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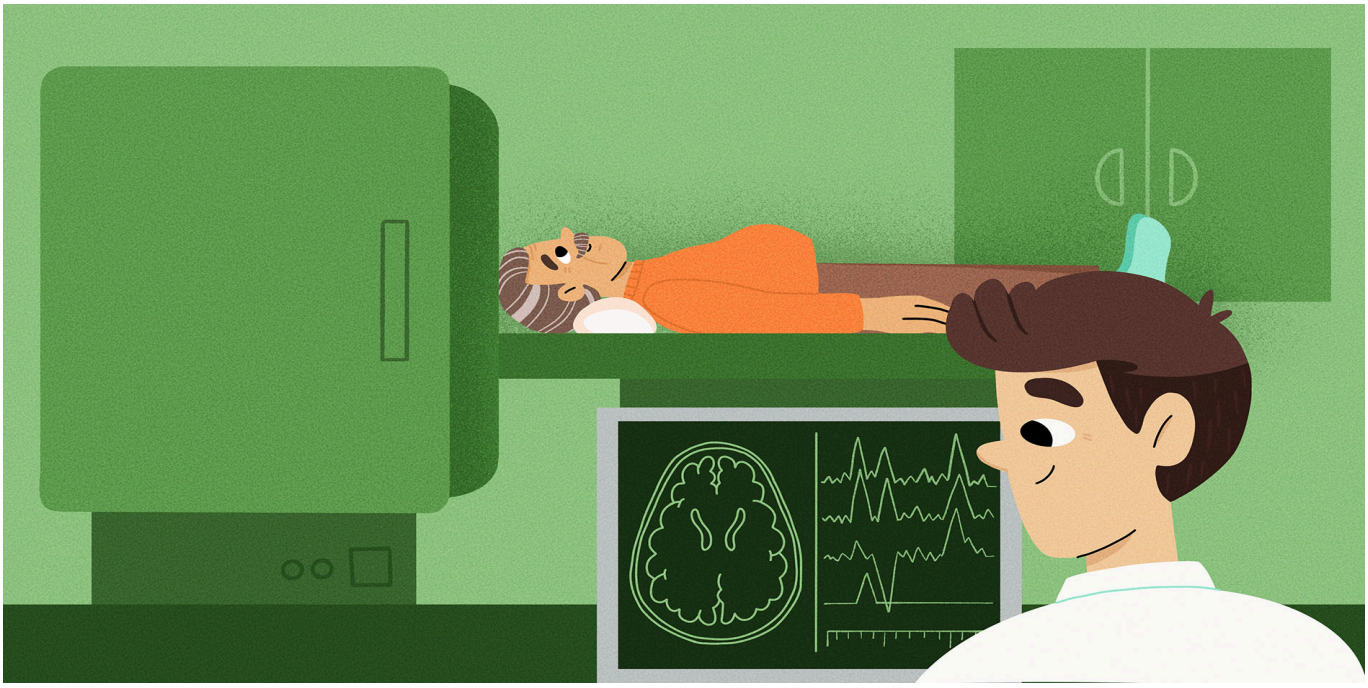

A MOLECULAR SUPERHERO THAT HELPS FIGHT AGING

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YOUNG REVIEWERS:

ALBAN
AGE: 13

EMILY
AGE: 13

As adults get older, their body functions decline. This can cause a build up of harmful substances, called reactive oxygen species, which can damage the cells: the process is called oxidative stress. Luckily, the body uses superhero chemicals called antioxidants to fight against oxidative stress, with the most common being a chemical called glutathione. We were curious to know whether glutathione levels change with age, and how. In previous studies, some researchers measured glutathione levels in the brains of healthy individuals and in the preserved brains of people that had passed away. Other researchers measured glutathione levels in the blood. We analyzed all the results to see how they fit together. Compared to young adults, glutathione levels in older people were either

higher, lower, or unchanged depending on the brain region scientists looked at. In blood, glutathione levels were usually lower with increasing age. This means that oxidative stress contributes to aging by damaging the cells in different parts of the brain and in the body, and that the superhero chemical provides protection by fighting oxidative stress.

