

Hypothesis

The GABA–Working Memory Relationship in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a highly debilitating neurodegenerative disease with no cure to date. Emerging evidence indicates aberrations of the primary inhibitory neurotransmitter GABA in the frontal, parietal and temporal cortices, and hippocampal regions of the AD brains. GABA levels have been reported to predict working memory (WM) load capacity in the healthy young population. Since working memory is impaired in AD, it opens an active area of research to investigate the influence of GABA on WM performance in AD. Advancements in neuroimaging techniques and signal processing tools can aid in neurochemical profiling of GABA in AD as well as facilitate in probing the role of GABA in AD-specific impairments of working memory.

Keywords: Alzheimer's disease, functional MRI, GABA, MR spectroscopy, working memory

Alzheimer's disease (AD) is a major neurodegenerative disease affecting millions of people worldwide [1]. Intensive basic and clinical research have yielded valuable information regarding AD-related structural aberrations, such as deposition of amyloid- β ($A\beta$) peptide and tau tangles [2], and neurochemical anomalies, such as dysfunction of acetylcholine and glutamate [3, 4]. Despite attempts on treating these structural and neurochemical pathologies, as evidenced from clinical trials attempting to reduce $A\beta$ peptide production [5, 6] and pharmacological interventions targeting glutamatergic and cholinergic systems [7], cognitive deficits continue to persist and the cause of AD remains to be identified. Recently, animal and postmortem studies have elucidated a key involvement of the primary neu-

roinhibitory neurotransmitter, gamma-aminobutyric acid (GABA), in AD pathology [8, 9]. Moreover, efforts are already under way in developing promising therapeutic strategies that target the GABAergic system in AD [10]. With GABA galvanizing support as a potential pathological factor and therapeutic approach in AD, it becomes worthwhile to investigate whether GABA is significantly involved in the cognitive deficits evident in AD. As a plethora of existing literature indicates a crucial role of GABA in working memory performance [11, 12], we posit a specific relationship between GABA aberrations and working memory impairments in AD patients.

GABA is widely spread in the mammalian brain and is believed to be involved in controlling cortical excitability [13]. Variations of GABA levels in AD brains has primarily been evidenced in post-mortem and animal studies [14]. Initial postmortem studies report reduced GABA levels in the frontal, parietal and temporal cortices as compared to healthy age-matched controls [15]. Although most of these studies indicate no change in GABA levels in the

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hippocampus, a few studies have reported a reduction of GABA levels in this region [15, 16]. Recent studies based on AD mice models and postmortem human brain tissue have reported significantly higher GABA levels in the reactive astrocytes of the dentate gyrus region of the hippocampus [8, 9]. It is important to note that postmortem studies predominantly measure the activity of the synthesizing enzyme of GABA, namely glutamic acid decarboxylase (GAD). GAD is sensitive to the premortem conditions (e.g., hypoxia and hypovolemia) [17], and can thus introduce variability in the GABA levels quantified from postmortem brain tissues.

The advent of the non-invasive imaging technique, magnetic resonance spectroscopy (MRS), has provided researchers a reliable method to measure absolute GABA concentrations in various brain regions [18]. To the best of our knowledge, hitherto only one study has measured GABA levels (in relation to Creatine; GABA+/Cr) in AD patients using the MRS imaging modality [19]. The results from this study indicate significantly lower GABA+/Cr levels in the parietal region of AD patients as compared to age- and gender-matched healthy control subjects.

In the healthy population, the MRS technique has been used in conjunction with behavioral measures of WM [11, 12]. GABA levels from the dorsolateral prefrontal cortex (DLPFC) has been shown to initially increase and then decrease with repetitions of a WM task [11]. Furthermore, while attempting to parse out the association between GABA levels and WM in terms of the WM components (load, maintenance and distraction resistance) and the associated anatomical brain regions (DLPFC and visual cortex), GABA levels measured specifically from the DLPFC region has been reported to predict the load processing capacity of WM [12].

GABA levels have been associated with vascular factors, including perfusion changes [11], blood-oxygen-level dependent (BOLD) activity [20, 21] and the hemodynamic response function (HRF) [22]. Baseline GABA levels acquired from the DLPFC region have been indicated to correlate inversely with changes in DLPFC perfusion during the performance of a WM task [11]. Baseline GABA concentrations have been shown to correlate negatively with task-based positive BOLD response [21], and correlate positively with task-based negative BOLD response [20]. Task-based changes in GABA levels have also been indicated in functional MRI (fMRI) studies, such that the initial increase and then decrease in the GABA levels has been found to be negatively

correlated with percentage BOLD signal change [23]. Higher GABA levels in the visual cortex have been indicated to have shorter and wider HRF distributions during the performance of a visual task [22]. Despite the abundance of research indicating a negative correlation between GABA levels and positive BOLD response, one recent study did not find a significant relation between baseline GABA concentrations and BOLD activations [24].

The emerging variety of measures and the accumulating empirical evidence for the role of GABA in WM open new avenues to investigate the link between GABA levels and aberrations of WM performance in the AD brain. Future studies are warranted to carry out longitudinal behavioral and vascular assessments of the GABA-WM relationship in mild cognitive impairment as well as early AD patients using advanced multimodal (MRS & fMRI) imaging modalities. It is also suggested that the influence of GABA on WM is assessed in terms of the distinct WM components. As research supports that working memory deficit in AD is multifactorial [25], the understanding of the GABA-WM relationship should be extended to incorporate potential mediating and/or moderating factors, such as A β aggregation and glutamatergic dysfunction [7]. Investigating the GABA-WM link will open further new pharmacological strategies aimed towards reducing, and perhaps even reversing, the working memory deficits prevalent in the escalating epidemic of AD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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