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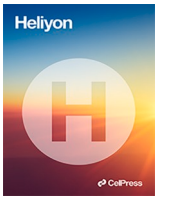

Effects of acute physical activity on brain metabolites as measured by magnetic resonance spectroscopy (^{1}H-MRS) in humans: A systematic review

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ABSTRACT

Physical activity (PA) promotes brain health in a variety of domains including cognition, mood, and neuroplasticity. At the neurochemical level, the mechanisms underlying these effects in the brain are not fully understood. With proton Magnetic Resonance Spectroscopy (^{1}H-MRS), it is possible to non-invasively quantify metabolite concentrations, enabling studies to obtain measures of exercise-induced neurochemical changes. This systematic review aimed to examine the existing literature on acute effects of PA on brain metabolites as measured by ^{1}H-MRS. Four databases (Cochrane Central Register of Controlled Trials, PubMed, Embase, and PsycINFO) were searched, identifying 2965 studies, of which 9 met the inclusion criteria. Across studies, Gamma-AminoButyric Acid (GABA) and lactate tended to increase after exercise, while no significant changes in choline were reported. For glutamine/glutamate (Glx), studies were inconclusive. Conclusions were limited by the lack of consensus on ^{1}H-MRS data processing and exercise protocols. To reduce inter-study differences, future studies are recommended to (1): apply a standardized exercise index (2), consider the onset time of MRS scans, and (3) follow standardized MRS quantification methods.

1. Introduction

There are widespread health benefits of physical activity (PA) across the human body. This includes the brain, as PA-induced effects can benefit cognition [1] and even reduce the risk, or delay the onset, of neurodegenerative diseases like dementia [2]. Although promising, our limited knowledge of the mechanisms behind these effects in humans have led to poorly targeted interventions. Three levels of evidence have been proposed for the effects of exercise on cognition: (a) cellular and molecular signalling pathways, (b) changes in brain structure and function, and (c) mental states [1]. Mechanisms at a biochemical level have been notoriously difficult to

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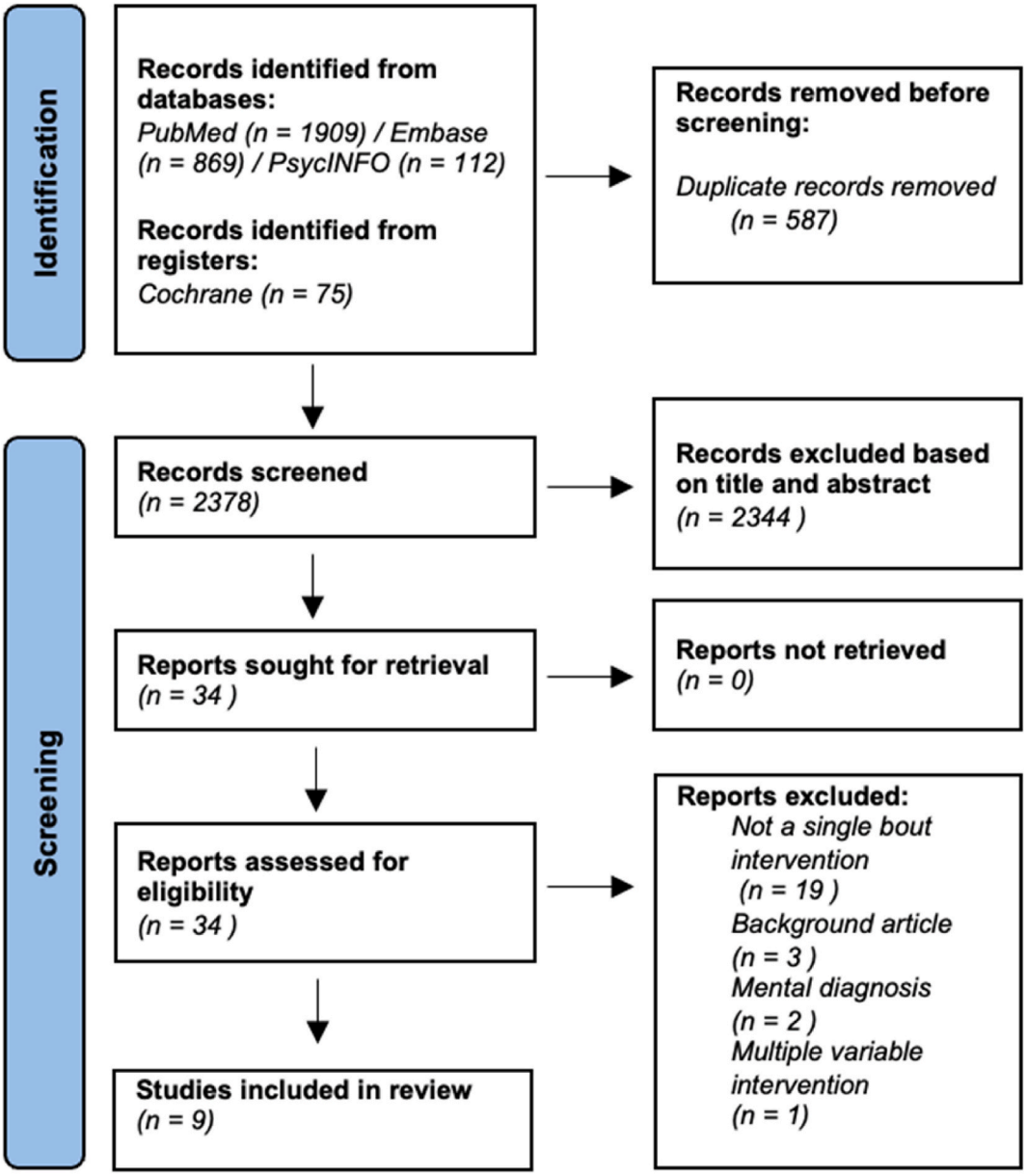

Fig. 1. Flow chart of included studies.

assess in vivo, limiting our understanding of the structural and functional pathways.