METABOLISM

All the chemical changes happening in the cells that convert food into energy, to support the life of an organism.

REACTIVE OXYGEN SPECIES

A family of unstable oxygen-containing molecules that are continuously created and can damage other molecules present in cells.

OXIDATIVE STRESS

Stress and damage that cells experience when reactive oxygen species build up faster than antioxidants can control them.

ANTIOXIDANTS

Molecules that protect cells against oxidative stress by neutralizing reactive oxygen species before they can damage cells.

GLUTATHIONE

The most common of the antioxidants that fights oxidative stress.

MAGNETIC RESONANCE SPECTROSCOPY

A brain imaging technique that safely and painlessly measures the concentrations of chemicals in the brain.

AGING CHANGES OUR BODIES

As we go from young adulthood to middle age and then to older adulthood, our bodies change physically. At older ages, some of our bodily processes start to break down. One such bodily process, known as **metabolism**, refers to all the chemical reactions that take place continuously in the body and make life possible. Problems with metabolism that naturally happen as people age can result in the overproduction of molecules called **reactive oxygen species**. At high levels, reactive oxygen species can trigger a harmful process known as **oxidative stress**, which damages cells and can result in increased risk of disease with age. Luckily, the body has a system in place to protect us from this harm. Superhero chemicals called **antioxidants** are produced to protect the cells of the body and brain from oxidative stress. The most common antioxidant is called **glutathione**.

Glutathione levels in the brain can be measured using a brain imaging technique called **magnetic resonance spectroscopy** (Figure 1A). This technique measures the different chemical concentrations inside the brain, and is painless and extremely safe. In addition, laboratory tests can be used to measure glutathione levels in various tissues of the body, such as the blood, or in the preserved brains of people who have passed away (Figure 1B). Researchers have previously found that aging causes changes in glutathione levels, but no one had ever looked to see whether all the completed studies were consistent with each other. Therefore, we searched previously published scientific papers to understand how glutathione levels change in the brain and blood in adulthood, which could tell us about changes in oxidative stress as we age. Adulthood is composed of young adults (18–39 years of age), middle-aged adults (40–59 years of age), and older adults (60+ years of age).

UNDERSTANDING GLUTATHIONE CHANGES IN BRAIN AND BLOOD

We systematically searched through all scientific articles about glutathione published to date in the PubMed scientific database. We used several keyword combinations in our search and found 32 studies that investigated how glutathione levels in the brain and blood vary in healthy aging [1]. Note that a person is considered a healthy ager

