention.

There has been extensive research on the relationship between illness characteristics and outcomes and the elapsed time between the first onset of psychotic symptoms and initiation of adequate treatment – termed duration of untreated psychosis (DUP) (Marshall *et al.* 2005; Perkins *et al.* 2005; Boonstra *et al.* 2012; Penttila *et al.* 2014; Rund, 2014; Anderson *et al.* 2015; Kane *et al.* 2016). This line of investigation is predicated on the neurotoxicity hypothesis, which suggests that delayed treatment of ongoing or repeated acute psychotic symptoms may be associated with biological and functional 'damage' and poorer treatment response (Sheitman & Lieberman, 1998; McGlashan, 2006; Cropley *et al.* 2013; Rund, 2014). An

alternative hypothesis is that longer DUP is a marker of a more severe form of illness characterised by greater neurodevelopmental and neurocognitive impairment (McGlashan, 1999, 2006). A recent systematic review of 48 neuroimaging studies concluded that there was equivocal evidence for an association between DUP and brain structure in FEP, providing little support for the neurotoxicity hypothesis at the neurobiological level (Anderson *et al.* 2015). On the other hand, evidence from several reviews suggests that longer DUP is associated with poorer cross-sectional and longitudinal symptomatic (particularly negative symptom) and functional outcomes (Marshall *et al.* 2005; Perkins *et al.* 2005; Boonstra *et al.* 2012; Penttila *et al.* 2014). This finding remains after controlling for factors such as premorbid functioning and age of onset (Marshall *et al.* 2005; Perkins *et al.* 2005; Penttila *et al.* 2014). While the mechanisms for the relationship between DUP and clinical outcomes remain unclear, this line of work validates the need for early psychopharmacological and psychosocial interventions to maximise symptomatic and functional outcomes, in line with a staging model of care (McGorry *et al.* 2006). There is also a need to better understand whether longer DUP is associated with poorer neurocognition, as neurocognitive impairment is a strong predictor of poorer functional outcome (Fett *et al.* 2011) and early neurocognitive interventions might be beneficial (McGorry *et al.* 2014).

Two previous systematic reviews have examined the relationship between DUP and neurocognition. In the first, only two of the eight included studies found longer DUP was associated with poorer neurocognition (Perkins *et al.* 2005). In the second most recent review, only six of the 22 included studies reported a significant relationship between longer DUP and poorer neurocognition (Rund, 2014). In both reviews, it was concluded that there is minimal evidence for a longer DUP having detrimental associations with neurocognitive performance; however, results across different neurocognitive domains were aggregated and significant findings between studies were tallied rather than meta-analysed. It is possible that certain neurocognitive functions may be more susceptible than others to the deleterious effects of untreated psychosis, which may be due to variations in their developmental maturation and the extent to which differing brain regions/networks recruited for particular neurocognitive abilities are impacted by psychosis-related pathological processes (Meier *et al.* 2014; Pantelis *et al.* 2015). Furthermore, these reviews only included studies that specifically examined the association between DUP and neurocognition, thus excluding studies that assess DUP and neurocognition as secondary variables, which can provide valuable complementary information for a quantitative analysis of this association. A comprehensive meta-analytic investigation utilising all published primary and secondary data on DUP and separate neurocognitive domains, which may vary in their susceptibility to 'toxicity', may produce greater precision of data synthesis.

The primary aim of this study was to conduct a systematic review and meta-analysis investigating whether DUP is associated with neurocognitive performance in specific domains or tasks in FEP, assessed cross-sectionally. The second aim was to examine the effect of demographic and clinical factors on the relationship between DUP and neurocognition in FEP. A final exploratory aim was to examine the relationship between DUP and neurocognition in studies with a mean DUP <360 days, to determine whether such a relationship might be more likely closer to illness onset. This exploratory aim was based on recent research showing that this period may represent a dynamic and critical treatment window (Boonstra *et al.* 2012; Kane *et al.* 2016).

Method

Search strategy

The systematic review and meta-analysis were conducted according to Meta-analysis of Observational Studies in Epidemiology guidelines (Stroup *et al.* 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher *et al.* 2009). PubMed and EMBASE online databases were searched from inception to June 2015. The initial search covered the combination of two concepts: 'FEP' (OR alternative terms) AND 'cognition' (OR alternative terms). The search was limited to FEP samples to minimise confounding effects of treatment on neurocognitive outcomes. Cognition search terms covered multiple neurocognitive domains and were based on those used in the meta-analysis on cognition in first-episode schizophrenia by Mesholam-Gately *et al.* (2009). These cognition terms were subsequently entered into the Medical Subject Headings online dictionary to ensure all relevant terms were captured (see online Supplementary Material). DUP was not included in the initial search to allow collection of secondary data included in papers that did not have a primary focus on the relationship between DUP and neurocognition. A second separate search of PubMed and EMBASE was conducted that combined 'FEP' (OR alternative terms) AND 'duration of untreated psychosis' OR 'DUP'. Finally, a manual search was performed on the reference lists of relevant reviews.

Screening and selection criteria

All papers were double-screened in author pairs from different cultural backgrounds in order to avoid potential educational/cultural bias. Screening occurred in three phases with discrepancies resolved by consensus. In phase 1, titles and abstracts were screened checking for broad eligibility (strict definitions were not applied in this phase). In phase 2, full-text articles surviving phase 1 were comprehensively reviewed for eligibility according to the following inclusion and exclusion criteria: (a) written in English; (b) peer-reviewed; (c) original empirical study; (d) *N* specified and ⩾5; (e) all participants had a diagnosis of psychotic disorder according to DSM or ICD criteria. Given the interest was on the role of untreated *psychotic symptoms*, the full spectrum of psychotic disorders were permitted, including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, mood disorders with psychotic features, psychotic disorder not otherwise specified and brief psychotic disorder. Any method of diagnostic assessment was permitted; (f) the sample was described as first episode, using any one of the following terms: FEP, recent onset psychosis, first onset psychosis, early psychosis, first-episode schizophrenia, FES, recent-onset schizophrenia, first onset schizophrenia, early onset schizophrenia or early schizophrenia. If a mixture of first-episode and multi-episode participants were included, data on the FEP group had to be reported separately; (g) DUP was measured. Any method of assessment was permitted; (h) neurocognition was assessed objectively, via standardised or experimental tests: (i) relevant statistics were provided. Studies reporting that participants had received >2 years of treatment were excluded. Up to 2 years of prior treatment was permitted because this would maximise