Proton magnetic resonance spectroscopy (^{1}H-MRS) enables us to non-invasively measure regional metabolite concentrations in the in vivo brain [3]. In the context of PA studies, this method can obtain measures of neurochemical changes in the brain in response to physical activity. Several metabolites can be quantified by ^{1}H-MRS, including Gamma-Aminobutyric Acid (GABA) and Glutamate/glutamine (Glx). Measures of GABA and Glx characterise cortical excitability, as they constitute the main inhibitory and excitatory neurotransmitters in the human cortex, respectively [4]. N-AcetylAspartate (NAA) is the most abundant metabolite on the MRS spectra and exists in high concentrations within neurons. As a result, NAA is often attributed to be a "neuronal marker" [5]. Accordingly, increases in NAA following PA interventions have been interpreted as greater neuronal integrity [6]. Another metabolite of interest is creatine, which functions as an energy supply during increased energy demands, as observed during physical activity [7]. In relation to the brain's metabolic rate, non-oxidized carbohydrates such as lactate are taken up by the brain during moderate-to-vigorous exercise [8], and quantification of lactate levels by ^{1}H-MRS might shed light on the link between peripheral and central responses. Further, other quantifiable metabolites such as myoinositol, choline, and glutathione, have been associated to cognitive function and may therefore contribute to understanding the neurocognitive mechanisms of the effect of exercise [9,10].

Human studies on the effects of PA on brain health often span weeks or months. Yet as intervention duration increases, so does the

number of variables confounding our understanding of underlying mechanisms. In contrast to long-term interventions, single-bout exercise interventions reduce the number of variables that accumulate during the intervention timespan. Further, there is evidence to suggest that changes elicited by a single-bout of exercise are indicative of changes from chronic exercise. In a recent study of both acute and long-term effects on working memory and brain network within the same individuals, changes observed after a single exercise session were predictive of changes in functional connectivity after 12 weeks [11]. Accordingly, acute exercise interventions may elicit some of the initial changes that adapt over time and provide an indication of the long-term effects on outcomes such as cognition and brain connectivity. Thus, single-bout interventions enable the assessment of acute neurochemical changes induced by exercise.

Over the last 20 years, studies of acute neurochemical changes in response to exercise have applied MRS to investigate these effects in humans. For example, one ultra-high field MRS study showed an acute decrease in creatine levels after PA [12]. This was in contrast to an earlier MRS study reporting no changes in creatine after acute exercise [13]. In light of variable findings and differences in methodology, a review of human studies investigating the acute effects of PA on brain metabolites as measured by MRS is warranted. To this end, this review aimed to systematically assess all studies investigating the acute effects of PA on brain metabolites as measured by ^{1}H-MRS.

2. Methods

This systematic review was conducted in line with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [14] and preregistered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022363790).

2.1. Eligibility criteria

Studies were considered eligible if they met the following criteria: (a) the intervention included measurements before and after a single bout of PA; (b) the study outcome included a measurement of metabolite concentrations in the brain obtained with ^{1}H-MRS; (c) the study was published in English in a peer-reviewed journal; (d) the study was conducted on humans. Studies were excluded if (a) the sample consisted solely of participants diagnosed with a neurological or psychiatric illness or (b) the exercise was combined with another intervention (e.g., cycling + hypoglycemic clamp).

2.2. Information sources and search strategy

The literature search was conducted on four independent databases: PubMed, Embase, PsycINFO, and Cochrane (Fig. 1). The search string consisted of terms supporting the eligibility criteria by incorporating a definition of intervention type along with terms searching for exercise-induced effects on brain metabolites as measured by ^{1}H-MRS. The string incorporated keywords and MeSH terms from other reviews assessing acute exercise on a variety of brain variables [15]. No filters were applied. The final search was done on the September 8, 2022 in all four databases using the following string:

["Brain"]

AND

["Exercis*" OR "Physical activity" OR "Physiology" OR "Acute exercise*" OR "Acute aerobic" OR "Acute resistance" OR "Single bout exercise*" OR "Single bout" OR "Acute training" OR "Single bout training"]

AND

["Magnetic resonance spectroscopy" OR "MRS"]

AND

["Metabolites" OR "Neurochemicals" OR "Neurotransmitters" OR "GABA" OR "Glutamate" OR "Lactate" OR "Gluthatione" OR "N-acetylaspartate" OR "Choline" OR "Creatine"]

2.3. Screening strategy and selection process

Each search result was imported to Rayyan software [16], with duplicates removed by comparison of title, author, year, and, if necessary, abstract. Identified abstracts were first independently screened by two co-authors (MR and ND). Remaining studies were then assessed for full-text screening.

2.4. Data extraction

Sample size, age, sex, and intervention regime were extracted from all included studies. If a study included multiple experiments, only the data from the relevant MRS sub-study was extracted [17]. The intervention regime was described by exercise type, duration, and intensity. Exercise intensity was categorized into constant, graded, or alternating intensity. In addition to intensity classification, maximal heart rate (%), aerobic capacity, or workload was also extracted as a description of exercise intensity. Data extraction