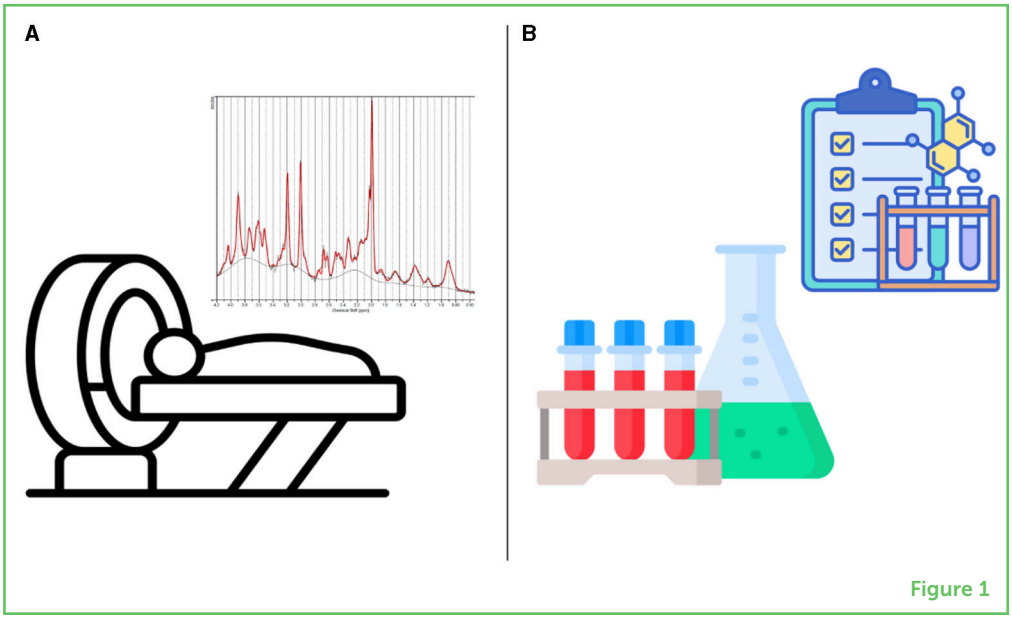

Figure 1

(A) The common antioxidant glutathione can be measured in the brains of living people using a safe, painless brain imaging technique called magnetic resonance spectroscopy. **(B)** Laboratory tests can be performed to measure glutathione in various body tissues, including the blood.

when his or her physical and mental health, independence, and quality of life are maintained throughout life (World Health Organization, 2020).

GLUTATHIONE CAN BE ACCURATELY MEASURED IN THE BRAIN

The human brain has four sections, called lobes. They are the occipital, temporal, parietal, and frontal lobes. Each lobe is made up of several sub-regions, which we will not describe in detail here. Some well-known functions of the four lobes are as follows: the occipital lobe is the master of vision; the temporal lobe is involved in listening and memory; the parietal lobe combines information from all our senses to understand what is happening around us; and the frontal lobe is the boss of planning, calculating, and controlling our emotions. The cerebellum, located in the back bottom part of the brain, is in charge of the coordination of movements (Figure 2).

REPRODUCIBILITY

Concept saying how accurate two (or more) measurements are. Something reproducible can be repeated multiple times.

Reproducibility is very important to scientists. It means that a scientific finding can be repeated or reproduced across multiple studies. To be reliable and accurate, scientific results must be reproducible. Twelve studies of healthy adults (18+ years of age) investigated the reproducibility of glutathione measurements in 12 sub-regions of the brain, using magnetic resonance spectroscopy (Figure 3A). The studies scanned the same participants at least twice, and evaluated how similar the results were to each other. If there was little to no difference between measurements from each scan, the results were considered to have good reproducibility. Overall, measures of glutathione levels were found to have good to excellent reproducibility across all brain areas studied. The reproducibility of glutathione measurements

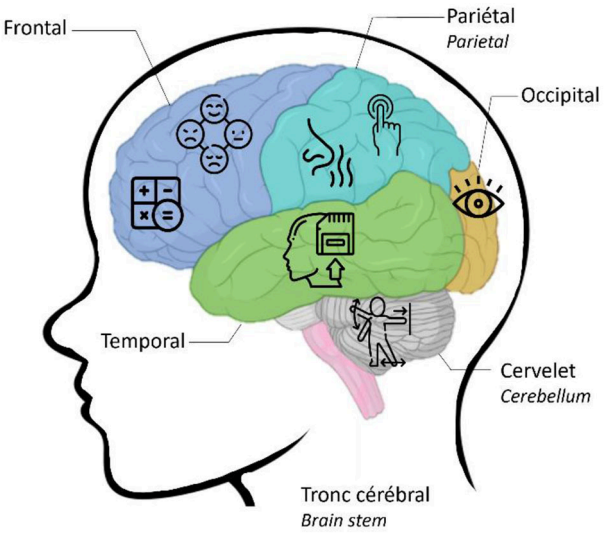

Figure 2

The human brain consists of four main lobes and the cerebellum. The frontal lobe is in charge of calculations, decision making and emotions. The parietal lobe combines and interprets sensations such as touch and smell. The temporal lobe is important for memory. The occipital lobe is the master of vision. The cerebellum, under the parietal lobe, coordinates movements. Finally, the brain stem connects the brain to the rest of the body via the spinal cord.

throughout the brain means that we can trust the results and use them to answer complex questions, such as how brain glutathione levels change with age.

