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Neuropsychological Function at First Episode in Treatment-Resistant Psychosis: Findings from the ÆSOP-10 Study

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Abstract

Background

Neuropsychological investigations can help untangle the etiological and phenomenological heterogeneity of schizophrenia, but have scarcely been employed in the context of treatment-resistant schizophrenia. No population-based study has examined neuropsychological function in the first-episode of treatment-resistant psychosis.

Methods

We report baseline neuropsychological findings from a longitudinal, population-based study of first-episode psychosis, which followed up cases from index admission to 10 years. At the 10-year follow up patients were classified as treatment responsive or treatment resistant after reconstructing their entire case histories. Of 145 cases with neuropsychological data at baseline, 113 were classified as treatment responsive, and 32 as treatment resistant at the 10-year follow-up.

Results

Compared to 257 community controls, both case groups showed baseline deficits in three composite neuropsychological scores, derived from principal component analysis: verbal intelligence and fluency, visuospatial ability and executive function, and verbal memory and learning (*P* values≤0.001). Compared to treatment responders, treatment-resistant cases showed deficits in verbal intelligence and fluency, both in the extended psychosis sample (t=-2.32; *P*=0.022) and in the schizophrenia diagnostic subgroup (*t*=-2.49; *P*=0.017). Similar relative deficits in the treatment-resistant cases emerged in sub-/sensitivity analyses excluding patients with delayed-onset treatment resistance (*P* values<0.01-0.001) and those born outside the UK (*P* values<0.05).

Conclusions

Verbal intelligence and fluency are impaired in patients with treatment-resistant psychosis compared to those who respond to treatment. This differential is already detectable – at a group level - at the first illness episode, supporting the conceptualisation of treatment-resistant psychosis as a severe, pathogenically distinct variant, embedded in aberrant neurodevelopmental processes.

Keywords: Cohort study; population-based; psychosis; schizophrenia; first episode; treatment resistant; neuropsychological

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Introduction

Schizophrenia and other psychoses are severe neuropsychiatric disorders, heterogeneous in aetiology, clinical trajectory and treatment response (Fanous & Kendler, 2005; van Os, 2016). In approximately 30% of schizophrenia patients, psychotic symptoms respond poorly, if at all, to most antipsychotics, with the notable exception of clozapine (Elkis & Buckley, 2016; Howes *et al*. 2017; Gillespie *et al*. 2017). This emerged as the gold-standard pharmacological intervention for 'treatment-resistant schizophrenia' (TRS) in 1988 (Kane *et al*. 1988). Since then, studies have varied considerably in their definitions of TRS (Howes *et al*. 2017), although there is a consistent minimum requirement of two periods of adherence to two different antipsychotics, each administered at adequate doses (variously defined) for at least 4 weeks, resulting in symptom reductions of less than 20% (Gillespie *et al*. 2017).

Recent evidence suggests that TRS is neurobiologically and categorically distinct from treatment-responsive schizophrenia (Gillespie *et al*. 2017). Unlike treatment-responsive patients, treatment-resistant (TR) ones do not exhibit elevation in dopamine synthesis capacity (Demjaha *et al*. 2012), and instead, show elevated glutamate levels in the anterior cingulate cortex (Demjaha *et al*. 2014). In addition, previous findings from the ÆSOP-10 study (Aetiology and Ethnicity in Schizophrenia and Other Psychoses) by our group showed that 84% of TR patients were resistant from illness onset (primary TRS), while the remaining 16% made an initial response to antipsychotics, but became TR

later (secondary TRS) (Demjaha *et al.* 2017). Lally and colleagues (2016) showed similar results in the GAP (Genetics and Psychosis) first-episode study, with 70% of TR patients having primary TRS.

Despite emerging evidence that specific combinations of cognitive deficits define disease heterogeneity as related to treatment response (Gilbert *et al*. 2014), neuropsychological investigations largely remain an untapped resource for characterising the origin and mechanism of TRS. To date, only six studies have compared neuropsychological function between treatment-resistant and treatment-responsive patients with psychosis, showing the former to have consistent relative deficits in verbal domains, such as language, verbal intelligence, verbal memory, verbal fluency and verbal interference (Joober *et al.* 2002; de Bartolomeis *et al*. 2013; Iasevoli *et al.* 2016), less consistently reported deficits in nonverbal domains, such as performance intelligence, processing speed, visuospatial function and visual memory (Joober *et al*. 2002; Bourque *et al*. 2013; Frydecka *et al*. 2016), and no cognitive differences from treatment-responsive patients in one study (Anderson *et al*. 2015).

All the above studies have involved cross-sectional investigations of chronically ill samples with schizophrenia or schizoaffective disorder, and with established group differences in treatment response and medication profiles. The respective research designs and methodologies have allowed limited conclusions with regard to two important questions: 1) Do neuropsychological differences between treatment-resistant and treatment-responsive individuals reflect premorbid differences, or the impact of non-remitting psychosis? 2) Do findings from TRS generalise to other psychoses?

To address these questions, we examined baseline neuropsychological data from ÆSOP-10, a population-based study of first-episode psychosis with a 10-year follow-up (Fearon *et al*. 2006; Morgan *et al*. 2006; Morgan *et al*. 2014). All neuropsychological assessments were carried out during the patients' first episode of psychosis, approximately 10 years before participants were characterised as TR or treatment responsive following detailed re-constructions of their case histories by the ÆSOP team (Demjaha *et al*. 2017). In line with the TRS literature and with additional neuropsychological

findings in support of dimensional models of psychosis (Kravariti *et al*. 2012), we predicted that TR patients would show deficits in verbal tasks of intelligence, fluency and memory compared to treatment-responsive patients and community controls, both among participants with schizophrenia and in the extended sample with various psychoses.

Methods

The ÆSOP-10 Study

The present analysis included baseline neuropsychological, sociodemographic and clinical data from ÆSOP-10 (Aetiology and Ethnicity in Schizophrenia and Other Psychoses), a 10-year longitudinal follow-up, population-based study of first-episode psychosis (FEP) (Fearon *et al*. 2006; Morgan *et al*. 2006). The study identified all individuals aged 16–65 years with FEP [codes F20–F29 and F30–F33 in the International Classification of Diseases, 10th Revision (ICD-10) manual (World Health Organisation: WHO, 1992a)], who presented to specialist mental health services in tightly defined catchment areas in Southeast London, Nottingham and Bristol between September 1997 and August 2000. Exclusion criteria were previous contact with health services for psychosis, organic causes of psychotic symptoms, transient psychosis due to acute intoxication (as defined by ICD–10) and IQ<50. [Due to the primary focus of this analysis on neuropsychological functions, we used a higher threshold of inclusion herein: IQ>69, as assessed by the Wechsler Intelligence Scale-Revised) (WAIS-R) (Wechsler, 1981)]. The study further included a random sample of community controls with no past or present psychotic disorder, recruited using mainly a sampling method that matched cases and controls by area of residence. Across the three centres, 568 cases with consensus diagnoses of psychotic illness who met the study inclusion criteria, and 412 community controls, were identified. Patients provided detailed contact information for themselves, their General Practitioners (GPs) and relatives, and consent to be re-contacted for follow-up. Ethical approvals for the baseline and follow-up studies were obtained from local research ethics committees. Detailed overviews of the ÆSOP

study design and procedures have been published elsewhere (Fearon *et al*. 2006; Morgan *et al*. 2006; Morgan *et al*. 2014; Demjaha *et al*. 2017).