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inclusion of studies from early psychosis services internationally, with some services allowing up 2 years prior to inclusion (e.g. Daban *et al.* 2005, Nuechterlein *et al.* 2011). Furthermore, this time period was selected because the outcomes in the first 2 years after illness onset predict long-term outcomes (Menezes *et al.* 2006). Self-reported or clinician-rated cognitive functioning (e.g. PANSS) was also excluded. Phase 3 screening involved identifying papers with overlapping samples to ensure the final set of papers included independent samples. Overlapping studies were not excluded if there was no duplication of the variables of interest and data on both DUP and neurocognition were available.

Data extraction and quality assessment

Two authors (KA, EP) independently extracted data from all included papers and discrepancies were resolved via discussion. Data extracted included: location and year of the study; descriptions of the study design; premorbid, demographic, clinical and treatment characteristics of the sample; details of DUP, including definition and measurement; and neurocognitive measures. The neurocognitive test data extracted from included studies were categorised according to widely accepted and conventional neurocognitive domains (Lezak *et al.* 2004; Mesholam-Gately *et al.* 2009) (see online Supplementary Table S1). Each paper was rated for methodological quality by two authors (KA, EP) using a 7-item scale adapted from Anderson *et al.* (2015) and purposefully designed for the current study (see online Supplementary Table S2). Each item was scored 2, 1 or 0, with maximum score out of 14 (higher scores indicating higher quality). Discrepancies were resolved by consensus.

Data synthesis and analysis

Data were analysed with a quantitative meta-analytical approach using Comprehensive Meta-Analysis Software version 3 (Biostat, Inc., Englewood, NJ). Two different types of meta-analytical approaches were performed, depending on whether original papers provided: (i) measures of correlation between DUP and neurocognition (e.g. Pearson *r*) or (ii) mean and S.D. for neurocognition and mean for DUP.

The primary and more statistically powerful approach involved meta-analysis of the correlation between DUP and neurocognition, which involved separate meta-analyses performed for each neurocognitive domain/index. Meta-analyses were conducted when at least three independent studies measured a given neurocognitive domain/index. As early intervention trials show there may be a critical treatment window within the first year of FEP (Petersen *et al.* 2005; Kane *et al.* 2016) additional exploratory meta-analyses were conducted on studies with a mean DUP <360 days to determine whether potential DUP-neurocognition relationships might be evident closer to illness onset. Effect size was estimated by calculating the correlation value [with 95% confidence interval (CI)] of each paper. In the case of studies stating that the correlation was not significant, but not reporting *r* value, $p = 1$ was assumed, as this results in an effect size of zero and avoids the need for an additional assumption about the direction of the effect and thus is parsimonious and conservative. The rigour of the findings was also checked by performing a jackknife sensitivity analysis, which consists of iteratively repeating the meta-analyses excluding one study at a time to establish whether the results are replicable (Radua & Mataix-Cols, 2009). Effect sizes were combined to produce a single summary estimate using random-effects techniques based on the DerSimonian & Laird (1986) method (method of maximum likelihood). Interpretation of the strength of correlations (*r*) was 0.10 = small, 0.30 = medium and 0.50 = large effect, while interpretation of the effect size (Cohen's *d*) was 0.2–0.5 = small, 0.5–0.8 = moderate and >0.8 = large (Cohen, 1992). To assess the heterogeneity among study point estimates, we calculated the *Q* statistic, with magnitude of heterogeneity being evaluated using the I^2 statistic (a measure of the proportion of variance in the summary effect size that is attributable to heterogeneity). I^2 indicates the percentage of total variation across studies due to heterogeneity rather than chance, with I^2 values of 25%, 50% and 75% considered to represent low, moderate and high heterogeneity, respectively. Publication bias was assessed by visually inspecting funnel plots. In addition, we used Orwin's (1983) FSN (fail-safe number). This generated the number of unpublished studies that would be needed to move estimates to a non-significant threshold. Further, we used the Duval & Tweedie (2000) trim-and-fill method to estimate an effect size corrected for publication bias.

The influence of demographic, clinical and study quality variables was tested using weighted linear meta-regression analyses (mixed effects regression, unrestricted maximum likelihood), with study effect size as the dependent variable and either quality of study (total quality score), age (mean age of participants), sex (percentage of males), specific diagnosis (percentage of patients with schizophrenia diagnosis), education level (years of education), premorbid IQ, antipsychotic-naïve (percentage of antipsychotic-naïve patients) and antipsychotic dose (mean chlorpromazine equivalents) as the independent variables. Given the exploratory nature of these analyses, a correction for multiple comparisons was not performed (Perneger, 1998).

The secondary analyses involved the studies that provided mean and S.D. for neurocognitive measures and mean for DUP. Separate meta-regression analyses examining the influence of DUP on neurocognition were performed on individual neurocognitive test or index scores (rather than domains). Meta-regressions were conducted when at least four independent studies reported on a given neurocognitive measure. The slope of the meta-regression line (β-coefficient: direct [+] or inverse [−]) indicates the strength of a relationship between the moderator (DUP) and outcome (neurocognitive test score). Interpretation of β weights was <0.2 = weak, 0.2–0.5 = moderate and >0.5 = strong (Acock, 2014).

Results

Study selection and characteristics

The literature search and screening process led to the inclusion of 43 independent studies (see online Supplementary Fig. S1) involving a total of 4647 individuals with FEP. Eighteen of the included studies directly examined the relationship between DUP and neurocognition and 31 studies reported means and S.D. for neurocognitive scores and mean for DUP (six studies provided both data types). The mean age of FEP patients across the 43 studies ranged from 15 to 32 years. The percentage of males across the included studies ranged from 32% to 100%, with males outnumbering females overall (65% male). Of the 34 studies that reported on specific diagnoses, the percentage of patients with a diagnosis of schizophrenia ranged from 0% to 100%, highlighting the heterogeneous diagnostic presentations across studies. Three of the correlation studies did not report the mean DUP (Joyce *et al.* 2002;

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Rund *et al.* 2004; Broussard *et al.* 2013). Of the remaining 40 studies, the mean DUP ranged from 34.0 (Faber *et al.* 2011) to 2737.5 (Bliksted *et al.* 2014) days. Only 12 studies reported median DUP, which ranged from 31 to 322 days. Complete details of the included studies are shown in Table 1.

