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Working Paper

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Publication date:
2024-05-21

Permanent link:
https://doi.org/https://doi.org/10.3929/ethz-b-000680621

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Originally published in:
SportRxiv, https://doi.org/10.51224/SRXIV.411

Beyond FITT: How Density Can Improve the Understanding of the Dose-Response Relationship Between Physical Activity and Brain Health

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Please cite as: Herold,F., Zou, L., Theobald, P., Manser, P., Falck, R. S., Yu, Q., Liu-Ambrose, T., Hillman, C. H., Kramer, A. F., Erickson, K. I., Cheval, B., Chen, Y., Heath, M., Zhang, Z., Ishihara, T., Kamijo, K., Ando, S., Gao, Y., Costello, J. T., Hou, M., Hallgren, M., Chen, Z., Moreau, D., Farrahi, V., Raichlen, D. A., Stamatakis, E., Wheeler, M. J., Owen, N., Ludyga, S., Budde, H., Gronwald, T. (2024). *Beyond FITT: How Density Can Improve the Understanding of the Dose-Response Relationship Between Physical Activity and Brain Health*. SportRχiv.

All authors have read and approved this version of the manuscript. This article was last modified on 21. May 2024.

Abstract

Research on physical activity and health, including planned and structured forms such as acute and chronic physical exercise, has focused on understanding potential dose-response relationships. Traditionally, the variables of (i) Frequency, (ii) Intensity, (iii) Time, (iv) and Type (known as the FITT principle) have been used to operationalize the dose of physical activity. In this article, we describe the limitations of FITT and propose that it should be complemented by the underappreciated variable density, which defines the temporal distribution of physical activity stimuli within a single bout of physical activity or between successive bouts of physical activity relative to time spent resting (e.g., in napping/sleeping or sedentary behaviors). Using the field of physical activity and brain health as an example, we discuss challenges and opportunities for further research to use density to improve our understanding of dose-response relationships between physical activity and health-related outcomes.

Keywords: physical exercise, sedentary behavior, brain, cognition, personalized interventions

1. Introduction

Physical activity (PA), which includes planned and structured forms such as acute and chronic physical exercise (see Table 1 for definition), is associated with improved brain health across various age groups, and with different health status [1–4]. Regular engagement in PA is beneficial for brain health at multiple levels [5–8], namely (i) the molecular and cellular level (e.g., expression of brain-derived neurotrophic factor [9–15]), (ii) the functional and structural brain level (e.g., brain activity patterns [16–18] or hippocampal volume [19–21]), (iii) the behavioral level (e.g., better cognitive performance [1, 2, 22–30]), and (iv) the risk of adverse health-related events (i.e., lower dementia risk [31–34]). However, the optimal dose of PA, including but not limited to the time point at which PA should be applied or repeated to trigger changes in specific health-related outcomes (i.e., brain health), is not fully understood [6, 8, 22, 26, 27, 35, 36].

There is currently a need for greater clarity in the definition of the dose of PA (including physical exercise) [37–42]. This extends to the call for a more complete reporting of dose in intervention studies using PA [41, 43–45]. From a practical perspective, elucidating the complex dose-response relationship of PA and health-related outcomes, comprising the interindividual response variability, is an important prerequisite when aiming to maximize the benefits of PA interventions (e.g., on brain health) by individualizing the PA prescription [37, 38, 40, 45–55].

Traditionally, the dose of PA has been characterized and prescribed using the FITT principle, an acronym representing: (i) Frequency, (ii) Intensity, (iii) Time (also referred to as duration), and (iv) Type of PA [51, 56–68]. The FITT principle can also be used to retrospectively analyze how the dose of free-living PA (e.g., unplanned and unstructured forms of PA) is associated with health-related outcomes, which can inform recommendations for a specific amount of PA to maintain or improve health. The FITT principle is also commonly used in systematic reviews and meta-analyses when analyzing the dose-response relationship between PA and measures of brain health [26–28, 60]. Some researchers have suggested extending the four elements of the FITT principle by the factors of: (v) Volume (V), which is defined as the total amount of PA spent in a given intensity zone that is typically operationalized as a product of the duration of the acute PA bouts spent in a particular zone of intensity x frequency [57]; and, (vi) Progression (P), which characterizes the gradual and systematic increase of the PA stimulus to maintain overload and, thus, provoke further adaptation(s) [69], into FITT-VP [58, 70]. However, adhering to the FITT-VP principle to prescribe and analyze PA has several disadvantages.

