A Meta-Analysis of Computerized Assessment Batteries in Schizophrenia Medication Trials

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Abstract

Introduction: A variety of computerized assessment batteries (CABs) have been utilized to assess cognitive impairment in schizophrenia; however, there is no consensus regarding CABs sensitivity to medication effects. This meta-analysis provides a quantitative overview of CABs used in schizophrenia research by examining medication trials with at least one pre and post cognitive assessment.

Methods: A structured search of the CAB literature using the PsycInfo, MEDLINE, PubMed, and Google Scholar databases yielded 15 suitable publications that met inclusion criteria for meta-analytic review. Each CAB website was also examined for relevant publications, resulting in a total of 81 separate pre-post effects. CABs reviewed included CANTAB, ANAM, CogState, CogLab, and MINDSTREAMS. Specific tests from each CAB were extracted and grouped into cognitive domains reflecting executive function, working memory, verbal and non-verbal memory, visuospatial reasoning and motor functioning. Effect sizes (ES) (Cohen's *d*) were then calculated for each CAB, their component subtests, and for each cognitive domain.

Results: Analysis of medication effects on cognitive functioning, across different medication types, revealed an overall moderate effect size (d = 0.523) for all CABs which was significantly heterogeneous (p < 0.001). Of the five CABs, CogLab yielded the largest effect size (d = 0.79) followed by ANAM and then CogState. Effect sizes were largely driven by battery composition with measures of attention (d = 0.809) and visuospatial reasoning (d = 0.702) yielding relatively higher ESs than non-verbal memory (d = 0.459) and executive functioning (d = 0.403); although these four domains did not differ significantly from each other. Type of treatment intervention also impacted ES with combination treatment (Haloperidol plus nicotine) yielding the largest ES (d =1.05) followed by Haloperidol alone, and then various antipsychotics and nooptropics. Important moderator variables included previous medication type, inpatient/outpatient status, number of follow-up cognitive assessments, PANSS negative symptomatology score, and patient age.

Conclusion: This meta-analysis suggests that it is possible to more confidently select CABs, their component subtests, and cognitive domains that are more likely to be sensitive in treatment trials; and that this sensitivity is moderated by medication type and important disease-related and demographic variables.

Methods

•Studies were identified through a search of the MEDLINE, PsychINFO, PubMed and Google Scholar databases. Each CAB website was also examined for relevant publications. CABs reviewed included CANTAB, ANAM, CogState, CogLab, and MINDSTREAMS.

▪The search yielded 81 publications and abstract/ presentations that were reviewed for inclusion by three authors (LE, LH and PJM). Of these 81 articles, 15 were found to be suitable for inclusion in the meta-analysis. Most articles were excluded due for lack of information allowing calculation of effect sizes.

Methods (cont.)

▪When possible, specific tests from each CAB were extracted and grouped into domains of neuropsychological function (attention, visual spatial reasoning, nonverbal memory, executive function etc.).

▪ Analyses were conducted using Comprehensive Meta-Analysis, Version 2.0. In order to standardize medication effects on cognitive performance, an effect size (Cohen's d) was calculated by calculating the mean difference in pre/post cognitive scores after pharmacologic treatment or challenge in schizophrenic patients and dividing this value by the pooled standard deviation.

$$ES = \frac{Mean_{t1} - Mean_{t2}}{\sqrt{(SD_{t1}^2 + SD_{t2}^2)/2}}$$

▪In order to assess homogeneity across studies for each cognitive domain, the Cochran Q-statistic was utilized. A random effects model was used to calculate effect sizes if the Q-statistic revealed significant within-group heterogeneity. In cases where significant heterogeneity was not indicated, fixed effects models were used.

▪ In domains with significant heterogeneity, possible effect size moderators were examined based on the Q-statistic. Continuous moderators were examined with meta-regression techniques.

Results

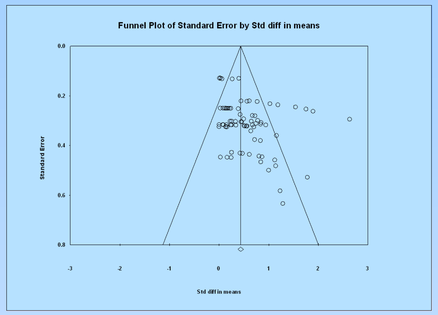
•Analysis of medication effects on cognitive functioning across different medication types, revealed an overall moderate effect size (d = 0.523) for all CABs which was significantly heterogeneous (p < 0.001).

▪An analysis of homogeneity including all studies revealed significant variance among study effect sizes that supported examining the effects of moderator variables (Q_B[80] = 257., p<0.001).

