GABA, Aging and Exercise: Functional and Intervention Considerations

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ABSTRACT: The global growth of an aging population is expected to coincide with an increase in aging-related pathologies, including those related to brain health. Thus, the potential for accelerated cognitive health declines due to adverse aging is expected to have profound social and economic implications. However, the progression to pathological conditions is not an inevitable part of aging. In fact, engaging in activities that improve cardiovascular fitness appears to be a means that offers the benefits of maintaining and/or improving cognitive health in older age. However, to date, the underlying mechanisms responsible for improved central nervous system health and function with exercise are not yet fully elucidated. Consequently, there is considerable interest in studies aimed at understanding the neurophysiological benefits of exercise on aging. One such area of study suggests that the improvements in brain health via exercise are, in part, driven by the recovery of inhibitory processes related to the neurotransmitter gamma-aminobutyric acid (GABA). In the present review, we highlight the opposing effects of aging and exercise on cortical inhibition and the GABAergic system's functional integrity. We highlight these changes in GABA function by reviewing work with in vivo measurements: transcranial magnetic stimulation (TMS) and magnetic resonance spectroscopy (MRS). We also highlight recent and significant technological and methodological advances in assessing the GABAergic system's integrity with TMS and MRS. We then discuss potential future research directions to inform mechanistic GABA study targeted to improve health and function in aging. We conclude by highlighting the significance of understanding the effects of exercise and aging, its influence on GABA levels, and why a better understanding is crucial to allow for more targeted and effective interventions aimed to ultimately improve age-related decline in aging.

KEYWORDS: Gamma-aminobutyric acid (GABA), magnetic resonance spectroscopy, transcranial magnetic stimulation, cortical inhibition

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Introduction

According to the World Health Organization (WHO) the global population over the age of 60 is projected to be over 2.1 billion by 2050. This growth is expected to coincide with an increase in aging-related pathologies, including those related to brain health. However, the progression to pathological conditions is not an inevitable part of aging. Engaging in a healthy lifestyle, particularly activities that improve cardiovascular fitness, is a means that appears to offer the greatest benefits for maintaining preserved cognitive health in older age.[1] However, to date, underlying mechanisms are not yet fully elucidated.

Recent evidence suggests that brain health may be associated with maintaining a homeostatic balance between excitatory and inhibitory functions. Cortical excitability, which refers to the strength of neuronal response to a stimulus, must be carefully balanced between excitatory and inhibitory activity to ensure normal brain function.[2] Inhibitory and excitatory neurotransmitters regulate this delicate balance, specifically gamma-aminobutyric acid (GABA) and glutamate (Glx), respectively. Disruptions to this balance, such as excessive excitation or insufficient inhibition, have been implicated in a range of neurological disorders, including epilepsy,[3] migraines,[4,5] and movement disorders.[6,7] However, gradual changes in cortical excitability have been demonstrated in the aging process.[8] As we age, the homeostatic cortical excitability may become disrupted due to changes in the balance of excitatory and inhibitory neural communication (E/I balance).[8] This disruption is associated with cognitive and motor declines related to aging and an increased risk for neurological disorders.[9]

Therefore, investigating cortical excitability and neurotransmitter levels helps better understand age-related changes in brain function, leading to effective interventions to maintain brain health and function throughout one's lifespan. Recent research suggests that exercise can modify GABA levels and thus affect cortical excitability.[10,11] However, the implications for changes in brain state following exercise on cognitive and motor systems in aging remain elusive. Thus, continued investigation into the complex interplay between cortical excitability, neurotransmitter levels, exercise, aging and behavioral outcomes is crucial for developing effective interventions that must be tailored to individual needs of older adults.

In the present review, we describe the effects of aging and exercise on the dominant inhibitory neurotransmitter GABA. We will start by introducing concepts of the functional relevance