First, the FITT-VP principle does not take into account all acute and chronic variables (e.g., movement frequency) that determine the dose of PA (especially of planned and structured forms such as acute and chronic physical exercise) [37, 38, 40, 71]. Second, the FITT-VP principle does not consider the temporal distribution of PA stimuli within a single bout of PA or

between successive bouts of PA relative to the time spent resting, which is conceptualized as density (see definition below) [37, 38, 40]. Third, each component of the FITT-VP principle is treated somewhat independently when in reality variables characterizing PA can be inter-related [37, 71] (e.g., intensity is significantly influenced by other variables such as acute duration [72, 73] and movement frequency [e.g., cadence operationalized as revolutions per minute when using a cycle ergometer] [74, 75]).
For example, one study provided evidence that exercise intensity influences the duration individuals can spend in a specific exercise intensity zone [72]. In particular, in healthy younger adults (i) the maximal duration (i.e., defined in minutes) that the participants were able to spend in a given exercise intensity zone during a constant-load exercise test, and (ii) the physiological responses characterizing distinct duration phases during this performance test show a high interindividual variability, while the relative duration (e.g., operationalized as % of maximal duration) was comparable among participants [72]. These findings suggest that a personalized exercise prescription should consider the individualization of the duration spent in specific exercise intensity zones [72, 73].
Regarding movement frequency, a study in trained cyclists showed that, at the same exercise intensity, cycling at a higher movement frequency (i.e., 120 revolutions per minute on a cycle ergometer) led to higher physical demands (i.e., operationalized by ratings of perceived exertion, peripheral blood lactate concentration, heart rate, indices of heart rate variability [74], or spectral parameters of the electroencephalography [76]) than cycling at a lower movement frequency (i.e., 60 revolutions per minute) [74, 76]. In addition to the acute differences in physiological markers, there is evidence that in trained cyclists endurance training at different movement frequencies (i.e., high vs. low cadence training for four weeks) may differently influence specific brain measures [77, 78]. In particular, in trained cyclists endurance training at either high or low cadence produces similar improvements in markers of endurance performance (i.e., maximal oxygen uptake and power at the individual anaerobic threshold) [77, 78]. However, training at high cadence led to more pronounced changes in several brain parameters (e.g., reduction in alpha-, beta- and overall-power spectral density [77] or increase in frontal alpha/beta ratio [78] assessed during an incremental exercise test).

The above-presented examples highlight the complexity of determining or providing a specific dose of PA and suggest that an oversimplification of dose may hinder accurate prediction and optimization of PA interventions on health [37, 38, 40]. This is also supported by the fact that different PA variables converge in the PA-induced stimulus (i.e., external load) that feeds into the response matrix, where it interacts with non-modifiable factors such as age, sex, or genetic predisposition, and (potentially) modifiable non-PA-related factors such as sleep, nutrition, general stress, and environmental factors, and then triggers specific biological processes that determine the dose (i.e., defined as (a) specific marker(s) of internal load that are involved in biological processes driving the desired changes in outcomes of interest – see Table 1) [37, 38, 40, 71, 79]. Thus accounting for such interrelations of PA variables must not only be considered when tailoring, programming, or progressing PA interventions [37, 38, 40, 71, 80] but also as part of the assessment and analytic approaches used.

Consequently, to advance the understanding of the dose-response relationship of PA with specific domains of health (i.e., brain health [40]), it is necessary to consider additional variables, such as density, which we will show can allow for a more precise determination of the dose of PA and provide a more nuanced approach beyond the FITT-VP principle.

