MND AUSTRALIA INTERNATIONAL RESEARCH UPDATE

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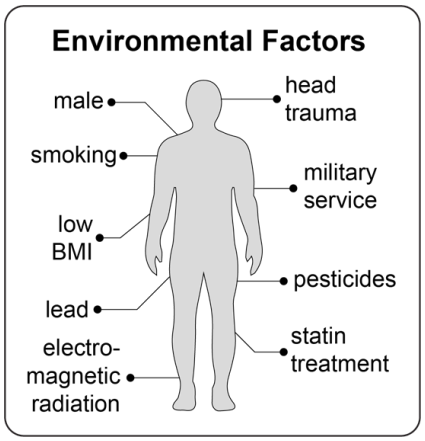
Dr Luke McAlary, Bill Gole MND Postdoctoral Fellow, University of Wollongong

The light at the end of the tunnel

Australia's current situation in regards to lockdowns and COVID-19 vaccination is by no means shared across the rest of the world. Other nations that either vaccinated extensively at the start of the year, or had fewer restrictions, have been continuing their research. However, even hampered by multiple lockdowns, Australian researchers have been busy planning and communicating with one another about new research to perform once we are able.

Soccer as a risk factor for MND[1]



It has been suggested that playing soccer is a risk factor for the development of MND. Researchers from Spain performed an investigation into players within the Spanish soccer league from 2000 to 2020 to identify if soccer players were at greater risk of developing MND than the general population. They found that soccer players were diagnosed roughly 23.7 years earlier than non-soccer playing MND patients, suggesting a role for soccer in earlier disease onset.

What is it about soccer? Sport is something that keeps us healthy and resistant to cardiovascular diseases, which are the biggest killers in the western world. However, we do know that some sports carry great risk with them. An example is that playing American football (NFL) significantly increases the risk of developing dementia. This is very likely due to repeated head injuries and repeated head strikes. The same may be true for soccer in the action of 'heading' the ball.

Trauma or something else? Although trauma is a likely component of developing neurological disorders, it may not be the only one. Professional sports players are not just exposed to more trauma than the average person, but also to more metabolic changes too. This can come in the form of strenuous exercise and even in the form of drugs to enhance performance. Likewise, close proximity to chemicals used on soccer fields may also play a role.

Future of epidemiological studies into MND Around 90% of MND cases are not related to a genetic mutation currently, which means we either do not have enough information to determine a gene or it happens from environmental factors. It is likely that MND is a consequence of both environmental and genetic factors, but the specific nature of those environmental factors still eludes us. In the coming years, as statistical analyses and large data sets get even larger, we should expect to develop more insights into what the MND risk factors are.

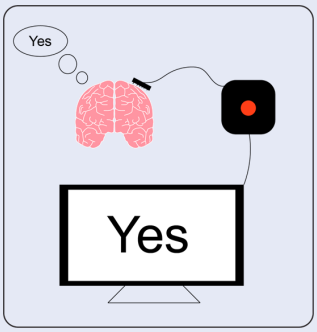
Brain-computer interfaces for improving MND patient communication[2]

In this work, researchers from the Netherlands present a type of brain-computer interface that is faster than the currently used model. These researchers are involved in an area that some might consider more science-fiction than research, where neuroscience meets engineering and software programming. We are increasingly improving our ability to both measure and understand an individual's brain signature, making brain output or signals capable of becoming input to control devices in some cases.

Brain-computer interface? A brain-computer interface is a system that measures output from the brain after a stimulation of some sort has been administered (stimulation is typically a sound or visual cue). By directly measuring the brain output via a headset in response to stimuli, one can define how that person's brain activity corresponds to their desired action very simplistically.

Use of a BCI in MND. By measuring a MND patient's brain while they attempt to carry out a specific task, such as saying "no" or "yes", a BCI can give a patient the ability to tell a computer yes or no just by thinking. The researchers here have specifically shown that they can improve the speed of this technology more than has been typically achieved, making it increasingly useful for MND patients being more like a "real-time" interaction.

A cyborg future. I often say that engineers and computer scientists will provide more short-term advances for those who suffer from MND than biologists or chemists will. The continued advances made in computing, especially with the incredibly rapid advances made in artificial intelligence, are likely to provide MND patients with an improved quality of life over the next few decades. A welcome outcome of this interesting field.



MND Research Australia - the research arm of MND Australia
PO Box 117 Deakin West ACT 2600
Ph: 61 2 8287 4989 email: research@mndaustralia.org.au
website: www.mndresearch.org.au

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How cellular stress can lead to aberrant RNA localisation[3]

Even cells can get stressed

Researchers from the University of California, lead by Dr Gene Yeo, have investigated what happens to RNA molecules when cells become stressed. Cellular stress can occur due to external forces inducing heat, changes in internal cell water content, unwanted oxidation, or proteins becoming misfolded. Cells are very dynamic and have evolved multiple mechanisms to prevent these stresses from causing harm.

