collaborative group pooling data on over 800 patients receiving placebo from 12 separate clinical trials[7].

A more serious consideration for why CIAS trials have been negative is the transition from early to later phase methodologies:

- *Noise*. Larger sample sizes have more statistical power, but larger trials often require methodologies that create noise and weaken power. Single site studies with dedicated investigators are adept at eliminating noise. Later trials with tens or even hundreds of site investigators are often not implemented at each site in the exact same manner.
- *Regulation*. Later phase trials, including pivotal trials, are more likely to adhere to stringent regulatory processes that eliminate some of the bias that is inherent to small studies conducted by individual investigators with conflicts of interests based upon financial and aspirational motives. Greater regulation leads to less bias and fewer positive findings.
- *Regulated endpoints*. A treatment signal is more likely when investigators can match a mechanism of action with an appropriate endpoint (e.g., choosing a processing speed endpoint with a short time frame of follow-up for a stimulant trial), but more difficult to detect with an endpoint determined by regulatory agencies to have general relevance.
- *Simple regression to the mean*. Early phase studies with positive results are forwarded to the next phase. Negative studies are not. Because of the small sample sizes of these trials necessitated by cost concerns, statistical power is low. Therefore, some investigators will lower the threshold for statistical significance of these studies to align their go/no-go decisions with their business priorities, and may include multiple comparisons and *post hoc* analyses without correction. These approaches lead to more type I statistical errors where null hypotheses of no treatment effect are mistakenly rejected. In the next phase of trial, with improved statistical power and the enhanced precision that it brings, no effect of the drug will be found.

Another important consideration for the negative trials to date is that almost all of them have targeted a chronic schizophrenia population with an average age around 40 years old. Has the opportunity to improve cognition passed at that age? Models of brain plasticity suggest that the propagative properties of neurons diminish over time, and it is reasonable that this aging process is accelerated in people with schizophrenia, who are more likely to have comorbid medical conditions, substance use and reduced physical and mental engagement with the environment. Some data have suggested that younger patients may be more responsive to CIAS treatments. The idea of treating CIAS in first episode patients has often been proposed, but completing these trials has been challenging. Several of us have urged for the remediation of cognitive impairment with highly safe treatments prior to the onset of psychosis in vulnerable populations[8,9], but again these trials are challenged by patient recruitment concerns and the length of time required to identify treatment response.

Beyond these questions of study design and implementation are darker considerations. Do we need to wait for a greater understanding of how complex human neural systems operate before we can discover pharmacological and behavioral treatments that interact with them favorably? Or perhaps CIAS is so elemental to the genetic manifestation of a diseased brain that we will never be able to alter it once an infant is born? All of these pessimistic perspectives are possible. However, the history of medicine includes a steady stream of examples where scientists and clinicians whose ideas and compassion were too great to listen to the herd mentality of financial investors and fear mongers. Those with the courage and resources to pursue reasonable hypotheses based upon the limited data we have available now will perhaps be viewed by history as resolute prospectors who invested in the reduction of suffering.

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# Innovative methods for improving cognition, motivation and wellbeing in schizophrenia

Neuropsychiatric disorders involve impairment of cognition, motivation and their interaction[1]. Cognitive manifestations include attentional biases, aberrant learning, dysfunctional reward processing, and lack of top-down cognitive control by the prefrontal cortex. These cognitive manifestations are both "cold" or non-emotional and "hot" or social and emotional[2]. From a neurobiological perspective, these relate to two partially segregated loops: the "cold" loop including the dorsal lateral prefron-

tal cortex and the "hot" affective loop including the orbitofrontal cortex and the ventral striatum, with strong connections to the "emotional brain" including the amygdala[2].

There are three major problems in schizophrenia: positive symptoms, cognitive symptoms and motivational deficits, which include negative symptoms. Green et al[3] make a compelling argument that cognitive impairments in both social and non-social domains are core features of the illness. Although antipsychotic medications treat hallucinations and delusions reasonably well, they have little impact on functional outcomes. One of the biggest challenges of this century is how to treat early and effectively the cognitive and motivational deficits in patients with schizophrenia in order to prevent their persistence and ensure the best possible outcome.