Table 1. Definition of key terms. PA: physical activity; MET: metabolic equivalent of the task; SB: sedentary behavior

Key terms	
Brain Health	…can be defined as the optimal development and maintenance of brain integrity which encompasses: (i) structural (e.g., hippocampal volume) and functional (e.g., changes in brain activity) brain parameters; (ii) functions that depend on the integrity of the brain, including but not limited to mental health, cognition, and movement; and (iii) the absence of neurological disorders (e.g., dementia). [81, 82]
Dose	…is characterized by three key components: (1) external load (i.e., defined as the work performed by the individual independent of internal characteristics), (2) influencing factors (i.e., all factors [e.g., including environmental factors] that can strengthen or weaken the stimuli of a single bout of PA), and (3) internal load (i.e., defined as the individual and acute physiological, psychological, motor, and biomechanical responses to the external load and the influencing factors during and/or after the cessation of a single bout of PA). Thus, the dose can be operationalized and monitored by using specific indicators of internal load involved in the biological processes that drive the desired changes in outcomes of interest. [37, 40, 79]
Physical Activity (PA)	…can be defined as any muscle-induced bodily movement (e.g., in occupational or leisure time) that results in an increase in the energy expenditure above ~1.5 metabolic equivalents of the task (MET; 1 MET = 1 kcal (4.184 kJ) • kg^{-1} • h^{-1}). This includes planned and structured forms such as acute and chronic physical exercise (see the following definition). PA can be divided into acute (single bout/session of) and chronic (multiple bout/session) PA based on temporal characteristics." [81, 83–90] Furthermore, PA can be differentiated based on the domains in which it occurs, including recreation/leisure time (such as household), transportation, education, or occupation [87, 88, 91–95].

Physical Exercise	…can be defined as a specific form of PA that is planned, structured, repetitive, and designed to improve or at least maintain the performance in one or more fitness dimensions. Physical exercise can be divided into acute (single bout/session) and chronic (multiple bouts/sessions) based on temporal characteristics, also referred to as physical training [83–86, 88, 89, 91]. In addition, physical exercise is typically performed in recreational/leisure time when it is not part of healthcare service (e.g., rehabilitation) or occupation (e.g., elite athlete). To delimit physical exercise from PA: Physical exercise is always PA, PA is not necessarily physical exercise [96].
Sedentary Behavior (SB)	…can be defined as any waking behavior characterized by a low energy expenditure (≤1.5 MET) while sitting or lying down [87–89, 92, 97, 98]. SB is ubiquitous, due to rapid changes in human environmental, economic, social, and technological contexts. Scientifically, SB has been identified as a newer component of the activity spectrum, which can adversely impact health [99–102]. SB can be categorized as cognitively active (e.g., reading) and cognitively passive (e.g., watching television) [81, 103]. For many adolescents and adults, daily time spent sedentary is ≥ 5 hours per day [104–106].

2. Method

Given that the German exercise and training variable “Belastungsdichte” [107] (hereafter referred to as “density”), which has its roots in the field of exercise science, is not well-recognized internationally, we aimed to improve its accessibility by introducing this variable to the broader scientific community. In this context, we extend the description and application of “density” to the field of free-living PA, where it has not previously been applied. As “density” is underappreciated in the scientific community, we opted to perform a narrative review, since there is not a large and specific enough literature base to conduct a systematic review (e.g., on the role of density of PA on brain health).

The author group comprises junior, mid-career, and senior researchers from different disciplines, and cultural and ethnic backgrounds.

3. Definition of density

Density can be defined as the distribution of PA bout(s) (also referred to as “work bout[s]”) or portions thereof over a specific time interval (e.g., within a single bout, day, week, month, or year) in comparison to the time spent resting (also referred to as “rest, recovery or relief bouts”) [8, 40, 80, 108]. Assuming the characteristics of work bouts remain similar (i.e., are identical in terms of acute and chronic variables that characterize PA), density is determined by the duration of rest bouts. In other words, density can be modified by changing the duration of such bouts to adjust the work-rest ratio.

In this context, we would like to highlight three important points. First, density is related to the construct of the work-rest ratio, but differs conceptually in that density is associated with changing the time spent at rest (i.e., duration of the rest bout[s]), whereas the work-rest ratio can also be adjusted by increasing the duration of the work bout(s). Second, the variables that characterize the work bout(s) and the rest bout(s), namely the type of activity, the intensity, and the duration, need to be considered to gain a more nuanced understanding of the influence of density and, in turn, the dose-response relationship of PA with measures of brain health. Third, density needs to be further differentiated based on the temporal context, namely (i) in acute density (i.e., in the context of acute PA; see Figure 1 a) and (ii) in chronic density (i.e., in the context of chronic PA; see Figure 1 b) [37].