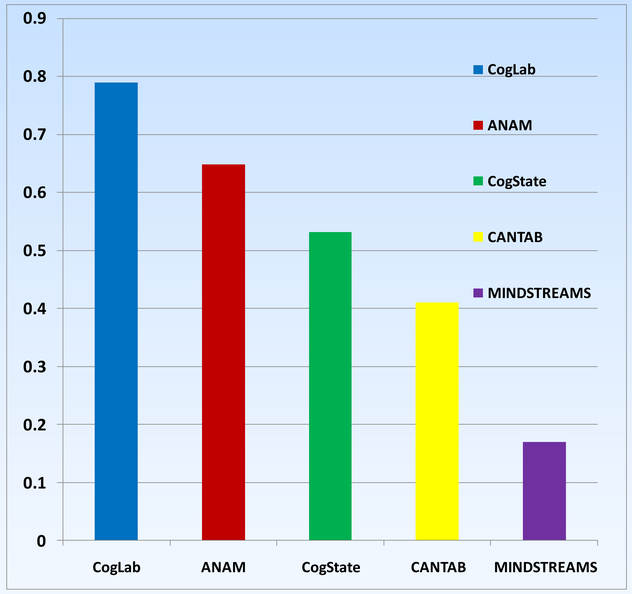
▪Possible publication bias was observed, as indicated by an asymmetric funnel plot and significant Begg test (p=0.00024, one-tailed) and Egger test (p=0.00028, one-tailed).

▪Calculation of a fail-safe N, however, revealed that 5,301 "null" studies would be required to negate the observed effects. These result suggest that the current findings are a valid representation of the current CAB medication trial literature.

Results (cont.)



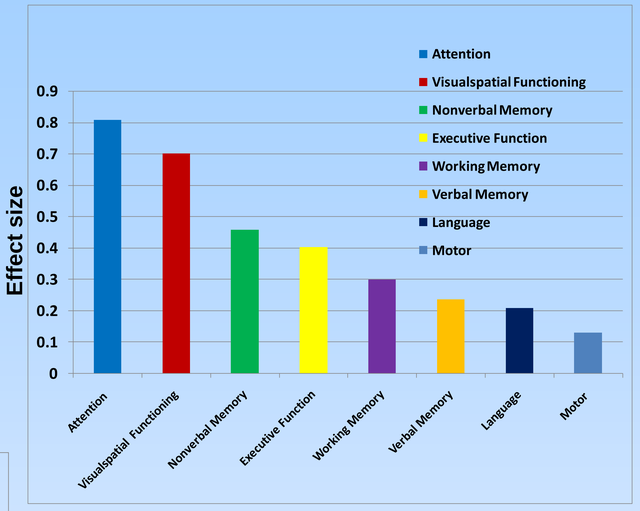
▪Of the five CABs, CogLab yielded the largest effect size (d = 0.79) followed by ANAM (d = 0.65), CogState (d = 0.53). CANTAB (d = 0.41) and MINDSTREAMS (d = 0.17).



•Despite nominal differences between the top three batteries, post-hoc analyses did not reveal significant differences between the CogLab, ANAM, and CogState batteries (p > .19). However, CogLab and ANAM had significantly higher ESs than CANTAB and MINDSTREAMS (p =.029, p<.001; and p=.029, p<.001, respectively).

• Individual CAB effect sizes were largely driven by battery composition with measures of attention (d = 0.809) and visuospatial reasoning (d = 0.702) yielding relatively higher ESs than non-verbal memory (d = 0.459) and executive functioning (d = 0.403). Lower ES were seen for measures of Working Memory (d = 0.299), Visual Memory (d = 0.237) and Language (d = 0.209).

Results (cont.)



•Post-hoc analyses revealed significant differences between the attention domain and that of verbal memory (p = 0.045) and language (p = 0.05). Similarly, visuospatial functioning yielded significantly larger ESs than those seen in executive (p = 0.035) and verbal memory domains (p=0.035). No other domain contrasts were significant.

▪Type of treatment intervention did not significantly moderate ESs. Specifically, atypical (d = 0.42), nootropics (d = 0.40) and combination (d = 0.61) therapies all yielded small to moderate effects on cognitive performance, but did not differ significantly from each other (Q_B[2] = 3.87, p = 0.14).

▪Other important moderator variables included inpatient/outpatient status, number of follow-up cognitive assessments, PANSS negative symptomatology score, and patient age.

▪For example, patients with higher levels of negative symptoms appeared to demonstrate a greater degree of change in cognitive performance with intervention (p = 0.006) than those patients with a greater degree of positive symptoms (p = 0.23).

▪Age was also a significant moderator (p = 0.015), with older patients showing larger changes in cognitive performance with medication intervention.

Conclusions

▪This meta-analysis suggests that it is possible to more confidently select CABs, their component subtests, and cognitive domains that are more likely to be sensitive in treatment trials.

▪This sensitivity is moderated by medication type and important disease-related and demographic variables including age and negative symptomatology..