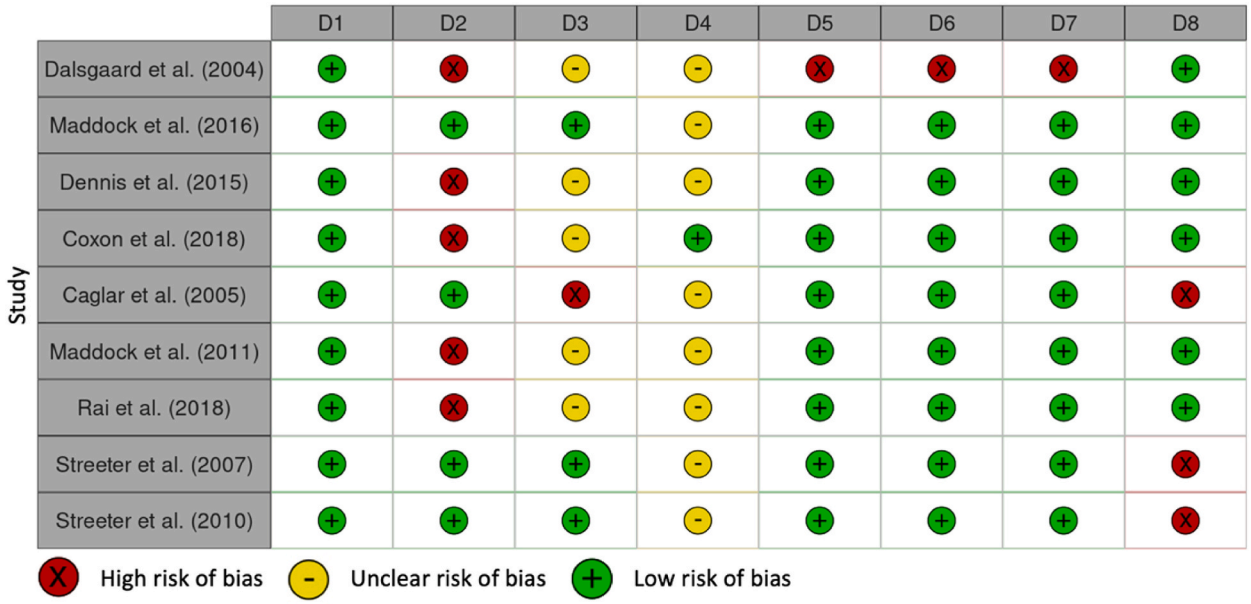

Fig. 2. Illustration of the risk of bias assessment of the included studies. The items posed the following questions: D1: Was the study question or objective clearly stated?; D2: Were eligibility/selection criteria for the study population prespecified and clearly described?; D3: Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?; D4: Was the sample size sufficiently large to provide confidence in the findings?; D5: Was the test/service/intervention clearly described and delivered consistently across the study population?; D6: Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?; D7: Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p-values for the pre-to-post changes?; D8: Was the onset of the MRS-measurements explicit and clearly stated?.

concerning MRS measurements included: Scanner type and field strength used in the study, description of the voxel placement, voxel size (cm^3), metabolite measured, and the directional change of the measured metabolites. When available, the time between exercise cessation and onset of MRS measurement was extracted (minutes). Some studies executed repeated measurements post-exercise to investigate possible time effects. Only changes between baseline and the first measurement post-exercise were presented, as this review aimed to assess acute effects.

2.5. Risk of bias

Risk of bias was assessed using a checklist developed by the National Institutes of Health (NIH) for before-after (pre-post) studies with no control group [18]. Here, the assessment tool was modified to an 8-item list to better fit the included studies. Given the context of acute effects and the importance of the time delay between measures, an item was added to indicate whether the onset of MRS measurement was reported. Each item was first assessed by one author (MR) and then checked by a second author (ND). In the event of disagreements, items were discussed with a third author (CJB) and a joint decision was then made. Items were classified as "Low risk of bias", "Unclear risk of bias", or "High risk of bias". Fig. 2 was created using online visualization software (Robvis) [19].

3. Results

Nine studies, including a total of 125 participants, were included in the review (Table 1). Seven studies had fewer than 12 participants (n = 7), and two studies had sample sizes larger than 30. Overall, 54% of all study participants were female (65/120). One study had a larger proportion of female participants (>65%) [20], and two studies consisted of only male participants [21,22]. One study did not report the sex of their 5 participants [17].

PA interventions were classified into categories of "graded" (n = 4), "alternating" (n = 2), or "constant" (n = 3) intensity. The interventions predominantly applied high-intensity paradigms with 7 out of 9 interventions having their participants working at ≥ 65% of either maximal individual heart rate, workload, or aerobic capacity. Scanner field strengths differed between studies. Metabolite concentrations were acquired with field strengths of either 1.5 T (n = 3), 3 T (n = 3), 4 T (n = 2), or 7 T (n = 1). The voxel of interest was placed in a variety of regions (see Table 1), whereas the only recurring regions were the anterior cingulate cortex (n = 2) or regions within the occipital cortex (n = 3).

Table 1
Overview of sample characteristics and exercise regimes of all included studies.

First author, ref.	N	Age	Sex (female n, %)	Exercise regime		
				Type	Duration (min)	Intensity
Caglar et al. (2005)(22)	7	16	0	Jogging on treadmill	20	(Con) 70% of max aerobic capacity
Coxon et al. (2018)(24)	10	29.4 ± 10.72	2, 20%			
Study 1	†			Bicycle ergometer	20	(AI) Alternating between 3 min at 50% of HRR and 2 min at 90% of HRR (Mean % of MHR during HI = 91 ± 8.2%)
Study 2	†			Bicycle ergometer	20	(AI) Alternating between 3 min at 50% of HRR and 2 min at 90% of HRR (Mean % of MHR during HI 91 ± 8.2%)
Dalsgaard et al. (2004)(17)	5	N.A.	N.A.	Bicycle ergometer + arm cranking or rowing ergometer	N.A.	(G) Increasing 10% every 2. min until individual max. capacity
Dennis et al. (2015)(12)	11	30 (Range: 22–41)	7, 64%	Bicycle ergometer	14 ± 3	(G) Start at 60W (F)/90 W (M) → Increasing by 30 W every 3. min until 85% of MHR (Mean % of MHR = 87% ± 3.6)
Maddock et al. (2011)(25)	8	25 (Range: 18–37)	5, 63%	Bicycle ergometer	11 ± 4	(G) Starting at 50–100 W and increasing 25–30 W every 3 min until 85% of MHR. (Mean % of MHR = 87 ± 5%)
Maddock et al. (2016)(13)	38		22, 58%			
Study 1	8	25.8 ± 6.4	5, 63%	Bicycle ergometer	8-17 (mean = 11.5)	(G) Starting at 50–100 W and increasing 25–40 W every 2–4 min until target HR. (Mean % of MHR = 85,5%)
Study 2 (V1)	8	28.1 ± 9.9	6, 75%	Bicycle ergometer	20 + 1 cooldown	(G) Graded until target heart rate → constant load until duration of 20 min was reached (Mean % of MHR = 85,5%)
Study 2 (ACC)	8	28.1 ± 10.7	6, 75%	Bicycle ergometer	20 + 1 cooldown	(G) Graded until target heart rate → constant load until duration of 20 min was reached (Mean % of MHR = 93,9%)
Study 3	8	26.6 ± 7.5	2, 25%	Bicycle ergometer	20 + 1 cooldown	(G) Graded until target heart rate → constant load until duration of 20 min was reached (Mean % of MHR = 89,3%)
Control	6	26.2 ± 5.4	3, 50%	Bicycle ergometer	20	Seated on the bike
Rai et al. (2018)(21)	4	25 ± 4				
Moderate	†			Bicycle ergometer	45	(AI) 3 min warm up at 40% MWL → 20 min at 65% of MWL+ 20 min at 55% of MWL → 2 min at 40% MWL
HIIT	†			Bicycle ergometer	21	(AI) 3 min warm up at 40% MWL → 4 × 30 s HI sprints at 200% MWL separated by 3 min at 40% MWL → 4 min cool down at 40% MWL
Streeter et al. (2007)(23)	8	25.75 ± 5.15	7, 88%	Yoga asana (Participants differed in the type and years of experience of yoga practice)	60	(Con) Low
Streeter et al. (2010)(20)	34	25.6 ± 4.9	22, 65%			
Yoga	19	23.9 ± 3.0	11, 58%	Yoga asana	60	(Con) Low
Walking	15	25.6 ± 4.9	11,73%	Walking	60	(Con) Walking pace: 2.5 mph

Abbreviations: ACC, Anterior cingulate cortex; AI, Alternating intensity; Con, Constant intensity; G, Graded intensity; HRR, Heart rate reserve; MHR, Maximal heart rate; MWL = Maximal workload; N.A., Not available; V1, Primary visual cortex. † indicates that the same participants completed multiple conditions or sub-studies.

3.1. GABA

A total of four studies measured GABA concentrations (Table 2). Overall, two studies found increases in GABA concentrations from baseline to post-exercise measures [13,23], one study found no changes [20], and one study reported both an increase and no change, depending on the voxel placement [24]. Across the four studies, four different regions of interest were specified: left sensorimotor cortex [24], right dorsolateral prefrontal cortex [24], bilateral placement over primary visual cortices [13], and left thalamus [20,23]. Metabolites were quantified from the different regions using field strengths of 1.5 T, 3 T or 4 T.

In the sensorimotor cortex, increases of 29% and 24% were observed relative to water and creatine, respectively, following exercise [24]. No significant changes were reported in the dorsolateral prefrontal cortex [24]. One study measured GABA concentrations bilaterally in the primary visual cortices and found increases in GABA when normalized to both creatine and NAA [13]. In the thalamus, results have been mixed. While a pilot study reported a 27% increase in GABA levels, the subsequent RCT found no

Table 2
Overview of MRS acquisition parameters and outcomes.

Study (First author, year)	Onset of scan (min)	Field strength (Tesla)	Voxel (cm^3)	Voxel location	Observed pre-/post- exercise changes in MRS outcomes
Caglar et al. (2005)(22)	N.A.	1.5 T	2 x 2 x 2	Left frontal lobe	No significant changes in NAA:Cr, NAA:Cho, NAA:Cho + Cr or Cho:Cr ratios.
Coxon et al. (2018)(24)					
Study 1	24 ± 3.5	3 T	2 x 2 x 2	Sensorimotor cortex (including hand knob region in left hemisphere)	GABA:H20 and GABA:Cr increased 29% and 24%, respectively. No sig. change in Glx:Cr, Ins:Cr, Cho:Cr NAA:Cr
Study 2	31 ± 3.5	3 T	2 x 2 x 2	Right dorsolateral prefrontal cortex	No change in GABA or Glx within DLPFC
Dalsgaard et al. (2004)(17)	<40 s	1.5 T	4 x 4 x 2.5	Supra-ventricular cortex	No significant change in lactate concentration. No other MRS outcomes reported.
Dennis et al. (2015)(12)	32 ± 10	7 T	3 x 2.5 x 2.5	Occipital cortex/visual cortex	Lac:Cr and Lac increased after exercise. No significant change in Glu:Cr or Gln:Cr, but [Glu], [Gln] and [Cr] decreased after exercise.
Maddock et al. (2011)(25)	20	1.5 T	3.0 x 2.5 x 2.5	Bilaterally over primary visual cortices	Lac:Cr, Lac:NAA, Glx:Cr and Glx:NAA increased after exercise. No significant change in NAA:Cr or Cho:Cr.
Maddock et al. (2016)(13)					
Study 1	14.6 ± 2.4	3 T	3 x 2.5 x 2.5	Bilaterally over primary visual cortices	GABA:Cr, GABA:NAA and Glu:Cr increased after exercise. There was no significant change in NAA:Cr Ins:Cr, Cho:Cr or [Cr].
Study 2a	12.8 ± 2	3 T	3 x 2.5 x 2.5	Bilaterally over primary visual cortices	Glu:Cr and NAA:Cr increased after exercise. There was no significant change in Ins:Cr, Cho:Cr or [Cr].
Study 2b	13.3 ± 2	3 T	3 x 2.5 x 2.5	Bilaterally over the rostrodorsal ACC	Glu:Cr and NAA:Cr increased after exercise. There was no significant change in Ins:Cr, Cho:Cr or [Cr].
Study 3	15.3 ± 1.1	3 T	3 x 2.5 x 2.5	Bilaterally over primary visual cortices	Glu:Cr and Glu:H20 increased after exercise. NAA:Cr, Cho:Cr, Ins:Cr and [Cr] did not change after exercise.
Rai et al. (2018)(21)					
Moderate	≤15	3 T	3.0 x 3.0 x 2.0	ACC	GSH decreased after exercise
HIIT	≤15	3 T	3.0 x 3.0 x 2.0	ACC	No significant changes in GSH
Streeter et al. (2007)(23)	N.A.	4 T	2 cm slab	The bottom of the slab of interest was aligned with the anterior commissural-posterior commissural line and then rotated 20°	GABA increased after yoga training. No other MRS outcomes reported.
Streeter et al. (2010)(20)					
Yoga	N.A.	4 T	2 x 2 x 2	Left thalamus	No signfiicant change in GABA:Cr. No other MRS outcomes reported.
Walking		4 T	2 x 2 x 2	Left thalamus	No significant change in GABA:Cr. No other MRS outcomes reported.

Abbreviations: ACC, Anterior cingulate cortex; GSH, glutathione; HIIT, High intensity interval training.

significant changes in GABA [20,23]. Both applied an exercise regime of 60 min Yoga Asana sessions.

3.2. Glutamine/glutamate (Glx)

Glutamate (Glu) and glutamine (Gln) can either be quantified separately or pooled together as glutamine/glutamate (Glx). Here, all results regarding Glu, Gln, and Glx will be considered together.

A total of four studies, one of which included 3 sub-studies, measured either Glu, Gln or Glx (Table 2). Two studies found increases in Glx and Glu [13,25], one study found no significant changes to Glx levels [24], and one study had varying results [12]. Across the four studies, five different regions of interest were specified: left sensorimotor cortex [24], right dorsolateral prefrontal cortex [24], occipital cortex [12], bilateral placement over primary visual cortices (V1) [13,25], and bilateral placement over the anterior cingulate cortex (ACC) [13].