Study quality

The quality ratings for the 43 included studies are presented in Table 1. Total scores out of a possible maximum of 14 ranged from 2 to 11, with a mean of 6.88 (S.D. = 2.32). Only nine of the 43 studies reported use of a standardised DUP measure.

Meta-analysis of correlation studies

Twelve separate meta-analyses (one for each neurocognitive domain/index) were conducted with data from the 18 studies that examined the correlation between DUP and neurocognition. One meta-analysis involving four studies ($N = 246$) showed a significant correlation between DUP and cognitive deterioration index (a calculation of current IQ minus premorbid/'hold' IQ) (mean ES −0.213, 95% CI −0.344 to −0.074, $p = 0.003$; Fig. 1). Specifically, shorter DUP was associated with a lower cognitive deterioration index. The remaining meta-analyses, including attention/vigilance, motor speed, speed of processing, working memory, executive functioning, verbal fluency, verbal learning and memory, visual learning and memory, verbal/language skills, visuospatial skills, global cognition, and all combined, were not significant (Table 2). As specified in the method, for studies stating that the correlation was not significant, but not reporting r value, $p = 1$ was assumed. Given this conservative approach may bias results towards the null hypothesis, we conducted a sensitivity analysis assuming $p = 0.5$ (Beretta & Santaniello, 2016); this led to equivalent results. Tests of heterogeneity were nonsignificant, with the exception of the visuospatial skills domain, and there was no evidence of publication bias. Meta-regressions to assess the influence of demographic and clinical variables showed that the effects of study quality, age, sex, specific diagnosis, education level, premorbid IQ, antipsychotic-naïve status and antipsychotic dose on the meta-analytical estimates were all non-significant (results available upon request).

Meta-regression analysis of studies reporting means and standard deviations

In the second set of analyses, the influence of DUP on performance on specific neurocognitive tasks or index scores using 20 separate meta-regressions was conducted (Table 3). Results showed that the influence of DUP on neurocognitive performance was significant for perseverative errors on the Wisconsin Card Sorting Test (WCST) (five studies, $N = 569$; mean ES −0.031, 95% CI −0.048 to −0.013, $p < 0.001$; Fig. 2), indicating that longer DUP was associated with fewer perseverative errors (incidentally this analysis only included studies with mean DUP <360 days). The remaining meta-analyses, including digit span forward, digit symbol coding, Trail Making Test (TMT) A and B, immediate and delayed scores on the Auditory Verbal Learning Test, semantic verbal fluency, categories on the WCST, and Verbal, Performance and Full-Scale IQ (FSIQ), were not significant.

Finally, exploratory meta-analyses restricted to studies with a mean DUP <360 days were conducted. In addition to WCST-perseverative errors reported above, in these studies DUP was associated with three neurocognitive scores: TMT-A (eight studies, $N = 442$; mean ES 0.052, 95% CI 0.025 to 0.079, $p < 0.001$), TMT-B (five studies, $N = 388$; mean ES 0.117, 95% CI 0.036 to 0.198, $p = 0.005$) and FSIQ (11 studies, $N = 555$; mean ES 0.051, 95% CI 0.015 to 0.087, $p = 0.006$). Specifically, longer DUP was associated with poorer performance (i.e. slower time to complete) on TMT-A and B, but higher FSIQ (see Table 3 and Fig. 2).

Discussion

Meta-analysis of FEP studies that examined the correlation between DUP and neurocognition found that there were no significant associations between DUP and most domains of neurocognition. The exception was that a longer DUP was associated with a higher cognitive deterioration index, which is a calculation of current minus premorbid/'hold' intellectual functioning. A confirmatory analysis using median DUP led to equivalent findings. Potentially important demographic, clinical and study quality moderating factors did not alter the results of these meta-analyses. Meta-regressions of DUP and neurocognitive test scores were mostly non-significant, except for WCST-perseverative errors (cognitive flexibility) with better performance being associated with longer DUP. Exploratory meta-regressions showed that in studies with DUP <360 days (but not in those with DUP >360 days), DUP was significantly related to poorer performance on TMT-A and B (processing speed and working memory) and higher FSIQ. Given there were few significant relative to non-significant associations, it may be reasonable to argue that there is minimal evidence for an association between DUP and neurocognition in psychosis, in line with previous reviews (Perkins *et al.* 2005; Rund, 2014). Previous reviews differed from the current meta-analysis in that neurocognition was examined as a single construct, generally without considering individual neurocognitive domains or tasks, and different ranges in the mean DUP between studies was not taken into account. Rund's (2014) critique of the studies he reviewed included that many were potentially underpowered to detect significant associations. The current meta-analysis was able to address these concerns, providing the most robust test to date of the relationship between DUP and neurocognition. The findings of the current review suggest that the relationship between DUP and neurocognition is complex and validates the need for hypothesis-driven longitudinal studies that examine specific domains.