Baseline Assessment of Sociodemographic and Clinical Characteristics

Sociodemographic data were collected by interviews with the participants using the Medical Research Council Sociodemographic Schedule (Mallett, 1997). Information gaps were filled using additional data sources, including case notes and other informants. Clinical data were collected as soon as possible after first contact with psychiatric services using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1992b). The SCAN incorporates the Present State Examination (PSE) - Version 10, which was used to elicit symptom-related data at presentation. Where a patient interview was not possible, case notes and, when available, information from informants, were used to complete the SCAN Item Group Checklist. Baseline symptom scores were further subjected to factor analysis, giving rise to five psychopathological dimensions: manic, reality distortion, negative, depressive and disorganization symptom dimensions (for full details, see Demjaha *et al*. 2009). Patients' ICD–10 diagnoses were determined using the SCAN data on the basis of consensus meetings involving a principal investigator (PI) and other members of the research team with satisfactory interrater reliability (kappa values ranged from 0.63 to 0.75, $P<0.001$). Duration of untreated psychosis (DUP) was defined as the period from the onset of psychosis to first contact with statutory mental health services (for full details, see Morgan *et al*. 2006). Data on illicit substance use before first presentation to mental health services were collected retrospectively using an ad hoc secondary data collection schedule, which collated data on prevalence and type of illicit substance use from relatives or carers, from the SCAN (WHO, 1992b) and from clinical case notes. Controls were screened for psychosis using the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995). Those with a positive rating were further assessed using the SCAN (WHO, 1992b) and, where appropriate, excluded.

Baseline Neuropsychological Assessment

The present analysis included neuropsychological data collected at baseline using the National Adult Reading Test-Revised (NART-R) (Nelson & Willison, 1991), assessing premorbid intelligence; the Vocabulary, Comprehension, Block Design and Digit Symbol subtests of the WAIS-R (Wechsler, 1981), assessing verbal and non-verbal intelligence; trials 1-5 and 7 of the Rey Auditory Verbal Learning Test (RAVLT) (Spreen & Strauss, 1991), assessing immediate and delayed verbal recall and learning; the immediate Visual Reproduction trials of the Wechsler Memory Scale – Revised (WMS-R) (Wechsler, 1987), assessing visual memory; the Trail Making A (Reitan, 1958), Trail Making B (Reitan, 1958) and Letter-Number Span (Gold *et al*. 1997) tests of processing speed, working memory and executive function; and Category and Letter Verbal Fluency (category: 'body parts', 'fruits' and 'animals'; letter: F, A, S), assessing verbal ability and executive control.

Follow-up Clinical Assessment

At approximately 10 years after inclusion, we made an attempt to trace, re-contact and re-assess 557 ÆSOP participants with psychosis, who had initially been identified in the Southeast London and Nottingham centres. Using an extended version of the WHO Life Chart Schedule (LCS) (WHO, 1992c) and a Medication History Timeline, comprehensive information on psychopathology, all prescribed antipsychotic medications (start and end date, dosage, adherence, reasons for change or termination), substance use and contact with mental health services was collected and rated for the entire follow-up period using a wide range of information sources: medical case records, follow-up interview with participant or informants (where possible), treating clinicians, ward and community prescriptions, medication charts and clinical documentation (including, where available, reports of drug level testing, and correspondence from the prescribing clinician/to general practitioners). Using the above sources, adherence to each prescribed antipsychotic throughout the period it was prescribed was rated on a three-point scale (1: 0-33%; 2: 34-67%; 3: 68-100%), using 68% as cut-off for 'adherence'. Presence of symptoms at follow-up was further assessed using the Scan - Version 2

(WHO, 1994). Based on all available information, case histories were reconstructed for the entire follow-up period to complete all sections of the Life Chart. A detailed overview of the follow-up clinical assessment procedures has been published elsewhere (Morgan *et al*. 2014; Demjaha *et al*. 2017).

Representativeness of the Follow-Up Sample

Of the 557 cases who were initially recruited, 434 (78%) underwent follow-up assessments. There were no marked differences in gender, ethnicity, duration of untreated psychosis, or diagnosis between the cases who underwent follow-up assessments and those who were lost to follow-up, except that the follow-up sample was younger (t=2.5; P=0.02).

Criteria for Treatment Response and Treatment Resistance

'Response to treatment' was defined as a state of no or mild symptoms (SCAN score<2), not interfering with daily functioning, lasting at least 6 months (Andreasen *et al.* 2005). In line with National Institute for Health and Care Excellence (NICE) criteria (National Institute for Health and Care Excellence, 2014), patients were classified as 'Treatment Resistant' (TR), if, despite recorded adherence to medication, they continued to show positive symptoms of at least moderate severity (SCAN score≥2) following two sequential trials of antipsychotic medication at a daily dose of 400–600 mg of chlorpromazine equivalence, each lasting at least 4 weeks. Patients were classified as 'Treatment Resistant from Illness Onset' (TRO) if they met resistance criteria after the first two trials of antipsychotic medication, and as 'Delayed Onset Treatment Resistant' (DOTR), if such criteria were met after a period of response to treatment. An individual meeting treatment resistance criteria, but later meeting treatment response criteria, would have been classified as treatment resistant. However, the ÆSOP-10 Study did not identify individuals whose response to medication improved during the course of illness. Of the 50 patients who received clozapine (by definition treatment resistant), 14 (28%) were clozapine responders, 12 (24%) were clozapine resistant, and the remaining

24 (48%) could not be classified, due to a suboptimal clozapine trial or insufficient clinical and response data (Demjaha *et al.* 2017).

Representativeness of the Follow-Up Sample that was evaluated for Treatment Response

Of the 434 cases who were assessed at follow-up, 212 (49%) met criteria for treatment response, 74 (17%) met criteria for treatment resistance (of whom 62: 84% were TRO) and 37 (9%) had never received an adequate trial of antipsychotic medication and could not be included in either category. The remaining 111 participants (26%) had incomplete clinical information documentation and could not be classified. Cases with complete information did not differ notably from the remainder of the follow-up sample in terms of age, gender, ethnicity, DUP or diagnosis (Demjaha *et al.* 2017).

