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Original Article

The Association Between Generalized Anxiety Disorder and Resting-State Prefrontal Cortex Oxygenation Is Modified by Self-Reported Physical Activity: Results From The Irish Longitudinal Study on Ageing

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Abstract

Individuals with anxiety disorders exhibit lower intrinsic functional connectivity between prefrontal cortical areas and subcortical regions. The prefrontal cortex (PFC) is sensitive to the acute and chronic effects of physical activity (PA), while the anxiolytic effects of PA are well known. The current study examined the association of generalized anxiety disorder (GAD) and its interaction with PA, with resting-state, left PFC oxygenation. This cross-sectional study used data from participants (N = 2444) from The Irish Longitudinal Study on Ageing, a nationally representative prospective study of community-living adults aged 50 and older in Ireland. The Composite International Diagnostic Interview Short-Form determined fulfillment of criteria for GAD. The short-form International Physical Activity Questionnaire determined adherence to the World Health Organization PA guidelines. Resting-state, left PFC oxygenation was continuously measured via a Portalite. Tissue saturation index (TSI) was calculated as the ratio of oxygenated hemoglobin to total tissue hemoglobin (expressed as a percentage) for the final minute of a 5-minute supine-rest period. Multivariable linear regression quantified associations of GAD with TSI in the total population and population stratified by PA status. Participants with GAD had lower TSI (b = −1.416, p = .008) compared to those without GAD. However, this association was modified by PA. Among participants who met the PA guidelines, TSI did not differ according to GAD status (b = −0.800, p = .398). For participants who did not meet the guidelines, TSI was significantly lower among those with GAD (b = −1.758, p = .004). These findings suggest that PA may help to protect brain health among older adults with GAD.

Keywords: Brain aging, Epidemiology, Exercise, Health

Late-life anxiety can be inherent to aging and an adaptive process to coping with social isolation, health issues, and mortality. However, exceeding "normal" levels of anxiety can lead to the development of an anxiety disorder which poses major challenges in late life. Generalized anxiety disorder (GAD) is a condition primarily characterized by excessive, uncontrollable, and often irrational worry about everyday matters for a period of 6 months or more (1). Lifetime prevalence is 1.6%, 2.8%, and 5.0% among low, middle, and high-income countries, respectively (2), and it can have a severe personal burden, including functional impairment, reduced health-related quality of life (3), impaired cognitive performance (4,5), and increased risk of cardiovascular events (6,7). In Europe, 12-month

prevalence is currently highest in those aged 65 and older; given the increasing aged population in Europe, the number of people with GAD will also likely increase (8). Predictors of GAD are lower subjective social status, female sex, exposure to childhood adversity, and certain health behaviors, including low physical activity (9–12).

Evidence from across the life span shows that heightened anxiety symptoms are associated with lower blood oxygen level-dependent signaling in prefrontal cortical areas and increased blood oxygen level dependent in the amygdala during emotional regulation tasks in task functional magnetic resonance imaging (fMRI) (13–17). Individuals with anxiety disorders also exhibit lower intrinsic functional connectivity between anxiety-attenuating prefrontal cortical areas and anxiety-inducing subcortical regions comprising a limbic circuit, including the amygdala, as measured by resting-state fMRI (18–21). Though these patterns provide promising insights into abnormal brain functional integration that may underlie anxiety disorders like GAD, the cost and analytic challenges associated with MRI-based data collection act as barriers to their therapeutic value.

Hemodynamic status of the dorsolateral (DL) prefrontal cortex (PFC) can also be assessed using functional near-infrared spectroscopy (fNIRS), a cheaper and computationally simpler technology than MRI as evidenced in recent studies from The Irish Longitudinal Study on Ageing (TILDA) (22,23). The DLPFC, an anterior node within a diffuse cognitive control brain network, is important for proper emotional and affective regulation (24,25). Hemodynamic status, measured using fNIRS placed over the DLPFC, has recently been both directly (26,27) and inversely (28) related to anxiety symptoms, partly reinforcing the complex and hierarchical organization of these brain circuits and their clinical relevance among treatment-seekers (29). The DLPFC is also sensitive to the acute effects of exercise in young adults (30,31) and chronic effects of physical activity in older adults postretirement (32), suggesting it may play an important role in the anxiolytic benefits of exercise and physical activity.

