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Research on schizophrenia – based on dementia, working memory and episodic memory deficits

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Abstract. Schizophrenia is associated with severe cognitive dysfunctions, including memory deficits that affect both working memory (WM) and episodic memory (EM). Memory deficits are also a typical symptom experienced by dementia patients that causes crucial functional problems in daily life. Meanwhile, past studies yielded evidence for the relationship between dementia and psychiatric disorders, indicating the emergence of psychotic symptoms during prodromal dementia. This article aims to investigate the relationship between schizophrenia and dementia plus the WM and EM deficits among schizophrenia patients. In the first part of this paper, the association between schizophrenia and dementia is examined based on a psychosocial study conducted among the Danish population, comparing the likelihood of developing dementia in patients with schizophrenia to that of individuals without schizophrenia. The review of previous research findings indicates a positive correlation between a diagnosis of schizophrenia and the later development of dementia. This phenomenon may be due to the reason that schizophrenia is positively associated with several established risk factors of dementia. Then, the topic of the potential deficits of WM and EM is discussed using self-ordered task results and neurobiological evidence. Studies have showed that schizophrenia is likely to lead significant WM and EM limitations that are closely related to prefrontal cortex impairment.

Keywords: schizophrenia, dementia, working memory, episodic memory, memory deficits.

1. Introduction

Schizophrenia and dementia are conditions that involve significant cognitive impairment and can lead to serious hinderance to individuals' daily functions. Both disorders impose a substantial caregiver burden, cause considerable patient suffering, and incur high societal costs. While the two conditions are often considered and treated as independent illnesses, studies have shown that progression of dementia often involves the emergence of neuropsychiatric symptoms (NPS) [1]. Furthermore, evidence from recent research suggested that psychosis in prodromal dementia is more common than previously understood and has negative impacts on clinical course [1]. Based on previous findings, this section of the paper aims to investigate the relationship between schizophrenia and dementia, as well as examining schizophrenia as a risk factor for dementia. The results aim to help identify vulnerable population to the development of dementia as well as enhance current understanding of dementia and schizophrenia.

The second part of this paper will focus on talking about the potential mechanisms of memory deficits among schizophrenia patients. It will incorporate discussions of the impact of schizophrenia on patients' WM and EM specifically, in which neurobiological evidence will be used for better demonstration.

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These discussions hope to help identify neural biomarkers and putative mechanisms of WM and EM impairment in patients with schizophrenia, which could be applied in future clinical settings.

2. Research Evidence for Schizophrenia Being a Risk Factor for Dementia

To determine the risk of dementia among patients with schizophrenia compared to the healthy population, Ribe et al. did research using individual data from 6 nationwide registers in Denmark that involved 2.8 million people, among which the data of 20,683 individuals aged 50 years or older with schizophrenia was collected [2]. Researchers obtained information on comorbid chronic conditions for dementia – such as diabetes mellitus, ischemic heart disease (IHD) and substance abuse (SA) – as well as individuals' civil status that was dichotomized into living with a partner or living alone; factors of age, and calendar period were also adjusted for baseline information [2]. Later, a follow-up study was conducted between 1995 and 2013, the data yielded was then analyzed using log-linear Poisson regression analysis [2].

The findings demonstrated that those with schizophrenia had a dementia risk that was more than two times greater, and this risk seemed to be especially significant in those with schizophrenia who were younger than 65 [2]. There are various explanations for this phenomenon. First, it has been shown that people with schizophrenia are also more likely to develop chronic illnesses including diabetes, IHD, and SA, all of which are known risk factors for dementia [2]. The risk of dementia in individuals with schizophrenia decreased after the factor of SA was adjusted, indicating that SA is an important mediating variable in the link between dementia and schizophrenia [2]. Concurrently, studies have demonstrated a high frequency of type II diabetes mellitus (T2DM) in individuals diagnosed with schizophrenia, which can be linked to both genetic and epidemiological variables. From an epidemiological perspective, weight increase is a common adverse effect of antipsychotics, and schizophrenia patients' poor diet, low socioeconomic position, and disordered lifestyle are linked to cognitive dysfunction [3]. Furthermore, stress is considered a possible contributing factor to chronic hyperglycemia in diabetes, and patients with schizophrenia frequently experience higher levels of stress [4]. Evidence from human and animal models also points to changed adrenergic sensitivity in the pancreas and other likely locations in T2DM patients, which may result in increased sensitivity in these individuals when confronted with stressful environmental triggers [4]. From a genetic perspective, there is growing evidence that schizophrenia and type 2 diabetes share susceptibility genes that lead to similar cascades and mechanisms in the brain or pancreas that cause the onset of both conditions [3].

