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Michigan Neural Distinctiveness project: investigating age-related behavioural and brain changes

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28/02/2019

Recruitment status
Suspended

Registration date
04/03/2019

Overall study status
Completed

Last Edited
18/12/2020

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Normal ageing is associated with pervasive declines in cognitive, motor, and sensory function, even in the absence of significant disease. Furthermore, the number of elderly people, as well as the proportion who are elderly, are both growing at an alarming rate. Consequently, tens of millions of healthy people are already experiencing age-related behavioural impairments, and that number is only going to grow.

Nevertheless, there are substantial individual differences in age-related behavioural impairments. Some otherwise healthy people experience significant age-related declines while others do not. What distinguishes those who age gracefully from those who experience significant impairments? The answer to that question could transform efforts to reduce, or even reverse, behavioural impairments associated with ageing.

Using functional neuroimaging, we have found that neural activation patterns in response to different stimuli are significantly less distinctive in older compared with younger adults, a phenomenon we refer to as age-related neural dedifferentiation. Based on recent research from our group and others, we hypothesize that impaired neural distinctiveness is an important factor in age-related declines and that reductions in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) as we age cause this impaired distinctiveness. We also predict that increasing GABA levels pharmacologically will increase neural distinctiveness.

We will examine how similar the neural activation patterns are in blocks of the same task condition (e.g., images of faces with images of faces) versus how similar activation patterns are in different task conditions (e.g., images of faces vs. images of houses). Neural distinctiveness refers to the difference in the average correlation between pairs blocks of the same type of stimuli and pairs of blocks of different types.

Who can participate?
Participants are healthy right-handed, native English speakers aged 18-29 (young adults) or 65 and older (older adults). No one will be excluded based on gender, race, or ethnic background.

What does the study involve?
For the main study, all participants complete the three study sessions (completed on three separate days), involving cognitive, visual, auditory, motor, and emotional processing tasks and two MRI scans.

During session one, participants complete 2 hours of behavioural and cognitive testing. In session two, participants complete 45 minutes of behavioural and cognitive testing and a 1-hour functional magnetic resonance imaging (fMRI) scan. The fMRI involves a tactile (touch) task, auditory (hearing) task, visual task, and a motor (movement) task. We will also measure participants' brain activity while at rest and scan images of brain structure and of the white matter connections.

During the third session, all participants complete a 1.5-hour Magnetic Resonance Spectroscopy (MRS) scan wherein we scan images of brain structure and measure individuals' levels of GABA in the brain. We collect six MRS voxels in the left and right auditory cortices, ventral visual cortices, and sensorimotor cortices.

For the drug study, all participants complete two study sessions (completed on two separate days) that involve taking a drug or placebo and completing two MRI scans.

Both sessions follow the same format. One hour before the MRI scan begins, participants take either a low oral dose of lorazepam or a placebo pill. The researchers will assign participants to the different conditions so that half of the participants complete the lorazepam fMRI before the placebo fMRI and vice-versa. The fMRI involves a tactile (touch) task, auditory (hearing) task, visual task, and a motor (movement) task. We will also measure participants' brain activity while at rest. We will compare neural distinctiveness during the lorazepam fMRI and during the placebo fMRI.

What are the possible benefits and risks of participating?
A potential benefit to participants is the satisfaction of contributing to scientific knowledge. The knowledge gained could improve our understanding of age-related behavioural impairments and potentially lead to new treatments to reduce or eliminate some of those impairments.

All of the procedures in this study are non-invasive and involve minimal risk. Risks associated with behavioural testing involve fatigue and boredom. Additionally, there are no known physiological risks associated with non-invasive MRI imaging. However, there is a potential for injury during scanning if the participant has metal in his or her body, but we will carefully screen all participants both in the initial web-based questionnaire and immediately before scanning. There is also a potential risk of claustrophobia, boredom, and fatigue from the MRI procedures, but these concerns are easily managed by removing the participant from the scanner briefly and /or discontinuing the experiment. Another potential risk associated with neuroimaging is the possibility of detecting a brain abnormality in the course of a scan.

The most common side effects associated with a single, oral dose of lorazepam include sedation and drowsiness, dizziness, weakness, slurred speech, and ataxia. Less common side effects include confusion, restlessness, depression, suppressed breathing, amnesia, reduced blood pressure, and allergic reactions.

Where is the study run from?
All sessions take place at the University of Michigan's Functional MRI Laboratory at the Bonisteel Interdisciplinary Research Building in Ann Arbor, Michigan (2360 Bonisteel Blvd, Ann Arbor, MI, 48109).

When is the study starting and how long is it expected to run for?
This study began on the 1st of June, 2016 and will continue to run for the next four to five years.

Who is funding the study?
The National Institutes of Health (NIH)

Who is the main contact?
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Additional identifiers

Clinical Trials Information System (CTIS)

N/A

ClinicalTrials.gov (NCT)
N/A

Protocol serial number
5R01AG050523-04

Study information

Scientific Title
Michigan Neural Distinctiveness project: investigating the scope, causes, and consequences of age-related neural dedifferentiation

Acronym
MiND

Study objectives
Impaired neural distinctiveness is an important factor in age-related declines, and that reductions in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) are what cause this impaired distinctiveness. Furthermore, we predict that increasing GABA activity via a low oral dose of a benzodiazepine (lorazepam, 0.5 mg) will lead to increased neural distinctiveness within individual subjects.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/10/2016, University of Michigan IRBMED (2800 Plymouth Road, Building 520, Suite 3214, Ann Arbor, MI 48109-2800; (734) 763 4768; (734) 763 9603; irbmed@umich.edu), ref: HUM00103117.