To the best of our knowledge, no studies have examined resting-state PFC oxygenation in older adults with GAD. It is plausible that older adults with GAD have had greater/longer total exposure to anxiety symptoms, thus underlying pathologies, such as dysfunctional cognitive control circuits, may be more pronounced. Therefore, the current study examined whether resting-state, left PFC oxygenation differs between older adults with and without GAD. It also examined whether this association was modified by physical activity. We hypothesized that people with GAD would have lower left PFC oxygenation but that this would not be apparent among those with higher physical activity levels.

Method

This study used Strengthening the Reporting of Observational Studies in Epidemiology recommendations to guide reporting (33).

Study Design

This study examined cross-sectional associations between GAD and resting-state, left PFC oxygenation, and whether physical activity modified this association, in a large cohort of participants (N = 2444; 54% female) from TILDA. Established in 2009, TILDA is an ongoing large population-based study of a nationally representative equal probability sample of community-dwelling older adults aged 50 and older. Data from Wave 3 of TILDA collected between 2014 and 2015 were utilized herein. Details of the methodology employed by TILDA are fully described elsewhere (34). Briefly, data for the current study were collected by (a) a Computer-Assisted Personal Interview (CAPI) completed by participants in their own homes with a trained professional social interviewer, (b) a self-completion questionnaire completed and returned after the visit, and (c) a comprehensive health assessment at a national center conducted by trained nursing staff.

Resting-State PFC Oxygenation

In the health assessment, left PFC oxygenation was continuously measured at a rate of 50 Hz using a Portalite (Artinis Medical Systems, Zetten, Netherlands) continuous-wave NIRS system (35). This portable, noninvasive device has 3 transmitters and 1 receiver; each transmitter emits 2 different wavelengths of light (760 and 850 nm), which are absorbed at different rates by oxygenated hemoglobin (O_2Hb) and deoxygenated hemoglobin (HHb). Measuring changes in light attenuation at different wavelengths enables changes in frontal lobe O_2Hb and HHb to be determined continuously via spatially resolved spectroscopy (36,37).

Recordings were carried out in a comfortably lit room maintained at an ambient temperature between 21°C and 23°C. Participants rested silently in the supine position for 5 minutes. A single probe was placed on the forehead, corresponding approximately to the FP1 position in the international 10–20 electrode placement system (38). Measurement was conducted on the left hemisphere to limit the time demand on participants, and previous findings indicate no variation in tissue oxygenation index (TSI) between left and right head hemispheres (39). The influence of environmental light was prevented by a light-proof black headband covering the sensor. Levels of O_2Hb and HHb were recorded continuously. Concentrations of cerebral chromophores measured by NIRS are correlated with the BOLD signal measured by fMRI (40) and cerebral blood flow measured by computerized tomography (CT) (41). The PortaLite system used in this study has been used to study cerebral de/oxygenation during hypercapnia (42) and exercise (43). TSI was the primary measure used in this study and is defined as the ratio of O_2Hb to total tissue hemoglobin and expressed as a percentage (44,45). TSI has been shown to reflect cerebral oxygenation to a high degree of sensitivity and specificity during carotid surgery, an indication that NIRS can show clinically relevant estimations of cerebral hemodynamic and oxygen changes in the adult head (46). Using MATLAB (2016b, version 9.1; The MathWorks Inc., Natick, MA), all data were downsampled to 5 Hz and a lowpass 0.5 Hz Butterworth filter was applied to the NIRS signals to reduce heartbeat contamination of the signal. Mean TSI values were calculated over the last minute of the 5-minute rest period.