Moreover, Douaud et al. identified patterns of macrostructural abnormalities that were observed in both Alzheimer's disease and schizophrenia [5]. Their finding suggests the connection between schizophrenia and dementia on a neurobiological level, indicating that brain abnormalities in schizophrenia patients may contribute to an increased risk of developing dementia.

Overall, Ribe et al. yielded significant evidence for the association between schizophrenia and dementia [2]. Future research could adopt a similar research structure to study schizophrenia as a risk factor for dementia among other populations. Meanwhile, additional studies could be done to elucidate pathophysiologic factors of the connection between schizophrenia and dementia.

3. The Potential Mechanisms of WM Deficits in Schizophrenia

Schizophrenia is known to cause cognitive impairment, and the neurological correlates of WM are still a major mystery when it comes to understanding the cognitive dysfunction and dorsolateral prefrontal cortex (DLPFC) abnormalities in schizophrenia patients. By monitoring subjects' brain activity and evaluating whether people with schizophrenia show a change in the inverted-U connection between WM load and activation in comparison to healthy controls, Van Snellenberg et al. sought to investigate WM deficiencies in the population of schizophrenia [6]. The underlying theory for this approach was that the normal DLPFC activation in response to parametric variations in WM load may not be monotonic; in other words, the DLPFC activation experienced at higher WM loads declines, by which the overall shape that depicts the relationship between WM load and DLPFC activation is an "inverted-U" curve [6].

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The researchers divided participants into three groups (i.e. medicated schizophrenia patients, unmedicated schizophrenia patients, and healthy control subjects). Patients were put into the unmedicated group if they were medication-free for at least two weeks [6]. Patients classified as medicated were those who had not visited a psychiatric emergency room or been admitted to a hospital for at least three months, were taking steady doses of mental drugs for at least four weeks, and did not have antipsychotic polypharmacy [6]. While in fMRI, each of the three subject groups was asked to finish a self-ordered WM task. The task findings demonstrated that at each stage of the task, people with schizophrenia, whether on medication or not, performed worse than the healthy controls [6]. In contrast to the control group, schizophrenia patients took longer to respond to the task questions [6]. Reaction times between patient groups were similar, but unmedicated individuals had higher WM capacities than medicated patients [6]. This difference may be due to weakened psychiatric conditions and fewer side effects from psychiatric medications among unmedicated patients.

The fMRI images showed that patients with schizophrenia show a left shift in the “inverted-U" curve, which is associated with increased DLPFC activation at lower WM loads and decreased activation at greater WM loads [6]. Participants' neurobiological responses revealed that patients' left DLPFC had a reduced inverted-U response, which was linked to behavioral deficiencies in WM capacity [6]. Additionally, patients showed a relative inability to deactivate mPFC during the WM task, a finding that has been extensively documented in cases of schizophrenia and linked to more severe deficiencies in WM capability [6,7]. Important biomarkers and potential mechanisms of WM impairments in individuals with schizophrenia were revealed by these findings. Future research could focus on the clinical aspect of these neurobiological cues among schizophrenia patients.

4. The Potential Mechanisms of EM Deficits in Schizophrenia

Besides WM impairments, EM deficits also represent a key limitation in the condition of schizophrenia that severely hinders patients’ daily functions. Ragland et al. hypothesized that these EM deficits are most often related to dysfunction in the prefrontal cortex [8]. From a total of 36 potential studies, they selected 18 whole-brain studies that involved a standard comparison sample and low-level baseline contrast [8]. Using the method of activation likelihood estimation (ALE), the researchers conducted a quantitative meta-analysis of functional imaging studies comparing schizophrenia patients with healthy subjects during episodic encoding and retrieval [8].

The results went along with the hypothesis made by Ragland et al.: during encoding, patients exhibited less prefrontal activation than healthy controls in the left frontopolar (BA 10, 32), DLPFC (BA 45), and VLPFC (BA 46); during retrieval, there was less activation in DLPFC and VLPFC in schizophrenia patients compared to comparison subjects [8]. Moreover, when encoding strategies were provided, studies showed that VLPFC encoding deficits were no longer present, while DLPFC deficits remained [8]. This sparing of VLPFC suggests that VLPFC may compensate for diminished DLPFC function during WM and episodic encoding [8]. On the other hand, other from a relative increase in activation in the patients' parahippocampal gyrus during encoding and retrieval, there was no discernible difference in the activation of the hippocampal and adjacent medial temporal lobes between the patients and the controls [8]. Based on these results, memory rehabilitation techniques developed for people with frontal lobe lesions as well as pharmacological techniques used to improve the function of prefrontal cortex in patients may hold promise for restoring EM function in patients with schizophrenia. Prefrontal cortex deficits were found to be the primary factor affecting episodic encoding and retrieval in schizophrenia patients [8].