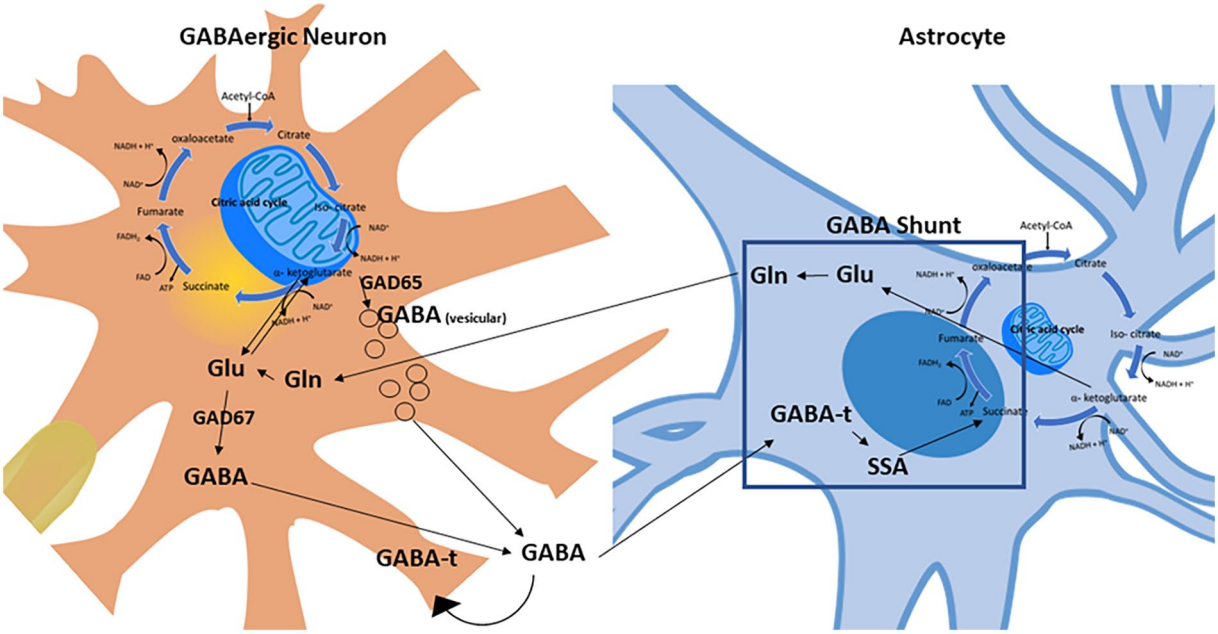

Figure 1. GABA metabolism and the GABA Shunt. GABA is created as a metabolite from the breakdown of glutamate via glutamic acid decarboxylase (GAD) in neuronal cells. Two GAD isoforms are present denoted by molecular weight in Daltons (GAD67 and GAD65). GAD67 breaks down glutamate (Glu) into GABA within the cytosol after which GABA diffuses across GABA transporters (GABA-t) into extracellular space. In addition, GAD65 catabolizes glutamate into GABA at the outer mitochondrial membrane in the neuron. It is believed that this GABA is packaged into synaptic vesicles for neurotransmission at the synaptic cleft (not represented). GABA is preserved, particularly, during periods of stress through the GABA shunt. The GABA shunt is afforded by the breakdown of GABA to succinic semialdehyde, which is entrant into the Krebs cycle in the astrocyte mitochondria producing glutamate, which transports to astrocytes for breakdown to glutamate completing the shunt.

of GABA in the aging nervous system, including measurement and clinical significance. We then describe the effects of exercise in the aging brain and highlight resent work examining changes in GABA with exercise. Lastly, because modulating cortical inhibition through aerobic exercise may be an effective therapeutic intervention to promote successful aging, we present future directions that can inform both mechanistic GABA study and rehabilitation research.

GABA in aging

The primary inhibitory neurotransmitter system in the brain is GABA, which exerts powerful control of cortical plasticity.[12,13] GABA is synthesized in the neuron through a metabolic pathway known as the GABA shunt (Figure 1), which occurs in conjunction with cellular respiration to help maintain sufficient extrasynaptic GABA tone. Importantly, frank disruption of GABAergic metabolism has been associated with several diseases that present severe central nervous system dysfunction.[14] The preserved metabolic stability of GABA in an aging model indicates that associated behavior declines are more likely a reflection of altered receptor dynamics and/or GABA density. The predominant techniques to noninvasively measure these aspects of GABA function in the human brain involve transcranial magnetic stimulation (TMS) and magnetic resonance spectroscopy (MRS), respectively. Consequently, these very different modalities have been employed in the study of cortical excitability in aging and have complementary findings that must be interpreted within the limits of each technology and target signal (see Table 1 for outline of relevant aging & TMS/MRS literature).

MRS

GABA concentrations can be measured in vivo in the human brain using proton 1-H MRS. In brief, 1-H MRS quantifies the chemical signal associated with bound proton (hydrogen atoms) configurations across a range of neurochemical compounds. Each compound has a magnetic resonance of a particular frequency largely dominated by water, which, when suppressed, yields a frequency spectrum that delineates proton configurations. The position of the proton moieties results in a specific frequency/chemical shift in the compounds. It is this chemical shift that is measured via spectroscopy. As the GABA signal in MRS cannot be separated from other metabolites (homocarnosine) at commonly measured field strengths (3T), we will refer to MRS concentrations of GABA as GABA+.

