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Changes in neural representations over time and in mild cognitive impairment

Submission date	Recruitment status	[_] Prospectively registered
01/11/2024	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
11/11/2024	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
12/11/2024	Other	[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Normal aging is characterized by cognitive, visual, hearing, and motor impairments. As the aging population continues to rise, it is imperative that we further our understanding on aging to improve treatments for older adults.
Part of the mystery of aging is individual differences in behavior and cognition: some adults age more gracefully while others experience more impairments. This study aims to understand what causes these differences and their implications for Alzheimer's pathology.
Previous work demonstrated that if neural activation patterns responding to different stimuli are similar, it is correlated with decreased behavioral performance. Distinctiveness of neural activation also declines with age, a phenomenon called age-related neural dedifferentiation. Lastly, age-related declines in an inhibitory neurotransmitter, GABA, were correlated with the decline of distinctiveness. This study investigates neural dedifferentiation, GABA levels and behavioral performance in older adults over time. The researchers will also study healthy and mildly cognitively impaired (MCI) adults to understand the role of neural mechanisms in Alzheimer's pathology.

Who can participate?
Healthy (CN) older participants must be right-handed, native English speakers, aged 65 years and older, and MRI scan compatible. Mild cognitively impaired (MCI) participants must be 65 years and older and MRI scan compatible.

What does the study involve?
Each participant will have three in-person sessions. Session 1 involves two hours of behavioral testing with a 10-minute break in between. Session 2 has 1 hour of behavioral testing and a 45-minute functional magnetic resonance imaging (fMRI) scan. During the fMRI scan, participants will complete an auditory, motor, visual and memory task to observe neural activation patterns. The researchers also collect a brain structural scan, a diffusion-weighted imaging scan and a scan at rest. Session 3 is 1 hour of behavioral testing and a 60-minute Magnetic Resonance Spectroscopy (MRS) scan. During the MRS scan, there is a brain structural scan and seven voxels to measure GABA levels. The voxels are placed in the left and right auditory cortices, left and right sensorimotor cortices, left and right visual cortices and one for memory.

What are the possible benefits and risks of participating?
A potential benefit is the contribution to scientific knowledge about age-related behavioral impairments and may lead to treatments to reduce impairments. All participants are monetarily compensated for their participation.
All potential risks of this study are non-invasive and are minimal. Risks associated with behavioral testing include fatigue and boredom. There are potential risks with MRI imaging if the participant has metal in or on their body. There is also a potential risk of claustrophobia, fatigue, and TMS from MRI scans. However, each participant is thoroughly screened to ensure MRI compatibility. Additionally, participants are allowed to leave the scanner at any time during the study. There is also a risk that the neuroimaging may detect/reveal a brain abnormality, and if this happens, the participant will be notified.

Where is the study run from?
University of Michigan (USA)

When is the study starting and how long is it expected to run for?
September 2021 to September 2026

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

Who is the main contact?
Dr Thad Polk, tpolk@umich.edu

Contact information

Type(s)
Public, Scientific, Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
R01AG050523

Study information

Scientific Title
Michigan Neural Distinctiveness Project Renewal: Investigating age-related neural dedifferentiation longitudinally and in Alzheimer's pathology

Acronym
MiND

Study objectives
Neural distinctiveness is related to age-related declines and is also associated with a reduction in the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). This study is investigating the relationship between neural distinctiveness, GABA and behavior longitudinally and with Alzheimer's pathology.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 20/09/2021, University of Michigan, IRBMED (2800 Plymouth Road, North Campus Research Complex, Building 520, Suite 3214, Ann Arbor, 48109-2800, United States of America; +1 (0)734 763 4768; irbmed@umich.edu), ref: HUM00199054

Study design
Observational longitudinal single-centre non-randomized study

Primary study design
Observational

Secondary study design
Longitudinal study

Study setting(s)
University/medical school/dental school

Study type(s)
Other

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Understanding mechanisms of aging, healthy and MCI groups, longitudinally

Interventions

The MiND Renewal Study investigates neural distinctiveness, GABA levels, and behavior, longitudinally and its relationship with Alzheimer's pathology.

In order to investigate longitudinally, participants are asked to return at multiple time points. The researchers investigate Alzheimer's pathology by administering neuropsych testing that results in a research diagnosis and using amyloid and tau data collected from a collaborating study.

Neural distinctiveness is measured by functional magnetic neuroimaging and GABA is measured by magnetic resonance spectroscopy. Both are investigated in auditory, motor, visual and memory brain regions. The researchers administer cognitive, auditory, motor, visual and memory tests to assess behavior.

Participants come in for three in-person sessions at the University of Michigan and the sessions are typically completed within 2-3 weeks. The researchers follow up with the participants with a picture of their brain to show their thanks for their participation. They also send out an annual newsletter with study progress updates to all participants.

