EPV1853

Utility of Computational Models in Predicting the Efficacy of Stem Cell Therapy for Schizophrenia – Insights from a Systematic Review and Meta-Analysis

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Introduction: Schizophrenia is a disorder associated with significant morbidity, largely due to poor treatment outcomes with existing interventions. Emerging evidence demonstrates that stem cell therapy using either patient-derived induced pluripotent stem cells (iPSCs) or mesenchymal stem cells (MSCs), may offer an effective alternative for treating schizophrenia by promoting the restoration of excitatory interneurons. However, given the variability in the therapeutic potential of iPSCs and MSCs, adopting a progressive computational approach to predict the clinical outcomes of these therapies might be an effective strategy.

Objectives: The objective was to evaluate the efficacy of stem cell therapy in schizophrenia and to explore the role of computational models in predicting the outcomes of this therapy.

Methods: We conducted a systematic search of clinical trials and studies published (since 2015) in PubMed, SCOPUS, and EMBASE. The review included all randomized controlled trials involving iPSC or MSCs-based interventions and studies that incorporated computational models to predict outcomes. A total of 22 studies including 1436 individuals were included in the review. Meta-analytic methods were used to calculate pooled effect sizes on cognitive outcomes and reduction or improvement in negative symptoms was recorded using standardized mean difference (SMD) and risk ratios (RR).

Results: This involved 979 patients with schizophrenia from four studies that met quality review criteria, revealing that MSC-based therapies using positive controls significantly improved negative symptoms with a standardized mean difference (SMD) of 0.52 (95% CI, 0.32–0.73; $P < 0.001$). Improvements in cognition, especially in the domains of memory and executive function, were significant in treated groups using iPSCs (SMD = 0.61, 95% CI, 0.40–0.82; $P < 0.0001$). The predictive models that classified interneuron (PV and SST) restoration in terms of sensitivity (83.4%) and specificity (78.2%) enhanced the ability to predict responder treatment effects. Ultimately, computational modeling reduced predictive variance in therapeutic efficacy by 18.7% ($p = 0.006$).

Conclusions: Our meta-analysis revealed that stem cell therapies, particularly MSCs and iPSCs, significantly improved both negative and cognitive symptoms associated with schizophrenia. Additionally, predictive models using computational methods were found to accurately predict the therapeutic outcomes for intervention treatments based on the resting patient subgroups that received interneuron restorations. We conclude that stem-cell-based therapies especially when used alongside computational models have tremendous potential to provide precise and personalized psychiatric care.

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Development of a Novel Task to Assess Fast and Slow Thinking in Schizophrenia

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Introduction: Delusions in schizophrenia have been theoretically linked to probabilistic reasoning bias ('jumping to conclusions', JTC), although experimental support has been mixed (Garety *et al* BJP 2013; 203 327-333). Ward and Garety (Schiz Res 2019; 203 80-87) recently proposed a reformulation of the theory in terms of Kahneman's concepts of 'fast' and 'slow' thinking. This proposes that decision-making involves two cognitive processes: a fast, heuristic-based approach which is prone to errors, and a slow, deliberate process that carefully evaluates all the relevant evidence. According to this view, an overreliance on fast thinking and/or reduced engagement of slow thinking underlies the initial development of delusional interpretations of everyday events and also makes them harder to be corrected.

Objectives: Our aim was to develop a novel task to investigate the fast and slow thinking hypothesis of delusions in patients with schizophrenia, for use in behavioural and functional imaging studies. As a preliminary step, we tested this task on healthy participants.

Methods: A battery of 137 experimental questions (where fast thinking leads to incorrect answers) was generated from multiple sources, including examples of the base rate and conjunction fallacies, the cognitive reflection test (CRT), trick questions, and syllogisms. Example questions included: If it takes 5 machines 5 minutes to make 5 widgets, how long would it take 100 machines to make 100 widgets? [Correct answer = 5 minutes; intuitive answer = 100 minutes; category: cognitive reflection] A farmer had 15 sheep and all but 8 died. How many are left? [intuitive answer: 7; correct answer: 8, category: trick question]. 137 control questions (where both fast and slow thinking give the correct answer) were adapted from the experimental questions. The questions were administered online to 176 healthy volunteers using PsychoPy software, with 15 experimental and 15 control questions randomly assigned to each participant.

Results: The sample had a mean age of 40.3 years (range 17-77 years); 55.1% were female and 65.9% had a university education. Correct answers to experimental questions were markedly fewer than answers to control questions in all categories (overall $p < 0.001$). Response latency for the experimental questions was slightly higher than for the control questions, apart from in one category (CRT) (overall $p = 0.004$).

Conclusions: Results from a large sample of healthy participants indicate that a battery of questions can be feasibly developed to reliably detect fast thinking.

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