Application of Computational Systems Pharmacology to the Postsynaptic Density (PSD)

Jeongchae Jeong*

Department of Psychology, Carnegie Mellon University, Pittsburgh, United States

ABOUT THE STUDY

About 40% to 60% of people with Alzheimer's disease (AD) experience psychotic symptoms. Compared to Alzheimer's disease without psychosis (AD-P), Alzheimer's disease with psychosis (AD+P) suffer from a faster rate of cognitive deterioration (AD-P). In the first stages of the disease, before the onset of psychosis, AD+P patients have a greater degree of cognitive dysfunction. Antipsychotics are currently used to treat psychosis in AD, however they have a limited efficacy, do not slow down the more rapid cognitive deterioration, and increase mortality. Additionally, compared to AD-P, AD+P is linked to worse outcomes, including greater rates of aggressiveness, caregiver distress, functional decline, institutionalisation, and mortality. The biology underpinning the risk of psychosis in AD is thus highly motivated to be discovered in order to create a focused, more effective intervention.

With an estimated heritability of 60%, the risk for psychosis in AD is mostly genetically determined, indicating a specific biologic vulnerability. As synapse loss has long been known to be the largest neuropathologic predictor of cognitive decline in AD, it has been proposed that AD+P is more susceptible to synaptic damage than AD-P. This hypothesis has been supported across neocortical regions, but not in medial temporal regions, by earlier studies comparing AD+P to AD-P subjects on a variety of indirect markers of synapse integrity, such as grey matter volumes, cerebral glucose utilisation or blood flow, or grey matter concentrations of the membrane breakdown products, glycerophosphoethanolamine and glycerophosphocholine.

Based on numerous investigations that evaluated indirect measures of synaptic integrity between AD+P and AD-P groups, both *in vivo* and in postmortem tissue, it has been hypothesised that AD+P result from a more severe synaptopathy than that which is present in AD-P. The PSD between AD+P and AD-P participants is directly compared for the first time in the current work, and we find that the PSD proteome is severely disrupted in AD+P. PSDs from AD+P subjects had lower concentrations of a network of protein kinases, Rho GTPase regulators, and other actin cytoskeleton regulators compared to PSDs from AD-P subjects. The changed load of neuropathologies could not explain the PSD protein decreases in AD+P compared to AD-P that were seen in various subsets of study participants.

It is not surprising that the PSD proteome of AD+P was preferentially depleted of proteins enriched for functions linked with actin regulation given the significant role post-synaptic regulation of the actin cytoskeleton plays in the maintenance and flexibility of dendritic spines. The discovery of defects in this signalling network presents a fresh possibility for the discovery of substances that could give novel, targeted treatment benefits for people with AD+P. To identify upstream genes susceptible to perturbation by existing compounds to potentially reverse the PSD proteome alterations in AD+P, we used a novel computational strategy to compare the overlap of gene knockout signatures with the AD+P PSD proteome alterations.

The predictions we made using this method are subject to a number of restrictions brought on by the available data that was utilised to make them. Instead of using an analysis of the proteome to characterise the consequences of manipulating these targets, the majority of research reporting the effects of gene knockdown depend on an evaluation of the transcriptome. These knockdown investigations, which almost always involve tissues and cells with non-neuronal origins, never evaluate the PSD. Although we used drug candidate signatures from CNS cell investigations, we once more focused on transcriptome rather than proteome modifications and did not include PSDs. Therefore, to assess their effects on the PSD, our candidates will need to be validated in intact neuronal model systems.

Correspondence to: Jeongchae Jeong, Department of Psychology, Carnegie Mellon University, Pittsburgh, United States, E-mail: jeongjchae@cmu.edu