Exploring participant-level trajectories of cognitive performance in patients with schizophrenia

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Background

- It is unclear whether the lack of clinical trial success and drug approval for cognitive impairment associated with schizophrenia (CIS) is due to compounds being ineffective, or whether trial methodology has been a limiting factor in successfully demonstrating the efficacy of these agents.
- Schizophrenia is a heterogeneous disorder and whilst cognitive deficits are a core feature, the profile and degree of neuropsychological impairment can vary across patients. Though most individuals with schizophrenia exhibit some general cognitive impairment compared to antecedent expectations, such as premorbid intelligence, up to a quarter display cognitive performance in the ‘normal’ range.
- Cognitive heterogeneity may pose a problem for pro-cognitive drug trials in this population as high performers may inflate baseline scores and reduce the scope to see improvement between treatment and placebo groups.
- In order to examine this potential issue, we investigated participant-level trajectories of cognitive performance among patients with schizophrenia enrolled in a multi-national, phase II clinical trial.

Methods

- We conducted a post-hoc analysis of existing trial data from 463 patients with schizophrenia who participated in a randomized, double-blind, placebo-controlled trial.
- Patients met established diagnosis for schizophrenia (DSM-5), were clinically stable (non-acute) and had no more than moderate severity ratings on the Positive and Negative Syndrome Scale (PANSS).
- Participants completed the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the MATRICS Consensus Cognitive Battery (MCCB), at 4 separate time points (screening, baseline, week 6 & week 12).
- Participant data were pooled across placebo and treatment groups to explore trajectories of cognitive performance, at the participant-level, across the course of the study.

Results

- Approximately 25% of the overall sample were performing within a clinically normal cognitive range at screening as determined by the MCCB composite score (t score >35-40).
- Participants performing within a clinically normal range at screening (on the MCCB composite) were also performing within the top 25% on domain specific subtests of CANTAB and MCCB for visual learning and memory, working memory and sustained attention/vigilance (Figure 1).
- Linear mixed model analyses revealed a significant time (baseline, week 6 & week 12) x group (high vs low performers at screening) interaction on the CANTAB test of episodic memory, PAL. Figure 2A illustrates the difference in performance across time points between participants who scored less than 10 errors on PAL at screening (top 25% of good performers) compared to those who scored more than 10 errors on PAL.
- As can be observed in Figure 2B, poorer performers on CANTAB PAL (>10 errors) at screening demonstrated an improvement in performance across baseline, week 6 and week 12 time points. In contrast, the top 25% of good performers on PAL at screening (<10 errors) demonstrated stable performance indicative of little or no change, across the remainder of the study visits.

Discussion

- Substantial variability was evident in cognitive performance among the current sample of patients with schizophrenia and a subsample of patients whose performance fell within a clinically normal range was identified.
- Improvement in cognitive performance based on CANTAB PAL was only seen in participants who exhibited an impairment on this measure at screening, bringing into question whether the inclusion of unimpaired patients in clinical trials minimizes chance to detect improvement in pro-cognitive drug trials.
- Further analyses will determine the interaction between different cognitive trajectories and the treatment arms included in this trial to explore whether there are individuals with a particular cognitive profile who are most likely to respond to treatment. This has potentially important methodological implications in the search to find a drug to treat CIS.

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Figure 1. Individual MCCB Composite Scores for participants plotted over 4 testing sessions. The data are presented for 3 different cognitive domains: visual learning and memory (A), working memory (B) and sustained attention/vigilance (C). Trajectories are colour coded according to performance at screening on the domain specific CANTAB (left) or MCCB (right) test. The top 25% of participants are plotted in green. The bottom 75% are plotted in red. Dashed lines highlight the composite score of participants performing within the bottom 75% on the specified test at screening. Dotted lines specify the normative mean for a schizophrenia population with +/- 1SD. Scores above the top bolded line represent individuals scoring above a clinically normal range on MCCB Composite Score.

Figure 2. (A) Individual and (B) mean PAL, total errors adjusted (PALTEA) scores for participants plotted over 4 testing sessions, colour coded by PALTEA scores at screening visit. Lower scores indicate better performance. Change lines specify individuals who scored less than 10 errors at screening whilst blue lines specify individuals who scored more than 10 errors at screening.

Visual Learning & Memory

CANTAB Paired Associates Learning
MCCB Visualspatial Memory Test - R

Working Memory

CANTAB Spatial Working Memory
MCCB spatial Span

Sustained attention/vigilance

CANTAB Rapid Visual Information Processing
MCCB Continuous Performance Test