Title: Profiling cognitive impairment in recovered Major Depressive Disorder.

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Methdological question being addressed: Characterisation of unmet medical need in recovered Major Depressive Disorder (MDD) patients.

Introduction

The clinical and socio-economic burden associated to MDD prompted interest for therapeutic drug interventions to specifically address cognitive impairment (CI) in major depressive episodes (MDEs). Cognitive deficits may persist even in patients with residual depressive symptoms across different MDD states (i.e. partial remission, full remission, recovery). The purpose of this study is to synthesize and characterize CI in MDD in order to aid in determining the degree in which CI is an unmet need in this patient subgroup.

Methods

We conducted a systematic literature review with meta-analysis to construct a profile of cognitive impairment associated to recovered MDD patients.

Results

Twenty-three studies (1.517 participants; 819 adult, non-elderly, euthymic, recovered, early onset MDD patients and 6988 healthy subjects) were included in the analysis. Data synthesis indicates a reduced performance in selected - rather than aspecific and widespread as in MDE - domains of cognitive functioning in MDD recovery state. This finding signals the presence of different cognitive impairment profiles by MDD disease state. Small magnitude ($20 \leq$ Hedges's d ≤ 50) and homogeneous effect sizes (ES) in a number of cognitive tasks and their derived measures were noted. The general absence of significant heterogeneity among ES across outcomes as well as indexes of publication bias support the robustness of these findings. Recovered MDD patients show several elements of cognitive impairment: reduced performance in tasks demanding elevated cognitive resourcing and rapid strategy shift to adapt to organisational rule changes; a decreased ability to utilise the underlying associative structure of items to be remembered, as indicated by the lower productivity of immediate or delayed (<1 hour) recalls of auditory-verbal structured item lists (i.e., a word list with items clustered by taxonomic semantic categories); less efficient in updating new learned information and retrieval according to specified a rule, as suggested by working memory measures; reduction of verbal fluency, but not of recognition memory measures; a decreased speed of visuo-motor processing - measured as reaction/response/latency times and

evaluated across a variety of tasks and paradigms - dependent on the duration of the task (shorter duration, < 7 minutes vs continuous performance). Accuracy measures of visuo-motor processing tasks, the ones derived from “Stroop” or from Digit Symbol Coding tasks do not indicate show differences. Generally, the clinical relevance of all these findings is unclear.

Conclusion

When applied to clinical drug development, MDD cognitive profiling contributes to the identification and stringent characterization of appropriate patient subgroups who may benefit the most from therapeutic intervention as well as specification of optimal treatment duration. The finest characterisation of the nature and extent of cognitive dysfunction in MDD informs the development of new diagnostic methods with superior cost-efficiency that can deliver suporior cost-efficiency throughout the drug development process. Advances are required to enable more accurate determination of transition between MDD disease states, evaluation of risk for recurrence as well as the monitoring and prediction of anti-depressant treatment response.