Statistical Analysis

Data Reduction and Generation of Composite Neuropsychological Scores

To avoid the caveats of multiple testing and of experimenter assumptions during the grouping of cognitive tasks into overarching constructs (e.g. executive function), we reduced an original set of 13 neuropsychological variables to a small number of components, using Principal Component Analysis (PCA) with promac oblique rotation in Stata/MP 14.0 (37stataCorp, 2015). This was performed on the present analytic cohort, i.e. 402 ÆSOP participants (145 cases, 257 controls) with available neuropsychological data at baseline (all participants), and with entire case history reconstruction at the 10-year follow-up (cases only). Where appropriate, variables were inverse transformed to achieve normality of distribution. The selected cut-off for the variable loadings on the PCA components was 0.30, in line with recommendations that this has practical significance for sample sizes of at least 350 (Hair *et al.* 1998, p. 112). The oblique method was preferred over the varimax solution for its superior capacity to identify a simple factorial structure, particularly in datasets where the latent traits are correlated (Finch, 2006). The Kaiser-Meyer-Olkin (KMO) test of sampling adequacy was used to determine the factorability of the data. To generate composite neuropsychological scores (each

reflecting a participant's composite ability across variables with primary loadings on a certain component), we estimated PCA scores using Stata's predict command with the score option immediately after the PCA command. The PCA scores are expressed in standardized units based on linear combinations of the retained components.

Comparison of Composite Neuropsychological Scores across Study Groups

Statistical analysis was performed in Stata/MP 14.0 (37stataCorp, 2015). Each of the main and sensitivity (see below) analyses was a multivariable regression analysis with robust standard errors, comparing selected study groups or subgroups in each composite neuropsychological score. All main and sensitivity analyses co-varied for sociodemographic and (where appropriate) clinical variables that were associated with each composite score at $P<0.1$ in preliminary univariable linear regression analyses (see **Supplementary Table S1**). Composite neuropsychological scores were compared across the treatment-resistant (TR), treatment-responder (non-TR) and community control groups, as well as between TR and non-TR cases in the full patient sample and in the diagnostic subgroup with schizophrenia.

Performing separate analyses for cases who were Treatment Resistant from Illness Onset (TRO) and those who had Delayed-Onset Treatment Resistance (DOTR) would enhance the interpretability of our findings. However, this was not possible due to the small size of the DOTR subgroup (n=6). We instead repeated all data analytic steps in sub-analyses which excluded the DOTR patients.

Sensitivity Analysis

All main statistical analyses uniformly controlled for the effects of ethnicity and education. However, as the TR group had a higher proportion of Black ethnic minorities (47%) than the non-TR (24%) and control (14%) groups (see Results and **Table 1**), it was important to further address potential confounding influences of language in our analysis. We therefore assessed the sensitivity of our

findings to excluding all participants who had been born outside the UK, regardless of ethnicity or first language (n=58; 15 non-TR, 6 TR, 37 controls). This left in the analysis an all-UK-born sample who had attended compulsory schooling in the UK.

Missing Data

The level of completeness of sociodemographic and clinical information at the time of the baseline neuropsychological assessment was high (96-100% for socio-demographic variables and 82-100% for clinical variables). The high level of completeness at baseline is partly attributable to the temporal proximity of the sociodemographic, clinical and neuropsychological assessments, which were typically completed within a few days of each other. Antipsychotic medication history was re-constructed in detail at the 10-year follow up. Exact recording of neuropsychological testing dates at baseline was available only in a subset of cases, allowing us to map the participants' complex medication histories onto the dates of their neuropsychological testing in a subgroup of 75 cases (52%, 57 non-TR, 18 TR). Detailed information on the medication received by this subgroup is presented in Supplementary **Table S2**.

Results

Representativeness of the Analytic Cohort

Of the 286 cases who were classified in terms of treatment response at follow-up (see *Methods*), 136 cases (48%) lacked neuropsychological data at baseline, and 5 (2%) had IQ<70, leaving 113 non-TR cases, 32 TR cases (of whom 26: 81% were TRO), and 257 community controls in the present analysis. There were no notable differences in age, gender, DUP or diagnosis between the patient analytic cohort (n=145), and those who lacked neuropsychological data at baseline or met exclusion criteria (N=141). However, the patient analytic cohort (treatment-responders and TR cases combined) comprised a lower proportion of black ethnic minorities (29%) than the cases who lacked neuropsychological data or who met exclusion criteria (51%; Chi-Square=14.563, *P*=0.001).

Sociodemographic and Clinical Characteristics

The sociodemographic and clinical characteristics of the analytic cohort are presented in Table 1. Compared to controls, both patient groups were younger, had fewer years of education, and a higher proportion of male and Black participants (P<0.01-0.0001). Compared to treatment-responders, TR cases were younger, had a higher proportion of male and Black participants, a higher score on the negative symptom dimension, and a longer duration of untreated psychosis (P<0.05-0.0001) (Table 1). The two patient groups did not differ statistically significantly in illicit substance use [positive lifetime history present in 27 (25%) non-TR- and in 4 (12.5%) TR participants; Chi-Square=2.237, P=0.135)].

Data Reduction and Estimation of Composite Neuropsychological Scores

The PCA gave rise to a three-component solution (eigenvalues 1.20-5.78) accounting for 0.65% of the variance. The results of the promax rotation of the solution are presented in **Table 2**. NART IQ, WAIS-R Vocabulary, WAIS-R Comprehension, Phonological Verbal Fluency and Semantic Verbal Fluency showed primary loadings (0.306-0.520) on Component 1, which was labelled *Verbal Intelligence and Fluency*. WAIS-R Block Design, WAIS-R Digit Symbol and Trail Making (A & B) showed primary loadings (0.332-0.565) on Component 2, which was labelled *Visuospatial Ability and Executive Function*. The immediate and delayed recall trials of the RAVLT showed primary loadings (0.598-0.698) on Component 3, which was labelled *Verbal Memory and Learning*. The Kaiser-Meyer Olkin measure of sampling adequacy indicated that the sample had very high factorability (KMO=0.875). Composite neuropsychological scores (PCA scores) were generated for the three components and used in the remaining analyses.

Comparison of Composite Neuropsychological Scores across Study Groups

Tables 3 and **4** present the means and standard deviations of the composite neuropsychological scores in the three study groups, as well as the results and effect sizes of selected group comparisons. **Figure 1** presents the distribution of the composite scores in *Verbal Intelligence and Fluency* in the full analytic cohort divided by study group. Both patient samples were impaired in all composite scores compared to controls ($P \leq 0.001$) (**Table 3**), with moderate to large effect sizes in the treatment-responsive patients and with large to very large effect sizes in the treatment-resistant cohort.