Generalized Anxiety Disorder

In the CAPI, the Composite International Diagnostic Interview Short-Form (CIDI-SF) determined fulfillment of criteria for GAD (47). Participants were classified as having GAD if they reported (a) a period of worry lasting at least 5 months, (b) severe worry, (c) difficult to control worry, and (d) at least 3 of 7 additional symptoms (ie, restlessness, keyed up/on edge, easily tired, difficulty concentrating, irritability, tense, sore, or aching muscles, and trouble falling or staying asleep). Compared to the full CIDI in the US National Comorbidity Survey, the CIDI-SF demonstrated sensitivity of 96.6%, specificity of 99.8%, positive predictive value of 96.8%, negative predictive value of 99.8%, and total classification accuracy of 99.6% for GAD (47). In a smaller European sample, it has demonstrated sensitivity and specificity of 71.4% and 74.3%, respectively (48).

Physical Activity

In the CAPI, the short-form International Physical Activity Questionnaire (IPAQ-SF) assessed physical activity (49). Respondents reported the number of days and duration of vigorous-intensity, moderate-intensity, and walking activities undertaken during the previous 7 days. The total number of minutes engaged in walking and moderate- and vigorous-intensity physical activity per week were summed, and respondents who reported engaging in activity for at least 16 hours per day were excluded. The remaining respondents were grouped according to whether they met WHO physical activity guidelines (ie, ≥150 minutes weekly of moderate physical activity or ≥75 minutes weekly of vigorous physical activity, or ≥600 metabolic equivalents minutes of weekly moderate- or vigorous-intensity physical activity). Walking was not included in assessing adherence to the WHO physical activity guidelines as the IPAQ-SF does not assess walking intensity.

Covariates

Covariates were selected based on logical, theoretical, and/or prior empirical associations between resting-state PFC oxygenation, anxiety, and physical activity and were assessed in the CAPI and self-completion questionnaire. These included self-reported sociodemographic information, including age (years), sex (male, female), education level (none/primary, secondary level, third level, or higher), marital status (married/living together as if married, not married, separated/divorced, widowed), and dominant hand (left or right). Waist–hip ratio and height were measured by a trained nurse. Participants were categorized as non-problem drinkers (≤1) or problem drinkers (≥2) based on established cutoffs on the CAGE alcohol scale (50). Smoking status was categorized as never, former, or current smoker. Medication records were examined for use of antihypertensive (ATC codes: C02, C03, C07, C08, or C09), antidepressant (ATC code N06A), anxiolytic (ATC code N05B), or antipsychotic (ATC code N05A) medications. Supine beat-to-beat blood pressure was measured at a rate of 200 Hz with a Finometer (Finapres Medical Systems, Arnhem, Netherlands) at the same time as the NIRS measurement. Depression was assessed using the CIDI-SF (47). Participants were asked if they had ever been diagnosed with any chronic (ie, lung disease, asthma, arthritis, osteoporosis, cancer, stomach ulcer, varicose ulcer, liver disease, or thyroid disease) or cardiovascular conditions (ie, stroke, angina, heart attack, heart failure, transient ischemic attack, high cholesterol, diabetes, heart murmur, or irregular heart rhythm). Participants were classified based on a number of chronic conditions (0, 1, ≥2) and cardiovascular conditions (0, 1, ≥2). The number of physical limitations was determined by asking about, and subsequently summing, the number of difficulties with walking, running, sitting, sit-to-stand, stair climbing, reaching overhead, stooping, kneeling, crouching, lifting heavy weights, pushing or pulling large objects, and picking small coins from table.

Statistical Analyses

Analyses were performed using Stata (v15.1; Stata Corp.). Participant characteristics are described using the mean and standard deviation for continuous variables and by frequency for categorical variables. Multivariable linear regression quantified associations (unstandardized betas [*b*] and associated 95% confidence intervals [95% CIs]) of GAD with TSI adjusting for age and sex (Model 1) and age, sex, education, problem drinking, smoking, use antihypertensive, antidepressant, anxiolytic, or antipsychotic medications, height, dominant hand, waist-to-hip ratio, supine systolic blood pressure, depression, cardiovascular conditions, other chronic conditions, and physical limitations (Model 2). Sensitivity analyses were subsequently run to examine the interaction between GAD and age and sex. To explore the effect of physical activity on this relationship, fully adjusted multivariable linear regression quantified associations of GAD with TSI within categories of meeting (ie, sufficient physical activity) and not meeting (ie, insufficient physical activity) minimum recommended physical activity levels. Participants in TILDA who attend the health center assessments were more likely to be younger, have a higher education level, and have less physical disability (51). Therefore, all data were weighted with an inverse probability weight using the *svy* command in STATA to be representative of the population of adults aged 50 and older in Ireland.