One study found varying results measuring glutamate and glutamine in the occipital cortex. They reported no changes when Glu and Gln were normalized to creatine but observed a decrease in absolute quantification [12]. Two other studies reported increases in Glu:Cr in the primary visual cortices [13,25]. Similar increases were found when expressed relative to NAA [25]. In one sub-study, Glu:Cr levels increased in the anterior cingulate cortex [13]. No significant changes in Glx:Cr were found in either the sensorimotor cortex or dorsolateral prefrontal cortex [24].

3.3. NAA

A total of four studies, one of which included 3 sub-studies, measured N-Acetylaspartate (NAA) concentrations (Table 2). All measurements were normalized to creatine. Three studies found no significant changes in NAA concentrations [22,24,25] and one study found varying results within its sub-studies [13]. Across the four studies, four different regions of interest were specified: Left frontal lobe [22], left sensorimotor cortex [24], bilateral placement over primary visual cortices [13,25], and bilateral placement over ACC [13].

No significant changes were found in the left frontal lobe or sensorimotor cortex [22,24]. Within the primary visual cortices, increases [13] and no changes have been reported [13,25]. An increase in NAA following exercise was also reported within the ACC [13].

3.4. Creatine

Only two studies measured creatine concentrations (Table 2). The two studies selected overlapping regions of interest: the occipital cortex [12] and the primary visual cortices [13]. One study reported significant decreases in absolute creatine values when measured in the occipital cortex [12]. In contrast, the other study found no changes in absolute concentrations in the primary visual cortices [25].

3.5. Lactate

Three studies measured lactate concentrations (Table 2). Two studies found significant increases in lactate concentration [12,25]. Across the three studies, three different regions of interest were specified: Supra-ventricular cortex [17], occipital cortex [12], and bilateral placement over primary visual cortices [25].

Measurements conducted by one study did not reach the detection limit in the supra-ventricular cortex, so no changes were reported in either absolute lactate or lactate normalized to creatine [17]. Absolute concentrations and Lac:Cr were found to increase in both the occipital cortex and bilaterally in the primary visual cortex [12](25).

3.6. Choline

Four studies measured choline (Table 2). Across the four studies, four different regions of interest were specified: Left frontal lobe [22], left sensorimotor cortex [24], bilateral placement over primary visual cortex [13,25], and bilateral placement over the ACC [13]. Metabolites were quantified from the different regions using field strengths of 1.5 T or 3 T. No studies reported significant changes in choline levels in any regions of interest. All choline concentrations were normalized to creatine.

3.7. Myoinositol

Two studies measured myoinositol (Table 2). Across the two studies, three different regions of interest were specified: Left sensorimotor cortex [24], bilateral placement over primary visual cortices [13], and bilateral placement over the ACC [13]. Metabolites were quantified from the different regions using field strengths of 3 T. No studies reported significant changes in myoinositol levels in any regions of interest. All myoinositol concentrations were normalized to creatine.

3.8. Glutathione

One study measured glutathione [21]. The voxel of interest was placed in the anterior cingulate cortex, and metabolites were quantified using a field strength of 3 T. The study reported a decrease in glutathione after a session of alternating exercise at moderate intensities but observed no changes in glutathione levels after a session of high-intensity intervals.

3.9. Risk of bias

All studies presented a clearly stated study question and 8 out of 9 studies delivered the intervention consistently over the study population (Fig. 2). While all studies prespecified their outcomes, one study arguably did not examine changes in one of their pre-post intervention outcomes as they did not reach the detection limit of the examined metabolite [17]. Most studies (n = 5) did not prespecify their eligibility criteria. Three studies screened their participants with a questionnaire on health (i.e., general health, medical screening, and electrocardiogram) or contraindications to exercise, but did not report how these measures influenced their eligibility criteria. Only one study justified their sample size with a power calculation [24]. Three studies did not state the onset of the MRS measurements, limiting the comparability and reliability of outcomes in these studies.

4. Discussion

The present review aimed to summarise and assess studies on the effects of acute PA on brain metabolites as measured by MRS. Across studies, GABA and lactate tended to increase after exercise, while no significant changes in choline were reported. For the remaining metabolites, the findings were either too scarce ($\leq$2 studies) or in disagreement. Across interventions, there was marked variability in MRS acquisition parameters - particularly in the time elapsed between exercise and data collection. With this in mind, the

findings for each metabolite will be discussed in turn, in the context of their brain function.

4.1. Excitatory and inhibitory neurotransmitters

GABA is the primary inhibitory neurotransmitter in the human brain [4]. It can be found intracellularly, in the cytoplasm or in pre-synaptic vesicles, and extracellularly. It is an amino acid of many functions, with reported roles on brain metabolism, neurotransmission and tonic cortical inhibition (for review, see Ref. [26]). In addition, GABA has been shown to be associated with brain connectivity and synaptic plasticity [27,28].

Brain connectivity is altered both in aging and in neurodegeneration [29]. In the face of ageing, remaining physically active can help maintain brain connectivity [30,31]. Accordingly, measuring GABA in relation to other markers of brain aging and neurodegeneration may help us to understand individual differences in connectivity effects – particularly since some studies show positive effects of exercise on connectivity [30,32], while others do not [33]. Exercise-induced GABA increases measured by MRS have been proposed to reflect intracellular increases utilized to support the energetic demands of the mitochondria [24]. Mechanisms of energy metabolism, including mitochondrial function, adaptively modify and protect neuronal networks. Therefore, interventions maintaining these functions have been suggested as a preventative strategy for Alzheimer's disease (AD) [34]. In male rats with AD, GABA-containing compounds have been shown to prevent mitochondrial dysfunction [35]. While three studies reported an increase in GABA after exercise, one study found no significant changes. Future PA-studies should investigate GABA changes in older individuals who experience a cognitive decline to better understand how these changes are potentially associated with benefits in cognition induced by exercise.

A combination of glutamate and glutamine can be expressed as "Glx". They are commonly reported together due to structural similarities of the metabolites making them difficult to distinguish on the MR-spectra [3]. Glutamate is the main excitatory neurotransmitter in the brain, and its influence on cognition and memory consolidation through long-term potentiation is well-established [36]. Given multiple reports of the effects of exercise on memory, both in younger and older adults [37], Glx modulation is a plausible candidate neuromechanism for the cognitive benefits of exercise. Glx levels have been shown to increase in the hippocampus of adolescents after 16 weeks of high intensity exercise [38]. Although cognitive benefits of acute exercise have been demonstrated [39], others have hypothesised that this effect increases with increasing intervention length [37], thus raising the possibility that longer intervention periods are necessary to reliably observe changes in Glx. In contrast, a recent study compared Glx levels between two groups: one group remained at rest and one group completed a single intense exercise session [40]. Interestingly, Glu:Cr and Glx:Cr concentrations were, respectively, 11.0% and 12.6% higher in the exercising group compared to the resting group. While both of these findings appear to lend support to an exercise-induced increase in Glx, there was no consensus in the reported direction of Glx changes after a single exercise session in the studies included in this review.