The significant association between DUP and cognitive deterioration index is intriguing. This finding suggests that the longer an individual goes without treatment for their psychotic symptoms, the greater the discrepancy between their estimated premorbid and current intelligence. Explanations for this include that untreated psychotic symptoms are neurotoxic or, that those who experience greater neurocognitive deterioration delay seeking treatment for their symptoms. Four studies were included in the cognitive deterioration index meta-analysis (Norman *et al.* 2001; Amminger *et al.* 2002; Caspi *et al.* 2003; Gaynor *et al.* 2009). The measurement of the deterioration index in these studies requires careful scrutiny. Caspi *et al.* (2003) calculated the magnitude of change on verbal and non-verbal intelligence tasks administered when participants were healthy at age 16–17 years and again following their first-episode of schizophrenia. However, the other three studies estimated cognitive deterioration cross-sectionally, after participants had reached full threshold for

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Table 1. Characteristics of studies included in the meta-analysis

Study (first author, year)	Country of Study	Sample *N*	Age mean (s.d.)	Male (%)	Scz (%)	Medication naïve %	Education years mean (s.d.)	DUP definition, Formal measure	DUP days mean (s.d.)	DUP days median	Quality score/14
Correlation studies											
Addington, 2004	Canada	200	24.8 (8.5)	68	68	NR	NR	First positive symptom to first effective treatment, IRAOS	589.4 (973)	196	9
Amminger, 2002[a]	Australia	42	22.3 (4.1)	71	NR	0	NR	First delusion or hallucination to admission, RPMIP	246.3 (525.2)	76.5	10
Ayres, 2007[a]	Brazil	179	32.2 (11.4)	48	NR	31	NR	Onset of psychotic phenomena to first contact with mental health services, None	264.7 (1083)	31	7
Broussard, 2013	USA	180	24.2 (4.9)	75	58	NR	11.8 (2.1)	Onset of hallucinations or delusions to first hospital admission, SOS	NR	NR	10
Caspi, 2003	Israel	44	22.5 (3.5)	75	100	0	12.1 (1.0)	Onset of first positive symptoms to initiation of antipsychotic treatment, None	94.6 (191.4)	NR	8
Chen, 2001	Hong Kong	56	32.8 (8.8)	45	100	54	10.3 (3.2)	NR, IRAOS	540.2 (940)	NR	6
Fraguas, 2014[a]	Spain	66	16.2 (1.6)	71	49	NR	11.2 (4.3)	First positive symptom recalled (delusion, hallucination, or disorganisation) and baseline assessment, Clinical questionnaire	65 (56)	47.5	8
Gaynor, 2009[a]	Ireland	47	30.0 (9.9)	72	NR	NR	NR	NR, Beiser Scale	519.6 (1167.6)	182.5	6
Goldberg, 2009	USA	102	23.9 (4.9)	70	73	80	NR	Emergence of psychotic symptoms to initiation of pharmacologic treatment, None	793.1 (1130.5)	322	5
González-Blanch, 2008	Spain	131	26.8 (7.3)	65	59	0	10.3 (3.2)	First continuous psychotic symptom (⩾4 on SAPS) to initiation of an adequate antipsychotic drug treatment, None	357 (717)	121.7	9
Heeramun-Aubeeluck, 2015[a]	China	38	25.9 (7.3)	55	100	NR	12.2 (3.5)	Onset of psychotic phenomena to first contact with mental health services, None	294 (318)	NR	11
Ho, 2003	USA	156	NR	62	73	80	NR		520.1 (1015.7)	91	8

								Onset of the full positive syndrome (any positive symptom rated moderate or worse) to initiation of antipsychotic treatment, None			
Hoff, 2000	USA	50	26.5 (5)	64	20	0	NR	Onset of delusions, hallucinations or formal thought disorder to treatment, None	342 (486)	NR	6
Joyce, 2002	UK	136	25.7 (8.0)	79	95	10	NR	NR	NR	NR	5
Lutgens, 2014	Canada	269	23.0 (3.9)	57	53	25	NR	Onset of psychotic symptoms to time of antipsychotic treatment, CORS	392 (798.6)	112	9
Norman, 2001	Canada	113	26.7 (NR)	74	41	NR	NR	Initial onset of psychosis to commencement of antipsychotic therapy, IRAOS	438 (NR)	173.4	9
Rund, 2004	Norway	207	28.1 (9.6)	58	27	NR	12 (2.4)	First onset of psychotic symptoms (week of PANSS score ⩾4 on positive scale items 1, 3, 5 or 6 or general item 9 to first adequate antipsychotic medication or hospital admission, None	NR	73.5	9
Ucok, 2014-B[a]	Turkey	90	23.2 (6.4)	NR	100	100	11 (2.9)	Onset of positive symptoms to adequate antipsychotic treatment, None	237 (288)	NR	8
Mean and s.d. studies											
Bartholomeusz, 2011	Australia	47	20.5 (3.3)	75	23	34	NR	NR	146.1 (188.7)	NR	5
Bliksted, 2014	Denmark	36	22.7 (NR)	53	100	0	12.1 (NR)	NR	2737.5 (NR)	NR	8
Bratlien, 2013	Norway	166	27.8 (8.5)	63	NR	NR	12 (2.2)	Onset of psychotic symptoms (week of PANSS score of ⩾4 on positive items 1, 3, 6 or general item 9 to first adequate treatment, None	959 (1463)	NR	9
Buchy, 2010	Canada	59	23.4 (3.7)	70	61	0	11.8 (2.6)	Onset of psychotic symptoms to time of adequate treatment with antipsychotics, None	53.2 (94.2)	NR	7

(*Continued*)

Table 1. (*Continued.*)