While early studies yielded somewhat inconsistent findings on cortical GABA+ concentration differences across the lifespan,[30,31] increased sample sizes and improved MRS editing/analyses from more recent work have shown with relative consistency that sensorimotor GABA+ levels decrease as a function of aging[32,33] (see Li et al[34] for excellent review). However, the uniformity of aging-induced changes in GABA+ levels

Table 1. A: All studies used healthy volunteers with no known motor or cognitive deficits for both young and old age groups. B: For motor tasks: FDI, first dorsal interosseous muscle; SRT, serial reaction time task; RT, reaction time task. C: For measurement techniques: iSP, ipsilateral silent period; ppIHI, paired-pulse interhemispheric inhibition; fMRI, functional magnetic resonance imaging; LIHI, long interhemispheric inhibition; SIHI, short interhemispheric inhibition; cSP, cortical silent period; SICI, short intracortical inhibition; LICI, long intracortical inhibition; MEP, muscle evoked potential; SP, silent period; MRS, magnetic resonance spectroscopy; tDCS, transcranial direct-current stimulation; YA, young adult; OA, old adult.

AUTHORS	AGE GROUP	SUBJECT #	CORTICAL MEASURES	MOTOR TASK(S)	PRIMARY FINDINGS
McGregor et al[15]	YA: 19-32 OA: 40-60	21 38	iSP, LIHI fMRI	9-Hole pegboard, simple RT, finger tapping	YA and physically active OA show longer iSP duration & more lateralized BOLD activity compared to sedentary OA. Motor measures correlated significantly with iSP & fMRI activity in M1/S1 in sedentary OA. Higher physical activity is associated with better motor performance and longer iSP with aging.
McGregor et al[16]	OA: 60-85	21	iSP, LIHI	Grip strength, finger tapping, Purdue Pegboard, 9-Hole Pegboard, simple RT, coin rotation	Aerobic exercise (12wk) increased iSP duration in sedentary OA. Post-intervention change in iSP duration correlated with improved motor performance and dexterity.
Talelli et al[17]	YA: 19-78	27	SIHI, LIHI	Isometric force tracking (FDI)	LIHI change from active to rest in ipsilateral M1 increased as a function of age, thus indicating an age-induced loss of IHI during volitional force output.
Fujiyama et al[18]	YA: 18-33 OA: 61-75	15/9F 15/9F	cSP	Iso/non-isodirectional rhythmic coordination (hand-foot)	YA showed differences in cSP duration between ipsilateral and contralateral coordination, while OA did not. OA also showed less stability in non-isodirectional coordination compared to the YA's.
Fujiyama et al[19]	YA: 26 ± 6.4 OA: 65.6 ± 6.5	13/10F 13/10F	TMS: SICI	Go/ no-go RT	SICI decreased in YA's during response preparation of a Go / no-go tasks, but not OA. Greater inhibition during movement preparation predicted faster reaction times within OA.
Peinemann et al[20]	YA: 20-38 OA: 48-71	13/5F 13/8F	SICI	Resting FDI	The magnitude of M1/S1 SICI at rest reduces with age.
Heise et al[21]	Adults: 20-88 Subgroup: 23-83	64/34F 23/9F	SICI	Simple/Choice Reaction Time Tasks	Resting M1 SICI, and task-dependent SICI modulation are both reduced with age. Diminished resting SICI and task-based SICI modulation predicted slower simple and choice RT performance.
Opie et al[22]	YA: 22.3 ± 3.8 OA: 73.7 ± 4.0	13 15	SICI, LICI, SICI primed by LICI	Isometric force tracking: Index finger abduction, pinch grip	SICI was greater during precision pinch grip task in OA, and LICI was reduced at rest compared to YA.
He et al[23]	YA: 24.66 ± 3.07	18/11F	SICI, LICI	Stop-signal, Go/no-go task	Individuals with greater resting SICI & LICI showed faster go/no-go reaction times, and more accurate in inhibiting their response in both stop-signal and go/no-go tasks.
Sale and Semmler[24]	YA:19-31 OA: 60-79	10/5F 10/5F	MEP, cSP	Purdue Pegboard, single tapping, alternating tapping, Isometric force	MEP was lower in the non-dominant hand of OA. cSP duration was shorter in OA compared to YA. For both groups, length of cSP demonstrated task dependence.