Compared to non-TR patients, the TR cases performed worse in *Verbal Intelligence and Fluency* in all main analyses ($P<0.05$) (**Tables 3 & 4; Figure 1**), sub-analyses ($P<0.01$-0.001) (excluding DOTR case: **Supplementary Tables S3-S4**), and sensitivity analyses ($P<0.05$) (excluding non-UK-born participants**: Supplementary Tables S5-S6**).

In the schizophrenia subgroup, TR cases performed worse than non-TR patients in *Visuospatial Ability and Executive* Function ($P<0.05$) (**Table 4**), but the finding did not persist in our sub-analyses or sensitivity analyses (**Supplementary Tables S3-S6**).

Discussion

Summary of Findings

Our analysis of baseline data from the ÆSOP-10 longitudinal, population-based study of first-episode psychosis provides a snapshot of neuropsychological function at the earliest stages of treatment-resistant psychosis. Both treatment-resistant and treatment-responsive patients with schizophrenia and other psychoses showed generalised neuropsychological deficits in verbal intelligence and fluency, visuospatial abilities and executive function, and verbal memory and learning compared to community controls. Furthermore, treatment-resistant patients showed, on average, impairments in verbal intelligence and fluency compared to treatment responders, replicating previous findings (Joober *et al.* 2002; Frydecka *et al.* 2016). This differential was an enduring finding of our analyses –

evident for individuals with schizophrenia, those with any psychoses, psychotic and schizophrenia patients born in the UK, and after excluding cases with delayed-onset treatment resistance.

Methodological Considerations

This is the first longitudinal, population-based study of first-episode psychosis that compared baseline neuropsychological function across patients with longitudinally-defined TR- and non-TR psychosis and community controls. The study draws on unique methodological advantages: The epidemiological source and robust size of the combined patient and community control groups increased the representativeness of our cohort and generalisability of our findings, whilst facilitating stringent statistical controls (including a sensitivity analysis) for a wide array of clinical, sociodemographic, and language confounders. Analysing neuropsychological data from the first episode minimised information bias (i.e. examiners did not know the participants' treatment response status at the time of testing) and reduced differentiation in clinical features between the two patient groups. Specifically, in contrast to all previous neuropsychological studies of TRS (Joober *et al.* 2002; de Bartolomeis *et al.* 2013; Bourque *et al.* 2013; Anderson *et al.* 2015; Frydecka *et al.* 2016; Iasevoli *et al.* 2016), our patient groups did not seem to differ notably in treatment profiles or medication doses at the time of testing (based on a subgroup analysis). These aspects served to further reduce confounding in our analysis.

Methodological limitations of our study include loss to follow up; limitations on clinical data accuracy associated with case history reconstruction; the availability of baseline neuropsychological testing dates for only a subgroup of patients; the lack of screening for family history of psychosis in community controls; and the moderate size of the treatment-resistant cohort. A deficit in verbal intelligence and fluency in TR patients compared to responders was a highly consistent finding across our main analyses, sub-analyses and sensitivity analyses. However, we cannot exclude the possibility that additional deficits are integral to TR psychosis, particularly in relation to schizophrenia (discussed below). Our selected cut-off for factor loadings (0.30) is among the lowest reported in the literature

(Peres-Neto *et al.* 2003), and may have reduced the clarity of the PCA components. Using a 0.40 cut-off would not have changed the pattern of findings (data available upon request). Finally, our analyses included baseline diagnoses. As with the extended ÆSOP sample (Heslin *et al.* 2003), most schizophrenia patients (77%) and 40% of those with 'other' diagnoses in our analytic cohort were classified as having schizophrenia at 10 years. Using diagnostic classifications at follow up, 31.5% of schizophrenia patients would have been classified as TR compared to 35.8% using baseline diagnoses.

Treatment-Resistant Psychosis as a Severe Neurodevelopmental Variant of Psychosis

The neurodevelopmental theory of schizophrenia posits the existence of a neurodevelopmental subtype of schizophrenia, which is the end product of aberrant neurodevelopmental processes unfolding from conception or early life (Murray *et al.* 1992). It has been suggested that primary TRS has a distinct neurodevelopmental origin, while secondary TRS may arise through the induction of dopamine super-sensitivity, or after periods of relapse, although a later emergence of an intrinsic treatment resistance, or a combination of underlying factors cannot be ruled out (Lally *et al.* 2016; Gillespie *et al.* 2017; Demjaha *et al.* 2017). The clinical and demographic profiles of the treatment-resistant cases in the present study largely encapsulate the defining features of 'neurodevelopmental schizophrenia' – younger, 'more male', with an earlier age of onset, more severe negative symptoms, more severe cognitive impairment and a longer duration of untreated psychosis (Murray *et al.* 1992). Three further observations suggest a pathogenic origin for the observed verbal deficit in the treatment-resistant group compared to treatment-responsive individuals. Firstly, the impairment was established by the first episode, arguing against the deficit being caused by non-remitting psychosis. Secondly, Vocabulary and NART-R, two tasks with primary loadings on Verbal Intelligence and Fluency, are reliable tests of premorbid ability, and are both resistant to brain pathological changes (de Oliveira *et al.* 2014; Bright *et al.* 2002). Finally, the pattern of deficits in verbal intelligence and fluency was accentuated (deficits were significant at a lower level of statistical significance) after removing cases with secondary treatment resistance.

Black participants were over-represented among treatment resistant patients. Although Black ethnicity is not a defining feature of 'neurodevelopmental schizophrenia' (Murray *et al.* 1992), the finding is in keeping with evidence that treatment resistance is associated with early first contact with psychiatric services (<20 years), and more so in Black (OR 3.71) than in White (OR 1.60) patients (Lally *et al.* 2016). Indeed, a closer look at our data revealed that only 9.4% of White patients, but 21.4% of Black patients had a first contact with psychiatric services before age 20, which may have increased disproportionately the outcome of treatment resistance in the Black ethnic group.

Treatment-Resistant Schizophrenia

An additional deficit in visuospatial ability and executive function emerged in TR- compared to non-TR patients in the schizophrenia subgroup. This finding did not generalise to the 'all-diagnoses' group and did not persist in our sub-analyses or sensitivity analyses. The finding is consistent with evidence that deficits in executive function, processing speed and verbal memory, albeit less salient in other diagnostic categories of psychosis, are prototypical of schizophrenia (Kravariti *et al.* 2009a; Kravariti *et al.* 2009b; Zanelli *et al.* 2010). As the size of the schizophrenia subgroup in the present study was modest, it is important to explore the significance of executive function and verbal memory deficits in treatment resistant schizophrenia in larger studies.