Results

Participant Characteristics

Participant characteristics of the analytic sample are presented in Table 1. Briefly, participants' mean ± *SD* age was 64.6 ± 7.8 years, and 53.89% (*n* = 1317) were female. Prevalence of GAD was 2.91%

Table 1. Participant Characteristics (*N* = 2444)

Variable	*N* (%) or Mean ± *SD*
Tissue saturation index (%)	73.84 ± 4.44
Generalized anxiety disorder	71 (2.91)
Meeting physical activity guidelines	1079 (44.15)
Age (years)	64.6 ± 7.8
Female	1317 (53.89)
Education	
Primary	405 (16.57)
Secondary	978 (40.02)
Tertiary	1061 (43.41)
Marriage	
Married	1875 (76.72)
Never married	160 (6.55)
Separated/divorced	169 (6.91)
Widowed	240 (9.82)
Problem drinker	334 (13.67)
Smoker	
Never	1148 (46.97)
Former	1072 (43.86)
Current	224 (9.17)
Waist-to-hip ratio	0.91 ± 0.08
Height (centimeters)	166.12 ± 9.21
Dominant hand (left)	230 (9.41)
Systolic blood pressure (mmHg)	135.99 ± 19.87
Depression	102 (4.17)
Taking antidepressants	183 (7.49)
Taking antihypertensives	902 (36.91)
Taking anxiolytics	26 (1.06)
Taking antipsychotics	28 (1.15)
Cardiovascular conditions	
0	1278 (52.29)
1	894 (36.58)
2+	272 (11.13)
Chronic conditions	
0	1190 (48.69)
1	864 (35.35)
2+	390 (15.96)
Number of physical limitations	1.8 ± 1.9

Note: mmHg = millimeters of mercury; *SD* = standard deviation.

(n = 71); 44.15% (n = 1079) met the physical activity guidelines. Prevalence of GAD was 2.14% (n = 22) and 3.59% (n = 49) among participants who did and did not meet the physical activity guidelines, respectively. Participants' mean ± *SD* TSI in the total analytic sample was 73.84% ± 4.44%.

Associations of GAD With Resting-State Frontal Lobe Cerebral Oxygenation

In the total sample, compared to participants without GAD, those with GAD had significantly lower TSI in Model 1 (b = −1.618, 95% CI = −2.542 to −0.694; p = .001; $F_{(3, 612)}$ = 7.57, p < .001, R^2 = 0.012) and Model 2 (−1.418, −2.465 to −0.370; p = .008; $F_{(26, 589)}$ = 3.24, p < .001, R^2 = 0.038). This association was modified by physical activity, as shown in Figure 1. Sensitivity analyses showed no interaction between GAD and age or sex (both $p \geq .60$). Among participants who met the physical activity guidelines, TSI did not differ according to GAD status in Model 1 (−0.842, −2.536 to 0.852; p = .329; $F_{(3, 541)}$ = 2.30, p = .077, R^2 = 0.009) or Model 2 (−0.800, −2.657 to 1.057; p = .398; $F_{(25, 519)}$ = 2.32, p < .001, R^2 = 0.056). Among participants who did not meet the guidelines, TSI was significantly lower among those with GAD in Model 1 (−1.954, −3.027 to −0.882; p < .001; $F_{(3, 569)}$ = 6.41, p < .001, R^2 = 0.015) and Model 2 (−1.758, −2.936 to −0.580; p = .004; $F_{(23, 549)}$ = 2.61, p < .001, R^2 = 0.046).