Study design
Interventional single-centre non-randomised study

Primary study design
Interventional

Study type(s)
Quality of life

Health condition(s) or problem(s) studied
Healthy ageing

Interventions
The MiND project consists of two separate studies: the main study and the drug study.

In the main study, we are evaluating the scope of neural dedifferentiation (measured by functional magnetic neuroimaging), whether age-related declines in GABA may be a cause (measured using magnetic resonance spectroscopy), and its behavioral consequences. To

investigate the role of GABA, we will measure GABA levels in visual, auditory, and sensorimotor regions using recently developed magnetic resonance spectroscopy (MRS) procedures and then investigate whether higher GABA levels are associated with greater neural distinctiveness in each cortical region. To assess behavioral consequences, we will measure individual differences in cognitive, visual, auditory, motor, and emotional processing using a standardized and validated set of tests.

Participants come in for three sessions at the University of Michigan's Functional MRI Laboratory (i.e., single-centre). Participants are assigned to one of four conditions balancing fMRI task order (tasks include tactile, auditory, resting, visual, and motor paradigms).

In the drug study, we are investigating the relationship between neural distinctiveness, as measured by functional magnetic resonance imaging, and GABA concentration in humans by administering low doses of lorazepam (LRZ), a benzodiazepine that is known to increase GABA receptor activity, and assessing the effect on neural distinctiveness. Participants in the main study do not participate in the drug study.

Participants come in for two sessions at the University of Michigan's Functional MRI Laboratory (i. e., single-centre). Participants are assigned to one of four conditions balancing fMRI task order (tasks include tactile, auditory, resting, visual, and motor paradigms) and drug/placebo administration order.

The drug study uses an intervention design. Participants are assigned by the researchers to one of four conditions balancing fMRI task order and drug/placebo order. We aim to manipulate GABA activity pharmacologically using a low oral dose of a benzodiazepine (lorazepam, 0.5 mg) and an oral placebo pill administered approximately 1 hour before the fMRI scanning session, and then investigate the effect on neural distinctiveness.

In group one, participants complete a placebo fMRI in the following task order during session one: tactile, auditory, resting, visual, motor. Then group one completes a lorazepam fMRI in the following task order during session two: tactile, auditory, resting, motor, visual.

In group two, participants complete a placebo fMRI in the following task order during session one: tactile, auditory, resting, motor, visual. Then group two completes a lorazepam fMRI in the following task order during session two: tactile, auditory, resting, visual, motor.

In group three, participants complete a lorazepam fMRI in the following task order during session one: tactile, auditory, resting, visual, motor. Then group three completes a placebo fMRI in the following task order during session two: tactile, auditory, resting, motor, visual.

In group four, participants complete a lorazepam fMRI in the following task order during session one: tactile, auditory, resting, motor, visual. Then group four completes a placebo fMRI in the following task order during session two: tactile, auditory, resting, visual, motor.

All participants complete the same Magnetic Resonance Imaging scan.

Participants typically complete all study sessions within 2-3 weeks. We follow-up with participants via Email about one week after completion to thank them for their participation with pictures of their brain. Additionally, we send out an annual newsletter to all completed participants. The newsletter describes preliminary results and major project aims to a lay-audience.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Lorazepam

Primary outcome(s)
Main study:
1. Neural distinctiveness will be determined from fMRI data at baseline during Session 2.
2. GABA levels will be determined from MRS data at baseline during Session 3.
3. Cognitive and behavioural test scores will be determined according to each test that was administered at baseline during Sessions 1 and 2.

Drug study:
1. Neural distinctiveness will be determined from fMRI data both at baseline and approximately 1 hour after administering a low (0.5mg) oral dose of Lorazepam. These measures will be collected on two separate days, at least two days apart (Sessions 1 and 2).

Key secondary outcome(s))
Main study:
1. Performance on the behavioural tasks and their relation to their respective fMRI task distinctiveness (e.g., comparing motor behavioural scores to the neural distinctiveness obtained in the motor fMRI task) within a few weeks of their completion of the study.

Completion date
31/01/2022

Eligibility

Key inclusion criteria
1. Right-handed
2. Aged 18-29 (young adults group)
3. Aged 65 and older (older adults group)
4. Native English speakers

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Sex
All

Key exclusion criteria
Criteria noted with an asterisk (*) only apply to the drug study.
1. Hearing problems or use of a hearing aid
2. Colour blindness
3. Motor control problems
4. Psychotropic medication
5. Current depression or anxiety, or occurrence of depression/anxiety within 5 years
6. Concussion with unconsciousness for 5 minutes or more
7. Pregnancy or attempting to become pregnant
8. More than 4 alcoholic drinks per week for women, more than 6 for men
9. History of drug or alcohol abuse or addiction
10. Weight greater than 250 pounds
11. MRI incompatibility (claustrophobic, foreign metallic objects, pacemaker, etc.)
12. Glaucoma*
13. Breathing problems*
14. Allergy to benzodiazepines*
15. Undergoing chemotherapy*
16. Immune system disorder*
17. Kidney disease*
18. Liver disease*

Date of first enrolment
14/10/2016

Date of final enrolment
30/11/2021

Locations

Countries of recruitment
United States of America

Study participating centre
Bonisteel Interdisciplinary Research Building, University of Michigan's Functional MRI Laboratory
2360 Bonisteel Blvd
Ann Arbor
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Sponsor information

Organisation

University of Michigan

ROR
https://ror.org/00jmfr291

Funder(s)

Funder type
Government

Funder Name
National Institutes of Health

Alternative Name(s)
US National Institutes of Health, Institutos Nacionales de la Salud, NIH, USNIH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the MiND project are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2019		Yes	No
Protocol article	protocol	12/04/2019	15/04/2019	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes