Glutathione: a molecular whistleblower for Alzheimer's disease

Alzheimer's disease: Neurons in select pockets of the brain begin to die off, slowly and incrementally erasing an individual's memory and eroding their individuality. It is a devastating disease, one that affects more than 36 million individuals today, and one for which no reliable and definitive diagnostic test is available. In hopes of identifying a molecular signature for Alzheimer's disease, there has been extensive research aimed at defining the early associated molecular events. One phenomenon that has gained a strong foothold as a lead player in Alzheimer's pathology is 'oxidative stress'. Oxidative metabolism – the process that yields all cells the energy required for survival – produces highly reactive oxidative byproducts, which if not curtailed wreak absolute havoc on a neuronal cell. To defuse these oxidizing products, the brain cells manufacture antioxidants, which act to police and neutralize these rabble-rousers. The predominant of these brain antioxidants – Glutathione aka GSH– has long been indirectly implicated in Alzheimer's: from post-mortem brains to cell models of the disease, research has repeatedly offered indirect evidence for depletion of GSH levels in Alzheimer's disease. But as yet, conclusive clinical association between brain GSH levels and Alzheimer's progression has been absent because directly measuring amounts of a molecule within specific brain areas of humans – well, it's not all that simple!

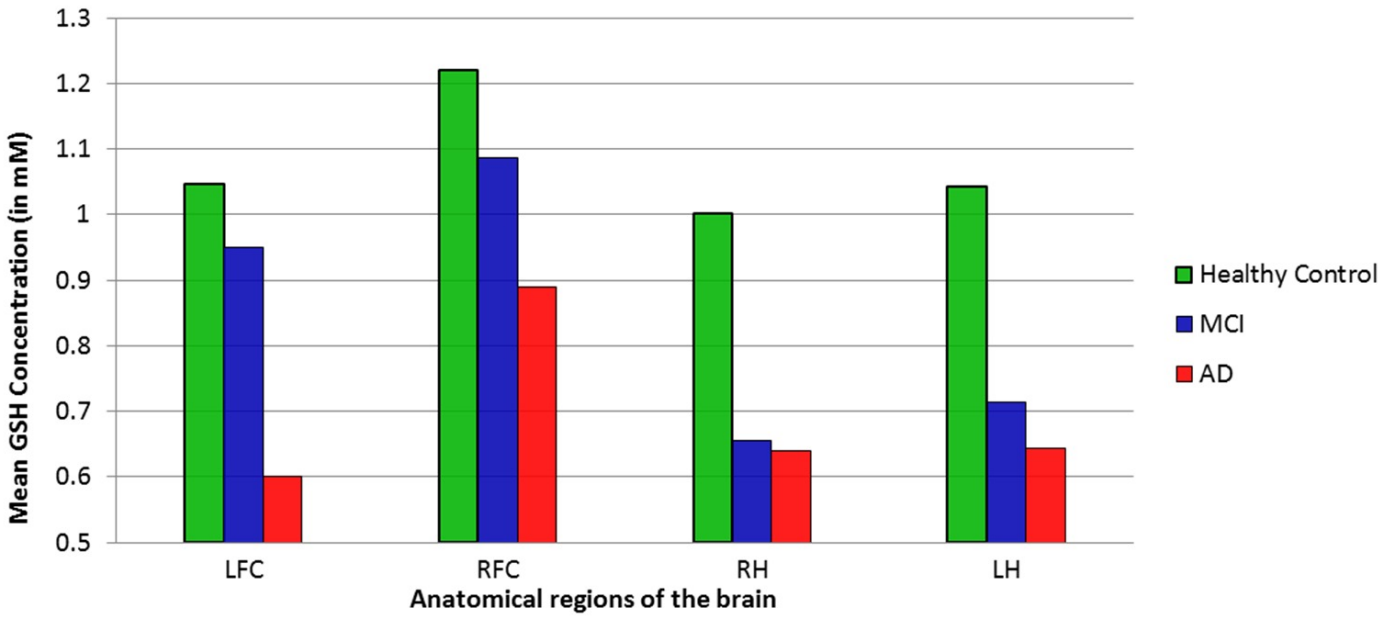

Fig.1. Glutathione levels plummet with Alzheimer's progression
LFC: Left frontal cortex; RFC: Right frontal cortex; RH: Right hippocampus; LH: Left hippocampus

Our team, led by Dr. Pravat K. Mandal, attacked this problem by using magnetic resonance spectroscopy – a remarkable technique that can quantify levels of certain molecules within a given brain region noninvasively by measuring their response to magnetic field fluctuations. Armed with this technique, we quantified GSH levels in brain regions acutely affected by the disease – the hippocampi and the frontal cortices – in Alzheimer's disease, as well as those with an early prodromal stage, namely mild cognitive impairment (MCI).