(Continued)

Table 1. (Continued)

AUTHORS	AGE GROUP	SUBJECT #	CORTICAL MEASURES	MOTOR TASK(S)	PRIMARY FINDINGS
Floyer Lea et al[25]	YA: 20-31	36	fMRS	Isometric force tracking	S1 GABA concentrations decrease during force learning task, but not during random force generation or at rest. GABA concentrations recovered rapidly (40% within 20 min), suggesting that GABA modulation may relate to encoding of task as opposed to longer-term consolidation.
Stagg et al[26]	YA: 19-40	12/9F	SICI MRS	None	GABA concentrations did not relate to 2.5 ms SICI component associated with synaptic GABA activity but was related to 1 ms component. This poses a question as to whether 1 ms SICI is related to extrasynaptic GABA tone.
Stagg et al[27]	YA: 21-31	12/6F	MRS tDCS	Visual RT	tDCS induced GABA change correlated positively with improved RT performance over practice. The authors propose a relation between GABA tone is relevant to short term motor learning.
Kim et al[28]	YA: 18-29	35/15F	MRS tDCS	Isometric Force Tracking	tDCS induced GABA change predicted individual differences in motor performance and recall.
Kolasinski et al[29]	YA: ~24	51/18F	MRS	SRT: Rest, Random, Learning	M1 GABA concentrations measured early in motor learning task correlated strongly with the degree of change in RT performance with practice. Higher initial GABA levels corresponded with poorer RT performance.

require further study, as regional differences in age group comparisons have been previously reported.[35-37] For example, Cuypers et al[38] reported aging-related decreases in GABA+ concentration in the dominant primary motor cortex (M1) but not the non-dominant M1. Nevertheless, a recent meta-analysis by Porges et al[39] shows that despite numerous sources of variance (different MRI platforms, acquisition parameters, spectral analyses), the measurement of cortical GABA+ in frontal regions tended to be lower in older adults (>65) across 8 studies (722 participants) when compared to younger adults.[39] As the reports of GABA+ expand in the literature, a consensus on region-specific effects of aging (likely decreases) in GABA levels will continue to emerge. As such, some degree of caution is warranted regarding the specificity of the GABA concentration changes based on bulk tissue distribution within the region of inquiry.[35] This is particularly notable in assessing prefrontal brain regions, which experience a higher degree of cortical atrophy.[40,41]

Importantly, the developments in MRS technology/methodology are affording its functional assessment (fMRS), and thus a growing body of literature is examining the dynamic relation between neurometabolic profiles and motor systems control (see Pasanta et al[42] for recent review). In a seminal study by Floyer-Lea et al, younger adults engaging in a motor learning task (targeted force production) showed progressive decreases in GABA+ levels as compared to resting conditions or during random force generation.[25] It was postulated that this decrease in GABA+ may co-vary with increasing glutamatergic activity to facilitate long-term potentiation. The mechanism by which this occurs is still not clear, but it may be associated with changes in receptor function in inhibitory interneurons, as dysregulation of these receptors (both GABA-a and GABA-b subtypes) have deleterious effects on motor learning in younger adults.[12,43] This likely reflects GABA's regulatory role in selectively increasing excitability to facilitate long-term potentiation. fMRS inquiry across the lifespan is a ripe target for study, particularly given more recent reports of functional sequelae of differences in cortical inhibition.[32,33,44,45] One cross-sectional study examined age effects on M1 GABA+ concentrations before, during, and after a series of uni-/bi-manual action-selection tasks. Both healthy younger and older adults exhibited transient reductions in GABA+ during online motor training, however, the older adults showed lower GABA+ levels across all 3 time points.[33,46] While this suggests that reduced resting-state GABA+ may not directly constrain the capacity to modulate GABA+, the variability in older individuals' GABA+ modulation was a strong predictor of their task performance. That is, individuals who exhibited a greater capacity to reduce GABA+ during online practice showed superior motor performance. Additional work using multiple acquisitions of GABA during a functional task could yield insight into a potential GABAergic contribution to individual differences in motor skill learning. These data would have significant implications for rehabilitation after neural injury, as neural aging may require more individualized approaches based on changes in neurometabolic profiles during therapeutic interventions.