Discussion

To the best of our knowledge, this is the first study to examine the association between GAD and PFC oxygenation in older adults and the extent to which meeting physical activity recommendations modifies this association. As hypothesized, following adjustment for relevant covariates, people with GAD had lower left PFC oxygenation than those without GAD. Also as hypothesized, subgroup analyses revealed that physical activity modified this association, as the significant difference in TSI between people with and without GAD remained only among people who did not meet minimum recommended levels of physical activity. Among those who did meet the physical activity guidelines, the difference in left PFC oxygenation between those with and without GAD was smaller and nonsignificant, suggesting that physical activity may be capable of promoting anterior brain vascular health among older adults with GAD.

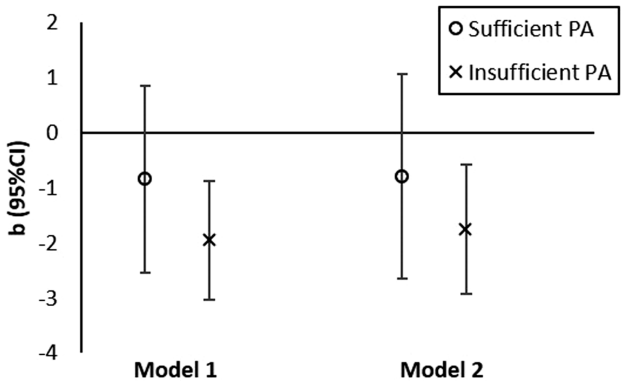

Figure 1. Unstandardized regression coefficients (b) and 95% confidence intervals (95% CIs) derived from multivariable linear regressions as indicators of associations between generalized anxiety disorder and tissue saturation index among participants meeting (n = 1079) and not meeting (n = 1365) physical activity (PA) guidelines.

Lower left PFC oxygenation among people with GAD shown here is consistent with available evidence for impaired PFC activity among adult GAD patients, particularly hypoactivation of the left DLPFC and hyperactivation of the right DLPFC in anxiety (16,52). Specific to GAD, fMRI studies have reported lower blood oxygen level-dependent signaling in the DLPFC in GAD patients which has been associated with emotional dysregulation and deficits in attentional control, suggesting that failing to engage the PFC during emotion regulation may be critical to the development and persistence of GAD (52). Given that the standardized placement of NIRS optodes in the current study indicates a high probability that the signal may represent resting-state, left DLPFC hemodynamic status, the current findings suggest a plausible etiological role of DLPFC hypoactivity in GAD; however, structural MRI would be required to test this hypothesis. Moreover, given recent evidence that excitatory stimulation of the left PFC may reduce symptom severity in anxiety disorders, the protective effect of physical activity on resting left PFC oxygenation among people with GAD shown here supports the plausibility that DLPFC activity may underlie/influence the anxiolytic effects of regular physical activity and exercise (52). Future mechanistic investigations of exercise and physical activity are warranted.

Although the magnitude of the difference in TSI between people with and without GAD (1.4%) appears relatively small, it is likely a meaningful difference for brain health as, unlike other measures such as blood pressure, small absolute changes in TSI can be associated with significant outcomes. For example, a drop in TSI of just 4.5% is sufficient to cause transient loss of consciousness during a tilt-table test (53), and resting cerebral oxygenation is lower by ~1%–4% among people with amnestic mild cognitive impairment (54). Moreover, the magnitude of the difference in TSI between people with and without GAD is larger than previous reports for other putative risk factors (eg, excess alcohol intake, diabetes, cardiovascular disease burden, increased cortisol, and depression) (22,23).

It may be plausible that declining cognitive abilities underlie the observed association between anxiety and lower left PFC oxygenation. For example, although declining cerebral oxygenation is a natural part of aging (55), chronic cerebral hypoperfusion may accelerate cognitive decline and increase the risk of cerebral atrophy, cognitive impairment, and subsequent dementia (56). Given that anxiety often cooccurs with dementia, it is plausible that it is a prodrome of dementia or it may occur as a reaction to declining cognitive abilities in a later phase of dementia. However, the current study excluded participants with diagnosed dementia; previous research has shown no effect of stratifying follow-up time on associations of anxiety with dementia, indicating that anxiety is not a prodrome of dementia (57); and hypoactivation of the frontal lobe in response to emotional stimuli has been observed in younger populations with GAD (16). Collectively, these findings suggest that GAD is associated with lower resting left PFC oxygenation independent of dementia and declining cognitive abilities. Thus, it is unlikely that cognitive decline underpinned associations between GAD and oxygenation shown herein.