5. Conclusion

The previous research revealed a positive relationship between schizophrenia and dementia, indicating that cases of schizophrenia were likely to be a crucial risk factor for the development of dementia. Such a correlation could be explained by the association between schizophrenia and well-known risk factors of dementia such as diabetes mellitus, IHD, and SA. However, this finding was limited as it was based on a single research source, lacking consensus from other studies. Meanwhile, researchers collected

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individual data from the Danish population only, which limits the study's to be representative of other populations. Future research could use similar experimental structure with participants from various races and cultural backgrounds to increase the validity of the test result in the overall population. Additional studies could also be done to investigate the pathophysiologic factors of the connection between schizophrenia and dementia.

Regarding the potential mechanisms of memory deficits in schizophrenia, researchers found that both medicated and unmedicated patients performed worse than controls in the self-ordered WM task, which the patients also spent more time reacting to the task compared to the healthy subjects. Meanwhile, they observed reduced inverted-U response in left DLPFC in patients with schizophrenia, which was related to behavioral deficits in WM capacity. Their study was limited by a small sample size (unmedicated schizophrenia patients, N=21), which may weaken the statistical power of the research. Additionally, while the inverted-U relationship has gained prevalence, it still lacks direct evidence to support it.

Furthermore, researchers found that during episodic encoding and retrieval, schizophrenia patients experienced significant reductions in prefrontal activation particularly in DLPFC and VLPFC compared to the controls. Their study, as well as the study done on WM deficits, identified crucial neural biomarkers for memory deficits in schizophrenia, which were significant for future pathophysiologic research as well as clinical applications.

Overall, this paper provides valid evidence for the association between dementia and schizophrenia as well as a general discussion of WM and EM deficits in schizophrenia. It helps advance people's understanding of dementia and schizophrenia as two correlated illnesses as well as deepen their knowledge of the potential mechanisms of memory deficits among schizophrenia patients. It is limited in the sense of a lack of primary evidence. Future research could focus on the investigation of the neural biomarkers that suggest the relationship between schizophrenia and dementia incidents as well as other kinds of memory impairment in people with schizophrenia.

References

[1] Fischer, C. E., & Agüera-Ortiz, L. (2017). Psychosis and dementia: Risk factor, Prodrome, or cause? International Psychogeriatrics, 30(2), 209–219. https://doi.org/10.1017/s1041610217000874.

[2] Ribe, A. R., Laursen, T. M., Charles, M., Katon, W., Fenger-Grøn, M., Davydow, D., Chwastiak, L., Cerimele, J. M., & Vestergaard, M. (2015). Long-term risk of dementia in persons with schizophrenia. JAMA Psychiatry, 72(11), 1095. https://doi.org/10.1001/jamapsychiatry.2015.1546.

[3] Mizuki, Y., Sakamoto, S., Okahisa, Y., Yada, Y., Hashimoto, N., Takaki, M., & Yamada, N. (2020). Mechanisms underlying the comorbidity of schizophrenia and type 2 diabetes mellitus. International Journal of Neuropsychopharmacology, 24(5), 367–382. https://doi.org/10.1093/ijnp/pyaa097.

[4] Surwit, R. S., Schneider, M. S., & Feinglos, M. N. (1992). Stress and diabetes mellitus. Diabetes Care, 15(10), 1413–1422. https://doi.org/10.2337/diacare.15.10.1413.

[5] Douaud, G., Groves, A. R., Tamnes, C. K., Westlye, L. T., Duff, E. P., Engvig, A., Walhovd, K. B., James, A., Gass, A., Monsch, A. U., Matthews, P. M., Fjell, A. M., Smith, S. M., & Johansen-Berg, H. (2014). A common brain network links development, aging, and vulnerability to disease. Proceedings of the National Academy of Sciences, 111(49), 17648–17653. https://doi.org/10.1073/pnas.1410378111.

[6] Van Snellenberg, J. X., Girgis, R. R., Horga, G., van de Giessen, E., Slifstein, M., Ojeil, N., Weinstein, J. J., Moore, H., Lieberman, J. A., Shohamy, D., Smith, E. E., & Abi-Dargham, A. (2016). Mechanisms of working memory impairment in Schizophrenia. Biological Psychiatry, 80(8), 617–626. https://doi.org/10.1016/j.biopsych.2016.02.017.

[7] Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH (2012): The role of default network deactivation in cognition and disease. Trends Cogn Sci 16:584–592.

DOI: 10.54254/2753-8818/66/2024.18010

[8] Ragland, J. D., Laird, A. R., Ranganath, C., Blumenfeld, R. S., Gonzales, S. M., & Glahn, D. C. (2009). Prefrontal activation deficits during episodic memory in Schizophrenia. American Journal of Psychiatry, 166(8), 863–874. https://doi.org/10.1176/appi.ajp.2009.08091307.