Ribonucleic Acid (RNA) and its role

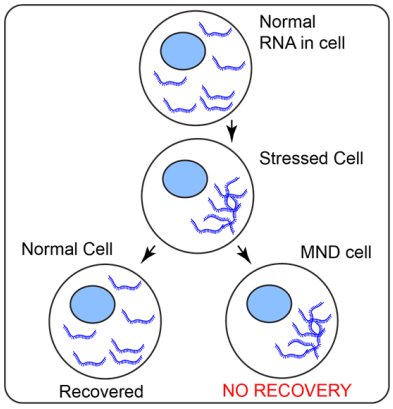
Most of us are probably a little familiar with RNA now that it is being exploited as a genetic vaccine technology against COVID -19. RNA molecules within a cell are as numerous as proteins and play just as important roles. This being the case, if RNA is damaged or cannot perform its role, cells can become sick.

Location, location, location!

A key part of cellular biology is that every molecule within a cell needs to be in the right place, at the right time, at the right amount. Under normal conditions, this is not difficult for a cell to do, but introduce hardship (perhaps in the form of mutations or stress) and cells can begin to have trouble doing this. The authors of this work found that although stressing cells that contained MND-associated mutations did not affect normal RNA processing, the cells did not recover as well as cells without these mutations once the stress was removed.

Future potential of this work?

A very impressive part of this work is that authors did not just identify that RNA was not being processed properly, but they identified which RNA molecules were being altered. This makes for a promising follow up in seeing if restoring these RNA molecules may somehow rescue the cells from the stress and thus perhaps reduce MND-associated damage.

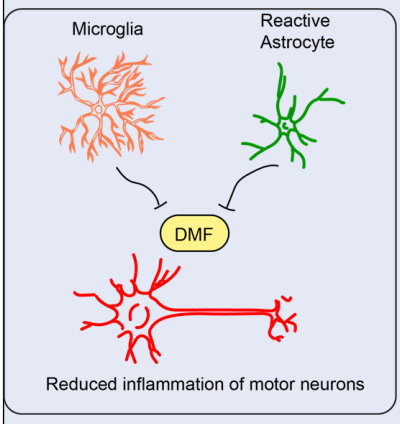


Targeting inflammation in ALS

Researchers from across Australia, lead by Professor Mathew Kiernan, recently finished a clinical trial of a compound called dimethyl fumarate as a potential treatment for MND. The study was a phase II, double-blind, placebo-controlled randomised trial that aimed to determine if dimethyl fumarate was safe for patients to take and if any efficacy could be observed.

Dimethyl Fumarate

Dimethyl Fumarate is a compound that is FDA-approved for the treatment of multiple sclerosis. It works by telling the immune system to become less inflammatory. A part of MND pathology is the activation of immune cells in the central nervous system called astrocytes and glia. It is thought that if we can tell these cells to switch off or at least reduce their activity, we may be able to slow MND progression.



Outcomes of this trial

Unfortunately, this trial did not show that dimethyl fumarate is efficacious as a treatment for MND. The authors note that they tested the compound against slow progressing MND and suggest that if they were to test this compound against fast progressing MND, they might see more promising results. Of note, this work did show that the treatment is safe and well-tolerated, meaning that other potential immune system modulators could be trialled in future too.

MND Research Shorts

- TDP-43 is an RNA-binding protein, and it is this very function that may underpin its role in MND pathogenesis. Researchers from France have shown that if TDP-43's ability to bind to specific types of RNA is lowered, TDP-43 becomes more likely to aggregate in cells. This holds particular importance when trying to understand TDP-43 aggregation as there are many mechanisms by which TDP-43 is thought to aggregate. This opens up the concept of introducing RNA into cells to reduce aggregation by retaining TDP-43 in its soluble form as a treatment approach.[4]
- Human endogenous retrovirus (HERV) has long been implicated in MND. Researchers from Italy have published work that suggests that HERV modulates the immune response by leading to the production of inflammation. Inflammation is associated with MND pathogenesis. HERV-mediated inflammation may therefore be a process we can target in developing new treatments.[5]
- There are some links to show that lipid (fat) metabolism is associated with the development of MND. Researchers from the UK have published work which suggests that aberrant blood lipid levels can lead to MND. This is particularly interesting because it supports growing evidence of metabolic dysfunction in MND, and also provides new potential biomarkers to assess for improving monitoring of disease progression and diagnosis[6].
- Familial MND is defined by the fact that there is a family history of disease. Sporadic means that there is no family history of disease. This does not mean that a sporadic case may not occur due to mutation. Researchers from Sweden have identified 4 cases where SOD1 has become mutated in an individual and produced MND without other family members being affected. This research shows that even sporadic cases of MND should be sequenced to determine if a mutation has occurred.[7] Treatments developed for specific mutations may then be used in these cases where appropriate.

References

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