The mental health benefits of physical activity are well-established. For example, in TILDA, physical activity has been associated with reduced odds of incident anxiety (58) and GAD (59), and short-term exercise training has improved the clinical severity of GAD among younger adults (60). Although no interventions have examined exercise effects on GAD among older adults, exercise has improved other mental disorders, such as depression, in this population (61). Moreover, the current findings suggest that even if a physical activity does not treat or protect against the development of

GAD, there may still be benefits to being physically active among people with GAD, such as maintenance of left PFC oxygenation. Therefore, the current findings regarding the influence of physical activity on resting left PFC oxygenation may have important implications for the maintenance of brain health among older adults with GAD.

Strengths and Limitations

There are several potential limitations. First, the cross-sectional design precludes causal inference. Thus, it is not possible to say that physical activity caused the differences observed here. A prospective cohort would help to establish causal inferences that are necessary to inform physical activity recommendations in a way that is clinically meaningful for GAD patients. Relatedly, these data only allowed for the examination of the relationships between these variables at one stage of the life course and cannot take into consideration participant characteristics and behaviors before they joined the TILDA study. Second, the NIRS measure is limited to capturing differences in oxygenation near the surface of the frontal lobe below the device. Although this brain region is particularly relevant to GAD, there are other regions of importance, particularly the amygdala, which warrant examination. It also is plausible that the frontal lobe as a whole, as measured by MRI, for example, may differ. Additionally, although NIRS has shown clinically relevant estimations of cerebral hemodynamic and oxygen changes in the adult head in previous studies (46), some differences exist between the Portalite and the device used in this previous study which delivers 4 wavelengths of light (775, 810, 850, and 910 nm) by 4 pulsed laser diodes and detects scattered light by 3 closely placed photodiodes (46). To the best of our knowledge, no studies have yet validated the Portalite to estimate changes in PFC oxygenation; however, it has monitored changes in skeletal muscle TSI with acceptable reliability (intraclass correlation coefficient [ICC]: 0.7–0.9) (62). Moreover, previous evidence supports that NIRS can show clinically relevant estimations of cerebral hemodynamic and oxygen changes in the adult head; however, to the best of our knowledge, no studies have yet validated the Portalite device to estimate changes in PFC oxygenation. Finally, physical activity was measured using a self-report questionnaire, the validity of which can be low which may predispose the results to over-reporting (63).

Nonetheless, there are important strengths, including a large, nationally representative, community-dwelling cohort of older adults. Second, the broad range of measures in TILDA allowed us to control for important sociodemographic, health, and anthropometric variables. Third, GAD was measured using a diagnostic measure as opposed to a self-report symptom assessment. Finally, NIRS is a noninvasive imaging method that requires little training to use and is relatively cheap compared to MRI, making it more accessible for clinical use.

Conclusions

Among a large, nationally representative, cohort of community-dwelling older adults, those with GAD showed lower left PFC oxygenation than those without GAD. Physical activity modified this association, such that people with GAD who met the WHO minimum physical activity recommendations did not differ in resting left PFC oxygenation compared to people without GAD. These findings may inform strategies to protect brain health among older adults with GAD.

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Conflict of Interest

None declared.

Ethics

TILDA was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin. All experimental procedures adhered to the Declaration of Helsinki. All participants gave informed written consent and assessments were carried out by trained research nurses.

Author Contributions

Study concept and design: C.M., M.H., L.N., J.O., and S.K.; analysis and interpretation of data: C.M., M.H., D.M., L.N., J.O., and S.K.; drafting of the manuscript: C.M., M.H., and D.M.; revision of the manuscript: all authors.

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