TMS

Over the past 20 years, TMS has been the primary modality for in vivo assessment of GABA receptor-mediated inhibition at the systems level. Two primary receptor subtypes of GABA, GABA-a and GABA-b can be assessed using paired-pulse TMS (ppTMS; Figure 2). Briefly, GABA-a and GABA-b receptors mediate fast and slow timescales of inhibition, respectively, and thus short and long inter-stimulus intervals have been employed to examine their specific contributions to intracortical (ICI)[47] and inter-hemispheric inhibitory (IHI) control[48] (Figure 2). There is mounting evidence that motor cortical ICI and IHI (GABA-a & GABA-b) are significantly reduced as a function of age, with a notable portion of older adults exhibiting a disinhibitory response to ppTMS[49,50] (Figure 2). Additional work has implemented single-pulse TMS during active muscle contraction to elicit a period of muscle quiescence in EMG activity[51] (Figure 2). The duration of this phenomenon, operationally termed the cortical silent period, can be induced via contralateral or ipsilateral M1 stimulation to measure intracortical (cSP) or interhemispheric inhibition (iSP), respectively. Consistent with the ppTMS literature, cortical silent-period durations have also been shown to reduce with age,[49-53] and while lower cSP duration is attributed primarily to altered GABA-b dynamics,[54] the receptor-specific contributions to diminished iSP duration is less well understood.

The above literature provides collective evidence of aging-induced alterations in GABA-a and GABA-b receptor-mediate neurotransmission within and between the primary motor cortices. Changes in circuitry so fundamental to neuroplasticity, particularly in a cortical network so relevant to motor coordination/control/skill acquisition, have led to the assumption that decreased inhibition may confer behavioral deficits known to occur in parallel with aging. Indeed, there is empirical evidence supporting the assertion that reduced interhemispheric inhibition may constrain motor function, as older individuals exhibiting shorter iSP durations and reduced SIHI & LIHI have demonstrated impaired psychomotor speed,[16] reaction-time performance,[19,55] and manual dexterity[45] compared to older individuals with relatively preserved inhibition. Thus, this loss of IHI attributed to transcallosal GABAergic circuitry may play a mechanistic role in the loss of functional segregation of the motor networks, a phenomenon predominantly described through fMRI-based studies showing that greater bilateral M1 activity is associated with poorer motor performance.[15,16]

Diminished ICI with aging has also been assumed to reflect a degradative process. However, support for this assumption