Study (first author, year)	Country of Study	Sample *N*	Age mean (s.d.)	Male (%)	Scz (%)	Medication naïve %	Education years mean (s.d.)	DUP definition, Formal measure	DUP days mean (s.d.)	DUP days median	Quality score/14
Carlsson, 2006-A	Sweden	49	26.8 (5.5)	63	NR	100	12.4 (2.4)	NR	655.9 (1348)	NR	8
Carlsson, 2006-B	Sweden	71	29.2 (7.9)	49	0	100	12.1 (2.2)	NR	261.8 (777.1)	NR	8
Chan, 2006	China	78	28.5 (9.8)	63	100	100	10.8 (2.5)	NR	248.6 (442)	NR	5
Chang, 2013-A	Hong Kong	41	31.5 (10.2)	32	NR	NR	10.5 (3.6)	Onset of positive psychotic symptoms to treatment initiation, IRAOS	49 (42.7)	NR	11
Chang, 2013-B	Hong Kong	43	31.5 (8.9)	54	NR	NR	10.5 (2.4)	Onset of positive psychotic symptoms to treatment initiation, IRAOS	878.6 (936.1)	NR	11
Daban, 2005-A	France	19	24.8 (4.3)	68	100	79	NR	Delay before first treatment, None	360 (390)	NR	5
Daban, 2005-B	France	19	26.6 (6.3)	79	100	0	NR	Delay before first treatment, None	150 (300)	NR	4
Faber, 2011-A	Netherlands	9	21.8 (3.6)	100	0	NR	NR	First manifestation of any positive psychotic symptom to start of antipsychotic treatment, None	34 (64)	NR	5
Faber, 2011-B	Netherlands	36	25.8 (6.7)	77	50	NR	NR	First manifestation of any positive psychotic symptom to start of antipsychotic treatment, None	294 (660)	NR	5
Guo, 2014	China	51	22.5 (4.1)	65	100	100	11.4 (3.3)	NR	252 (204)	NR	5
Hill, 2008	USA	367	24.5 (5.6)	73	NR	24	NR	NR	128.9 (35.2)	NR	5
Keshavan, 2003	USA	104	25.6 (8.2)	62	61	NR	NR	Onset of psychotic symptoms (hallucinations, delusions, disorganisation of thinking, bizarre or catatonic behaviour) to index admission into study, None	670 (1143.6)	238	8
Kravariti, 2012	UK	166	30.0 (10.7)	57	39	NR	NR	NR	404.7 (1120.8)	NR	5

Lappin, 2007-A	UK	180	28.8 (10.1)	68	100	NR	NR	Onset of psychotic phenomena (hallucinations, delusions, marked thought disorder, psychomotor disorder or bizarre behaviour; or definite change of personality or behaviour manifesting as two of serious deterioration in function, marked social withdrawal, persistent gross self-neglect, episodic marked excitement or anxiety) to first contact with statutory mental health services, PPHS	434 (938)	NR	11
Lappin, 2007-B	UK	93	32.7 (11.1)	59	0	NR	NR	Onset of psychotic phenomena (hallucinations, delusions, marked thought disorder, psychomotor disorder or bizarre behaviour; or definite change of personality or behaviour manifesting as two of serious deterioration in function, marked social withdrawal, persistent gross self-neglect, episodic marked excitement or anxiety) to first contact with statutory mental health services, PPHS	273 (1183)	NR	11
Molina, 2014	Spain	31	24.9 (5.2)	71	NR	NR	NR	NR	298.8 (676.2)	NR	5
Parellada, 2011-A	Spain	53	15.4 (2.0)	74	83	NR	NR	First positive, negative or disorganisation symptom recalled to baseline assessment, None	66.8 (54.7)	NR	7
Parellada, 2011-B	Spain	57	15.6 (1.6)	61	0	NR	NR	First positive, negative or disorganisation symptom recalled to baseline assessment, None	63.8 (50)	NR	7
Pedersen, 2008	Germany	37	28.3 (8.2)	78	100	0	11.5 (1.4)	First continuous (present most of the time) psychotic symptoms to initiation of adequate	339 (363)	NR	7

(*Continued*)

Table 1. (*Continued.*)

Study (first author, year)	Country of Study	Sample *N*	Age mean (s.d.)	Male (%)	Scz (%)	Medication naïve %	Education years mean (s.d.)	DUP definition, Formal measure	DUP days mean (s.d.)	DUP days median	Quality score/14
								antipsychotic medication, None			
Pena, 2011	Spain	86	28.5 (7.5)	69	6	0	11.5 (3.5)	NR	144.9 (369.6)	NR	4
Rigucci, 2013	Italy	19	22.2 (3.7)	63	100	0	12.1 (3.1)	First continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic treatment, None	240 (99.3)	NR	9
Tsui, 2013	Hong Kong	36	22.0 (4.6)	50	100	0	13 (2.2)	NR	249 (390)	NR	2
Ucok, 2014-A	Turkey	15	21.2 (7.2)	NR	100	100	8.2 (2.8)	Onset of positive symptoms to adequate antipsychotic treatment, None	390 (612)	NR	8
Ussorio, 2015-A	Italy	28	21.1 (4.0)	75	NR	NR	13.5 (2.2)	NR	282 (63.1)	NR	2
Ussorio, 2015-B	Italy	28	23.4 (5.2)	71	NR	NR	14 (2.4)	NR	660 (258)	NR	2
Vohs, 2015	USA	40	24.0 (4.3)	80	NR	0	12.3 (2.1)	NR	211.7 (449)	NR	3
Wang, 2010	China	214	23.2 (7.5)	44	100	100	11.8 (3.8)	NR	236.7 (67.5)	NR	7
Zhuo, 2013	China	22	26.6 (7.2)	68	100	100	12.6 (2.5)	NR	423 (414)	NR	5
Zhou, 2014	China	55	25.6 (7.3)	60	100	46	13.7 (2.2)	NR	366 (324)	NR	5

s.d., standard deviation; NR, not reported; Scz, schizophrenia diagnosis; IRAOS, Interview for the Retrospective Assessment of the Onset of Schizophrenia; RPMIP, Royal Park Multidiagnostic Interview for Psychosis; SOS, Symptom Onset in Schizophrenia; CORS, Circumstances of Onset and Relapse Schedule; PPHS, Personal and Psychiatric History Schedule

Note: A and B denote that sample characteristics were reported according to two subgroups in the original paper

[a]Also included in mean and s.d. studies

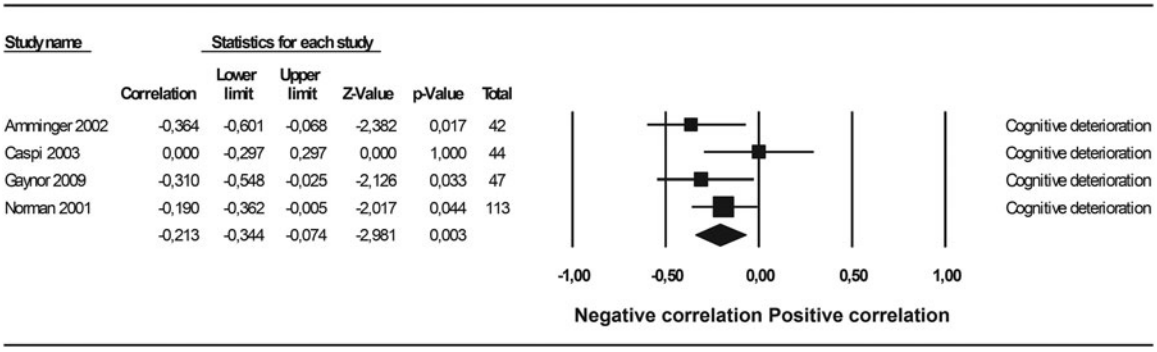

Fig. 1. Meta-analysis of relationship between DUP and cognitive deterioration index.