Our group has focused on episodic memory impairments in neuropsychiatric disorders. Impaired episodic memory occurs early and strongly relates to functionality in patients with amnestic mild cognitive impairment, Alzheimer's disease and schizophrenia. Episodic memory is also a functional correlate that is impaired in patients with a first episode of psychosis and further declines as the illness becomes more chronic.

This form of new learning and memory has been shown to utilize a neural circuitry including the hippocampus. Changes in hippocampal subfields, including volume loss in the hippocampal stratum layers and the dentate gyrus, have been implicated in memory dysfunction in first-episode and chronic schizophrenia[4].

Although cognitive dysfunction is acknowledged as a target for treatment by the US Food and Drug Administration (FDA), there are no licensed medications currently available. We thus propose that innovative pharmacological and non-pharmacological methods should be developed and implemented further to target *both* cognitive and motivational dysfunction in the symptomatic treatment of schizophrenia and other neuropsychiatric disorders, rather than focussing on diagnostic status.

Interest in the cognitive-enhancing properties of modafinil has been the focus of considerable experimental medicine research over the last two decades. Modafinil is a wakefulness-promoting agent that has been shown to enhance cognitive performance and task-related motivation in healthy volunteers. Modafinil has also been found to have positive effects in clinical populations such as adults with attention-deficit/hyperactivity disorder (ADHD). The precise mechanism for the cognitive-enhancing effects is not clear, but this agent is thought to activate the dopaminergic, glutamatergic, noradrenergic and serotonergic systems in several brain regions, including the prefrontal cortex, hippocampus, hypothalamus and basal ganglia.

It has been shown that modafinil improves episodic memory in patients with schizophrenia[5]. This agent has also been reported to selectively improve spatial working memory and emotional processing (e.g. affect recognition, which might help social and occupational functioning) in first-episode schizophrenia, as well as a range of cognitive domains – including attentional set shifting, visual memory and spatial planning – in chronic schizophrenia[6]. Importantly, there have been no safety concerns about exacerbating psychotic symptoms, and there is no evidence of abuse potential when administering modafinil at 200 mg/day. Simultaneously enhancing cognition and motivation may have broad down-stream effects on patients' functioning, quality of life and wellbeing[6]. It is also possible that improving memory or functioning more generally through cognitive enhancement could help protect against psychotic relapse.

In addition to novel cognitive-enhancing drugs, non-pharmacological interventions also have the potential to target symptoms as low-risk non-invasive options for patients with schizophrenia. Cognitive remediation strategies generate moderate effect sizes on cognition and psychosocial functioning and a smaller effect size on psychiatric symptom severity in schizophrenia[7]. Cognitive training, in particular, has been shown to increase dopamine $D_1$ receptor density in the brain and produce functional changes in the fronto-parietal network[8].

However, compliance with cognitive training may be problematic, leading to high drop out rates, thus requiring a more motivational approach. To overcome this challenge, a study from our laboratory recently combined cognitive training with gaming technology, showing that playing eight hours of the novel Wizard memory game (www.peak.net) on an iPad improved episodic memory and global functioning in patients with schizophrenia[1]. Importantly, high levels of enjoyment and task-related motivation were maintained throughout all hours of gameplay. Our game was also titrated in difficulty in real-time, akin to personalized medicine, to promote a sense of achievement whilst maintaining high levels of motivation and improving performance over time. We therefore maximized the effects of cognitive training by directly increasing active engagement with the intervention.

Advantages of incorporating a cognitive training programme into a game are that it helps de-stigmatize treatment, since everyone plays games; it is convenient, as travel to a hospital or clinic is not necessary and specialist equipment is not required; it is not associated with side effects; and it is highly rewarding. Use of exciting new technology in mental health, in particular gaming platforms, could reach more patients inexpensively, including adolescents at ultra-high risk of schizophrenia. Gamified cognitive training could also yield benefits for mood and self-esteem, as improvements in memory function following gameplay could be attributed to the self rather than a drug.

In order to identify changes in cognition, emotion and motivation, there is a need for objective and reliable measures for evaluating affective domains. EMOTICOM (www.cambridgecognition.com) is a novel neuropsychological test battery of emotion processing, motivation, impulsivity and social cognition. Recent evidence has shown that this battery is likely to be highly relevant to "hot" cognitive processes in paranoid schizophrenia, as one key aspect implicated in the formation and maintenance of a persecutory delusion is the hostile perception of others, including their beliefs and intentions[9]. EMOTICOM could also be used

in treatment development and efficacy research, such as the evaluation of the neuropeptide oxytocin, which has shown some effects on social cognition in schizophrenia.

Interventions such as oxytocin or modafinil, used in combination with gamified cognitive training, may synergize to increase plasticity and learning, promoting improvement in both "hot" and "cold" cognition as well as in social functioning. Augmentation therapies would be particularly useful for rehabilitating patients who have cognitive impairments that persist even after remission of the more acute symptoms.

If young people with schizophrenia are to have the best chance of realizing their potential and of having good functionality and wellbeing, we will have to move to game-changing initiatives that prioritize early detection and early effective intervention. With a move to first-episode psychosis clinics and research studies focusing on children and adolescents with an ultra-high risk of schizophrenia, interventions that target cognition and motivation can be implemented much earlier in the course of the illness, before "rescuing" cognition is the only option. Good cognition and positive wellbeing are closely linked and both are required for a flourishing society.

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# The need to develop personalized interventions to improve cognition in schizophrenia

Green et al[1] provide a review of the evidence on neurocognitive and social cognitive deficits in schizophrenia. These deficits span the course of the disease, starting from the prodrome, and are stable over time. Impairments in neurocognition involve learning and memory, vigilance/attention, speed of processing, reasoning and problem solving, and working memory. Social cognition deficits affect psychological processes implicated in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves. The underlying neurobiological disturbances have their origin in brain networks involving the hippocampus as well as temporal, parietal and prefrontal cortex. Here we discuss the central role of the hippocampus in cognitive processes and the impact of non-pharmacological treatments on this brain structure in schizophrenia patients.

The hippocampus has been implicated in episodic and working memory. In schizophrenia patients, associations were recently detected between hippocampal subregion volumes and cognitive performance in visual and verbal memory as well as working memory domains[2]. Among the most prominently altered hippocampal subregions in schizophrenia are cornu ammonis 4 (CA4)/dentate gyrus (DG) and CA2/3. In post-mortem brains of schizophrenia patients, along with reduced volumes of these subregions, we detected a reduced number of oligodendrocytes (the myelin-forming glia cells) in the left CA4 and a reduced number of neurons in the DG[3]. The reduced number of oligodendrocytes in the left CA4 was related to cognitive deficits in these patients.

These changes might in part be a consequence of disturbed neuro-regenerative mechanisms in the brain[4]. This hypothesis is supported by findings of reduced synaptic proteins and dysregulation of structural synaptic elements in the temporal lobes in schizophrenia. The converging lines of evidence suggest that episodic memory dysfunction in schizophrenia might well be caused by a disturbance of synaptic and neuronal plasticity and disconnectivity[4].

Understanding the underlying neurobiology of cognitive dysfunction is critical to allow researchers to develop pathophysiology-based innovative treatment strategies. So far, however, efforts to develop new pharmacological treatments have been disappointing. Among promising non-pharmacological add-on interventions for cognitive impairments, Green et al[1] propose aerobic exercise. This treatment has been suggested to promote neuroplasticity at the synaptic level and to improve neurogenesis, at least in animal models. Moreover, epigenetic mechanisms may also be involved.

Green et al[1] mention a recent meta-analysis of controlled trials investigating cognitive outcomes of aerobic exercise interventions in schizophrenia. Meta-regression analyses indicated that greater amounts of exercise were associated with greater improvements in global cognition. Among the cognitive domains, aerobic exercise improved working memory, social cognition, and attention/vigilance[5]. Effects on verbal memory were not among the significant results, but this subdomain was only measured in six studies, which limits the strength of findings in this meta-analysis.

To achieve meaningful real-world functional benefits, Green et al suggest to combine cognitive remediation with aerobic exercise. In fact, in a three-month aerobic exercise study, in which bicycle ergometer training augmented with cognitive