Effect of Antidepressant Medication on Alzheimer's Disease Patients

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ABSTRACT

Alzheimer's is a chronic neurodegenerative disease. This editorial presents a study by Klaassens and collaborators, where Functional Magnetic Resonance Imaging was used to project cholinergic and serotonergic neurotransmitters in Alzheimer's disease patients and age-matched controls. The aforementioned study relied on the hypothesis that single-dose Acetylcholinesterase Inhibitors and Selective Serotonin Reuptake Inhibitors administration would act on different brain regions in Alzheimer's disease patients versus controls. It was hypothesized that in Alzheimer's disease patients, the above drugs would act on brain areas where the disease has been found to predominate. The single-dose method and the study's small sample size, however, make it difficult to directly relate connectivity changes to behavioral changes after drug administration. In this editorial, I present suggestions for addressing this limitation, such as improved sampling and the use of long-term dose approaches with subjects.

INTRODUCTION
KLAASSENS AND COLLABORATORS' STUDY

Twelve patients diagnosed with mild Alzheimer's disease and twelve control subjects matched for gender and age were recruited for this study by Klaassens *et al.*[1]. Each participant was administered citalopram, galantamine, and a placebo on three separate occasions, with interceding intervals of at least seven days. On each study day, six Resting State fMRI scans were conducted: two at baseline and four following drug administration. Post-scan, participants engaged in computerized cognitive tasks. During each study day, nine blood samples were collected to ensure reliable comparison between groups, accounting for absorption rates and hormonal fluctuations.

The SSRI citalopram did not produce differential regional connectivity changes between groups. However, the widespread reduction in connectivity across networks observed in controls was absent in Alzheimer's disease patients. Additionally, an enhanced connection between the citalopram and the precuneus within the Default Mode Network (DMN) was exclusively observed in Alzheimer's disease patients. This connection, previously shown to be reduced in Alzheimer's disease[2], suggests that SSRIs may have the potential to improve memory, self-referential processing, and/or visual-spatial functionalities.

SUGGESTIONS ON FUTURE RESEARCH ORIENTATION

The single-dose approach and small sample size make it difficult to directly link connectivity changes to behavioral effects after drug administration.

Selective Serotonin Reuptake Inhibitors (SSRIs) are recognized for inducing minimal behavioral and cognitive alterations in wakeful resting conditions following single-dose administration[3], in contrast to their immediate neural effects. The monoaminergic hypothesis is employed to elucidate the delayed onset of SSRI-induced cognitive and behavioral effects. This hypothesis posits that such responses typically occur after two to three weeks of treatment. It is hypothesized that the desensitization of certain neurotransmitter receptors is associated with the delayed therapeutic action of SSRIs, whereas downregulation of other receptors may account for diminished side effects. Based on this hypothesis, I recommend further research into the long-term cognitive and behavioral effects of SSRI medication in patients with Alzheimer's disease, focusing on treatment durations of at least two weeks, rather than the single-dose approach.

Furthermore, Citalopram did not significantly alter any behavioral or cognitive state, as measured by the NeuroCart battery, between the two groups. This lack of observed difference may be attributable to the limited sample size. A Type II error occurs when the results support the hypothesis upon which the study was based, despite the possibility that an alternative hypothesis may be correct. An insufficient sample size markedly increases the likelihood of a Type II error and reduces the study's capacity to detect an effect when one exists. To address this limitation, I advocate for improved sample size planning. The purpose of sample size planning is to determine an appropriate number of subjects to maintain low levels of Type II errors without rendering the study prohibitively expensive or difficult to conduct.

In conclusion, it remains unclear whether dysfunction of the serotonin system constitutes a contributing factor in Alzheimer's disease. While serotonin is undeniably a neurotransmitter involved in numerous cognitive and behavioral functions, its role in the pathology of Alzheimer's disease, in contrast to acetylcholine, has yet to be elucidated. Future investigations should be conducted with enhanced sampling methodologies and subjects undergoing long-term dosing regimens to further explore this association.

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