4.2. Neuronal and glial markers

As NAA exists in high concentrations within neurons, it is often interpreted as a "a neuronal marker" [5]. For instance, findings of increased or decreased NAA levels are, respectively, interpreted as being indicative of neurogenesis and neurodegeneration - conditions at opposite ends of the neuronal integrity spectrum [41,42]. One prominent hypothesis in the exercise-brain literature is that exercise enhances hippocampal neurogenesis, which is in turn conducive to improved cognitive function [43]. If NAA is interpreted as a neuronal marker, then findings of increased NAA levels following exercise could be interpreted in support of the hypothesis that exercise promotes neuronal integrity.

Only one of the included MRS studies found NAA levels to increase after a single bout of exercise [13]. Outside of the acute-exercise literature, aerobic fitness has been observed to positively correlate with NAA levels in the hippocampus [44]. Likewise, higher NAA:Cr levels in the frontal grey matter have been observed in endurance-trained compared to sedentary adults, wherein physical fitness was significantly correlated with NAA:Cr levels in the same brain region [6]. Further, age-related decline in NAA levels may be offset in individuals with higher levels of aerobic fitness, though only in the older participants [45]. Despite promising evidence of a link between NAA levels and exercise from observational and long-term interventions, our review found no overwhelming evidence to suggest that physical activity, at least acutely, alters NAA levels.

In the in vivo brain, myo-inositol and choline concentrations are suggested to be higher within glial cells than neurons [46]. Both metabolites have been found to be elevated in older adults, in a pattern suggestive of neuroinflammation [47]. Choline measurements obtained by MRS are considered to reflect membrane turnover and cell density [48]. During long sessions of endurance sports, choline levels have been shown to drop significantly [49]. In contrast, none of the included MRS studies reported changes to choline levels. This inconsistency in findings could be due to the shorter duration of the exercise regimes typically implemented in acute MRS studies. Higher choline levels at older ages have previously been associated with lower cognitive performance [10]. In contrast, impaired declarative memory has been associated with choline depletion after a 5-day military combat program [50]. Future studies should investigate choline levels in relation to longer exercise sessions, as no support for changes to choline levels is reported in this review of short-duration interventions.

Myo-inositol concentration, as measured by brain MRS, is often interpreted as a glial marker (but see Rae [48]). Higher levels of myo-inositol have been linked to both normal cognitive aging and AD, while depletion of myoinositol levels have been implicated in affective disorders, such as depression [51]. Although no evidence of exercise-induced changes to myo-inositol was observed in the studies included in this review, only two studies to date have examined these changes and further investigation on myo-inositol levels is warranted.

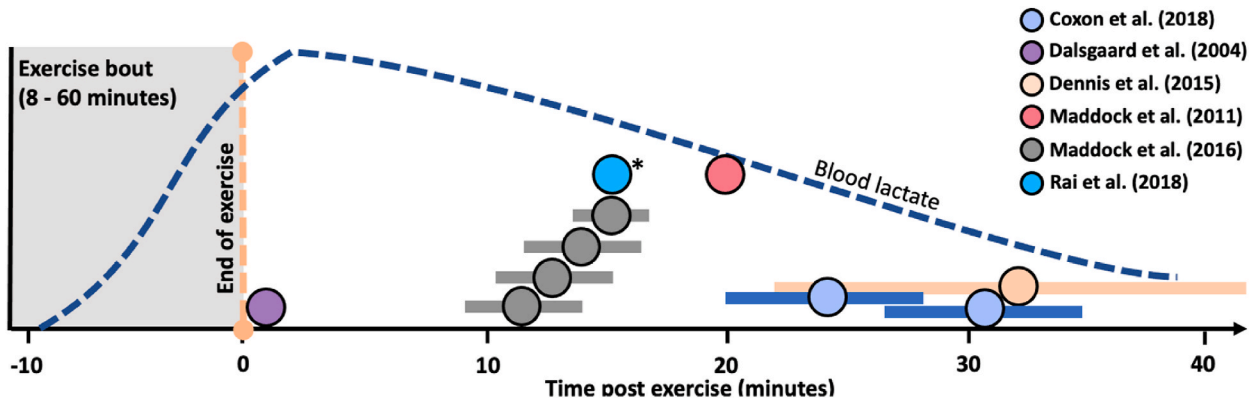

Fig. 3. Illustration of range of onset time of MRS data collection from the included studies. The mean and SD of reported onset times are depicted by circles and bars. Three studies did not report the onset time of MRS data collection. The timeframe of changes in blood lactate levels following a high intensity exercise have been obtained from a separate study [17], and are included only as a depiction of how the onset times of the included studies may compare to the timing of peripheral changes, such as lactate. * The MRS onset time was reported as ≤15 min.

4.3. Energy metabolism: lactate

In the working muscle cell under anaerobic conditions, glycolysis leads to a release of lactate into the blood [52]. In the brain, lactate is produced through glycolysis by glia cells [8]. During exercise, particularly exhaustive exercise, the lactate originating from the muscle is taken up by the brain, likely through increased arterial lactate concentrations [17]. This increase in lactate has been suggested to supplement glucose as a fuel for the brain during a bout of vigorous exercise [8].

Findings from this review support the hypothesis that lactate increases in the brain during exhaustive exercise. Two MRS studies have found increases in lactate [12,25], while measurements in one study did not reach the detection limit [17]. To optimally detect lactate, it is advisable to optimize acquisition sequences by, for example, applying longer echo times (TE) of 144 ms or 288 ms [3]. The study which did not reach the detection limit for lactate used a shorter TE of 20 ms [17].

In animals, lactate has been shown to function as a key regulator of Vascular Endothelial Growth Factor (VEGF) and angiogenesis in the brain and may therefore serve as an initial mediator of the cerebral effects of exercise [53]. With increasing evidence of exercise-induced lactate uptake in the brain, future research would benefit for examining the link between lactate and exercise-induced changes in cognition.