Intervention Type
Mixed

Primary outcome measure
1. Neural distinctiveness is determined from fMRI data at baseline during Session 2. Each participant will complete the fMRI scan each time they participate and will complete a visual, auditory, motor, and memory task that is then used to calculate their distinctiveness score. Neural distinctiveness score is calculated at the end of their participation. Neural distinctiveness is a subtraction of activation correlations, specifically: the difference between the average within-condition correlation and the average between-condition correlation. The researchers gather the activation data from the fMRI scan tasks and the condition blocks from each task. They calculate the within-condition by computing correlations to estimate how similar activation patterns are to the same stimulus type (activation patterns stimulated by different face blocks). Then, all the within-condition correlations are averaged to estimate within-condition similarity. Between-condition activation patterns are calculated by computing correlations between different conditions (face block vs house block) and then all values are averaged to get an estimate of between-condition similarity.
2. GABA levels are determined from MRS data at baseline during Session 3. Each participant will complete the MRS scan each time they participate and their GABA level measures are calculated at the end of their participation. To quantify GABA, the researchers utilize the Gannet 3.3.1 MATLAB toolbox for each of the seven MRS voxels collected during the MRS scan.
3. Cognitive and behavior test scores are determined according to behavioral testing at baseline, done at all three sessions. The NIH toolbox, NACC battery, AudioConsole testing and in-house created tasks are all administered.

Behavioral performance, fMRI task neural distinctiveness, and GABA level associations are assessed once each participant finishes their sessions.

Secondary outcome measures
1. GLX: Glutamate + glutamine (GLX) levels are also measured from MRS data at baseline during Session 3 and the measures are calculated at the end of their participation. Gannet 3.3.1 MATLAB does this automatically alongside GABA calculations.
2. Demographic information: to observe behavioral variables, the researchers additionally collect

demographic data via an online survey at baseline prior to starting their in-person sessions. They collect education levels, amount of exercise, average weekly alcohol intake and learned musical ability.
3. Emotions scales: to ascertain general emotional status and stress levels, the researchers administer an online survey during Session 1 at baseline. A raw score is generated via R script.
4. Brain volume: the researchers additionally calculate the volume for numerous different brain regions (mm^3) using FreeSurfer, from data collected from the MRI scan conducted in session 2 at baseline.

Overall study start date
19/09/2021

Completion date
19/09/2026

Eligibility

Key inclusion criteria
Healthy older adults:
1. MRI scan compatible
2. Aged 65 years and older
3. Normal (or corrected-to-normal) vision, hearing, and motor control
4. Right-handed
5. Native English speaker

Mildly cognitively impaired (MCI) adults:
1. MRI scan compatible
2. 65 years and older

Participant type(s)
Healthy volunteer, Patient

Age group
Senior

Lower age limit
65 Years

Upper age limit
100 Years

Sex
Both

Target number of participants
MCI = 100, CN = 150, Total = 250

Total final enrolment
250

Key exclusion criteria
Healthy older adults:
1. Use of hearing aids
2. Color blindness
3. Motor control problems
4. Psychotropic medication
5. Use of estrogen therapy
6. Current depression/anxiety or occurrence within the past 5 years
7. Concussion with unconsciousness for 5 minutes or more
8. Drinks more than 7 alcoholic drinks per week
9. History of drug or alcohol abuse or addiction
10. Weight greater than 250 lbs
11. MRI scan incompatibility
12. Familiar with languages with auditory task (Sinhalese, Macedonian, Marathi/Hindi, Persian, Ukrainian, Swahili)

Mildly cognitively impaired (MCI) adults:
1. MRI scan incompatibility

Date of first enrolment
21/09/2021

Date of final enrolment
21/09/2021

Locations

Countries of recruitment
United States of America

Study participating centre
East Hall
530 Church Street, B033
Ann Arbor
United States of America
48109

Study participating centre
Bonisteel Interdisciplinary Research Building, University of Michigan's Functional MRI Laboratory
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Study participating centre

Ann & Robert H. Lurie Biomedical Engineering Building (LBME)
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Study participating centre
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Sponsor type
University/education

ROR
https://ror.org/00jmfr291

Funder(s)

Funder type
Government

Funder Name
National Institutes of Health

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Publication and dissemination plan
The researchers plan to publish multiple manuscripts for the data generated from the MiND renewal project, publishing the results of the research questions. They have already published one paper in Imaging Neuroscience on 15/07/2024 (see citation below). The researchers will continue to publish study results for the next couple of years.

Citation = Mark D. Zuppichini, Abbey M. Hamlin, Quan Zhou, Esther Kim, Shreya Rajagopal, Adriene M. Beltz, Thad A. Polk; GABA levels decline with age: A longitudinal study. Imaging Neuroscience 2024; 2 1–15. doi: https://doi.org/10.1162/imag_a_00224

Intention to publish date
20/09/2027

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?
Interim results article		15/07/2024	12/11/2024	Yes	No