psychotic disorder (Norman *et al.* 2001; Amminger *et al.* 2002; Gaynor *et al.* 2009). Previous research has shown that assessing premorbid intellectual functioning after illness onset might be misleading (Russell *et al.* 2000). Indeed, examination of the forest plot (Fig. 1) shows no correlation in the study by Caspi *et al.* (2003) compared with the negative correlations of the other three studies. In two of the included studies, cognitive deterioration was assessed by examining the discrepancy between 'hold' (Vocabulary/Information) and 'non-hold' (Digit Symbol Coding) tests (Amminger *et al.* 2002; Gaynor *et al.* 2009). Comparing crystalised verbal abilities with processing speed may not be valid for estimating cognitive deterioration because processing speed (as assessed by coding tasks) is arguably a more fluid mental function that is susceptible to current mental state and thus, may not reflect global or permanent deterioration. This may be especially true for first-episode patients entering treatment for the first time. Interestingly, longitudinal research spanning ages 7–38 in people who develop schizophrenia suggests that declines are observed in processing speed and working memory (Digit Symbol Coding, TMT A and B), verbal learning (Rey Auditory Verbal Learning Test), and motor function (Grooved Pegboard), but not in 'crystalised' verbal skills (Similarities), which are already impaired at an early age (Meier *et al.* 2014). These declines were not associated with use of antipsychotic medication or substances (Meier *et al.* 2014). Given premorbid IQ was an estimate (rather than real-time measure) in one study (Norman *et al.* 2001) and cognitive deterioration was based on 'non-hold' tasks of neurocognitive function in two studies (Amminger *et al.* 2002; Gaynor *et al.* 2009), the finding of an association between DUP and cognitive deterioration index needs to be interpreted cautiously. Nevertheless, the current findings in combination with those of Meier *et al.* support the need for hypothesis-driven prospective studies examining processing speed in relation to untreated psychotic symptoms.

The remaining significant findings between DUP and neurocognitive measures were only observed in samples with a mean DUP <360 days (including the WCST-perseverative errors finding). This suggests that the relationship between neurocognitive performance and psychosis may be strongest closer to the onset of illness. Neurocognitive performance on specific tests was not reported as poorer (or better) in studies with a DUP >360 days. This finding highlights that the first year after illness onset may be especially critical for treatment and supports the rationale for early intervention in psychosis.

The finding of an association between longer DUP and poorer performance on the TMT-A and B in studies with mean DUP <360 days indicates that onset of psychosis may be particularly associated with a decline in functions mediating performance on this task, including visuomotor processing speed (Part A) and divided attention and working memory (Part B) (Lezak *et al.* 2004). The aforementioned longitudinal study showed that measures of processing speed are especially sensitive to neurocognitive decline prior to illness onset (Meier *et al.* 2014). Furthermore, processing speed has been found to be the most impaired neurocognitive domain in established psychotic disorder (Dickinson *et al.* 2007; Mesholam-Gately *et al.* 2009). What is unclear is whether these deficits are state-related impairments in association with symptomatology, whether they reflect progressive decline in association with a 'neurotoxic' process, or whether they represent developmental lag in neurocognitive functions underpinning TMT performance (Reichenberg *et al.* 2010). Another possible explanation is that longer DUP and poorer TMT performance are markers of a more severe subtype of illness (McGlashan, 1999, 2006). Again, hypothesis-driven studies with a specific focus on TMT performance are needed.

In studies with mean DUP <360 days, the finding that fewer WCST-perseverative errors (a putative index of cognitive flexibility) and higher FSIQ (general intelligence) were associated with longer mean DUP is unexpected. Interestingly, research in healthy adolescents and young adults has found that WCST-preservative errors and measures of intelligence are highly negatively correlated (Ardila *et al.* 2000; Kafadar & Orhan, 2016), so the converging findings between these two measures may not be co-incidental. There are several speculative explanations for these findings, including that both DUP and WCST/IQ measures might be correlated with a third variable (Marshall *et al.* 2005). For example, delayed help-seeking may occur due to factors that are associated with having higher cognitive flexibility (i.e. less perseveration) and higher IQ. Such factors may include better insight (Nair *et al.* 2014), higher perceived stigma, substance use (Donoghue & Doody, 2012), increased social support and/or the use self-help or alternative treatment approaches.

Fewer perseverative errors on the WCST have been found to be highly correlated with better insight, particularly appropriate relabelling of symptoms, in acutely psychotic individuals with early psychosis (Drake & Lewis, 2003). It is possible that higher insight combined with better cognitive flexibility equips an individual with the capacity for implementing effective coping and problem-solving strategies or trialling alternative approaches to manage their illness, before seeking treatment from specialist psychosis services. It is also possible that this combination is associated with higher perceived stigma and heightened

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Table 2. Meta-analysis of the correlation between DUP and neurocognitive domains

				Meta-analysis (random model) correlation mean (95% CI)						Test of heterogeneity			
Neurocognitive domain	Study *N*	Not reporting correlation *N*[a]	Participants *N*	Cohen's *d*	Correlation	Lower	Upper	*Z*	*p*	*Q* test	*p*	I^2	Fail safe *N*
Attention/Vigilance	9	5	1282	−0.058	−0.030	−0.085	0.026	−1.049	0.294	6.157	0.630	0.000	0
Motor Speed	5	1	732	−0.091	−0.046	−0.150	0.059	−0.862	0.389	7.524	0.111	46.837	0
Speed of Processing	10	1	1219	−0.028	−0.016	−0.077	0.046	−0.499	0.618	10.230	0.332	12.020	0
Working Memory	9	5	1275	−0.036	−0.018	−0.073	0.038	−0.633	0.527	2.248	0.972	0.000	0
Executive Functioning	12	4	1394	−0.092	−0.046	−0.106	0.015	−1.486	0.137	13.727	0.248	19.866	0
Verbal Fluency	6	3	981	0.063	0.032	−0.031	0.095	0.991	0.322	2.426	0.788	0.000	0
Verbal Learning & Memory	10	2	1446	−0.005	−0.002	−0.054	0.050	−0.089	0.929	7.129	0.624	0.000	0
Visual Learning & Memory	6	0	755	−0.026	−0.013	−0.094	0.067	−0.322	0.747	6.087	0.298	17.861	0
Verbal/Language Skills	6	0	699	−0.125	−0.064	−0.138	0.011	−1.675	0.094	4.747	0.448	0.000	4
Visuospatial Skills	5	2	778	0.020	0.011	−0.108	0.130	0.187	0.852	11.001	0.027	63.640	0
Global Cognition	3	0	526	−0.062	−0.031	−0.138	0.076	−0.567	0.571	2.767	0.251	27.711	0
Cognitive deterioration index[b]	4	1	246	−0.325	−0.213	−0.344	−0.074	−2.981	0.003	3.523	0.318	14.840	8
All combined	18		2106	−0.057	−0.033	−0.077	0.012	−1.421	0.155	18.020	0.388	5.661	0

DUP, duration of untreated psychosis; CI, confidence interval.
[a]When the correlation was not reported we used a conservative estimation of $p = 1$ and also conducted a sensitivity analysis with $p = 0.5$; these confirmed that results did not change.
[b]Cognitive deterioration index is a cross-sectional calculation of current IQ minus estimated premorbid IQ, with a higher discrepancy between the two indicating greater cognitive deterioration.

Table 3. Meta-regression analysis of the influence of DUP on neurocognitive task performance

			Meta-regression (random model) β coefficient, mean (95% CI)				
Neurocognitive test	Study *N*	Participants *N*	β[a]	Lower	Upper	*Z*	*p*
Digit span forward (raw)	4	318	0.002	−0.002	0.004	1.02	0.309
Digit symbol coding (raw)	5	716	0.005	−0.019	−0.030	0.41	0.685
TMT – Part A (raw)[b]	11	754	0.013	−0.011	0.037	1.05	0.295
TMT – Part B (raw)[b]	7	520	0.036	−0.011	0.083	1.51	0.132
AVLT – immediate recall total (raw)	7	769	0.001	−0.005	0.007	0.19	0.848
AVLT delayed recall (raw)	4	124	−0.002	−0.011	0.007	−0.51	0.610
Semantic verbal fluency (raw)	6	490	−0.002	−0.012	0.007	−0.49	0.625
WCST-completed categories (raw)	11	819	0.002	−0.006	0.009	0.43	0.668
WCST-perseverative errors (raw)[b,c]	5	569	−0.031	−0.048	−0.013	−3.36	<0.001
Verbal IQ	7	478	−0.005	−0.031	0.022	−0.34	0.735
Performance IQ	7	478	−0.017	−0.044	0.009	−1.28	0.202
Full-Scale IQ	17	1199	−0.0004	−0.005	0.005	−0.17	0.865
DUP <360 days							
TMT – Part A (raw)[b]	8	442	0.052	0.025	0.079	3.82	<0.001
TMT – Part B (raw)[b]	5	388	0.117	0.036	0.198	2.83	0.005
AVLT – immediate recall total (raw)	4	525	0.031	−0.100	0.163	0.47	0.642
Semantic verbal fluency (raw)	4	392	−0.003	−0.032	0.027	−0.18	0.853
WCST-completed categories (raw)	9	749	0.008	−0.000	0.017	1.91	0.056
Verbal IQ	4	202	0.007	−0.042	0.055	0.27	0.788
Performance IQ	4	202	0.018	−0.047	0.083	0.55	0.583
Full-Scale IQ	11	555	0.051	0.015	0.087	2.76	0.006

DUP, duration of untreated psychosis; CI, confidence interval; TMT, Trail Making Test; AVLT, Auditory Verbal Learning Test; WCST, Wisconsin Card Sorting Test; IQ, Intelligence Quotient.
[a]Positive β values mean that the longer the DUP the higher the cognitive score. $\beta < 0.2$ is considered a weak, $\beta < 0.2$ to <0.50, a moderate and $\beta > 0.5$, a strong effect.
[b]Higher score means a poorer performance.
[c]All included studies had mean DUP <360 days.

awareness regarding potentially negative long-term implications related to being treated for psychosis (Brekke *et al.* 2001), which may lead to avoidance of and delayed treatment seeking. In support of this, concealing one's diagnosis due to anticipated discrimination was predicted by being younger and having a higher level of education (a possible proxy for IQ), in a large multi-site cohort of individuals with schizophrenia (Ucok *et al.* 2012).

It is known that early detection efforts can reduce delays in psychosis treatment, which is associated with better long-term clinical and functional outcomes (Petersen *et al.* 2005; Hegelstad *et al.* 2012; Kane *et al.* 2016). However, it is currently unclear whether earlier intervention for psychosis is associated with better neurocognitive outcomes. While this meta-analysis cannot address this question directly, it provides tentative evidence suggesting that the year following onset of frank psychotic symptoms may be a heightened critical period ('window'), when interventions may maximally benefit neurocognitive course. Studies are needed to test this. While challenging from an ethical and practical perspective, study designs could 'manipulate' the DUP by delaying aspects of treatment such as antipsychotic prescription, to determine whether this impacts on subsequent neurocognitive outcomes (Francey *et al.* 2010).