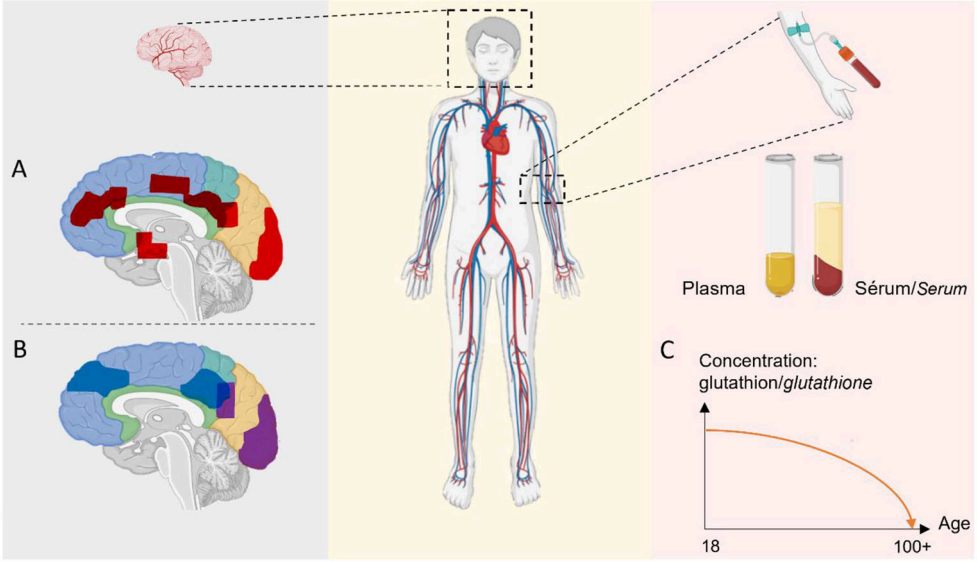

Figure 3

(A) The brain regions investigated using magnetic resonance spectroscopy to measure the reproducibility of glutathione levels are highlighted in red. **(B)** The brain regions in which glutathione levels decrease with increasing age are shown in purple, and regions in which glutathione levels increase with age are shown in blue. **(C)** Results using blood plasma and serum generally show that glutathione levels decrease with age.

CHANGES IN BRAIN GLUTATHIONE LEVELS WITH AGE

From studying published papers, we found that changes in brain glutathione levels depended on which brain region was examined. Specifically, we found that glutathione levels were *decreased* in 4 out of 10 of the brain sub-regions evaluated in older (60+ years of age) adults compared to young (18–39 years of age) adults. Glutathione levels *increased* in 3 out of 10 brain regions and *did not change* in

3 out of 10 regions (Figure 3B). Our hypothesis is that glutathione may increase with age in some brain regions as the brain's way to fight the increasing production of reactive oxygen species. Reduced glutathione in other areas might mean that the brain's glutathione production cannot keep up, probably leading to oxidative stress. This hypothesis still needs to be tested experimentally to see if it is correct. It is important to note that glutathione levels might also vary in other brain regions that have not yet been investigated, so we recommend additional work on this topic.

WHAT ABOUT THE BLOOD?

Since blood travels around the body to reach every organ, glutathione levels in the blood tell us about the amount of oxidative stress experienced over the entire body. The scientific papers we examined looked at changes in glutathione levels in two parts of blood: plasma and serum. Plasma is a yellow fluid in which molecules and chemical compounds such as nutrients and proteins are suspended (Figure 3C). Serum is the pale-yellow liquid that remains after all cells and the clotting proteins that help stop bleeding are removed from the plasma (Figure 3C). In both plasma and serum, glutathione level changes in the blood were more consistent than the changes seen the brain. A majority of the papers we examined reported lower levels of glutathione in older adults compared to young adults (Figure 3C). Since glutathione is produced throughout the body, the findings in blood tell us about what is happening in the entire body, not just the brain.