*4.4. **Methodological considerations***

*4.4.1. **Sample characteristics***

Metabolite outcomes might be influenced by various parameters, including sample characteristics. A clear gap in the literature was the lack of studies measuring brain metabolites in older adults, as all included participants were under 45 years old. Studies have found age-related cognitive decline to be linked with alterations in metabolite concentrations [54]. Given the evidence for the enhancing effects of exercise on cognition in older adults [55], studies on the acute effects of PA on brain metabolites in older individuals are warranted.

Sex differences have previously been proposed as a moderator of the effects of PA on cognition. For example, larger effect sizes in executive function have been suggested for older females compared to older male participants [56]. While most included samples were too small to test for sex differences in observed effects, the potential influence of sex differences was considered in two of the included studies – mainly in reference to the menstrual cycle [20,23]. This was in light of reported GABA differences across the menstrual cycle, as cortical GABA levels decrease during the follicular phase of the menstrual cycle in healthy women [57].

Beyond age and sex, other moderators may play a role in the exercise-brain relationship. For instance, individual fitness level has previously been shown to influence the effect that exercise has on cognition [58]. To reliably account for individual differences, future studies should be more consistent in specifying eligibility criteria and implementing the intervention on participants representative of the intended population of interest.

4.4.2. Onset of MRS measurements

The time between the cessation of the intervention and the onset of MRS measurements varied between studies (Fig. 3). The two studies reporting increases to Glx initiated their first measurement with a maximal scanning delay of 20 min [13,25]. Both studies found the increases had subsided to non-significant levels in the second measurement: approximately 30 min post-exercise. In comparison, one study reported a decrease in [Glu] and no change in Glu:Cr. This study executed the first post-exercise scan with an average delay of 32 min [12].

Blood lactate levels return to baseline within approx. 30 min of recovery from high-intensity training [59]. In response to visual stimulation, MRS measurements from the visual cortex returned to baseline within 20 min [60]. Likewise, the best acute effects of

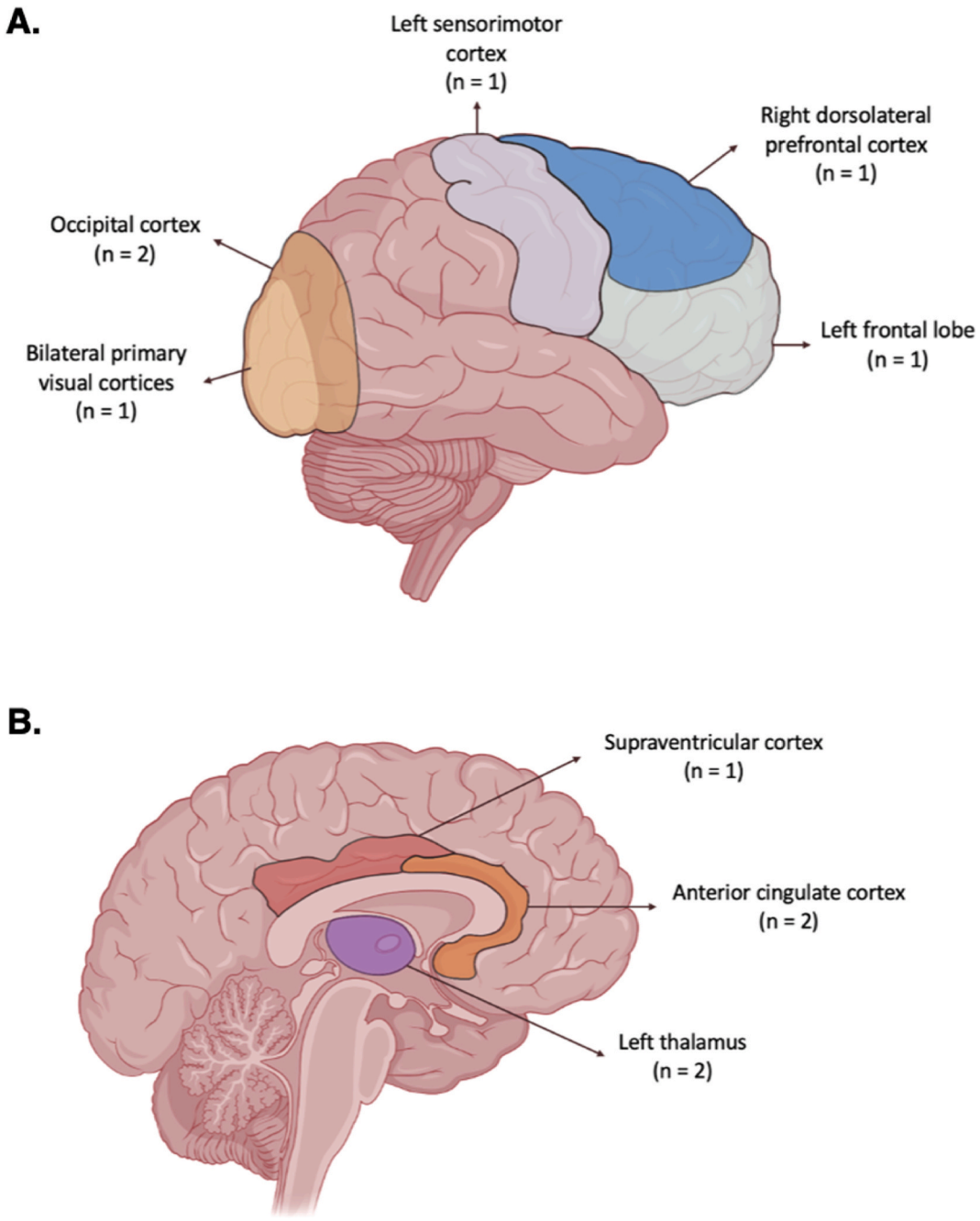

Fig. 4. A schematic overview of (A) cortical and (B) subcortical brain regions investigated in the included MRS studies. A single hemisphere was used for illustrative purposes, but regions examined unilaterally are specified in the labels. The figure was prepared using BioRender (2022), https://app.biorender.com/biorender-templates.

exercise on cognition have been demonstrated when cognitive tests are administered within 11–20 min post-exercise, with effects subsiding after a 20-min delay [58]. On this basis, it is suggested that results should be measured within 20 min to be reliably interpreted and prevent time-dependent declines in metabolite levels. Further, it would be advantageous for future studies to clearly state the onset of their MRS measurements so that the literature can move forward with a clearer understanding of the dynamic MRS changes following exercise.