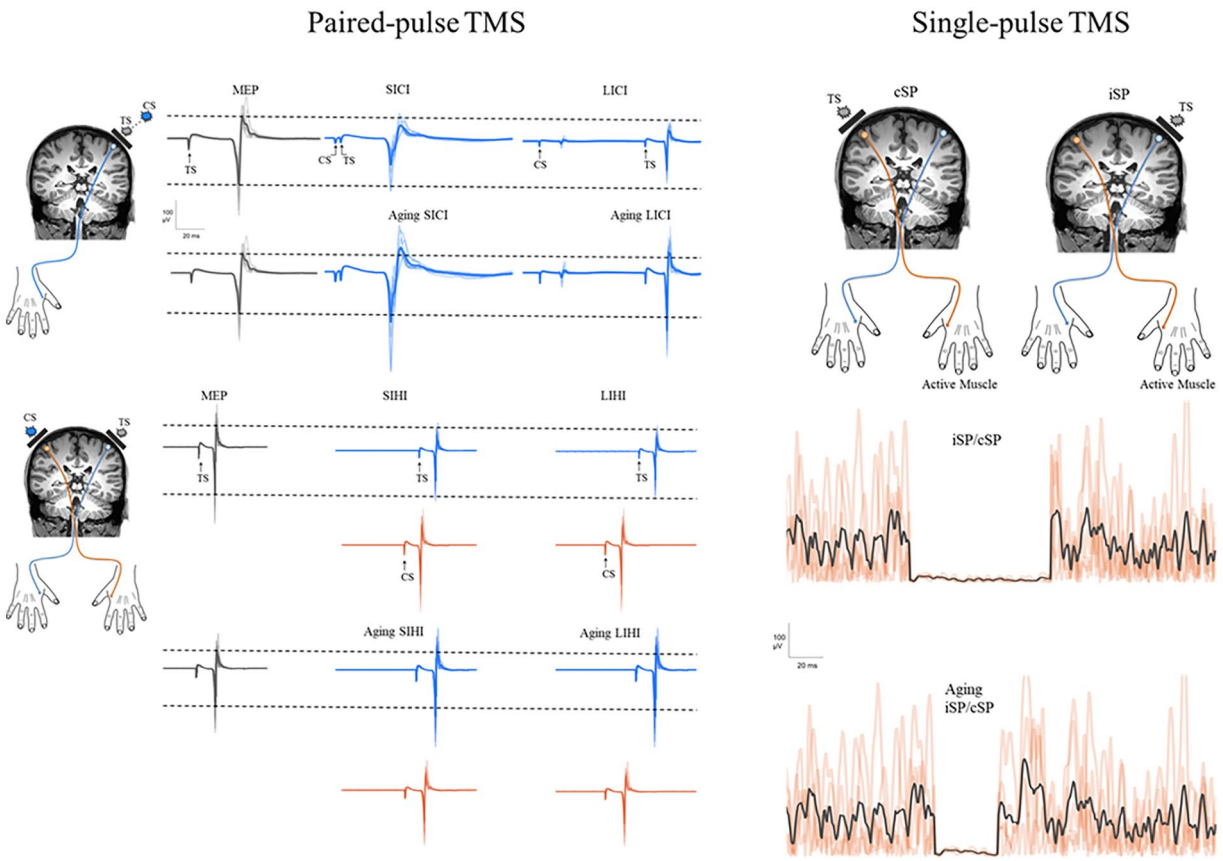

Figure 2. Graphical illustration of the paradigms used to assess GABA receptor-specific cortical inhibition within (SICI, LICI, cSP) and between (SIHI, LIHI, iSP) the primary motor cortices. For Paired-pulse TMS paradigms (SICI/LICI & SIHI/LIHI), single magnetic pulse stimulation (TS) is delivered to the motor cortex to induce a motor evoked potential (MEP). This MEP amplitude (gray EMG signal) is then used as a comparator to MEP amplitudes from the same target muscle (blue EMG signals) under various paired-pulse TMS (ppTMS) conditions. In healthy younger adults (illustrated by SICI/LICI & SIHI/LIHI EMG) MEP amplitudes are reduced during ppTMS due to GABA receptor mediated inhibition. Aging SICI/LICI/SIHI/LIHI plots illustrate an example of an older adult showing disinhibition (increased MEP with ppTMS), which is thought to reflect diminished GABA receptor function. For single-pulse TMS paradigms, a single magnetic pulse is administered to the contralateral (cSP) or ipsilateral (iSP) motor cortex during active contraction of a target hand muscle. This stimulation evokes transient cessation of EMG activity, the duration of which is denoted as the cortical silent period. The aging iSP/cSP plot illustrates aging-related reductions in the duration of this silent period, which is also associated with diminished GABA receptor function.

has been largely based on studies showing reduced SICI/LICI along with poorer motor performance outcomes when comparing group-level differences between younger and older adults.[22,56,57] Heise et al,[21] one of the seminal works demonstrating SICI reductions across the lifespan, examined the functional significance of this phenomenon by collecting simple and choice reaction-time performance from a subset of their participant pool (n = 23; 23-83 years). They found that individuals with reduced SICI showed slower reaction times in both simple and choice tasks. Conversely, a study by Clark et al found that older individuals with reduced LICI levels exhibited superior hand grip strength (a motor action largely mediated via increased excitatory drive) compared to individuals showing LICI values more consistent with healthy younger adults.[58] Such findings align with the contending theory that reduced intracortical inhibition may be a compensatory process that maintains excitatory: inhibitory balance in lieu of aging-related reductions in excitatory drive.[59] Consequently, a great deal of additional study is necessary to understand the functional significance of change in GABAergic neurotransmission within, between, and across cortical networks.

Exercise in aging

Although "aging" has not typically been considered a target for rehabilitation, the literature consistently shows that cognitive and motor declines are not only particularly prevalent in sedentary older adults[60] but can also be mitigated by exercise. In the cognitive domain, exercise has been demonstrated to improve various aspects of function throughout the entire cognitive system, as indicated by improved performance in psychomotor and processing speed, working memory, and cognitive-executive functions.[15,61-66] Further confirmation of exercise's influence is derived from task-based fMRI models, which consistently show that older adults who are aerobically fit exhibit brain activity patterns similar to those of younger adults, suggesting that exercise can counteract age-related cognitive decline.[67,68] For example, older adults with higher

aerobic capacity produce cortical activity patterns similar to young adults in the dorsolateral prefrontal area during an executive function task.[69] Furthermore, sedentary individuals, who are at an increased risk of cognitive decline, participated in a 6-month exercise intervention. Their results revealed that these individuals exhibited brain activity patterns typical of aging at baseline, However, after exercise training, their brain activity patterns resembled those of young and healthy adults, indicating that exercise can enhance brain function and prevent cognitive decline in sedentary older adults.[70]