A limitation of this meta-analysis is that the assessment of DUP in the included studies depended on retrospective recall, which may not be reliable. Furthermore, definitions of DUP and methods for assessing it varied widely across studies and few studies used standardised assessment methods, which may influence DUP estimates (Polari *et al.* 2011). Further, the severity and persistence of untreated psychotic symptoms was not taken into account and may be important, particularly in relation to the neurotoxicity hypothesis (Cropley *et al.* 2013). Our inclusion of studies with up to 2 years of prior treatment could be viewed as a limitation. Twenty-four of the 43 included studies reported <6 months of prior medication exposure, while the remaining 19 studies did not provide this information (but described their sample as FEP). While we assessed medication-naïve status and dose as a potential moderator of the relationship between DUP and neurocognition, as many studies did not report on medication exposure there is some uncertainty regarding medication effects. Moreover, as the second part of our meta-analysis involved use of secondary data, those studies were not hypothesis-driven and thus, not designed to specifically test the neurotoxicity hypothesis. We did not correct for multiple comparisons, which would have resulted in an alpha of 0.05/32 = 0.0016, resulting in only significant findings for TMT-A and WCST-perseverative errors. The

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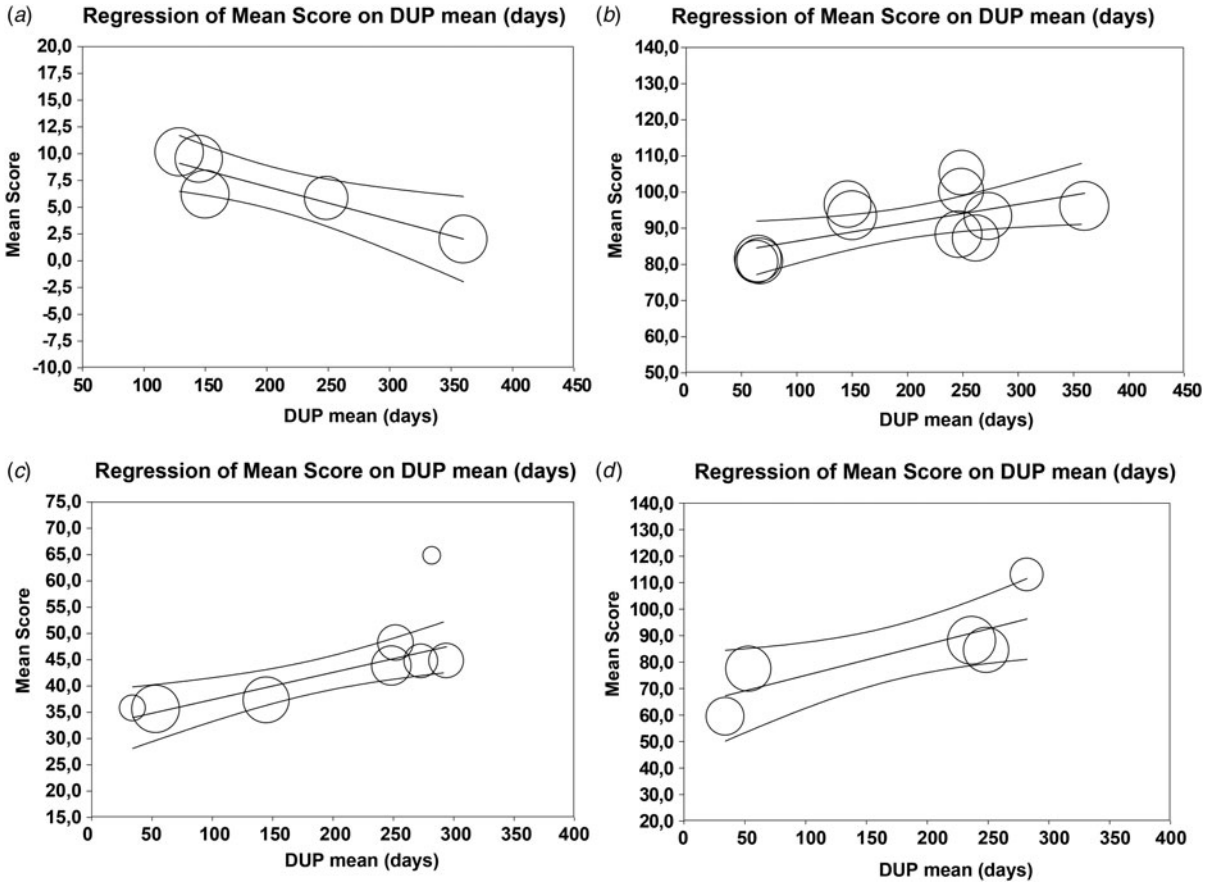

Fig. 2. Significant associations between DUP and neurocognitive performance in studies with DUP <360 days. (*a*) WCST – Perseverative Errors (*b*) Full-Scale IQ (*c*) TMT-A (*d*) TMT-B. DUP, duration of untreated psychosis; WCST, Wisconsin Cart Sorting Test; IQ, intelligence quotient; TMT, Trail Making Test.

significance level was not reported in some correlation studies that reported non-significant relationships between DUP and neurocognition, which may bias the meta-analysis. In this case, it is recommendable to use a conservative method to diminish risk of bias. We conducted a sensitivity analysis using $p = 0.5$ to confirm that the results were replicable. The data in this meta-analysis were cross-sectional [with the exception of Caspi *et al.* (2003)] and therefore, causality cannot be determined. Rigorous hypothesis-driven studies aimed at testing the neurotoxicity hypothesis need to comprise prospective longitudinal designs recruiting individuals before the onset of psychotic symptoms and assess whether the onset and persistence of symptoms is associated with poorer neurocognitive outcomes (Woodberry *et al.* 2013; Meier *et al.* 2014; Rund, 2014).

To conclude, this meta-analysis provides evidence for a significant association between longer DUP and larger cognitive deterioration index and poorer performance on the TMT in FEP. In contrast, longer DUP was associated with higher general intelligence and cognitive flexibility as indexed by FSIQ and WCST-perseverative errors. With the exception of the cognitive deterioration index, these relationships were only evident in studies with a mean DUP <360 days. Converging evidence suggests that this period reflects a critical treatment window for the prevention of poor long-term outcomes in FEP. Hypothesis-driven prospective studies are needed to clarify whether these findings are due to longer periods of untreated psychosis having a deleterious effect in patients with FEP or both factors characterising a subgroup of patients with greater severity. Future research should also aim to identify the factors associated with higher IQ and cognitive flexibility that may lead to delayed help-seeking.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717003002.

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