4.4.3. Physical activity interventions

In comparison to sample characteristics, the intensity of PA regimes was relatively comparable across studies. Most studies (n = 7)

Table 3
Overview of reported quality metrics of the metabolite measurements.

First author, ref.	Reported quality metric	Criteria for quality metrics	Correction for tissue type
Caglar et al. (2005)(22)	None	None	No
Coxon et al. (2018)(24)	[1] Full-width half-maximum of the creatine linewidth (Cr FWHM), [2] SD of the water frequency in Hz and [3] GABA signal fit error ($E_{GABA\text{-}Water}$)	[1] Cr FWHM <10 Hz [2] SD of water frequency <1 Hz [3] $E_{GABA\text{-}Water}$ <15%	Yes
Dalsgaard et al. (2004) (17)	CRLB	CRLB <20%	No
Dennis et al. (2015)(12)	CRLB	CRLB <25%	No
Maddock et al. (2011) (25)	CRLB	CRLB <20%	No
Maddock et al. (2016) (13)	[1] Mean and range SNR ratio [2] CRLB [3] Linewidth (FWHM)	CRLB <20%	No
Rai et al. (2018)(21)	None	None	Yes
Streeter et al. (2007)(23)	None[a]	None	No
Streeter et al. (2010)(20)	SNR	Not specified	Yes

CRLB, Cramer-Rao lower bounds; SNR, signal to noise.
[a] Spectral data from one subject was deleted due to poor quality, but the applied quality criteria were not reported.

had participants working at $\geq$ 65% of either maximal individual heart rate, workload, or aerobic capacity at some point during the intervention. Therefore, it can be interpreted that the literature predominantly investigated metabolite changes in response to moderate-to-vigorous exercise, although the duration of exercise at high intensity and the progression towards obtaining this intensity varied (i.e, graded, alternating, and constant regimes). Eliminating between-study differences in the description of intensity is crucial for future studies to explore any correlation between specific intensities and effects on brain metabolites. A review by Basso & Suzuki (2017) suggested that future studies report intensity as a percentage of individual VO_2-max. This percentage could then serve as a standardized exercise index for between-study comparison, which was proposed in the same review [61]. Agreement is needed in the context of how to standardize graded and alternating exercise regimes applying variance in intensity along the intervention timespan.

4.4.4. MRS acquisition parameters and data processing

Within MRS acquisition parameters, differences regarding the analysis, scanners and regions of interest are of note (Fig. 4). Metabolite levels are typically quantified to either creatine or water. This decision is not arbitrary, however. In one study, Glx changes differed when metabolites were quantified to either creatine or water [12]. Although creatine is assumed to remain stable in healthy and pathological brains [62], others have argued that creatine may vary with age and tissue type [10,63], making it ill-suited as a denominator. Creatine levels may also vary with exercise, as suggested by the only 7 T study included in the review [12]. Future studies should evaluate whether creatine remained stable during the exercise intervention or report concentrations based upon normalization to the unsuppressed water spectrum. In some instances, studies reported absolute concentrations instead of ratios [12,13]. While the pitfalls and benefits of absolute quantification are beyond the scope of this review (see Refs. [64,65]), it is important to note that the comparability across studies is limited by the differences between the techniques used to derive absolute metabolite concentrations, as well as differences between ratios and absolute concentrations.

Increases in field strengths improve signal-to-noise ratio and are inherently associated with increased spectral resolution. Higher field strengths enable the quantification of more metabolites and increase precision in quantifying Glu and Gln separately [3,66]. In terms of regions of interest (ROI), a total of 8 different ROIs were included in the reviewed studies. Here, we presented the direction of reported results independent of brain region. However, since metabolite levels can vary between regions and tissue types [63,67], variations in regions of interest and tissue concentration may also account for heterogeneity in findings.

Finally, a range of criteria is recommended to assess the quality of metabolite measurements [3]. These include: metabolite SNR, linewidth estimates (FWHM), residual water signal and Cramer-Rao lower bounds of the data fit. Further, visual assessment of the phased spectra is advised. Of the 9 included studies, 3 reported no quality metrics and only 2 studies reported more than one quality assessment (Table 3). Moving forward, we strongly encourage future studies to assess and report the quality metrics of metabolites, as recommended by Wilson and colleagues (2019) [3].

5. Conclusion

There is a small, and arguably still inconclusive, body of literature on acute effects of PA on MRS outcomes. As reviewed here, a few gaps in the field have become apparent, warranting attention of future research. First, given the evidence of exercise-induced lactate uptake in the brain, future research would benefit from examining the link between changes in lactate and exercise-induced changes in cognition. Similarly, given the link with cognition, exercise-induced changes in Glx are of particular interest. To date, no studies have investigated PA acute effects on the brain metabolites of adults over the age of 45. Future studies should investigate the effects of PA in different age groups and the moderating role of exercise intensity, as interventions predominantly have applied high-intensity exercise regimes. Further, since the Glx/Glu distinction can be challenging at lower field strengths, a higher field strength would be desirable to

separate these two metabolites. Finally, the large variability in the time of onset of MRS measurements is a notable limitation of this field. A better understanding of the timeframe of MRS changes following exercise is crucial. Without characterizing the time window of exercise-induced changes, we cannot be sure when to expect, or no longer expect, "acute" effects.

Most people know that physical activity is good for their physical health. Although the same is widely accepted for brain health, we still do not know how and why physical activity benefits the brain. With MR spectroscopy, it is possible to study the neurochemical effects of acute exercise in vivo. Here, we identified 9 studies that have investigated the acute, exercise-induced, changes in brain metabolites with MRS. The marked variation in MRS acquisition parameters (e.g., onset time and region of interest) may account for the marked variability in reported findings. However, some overlapping patterns in the direction of exercise-induced changes could be observed, including increases in GABA and lactate. Only with the better understanding of how exercise improves brain health, will we be able to develop and implement effective physical activity interventions.

CRediT authorship contribution statement

Mathias Ryberg: Data curation, Formal analysis, Writing – original draft. **Carl-Johan Boraxbekk:** Conceptualization, Supervision, Writing – review & editing. **Michael Kjaer:** Resources, Supervision, Writing – review & editing. **Naiara Demnitz:** Conceptualization, Formal analysis, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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