The influence of exercise extends systemically, as indicated by works from MRI and voxel-based morphometry that have highlighted the capabilities of exercise to exert powerful effects on general brain function in physically active versus sedentary older adults, including cortical re-structuring[70,71] and increased volume in overall brain mass, as well as white and gray matter at the frontal cortex and hippocampus.[71,72] Additionally, electroencephalography has revealed changes in oscillatory frequencies in older adults depending on level of physical activity[73,74] and after exercise interventions.[75,76]

The above findings support the beneficial impact of exercise on both brain structure and function in aging adults. However, it is important to note that studies examining the impact of exercise on brain health in aging have reported findings where exercise did not lead to significant improvements in cognition[77,78] or brain structure.[79] For example, the Aerobic Center Longitudinal Study followed a large cohort of middle-aged and older adults to assess the effects of aerobic fitness on health outcomes, including cognitive function. While the study found associations between higher aerobic fitness and better cognitive function cross-sectionally, the longitudinal analyses did not demonstrate that changes in aerobic fitness over time were associated with changes in cognitive function.[80] The conflicting research highlights the complexity of studying cognitive outcomes in relation to exercise and the importance of better understanding of individualized variability in such studies. Therefore, it is important to better understand individual parameters such as baseline cognitive function, genetics, and overall health status, each may contribute to whether exercise definitively leads to cognitive benefits in older adults. Of additional importance, the intensity, duration, and type of exercise may influence the outcomes. Studies that did not find cognitive improvements often used different exercise protocols compared to those showing positive effects (eg, walking[81] vs high intensity stationary cycling[67]). This suggests that the specifics of exercise regimen could play a role in determining cognitive outcomes which requires further investigation.

The exposition of the vast literature on exercise and aging is beyond the scope of this work. We will focus now on the specific effects of exercise on GABA and refer the reader to excellent recent reviews of exercise in aging.[9,82-84]

Exercise & GABA

Interestingly, exercise has been shown to influence GABA concentrations, with research suggesting that exercise can maintain or even enhance GABA levels in the brain. For example, Maddock et al looked at the visual cortex before and after a single dose of stationary cycling in healthy young adults and demonstrated that GABA levels increased by 7% after exercise, with glutamate following a similar trend at the anterior cingulate cortex (executive region).[11] This research also recorded physical activity levels in the week preceding exercise and found that more physically active participants exhibited higher levels of resting glutamate (Glx). As an extension, Coxon et al demonstrated that M1 GABA levels increase by an average of 20% after a single bout of high intensity interval training (HIIT), and importantly, the individualized degree of GABA change correlated positively with blood lactate accumulation.[10]

Relating GABA to cortical excitability, TMS studies have shown differences in measures of intra-hemispheric inhibition after acute aerobic exercise. Specifically, a recent meta-analysis demonstrated that acute aerobic exercise exerts transient reductions in SICI outcomes in young healthy adults.[85] Importantly, recent work by Hendy et al[86] observed similar reductions in SICI from sedentary older adults after a single bout of high-intensity interval cycling. Consistent with previous findings from the young healthy population, this sedentary group also exhibited increased cortical excitability as assessed by suprathreshold single-pulse TMS. While it is postulated that this net increase in cortical excitability may produce optimal conditions for augmenting cortical neuroplasticity, the longer-term neuroplastic effects from chronic exercise on intracortical GABAergic circuitry is currently unknown.

There is preliminary evidence suggesting that interhemispheric inhibition is also transiently reduced with acute exercise in healthy young adults.[87] While acute exercise effects on IHI in the aging cortex is currently unknown, there is supporting evidence for GABAergic plasticity from chronic exercise. Specifically, McGregor et al[55] compared ipsilateral silent-period (iSP) durations and task-based fMRI-BOLD activity in a sample of healthy younger, physically active older, and sedentary older adults. They found that sedentary older adults exhibited reduced interhemispheric inhibition (shorter iSP's), and greater ipsilateral M1 BOLD activation during motor tapping. This suggests that increased physical activity may play a role in decreasing aging-related losses of interhemispheric inhibition and subsequently cortical desegregation. In further examining effects of longitudinal exercise on interhemispheric inhibition, McGregor et al[45] found that 12-weeks of aerobic exercise effectively increased iSP durations in sedentary older adults. Moreover, the degree of increase in iSP duration correlated positively with the extent of motor dexterity improvements

observed at the individual level. This work collectively supports the notion that GABAergic circuitry may be preserved and/or recovered through exercise. However, futire research must aim to understand the specific mechanisms that promote healthy inhibition (ie, increased GABA-a and GABA-b receptor density, receptor sensitivity, etc).