Integrating Neurodevelopmental and Glutamatergic Hypotheses of Treatment-Resistant Psychosis

Some recent findings implicate glutamate rather than dopamine as the primary neurotransmitter system impaired in treatment-resistant schizophrenia (Demjaha *et al.* 2012; Demjaha *et al.* 2014; Gillespie *et al.* 2017). Glutamate plays an important role in several language-related neurodevelopmental processes. This highlights the possibility that core deficits in verbal intelligence and fluency, a neurodevelopmental aetiology, and a primary glutamatergic dysfunction may converge in a single model of treatment-resistant psychosis. Several lines of evidence support this possibility: pre-reading language abilities (e.g. phonological processing) show significant correlations with

glutamate in the anterior cingulate of healthy preschool-aged children (Lebel *et al.* 2016); microdeletions in glutamate receptors have been implicated in developmental delays predominantly affecting language and fine motor skills (Takenouchi *et al.* 2014); the high-risk metabotropic glutamate receptor 3 (GRM3) haplotype is associated with schizophrenia, as well as with deficits in verbal fluency and verbal list-learning (Spangaro *et al.* 2012); and poor-functioning subjects at ultra-high-risk for psychosis show a negative relationship between thalamic glutamate levels and prefrontal-striatal activation during a verbal fluency task (Allen *et al.* 2015).

Clinical and Research Implications

Neuropsychological deficits weigh disproportionally on the psychosocial and functional toll of psychosis (Kaneda *et al.* 2010; Shamsi *et al.* 2011; Iasevoli *et al.* 2016). Encouragingly, verbal fluency and executive function deficits, which differentiated TR from non-TR patients in the present study, do not seem refractory to pharmacological interventions. Indeed, there is strong evidence that clozapine improves attention and verbal fluency, and moderate evidence that it improves some types of executive function (Meltzer & McGurk, 1999; Woodward *et al.* 2005). In the only studies to report equivalent verbal performances in TRS- and non-TRS patients to date, TR cases were uniformly treated with clozapine (Anderson et al. 2015; Bourque et al. 2013). These findings re-iterate the necessity of timely detection and tailored pharmacological interventions as early as possible in the course of treatment-resistant psychosis (Lally & MacCabe, 2016). They further highlight the importance of neuropsychological constructs in designing multimodal research and clinical approaches to improving prognosis and personalised treatment (Gilbert *et al.* 2014).

Conclusion

A constitutional deficit in verbal intelligence and fluency, significantly exceeding – at a group level - the levels manifest in the general population of patients with psychoses, is a phenotypic indicator of treatment-resistant psychosis. Our findings are in keeping with emerging evidence that treatment-

resistant psychosis is a pathogenically distinct and severe variant, embedded in aberrant neurodevelopmental processes.

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Conflict of interest

There are no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

REFERENCES

Anderson VM, McIlwain ME, Kydd RR, Russell BR (2015). Does cognitive impairment in treatment-resistant and ultra-treatment-resistant schizophrenia differ from that in treatment responders? *Psychiatry Research* **230**, 811-818.

Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR (2005). Remission in schizophrenia, proposed criteria and rationale for consensus. *American Journal of Psychiatry* **162**, 441–449.

Allen P, Chaddock CA, Egerton A, Howes OD, Barker G, Bonoldi I, Fusar-Poli P, Murray R, McGuire P (2015). Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. *Schizophrenia Bulletin* **41**, 429-439.

de Bartolomeis A, Balletta R, Giordano S, Buonaguro EF, Latte G, Iasevoli F (2013). Differential cognitive performances between schizophrenic responders and non-responders to antipsychotics, correlation with course of the illness, psychopathology, attitude to the treatment and antipsychotics doses. *Psychiatry Research* **210**, 387-395.

Bebbington PE, Nayani T (1995). The psychosis screening questionnaire. *International Journal of Methods in Psychiatric Research* **5**, 11–20.

Bourque J, Lakis N, Champagne J, Stip E, Lalonde P, Lipp O, Mendrek A (2013). Clozapine and visuospatial processing in treatment-resistant schizophrenia. *Cognitive Neuropsychiatry* **18**, 615-630.

Bright P, Jaldow E, Kopelman MD (2002). The National Adult Reading Test as a measure of premorbid intelligence, a comparison with estimates derived from demographic variables. *Journal of the International Neuropsychological Society* **8**, 847-854.

Crawford JR, Besson JA, Bremner M, Ebmeier KP, Cochrane RH, Kirkwood K (1992). Estimation of premorbid intelligence in schizophrenia. *British Journal of Psychiatry* **161**, 69-74.

Demjaha A, Morgan K, Morgan C, Landau S, Dean K, Reichenberg A, Sham P, Fearon P, Hutchinson G, Jones PB, Murray RM, Dazzan P (2009). Combining dimensional and categorical representation of psychosis, the way forward for DSM-V and ICD-11? *Psychological Medicine* **39**, 1943-1955.

Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD (2012). Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *American Journal of Psychiatry* **169**, 1203-1210.

Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, McGuire PK (2014). Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biological Psychiatry* **75**, e11-13.

Demjaha A, Lappin JM, Stahl D, Patel MX, MacCabe JH, Howes OD, Heslin M, Reininghaus UA, Donoghue K, Lomas B, Charalambides M, Onyejiaka A, Fearon P, Jones P, Doody G, Morgan C, Dazzan P, Murray RM (2017). Antipsychotic treatment resistance in first-episode psychosis, prevalence, subtypes and predictors. *Psychological Medicine* **47**, 1981-1989.

Elkis H, Buckley PF (2016). Treatment-Resistant Schizophrenia. *Psychiatric Clinics of North America* **39**, 239-265.

Fanous AH, Kendler KS (2005). Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness, searching for a framework. *Molecular Psychiatry* **10**, 6-13.

Fearon P, Kirkbride JB, Morgan C, Dazzan P, Morgan K, Lloyd T, Hutchinson G, Tarrant J, Fung WL, Holloway J, Mallett R, Harrison G, Leff J, Jones PB, Murray RM, AESOP Study Group (2006). Incidence of schizophrenia and other psychoses in ethnic minority groups, results from the MRC AESOP Study. *Psychological Medicine* **36**, 1541-1550.

Finch H (2006). Comparison of the Performance of Varimax and Promax Rotations, Factor Structure Recovery for Dichotomous Items. *Journal of Educational Measurement* **43**, 39–52.

Frydecka D, Beszlej JA, Goscimski P, Kiejna A, Misiak B (2016). Profiling cognitive impairment in treatment-resistant schizophrenia patients. *Psychiatry Research* **235**, 133-138.