The hippocampi – the brain centres for learning and memory – are one of the earliest regions to be sabotaged by Alzheimer's pathology. Our data revealed that GSH levels plummet in the hippocampi of patients with Alzheimer's as well as those with MCI (Fig.1). The frontal cortices – brain CEOs responsible for a variety of executive functions – are chronologically affected later in Alzheimer's. GSH levels mimic this chronology with no changes in the cortices of MCI patients, but significant reduction in those of Alzheimer's patients (Fig.1). Interestingly, GSH remains unaffected in the cerebellum – a brain region unaffected by Alzheimer's till late stages. It appears GSH decline is not ubiquitous but rather a region-specific phenomenon that appears to precisely map the progression of Alzheimer's in our brains.

Could it then be that GSH levels would be able to act like a detector test for MCI and Alzheimer's? It appears that may well be the case. Using only GSH levels in the hippocampi and frontal cortices as indicators, we were able to differentiate between healthy subjects and MCI patients as well as between patients with MCI and Alzheimer's with a remarkably high accuracy.

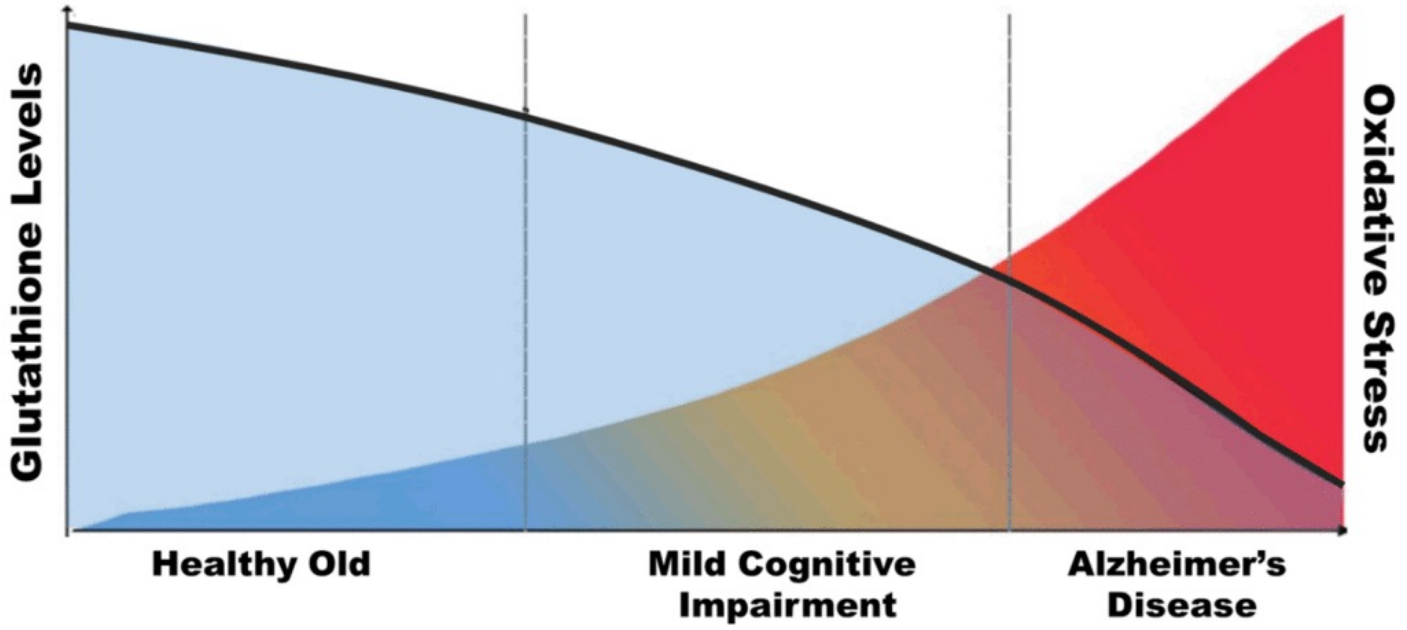

Fig.2. The Relationship between Glutathione, Oxidative Stress, and Alzheimer's

Our findings reveal GSH levels to be tightly associated with and diagnostically reflective of Alzheimer's progression (Fig. 2). They make a loud and strong case for GSH as a potential diagnostic marker for Alzheimer's – a possible whistleblower that uncovers the disease. Given that GSH appears to be a key character in the molecular script that incubates and propagates Alzheimer's, we are presently working towards conducting a clinical trial aimed at assessing GSH as therapeutic target. GSH may well turn out to be the therapeutic 'anti(oxi)dote' to this deadly disease.

Dr. Sumiti Saharan

Publication

Brain Glutathione Levels - A Novel Biomarker for Mild Cognitive Impairment and Alzheimer's Disease.
Mandal PK, Saharan S, Tripathi M, Murari G
Biol Psychiatry. 2015 Nov 15