GABA helps regulate neuronal excitability and synaptic plasticity, which are essential mechanisms for cognitive and motor functions. Considering the relationship between GABA changes and exercise's benefits, exploring the underlying mechanism of action by which exercise preserves GABA is important, particularly in aging. A possible link between exercise and changes in GABA concentration may be due to the metabolic load placed on the brain from exercise. Rigorous physical activity is one of the most energy-consumptive tasks the brain can encounter.[88] Higher-intensity activity is particularly taxing, with the brain metabolic rate (O_2 consumption/glucose consumption) shifting to burn 30% to 50% more glucose (as compared to only 5%-10% more oxygen).

Interestingly, not all glucose production can be accounted for by simple energy demands. The enhanced neuronal activity stimulated by more intense exercise activates neurotransmitter cycling in the astrocytes. Even a small increase in the size of these neurotransmitter pools, which includes GABA, would correspond to a notable amount of glucose being utilized.[88] It is postulated that due to the correlation between GABA concentration and blood lactate levels during exercise (as demonstrated by Coxon et al), non-oxidative metabolism converts lactate to GABA by α-ketoglutarate transamination.[11] This stimulation of acute neurotransmitter cycling, and increased demand of these chemicals, may help explain the increase that exercise exhibits on resting levels of glutamine and GABA. This notion supports the hypothesis that increased nonoxidative carbohydrate metabolism during exercise supports the de novo synthesis of neurotransmitters.[89,90] Therefore, glutamate and GABA are readily synthesized from carbon skeletons derived from CHO substrates utilized during exercise. Overall, exercise's ability to preserve and enhance GABA function offers a potential mechanism for its positive effects on cognitive and motor function in aging individuals.

Future directions for GABA and exercise in aging research

Understanding the effects of exercise and aging, specifically its influence on GABA levels, is crucial for rehabilitation research. Knowing how exercise affects GABA levels in an aging population could allow for more targeted and effective interventions, ultimately improving rehabilitation outcomes. To achieve this, future research on the development of techniques to acquire dynamic task-dependent GABA signals using MRS is warranted. An additional avenue of benefit would involve probing the dynamic relations between neurotransmitter concentrations and receptor function using combined MRS and TMS during neuromodulation (endogenous: motor learning, exogenous: TMS, transcranial direct-current stimulation or tDCS). For example, employing an edited MRS sequence to index GABA dynamics (resting levels, direction/magnitude of change) during motor skill training in older adults can inform the behavioral significance of GABA tone to induce neuroplastic change (learning). These MRS data and motor skill performance metrics could then be correlated with measures of GABA receptor function as characterized by TMS. As aging may associated with decreased levels of tonic GABA, we expect MRS measures of GABA concentration will predict group differences in measures of intracortical inhibition in TMS (SICI, LICI, SICF), possibly due to aging-related increases in receptor concentration.[38,91,92]

Lastly, our work (and others) continues to substantiate the benefits of aerobic exercise to improve behavioral and physiological outcomes in multiple populations. However, we have yet to identify the neurophysiological mechanism responsible, and we have yet to uncover how exercise modifies neurotransmitter function in the context of learning. Future studies should identify the interrelationship of GABA and exercise in promotion of a healthy neurochemical environment. These efforts could pave the way for the development of improved, evidence-based rehabilitation strategies that optimize the potential benefits of exercise for the aging brain.

Abbreviations

WHO, World Health Organization; GABA, gamma-aminobutyric acid; MSR, magnetic resonance spectroscopy; TMS, transcranial magnetic stimulation; ICI, intracortical inhibition; IHI, inter-hemispheric inhibition; HIIT, high intensity interval training; tDCS, transcranial direct-current stimulation

Author Contributions

TN, KM, LK, CW, AE, AW, KM, and JN contributed to manuscript writing. TN, KM, and JN, performed manuscript revision. TN, KM, LK, CW, AE, AW, KM, and JN performed search and collation of relevant literature. TN created figures. TN and CW created a supplementary table. KM, and JN provided financial support. All authors contributed to this article and have approved the submitted version.

Significance Statement

Understanding the effects of exercise and aging, specifically its influence on GABA levels, is crucial for rehabilitation research and the field of neuroscience. Knowing how exercise affects GABA levels in an aging population could allow for more targeted and effective interventions, ultimately improving rehabilitation outcomes.

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