549 **Gilbert E, Merette C, Jomphe V, Emond C, Rouleau N, Bouchard RH, Roy MA, Paccalet T, Maziade**
550 **M** (2014). Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms
551 of outcome and response to treatment. *European Archives of Psychiatry & Clinical Neuroscience*
552 **264**, 333-343.
553 **Gillespie AL, Samanaite R, Mill J, Egerton A, MacCabe JH** (2017). Is treatment-resistant schizophrenia
554 categorically distinct from treatment-responsive schizophrenia? a systematic review. *BMC*
555 *Psychiatry* **17**, 12.
556 **Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR** (1997). Auditory working memory
557 and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of General Psychiatry*
558 **54**, 159-165.
559 **Hair JF, Tatham RL, Anderson RE, Black W** (1998). Multivariate data analysis. (Fifth Ed.)
560 Prentice-Hall: London.
561 **Heslin M, Lomas B, Lappin JM, Donoghue K, Reininghaus U, Onyejiaka A, Croudace T, Jones PB,**
562 **Murray RM, Fearon P, Dazzan P, Morgan C, Doody GA** (2015). Diagnostic change 10 years after
563 a first episode of psychosis. *Psychological Medicine* **45**, 2757-2769.
564 **Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield**
565 **MA, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson**
566 **M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F,**
567 **Glenthoj BY, Graff-Guerrero A, Hallak JE, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J,**
568 **Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Moller HJ, Nakajima S, Pantelis C, Reis**
569 **Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas**
570 **N, Ucok A, Umbricht D, Walters JT, Kane J, Correll CU** (2017). Treatment-Resistant
571 Schizophrenia, Treatment Response and Resistance in Psychosis (TRRIP) Working Group
572 Consensus Guidelines on Diagnosis and Terminology. *American Journal of Psychiatry* **174**, 216-
573 229.

Iasevoli F, Giordano S, Balletta R, Latte G, Formato MV, Prinzivalli E, De Berardis D, Tomasetti C, de Bartolomeis A (2016). Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* **65**, 34-48.

Joober R, Rouleau GA, Lal S, Dixon M, O'Driscoll G, Palmour R, Annable L, Bloom D, Lalonde P, Labelle A, Benkelfat C (2002). Neuropsychological impairments in neuroleptic-responder vs. -nonresponder schizophrenic patients and healthy volunteers. *Schizophrenia Research* **53**, 229–238.

Kane J, Honigfeld G, Singer J, Meltzer H (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry* **45**, 789-796.

Kaneda Y, Jayathilak K, Meltzer H (2010). Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder, cognitive impairment and clozapine treatment. *Psychiatry Research* **178**, 57-62.

Kravariti E, Morgan K, Fearon P, Zanelli JW, Lappin JM, Dazzan P, Morgan C, Doody GA, Harrison G, Jones PB, Murray RM, Reichenberg A (2009a). Neuropsychological functioning in first-episode schizophrenia. *British Journal of Psychiatry* **195**, 336-345.

Kravariti E, Reichenberg A, Morgan K, Dazzan P, Morgan C, Zanelli JW, Lappin JM, Doody GA, Harrison G, Jones PB, Murray RM, Fearon P (2009b). Selective deficits in semantic verbal fluency in patients with a first affective episode with psychotic symptoms and a positive history of mania. *Bipolar Disorders* **11**, 323–329.

Kravariti E, Russo M, Vassos E, Morgan K, Fearon P, Zanelli JW, Demjaha A, Lappin JM, Tsakanikos E, Dazzan P, Morgan C, Doody GA, Harrison G, Jones PB, Murray RM, Reichenberg A (2012). Linear and non-linear associations of symptom dimensions and cognitive function in first-onset psychosis. *Schizophrenia Research* **140**, 221-231.

Lally J, Ajnakina O, Di Forti M, Trotta A, Demjaha A, Kolliakou A, Mondelli V, Reis Marques T, Pariante C, Dazzan P, Shergil SS, Howes OD, David AS, MacCabe JH, Gaughran F, Murray RM (2016). Two distinct patterns of treatment resistance, clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychological Medicine* **46**, 3231-3240.

Lally J, MacCabe JH (2016). Personalised approaches to pharmacotherapy for schizophrenia. *BJPsych Advances* **22**, 78-86.

Lebel C, MacMaster FP, Dewey D (2016). Brain metabolite levels and language abilities in preschool children. *Brain and Behavior* **6**, e00547.

Mallett R (1997). *Sociodemographic Schedule*. Section of Social Psychiatry, Institute of Psychiatry.

Meltzer HY, McGurk SR (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophrenia Bulletin* **25**, 233-255.

Morgan C, Dazzan P, Morgan K, Jones P, Harrison G, Leff J, Murray R, Fearon P, AESOP study group (2006). First episode psychosis and ethnicity, initial findings from the AESOP study. *World Psychiatry* **5**, 40-46.

Morgan C, Lappin J, Heslin M, Donoghue K, Lomas B, Reininghaus U, Onyejiaka A, Croudace T, Jones PB, Murray RM, Fearon P, Doody GA, Dazzan P (2014). Reappraising the long-term course and outcome of psychotic disorders, the AESOP-10 study. *Psychological Medicine* **44**, 2713-2726.

Murray RM, O'Callaghan E, Castle DJ, Lewis SW (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin* **18**, 319-332.

Nelson, HE Willison JR (1991). *The Revised National Adult Reading Test–Test manual*. NFER-Nelson: Windsor.

National Institute for Health and Care Excellence (NICE) (2014). *Psychosis and Schizophrenia in Adults, Treatment and Management* (Clinical Guideline 178). Royal College of Psychiatrists: London.

623 **Ojeda N, Pena J, Sanchez P, Bengoetxea E, Elizagarate E, Ezcurra J, Gutierrez Fraile M** (2012).
624 Efficiency of cognitive rehabilitation with REHACOP in chronic treatment resistant Hispanic
625 patients. *Neurorehabilitation* **30**, 65-74.
626 **de Oliveira MO, Nitrini R, Yassuda MS, Brucki SM** (2014). Vocabulary is an appropriate measure of
627 premorbid intelligence in a sample with heterogeneous educational level in Brazil. *Behavioural*
628 *Neurology* **2014**, 875960.
629 **van Os J** (2016). "Schizophrenia" does not exist. *BMJ* **352**, i375.
630 **Patel MX, Arista IA, Taylor M, Barnes TR** (2013). How to compare doses of different antipsychotics,
631 a systematic review of methods. *Schizophrenia Research* **149**, 141-148.
632 **Peres-Neto PR, Jackson DA, Somers KM** (2003). Giving meaningful interpretation to ordination axes:
633 assessing loading significance in principal component analysis. *Ecology* **84**, 2347-2363.
634 **Rehse M, Bartolovic M, Baum K, Richter D, Weisbrod M, Roesch-Ely D** (2016). Influence of
635 Antipsychotic and Anticholinergic Loads on Cognitive Functions in Patients with Schizophrenia.
636 *Schizophrenia Research and Treatment* **2016**. (http//dx.doi.org/10.1155/2016/8213165).
637 Accessed 4 March 2018**.**
638 **Reitan RM** (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual*
639 *and Motor Skills* **8**, 271–276.
640 **Shamsi S, Lau A, Lencz T, Burdick KE, DeRosse P, Brenner R, Lindenmayer JP, Malhotra AK** (2011).
641 Cognitive and symptomatic predictors of functional disability in schizophrenia. *Schizophrenia*
642 *Research* **126**, 257-264.
643 **Spangaro M, Bosia M, Zanoletti A, Bechi M, Cocchi F, Pirovano A, Lorenzi C, Bramanti P, Benedetti**
644 **F, Smeraldi E, Cavallaro R** (2012). Cognitive dysfunction and glutamate reuptake, effect of EAAT2
645 polymorphism in schizophrenia. *Neuroscience Letters* **522**, 151-155.
646 **Spreen O, E Strauss** (1991). *A Compendium of Neuropsychological Tests, Administration, Norms and*
647 *Commentary*. Oxford University Press: New York.
648 **StataCorp** (2015). *Stata Statistical Software, Release 14*. College Station, StataCorp LP: TX.

Tabares-Seisdedos R, Balanza-Martinez V, Sanchez-Moreno J, Martinez-Aran A, Salazar-Fraile J, Selva-Vera G, Rubio C, Mata I, Gomez-Beneyto M, Vieta E (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of Affective Disorders* **109**, 286-299.

Takenouchi T, Hashida N, Torii C, Kosaki R, Takahashi T, Kosaki K (2014). 1p34.3 deletion involving GRIK3, Further clinical implication of GRIK family glutamate receptors in the pathogenesis of developmental delay. *American Journal of Medical Genetics* **Part A. 164A**, 456-460.

de la Vega A, Brown MS, Snyder HR, Singel D, Munakata Y, Banich MT (2014). Individual differences in the balance of GABA to glutamate in pFC predict the ability to select among competing options. *Journal of Cognitive Neuroscience* **26**, 2490-2502.

Wechsler D (1981). *Manual for the Wechsler Adult Intelligence Scale – Revised*. Psychological Corporation: New York.

Wechsler D (1987). *Wechsler Memory Scale – Revised Manual*. Psychological Corporation: New York.

Woodward ND, Purdon SE, Meltzer HY, Zald DH (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology* **8**, 457-472.

World Health Organization (WHO) (1992a). *The ICD–10 Classification of Mental and Behavioural Disorders, Clinical Descriptions and Diagnostic Guidelines*. World Health Organization: Geneva.

World Health Organization (WHO) (1992b). *SCAN (Schedules for Clinical Assessment in Neuropsychiatry)*. World Health Organization: Geneva.

World Health Organization (WHO) (1992c). The Life Chart Schedule. Developed by Ezra Susser, Sarah Conover, Carole Siegel and an International Team of WHO Investigators. World Health Organization: Geneva.

World Health Organization (WHO) (1994). SCAN (Schedules for Clinical Assessment in Neuropsychiatry), Version 2. World Health Organization: Geneva.

Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, Morgan C, Zanelli C, Demjaha A, Jones PB, Doody GA, Kapur S, Murray RM (2010). Specific and generalized neuropsychological deficits, a comparison of patients with various first-episode psychosis presentations. *American Journal of Psychiatry* **167**, 78-85.

678 **Table 1** Sociodemographic and Clinical characteristics in the Treatment-Responder, Treatment-Resistant and Community Control Groups

	Treatment-Responder (n=113)		Treatment-Resistant (n=32)		Community Control (n=257)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	***P≤***
Education (years) [a]	12.60	2.36	12.10	1.90	13.26	2.55	5.97	**0.003**
Age at Assessment (years) [b]	30.75	10.60	26.63	9.07	39.73	13.16	62.81	**0.0001**
Age at Illness Onset (years)	30.23	10.67	25.41	9.02	-	-	5.71	**0.018**
Days of Untreated Psychosis	197.58	528.52	633.04	1097.00	-	-	4.81	**0.030**
Antipsychotic Defined Daily Dose (DDD) [c]	334.66	238.56	427.81	229.71	-	-	1.89	0.174
Reality Distortion	3.41	2.55	4.00	3.24	-	-	0.70	0.405
Disorganisation	0.69	0.96	0.83	0.82	-	-	0.52	0.471
Negative Symptoms	1.21	1.76	2.38	2.62	-	-	4.36	**0.039**
Mania	1.94	2.73	1.63	2.32	-	-	0.33	0.568
Depression	1.43	1.85	1.09	1.84	-	-	0.70	0.405
	N	**%**	**N**	**%**	**N**	**%**	**Pearson χ^2**	***P≤***
Gender: [d]							17.39	**0.0001**
Male	63	55.8	25	78.1	109	42.4		
Female	50	44.2	7	21.9	148	57.6		
Ethnicity: [e, f]							Fisher's [f]	**0.001**
White	72	63.7	13	40.6	211	82.1		
Black	27	23.9	15	46.9	37	14.4		
Other	14	12.4	4	12.5	9	3.5		
Level of Completed Education: [g]							7.604	0.107
School	65	63.1	19	67.9	131	51.4		
Further	19	18.4	7	25.0	69	27.1		
Higher	19	18.4	2	7.1	55	21.6		
Diagnosis: [f]							Fisher's [f]	**0.004**
Schizophrenia	43	38.1	24	75.0	-	-		
Bipolar Disorder or Mania	24	21.2	2	6.3	-	-		
Depressive Psychosis	18	15.9	2	6.3	-	-		
Other Psychotic Disorder	28	24.8	4	12.5	-	-		
Antipsychotic Type [c, f]							Fisher's [f]	0.725
Typical	22	38.6	8	44.4	-	-		
Atypical	33	57.9	9	50.0	-	-		
Combination of Typical & Atypical	2	3.5	1	5.6	-	-		

679 [a] TR, non-TR<CC, [b] TR, non-TR<CC, TR<non-TR. [c] Data was available for a subset of 75 cases (52%). [d] Proportion Male: TR, non-TR>CC; TR>non-TR. Proportion Black: TR, non-TR>CC; TR>non-TR.
680 [f] As the statistical assumptions for the chi-square test were violated, Fisher's Exact Test was performed. [g] Level of completed education was missing for 16 participants (4%).

Table 2 Obliquely Rotated Component Loadings [1] for 13 Neuropsychological Variables in the analytic cohort [2] (n=402)

	Component Loadings		
	1	2	3
WAIS-R Vocabulary	0.520	0.103	0.025
WAIS-R Comprehension	0.487	0.124	0.067
NART-R IQ	0.485	0.045	-0.017
Phonological Verbal Fluency (Letter)	0.322	-0.122	-0.169
Semantic Verbal Fluency (Category)	0.306	-0.178	-0.119
Trail Making A	0.113	0.565	0.113
Trail Making B	0.064	0.505	0.030
WAIS-R Digit Symbol	0.027	0.416	0.016
WAIS-R Block Design	0.019	0.332	0.133
RAVLT Trials 1-5	0.090	0.046	0.598
RAVLT Trial 7	-0.047	0.052	0.698
WMS-R Visual Reproduction (Total Score)	-0.052	-0.254	0.236
Letter-Number Span	0.203	-0.126	0.155

Abbreviations: NART-R: National Adult Reading Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; WAIS-R: Wechsler Adult Intelligence Scale-Revised;

[1] Variables with primary loadings of >0.30 are set against a grey background, and high loadings of >0.50 are highlighted in red font. [2] The sample included participants who had undergone neuropsychological testing at baseline, had IQ ≥70, and could be classified (in the case of patients, retrospectively, i.e. at the 10-year follow-up) as treatment responders (n=113), treatment resistant (n=32), or community controls (n=257).

703 **Table 3** Comparison [a] of Composite Neuropsychological Scores across the Treatment-Responder, Treatment-Resistant and Community Control Groups

	Responder (n=113)		Treatment-Resistant (n=32)		Community Control (n=257)		Regression Model [a]	
	Mean	SD	Mean	SD	Mean	SD	$F_{(D.F.)}$	*P*≤
Verbal Intelligence & Fluency	-0.81	1.81	-1.91	1.68	0.59	1.64	$40.15_{(7, 386)}$	**0.0001**
Visuospatial Ability & Executive Function	-0.71	1.79	-1.29	2.00	0.47	1.66	$37.12_{(7, 387)}$	**0.0001**
Verbal Memory & Learning	-0.37	1.29	-1.13	1.43	0.30	1.37	$21.99_{(7, 386)}$	**0.0001**

	Cohen's *d* [b]		Cohen's *d* [c]		Post-Hoc Comparisons [a]					
					Responder vs. Control		Treatment Resistant vs. Control		Responder vs. Treatment Resistant	
	d	95% CI	*d*	95% CI	t	*P*≤	t	*P*≤	t	*P*≤
Verbal Intelligence & Fluency	-0.83	-1.06 -0.60	-1.52	-1.91 -1.13	-4.12	**0.001**	-5.22	**0.001**	2.35	**0.019**
Visuospatial Ability & Executive Function	-0.69	-0.92 -0.47	-1.04	-1.41 -0.66	-6.60	**0.001**	-5.32	**0.001**	1.44	0.150
Verbal Memory & Learning	-0.50	-0.72 -0.27	-1.04	-1.42 -0.66	-4.36	**0.001**	-4.38	**0.001**	1.94	0.053

704 [a] The effect of Group (Treatment Responder, Treatment Resistant, Community Control) on each Composite Score was examined using multivariable regression analysis with
705 robust standard errors, co-varying for demographic variables that emerged as significant (P<0.05) or suggestive (P<0.1) predictors of each Composite Score in preliminary
706 univariable linear regression analyses (Supplementary Table S1): Age, Ethnicity, Years of Education (all Composite Scores) and Gender (Verbal Intelligence & Fluency; Verbal
707 Memory & Learning). [b] Standardised mean difference the between treatment-responder and community-control groups; [c] Standardised mean difference between the
708 treatment-resistant and community-control groups.

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Table 4 Comparison of Composite Neuropsychological Scores between the Treatment-Responder and Treatment-Resistant Groups

	Independent Effect of Group (Responder vs. Treatment Resistant)					
	Coefficient	**Stand. Err.**	**95% CI**		**t**	***P≤***
						All Diagnoses
Verbal Intelligence & Fluency [a]	-0.76	0.32	-1.40	-0.12	-2.35	**0.020**
Visuospatial Ability & Executive Function [b]	-0.70	0.57	-1.84	0.45	-1.23	0.226
Verbal Memory & Learning [c]	-0.40	0.52	-1.46	0.66	-0.76	0.453
						Schizophrenia
Verbal Intelligence & Fluency [a]	-0.96	0.38	-1.72	-0.20	-2.56	**0.014**
Visuospatial Ability & Executive Function [b]	-1.55	0.61	-1.95	0.28	-2.55	**0.019**
Verbal Memory & Learning [c]	-0.35	0.74	-1.90	1.20	-0.48	0.640

[a] The effect of Group (Treatment Responder vs. Treatment Resistant) on *Verbal Intelligence & Fluency* was examined using multivariable regression analysis with robust standard errors, co-varying for demographic and clinical variables that emerged as significant (*P*<0.05) or suggestive (*P*<0.1) predictors of *Verbal Intelligence & Fluency* in preliminary univariable linear regression analyses (**Supplementary Table S1**): Age, Gender, Ethnicity, Years of Education, Negative Symptoms, Mania and Depression. The analysis for 'All Diagnoses' additionally co-varied for 'Diagnosis'.

[b] The effect of Group (Treatment Responder vs. Treatment Resistant) on *Visuospatial Ability & Executive Function* was examined using multivariable regression analysis with robust standard errors, co-varying for demographic and clinical variables that emerged as significant (*P*<0.05) or suggestive (*P*<0.1) predictors of *Visuospatial Ability & Executive Function* in preliminary univariable linear regression analyses (**Supplementary Table S1**): Age, Ethnicity, Years of Education, Age at Illness Onset, Negative Symptoms, Mania, Medication Dose (expressed in Defined Daily Dose units) and Illicit Substance Use [positive/negative lifetime history of, based on information collected from relatives or carers, the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; WHO, 1992b), clinical case notes and an extended version of the WHO Life Chart Schedule (WHO, 1992c)]. The analysis for 'All Diagnoses' additionally co-varied for 'Diagnosis'.

[c] The effect of Group (Treatment Responder vs. Treatment Resistant) on *Verbal Memory & Learning* was examined using multivariable regression analysis with robust standard errors, co-varying for demographic and clinical variables that emerged as significant (*P*<0.05) or suggestive (*P*<0.1) predictors of *Verbal Memory & Learning* in preliminary univariable linear regression analyses (**Supplementary Table S1)**: Age, Gender, Ethnicity, Years of Education, Duration of Untreated Psychosis, Reality Distortion, Negative Symptoms, Mania and Medication Dose (expressed in Defined Daily Dose units). The analysis for 'All Diagnoses' additionally co-varied for 'Diagnosis'.