WHY IS THIS WORK IMPORTANT?

So now you know that glutathione is the most abundant of the superhero chemicals called antioxidants, and it helps to fight and prevent damage to cells caused by oxidative stress. Our review of scientific papers showed that glutathione measurements in the brain are reproducible, and that glutathione levels can be reliably measured in both brain and blood. Glutathione levels are altered in the brain as people age, and glutathione levels in the blood tend to decrease with increasing age, which might reflect the presence of oxidative stress.

Since everyone gets older, people might think that there is nothing they can do about these changes. Luckily, some studies have shown that it is possible to increase the levels of glutathione in the brain and blood, for example by taking dietary supplements [2, 3] or by exercising. These studies give us hope for the future, as they demonstrate that we might not have to suffer from decreasing glutathione levels as we age. In addition, new techniques and new knowledge are emerging, such as more powerful brain scanners that

provide doctors and scientists with high-quality images of glutathione levels in the living brain. Finally, many fruits and vegetables naturally contain antioxidants, so eating a healthy diet can help maintain good health. So remember to eat your grapes, berries, and broccoli, because after all, who would not want to be a superhero and fight oxidative stress?

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

ALBAN, AGE: 13

My name is Alban, I am 13 years old. I am a passionate of football and I am also a Brown belt in karate. I am a serious student, I work well in school and I have good results. I am a rather calm guy, but I am also quite funny. I love to travel and learn new things. I like video games, dinosaurs, and Roller coasters. But, what interests me above all is spending time with family and friends.

EMILY, AGE: 13

I am Emily, a passionate young scientist specialized in computer science. With 5+ years of coding experience, I am proficient in Python, JavaScript, CSS, and HTML. I've received awards like Technovation Montreal 2023 Competition's Jury's Favorite–Junior prize and Best Technical Application prize, and the Innovation Award "Coup de cœur 2021" from FEEP. Currently, I am focused on AI, developing a U-Net Deep Learning model for lesion in-painting on brain MRI scans. My dream is to be a doctor and scientist, making ground breaking discoveries to cure diseases.

AUTHORS

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Flavie E. Detcheverry was born on a small island where she loved going fishing and playing board games with her family. She is a PhD student in Biomedical Engineering at the University of Montreal under the co-supervision of Drs. Badhwar and Narayanan, and is studying metabolite changes in brain and blood of healthy adults and Alzheimer's disease patients, using brain neuroimaging techniques and blood biochemical assays. *flavie.detcheverry@umontreal.ca

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Sneha Senthil is currently a PhD student in Neuroscience at McGill University, who came to Canada to pursue her master's. She is interested in conducting research in Multiple Sclerosis, which can affect the way people move and feel. Before that, she developed rapid high-resolution techniques that can be applied to diseases that affect different regions of the brain. Apart from science, she enjoys reading and traveling.

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Dr. Sridar Narayanan obtained a Ph.D. in Neuroscience from McGill University. He is now an Assistant Professor in the Department of Neurology and Neurosurgery at McGill University, and is a scientist in the McConnell Brain Imaging Center of the Montreal Neurological Institute. His main research is on developing new ways to scan the brain, and on how to extract as much information as possible from brain images to help study neurological diseases, such as multiple sclerosis and Alzheimer's disease.

AMANPREET BADHWAR

Dr. AmanPreet Badhwar grew up in India, where she loved climbing mango trees and caring for monkeys. She came to Canada as a teenager and went on to get her Ph.D. from McGill University. She is currently an Assistant Professor in the Department of Pharmacology and Physiology at the University of Montreal in Montreal, Canada. Dr. Badhwar combines different methods to better understand Alzheimer's disease. These methods vary from looking at the entire brain using imaging to looking at small molecules that make up the brain. Dr. Badhwar also explains science using her paintings. *amanpreet.badhwar@umontreal.ca