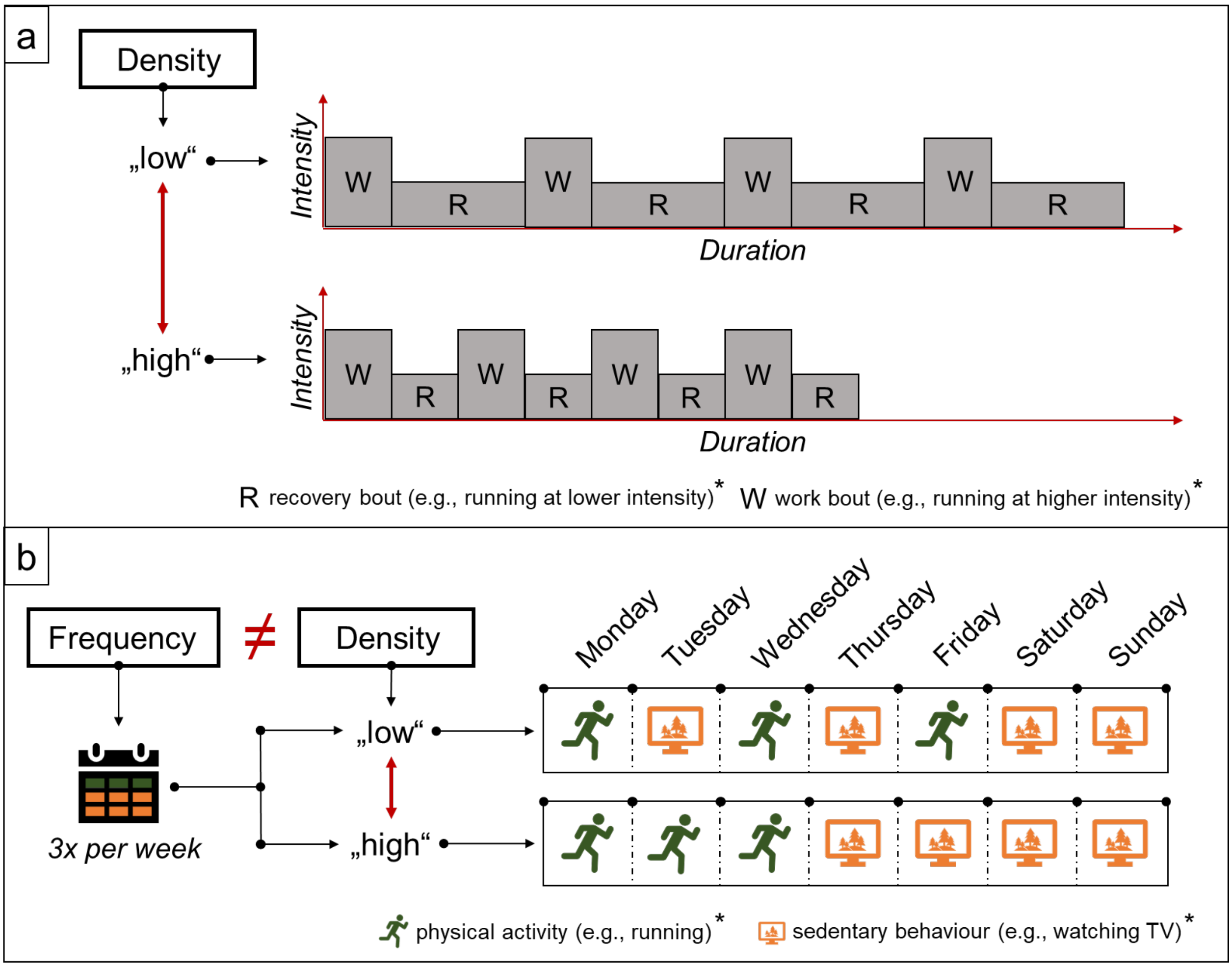

Figure 1: (a) Schematic illustration of different acute densities using an acute bout of physical exercise in interval mode as an example. In our example, the number of the work bouts (4x) and rest bouts (4x) is equal whereas the duration of the rest bout in the upper example (i.e., low acute density; the work-rest ratio of 1:2) is twice as long as in the lower one (high acute density; the work-rest ratio of 1:1) resulting in a different acute density and, in turn, dose. In this example, an active rest bout, which is conducted at half of the intensity as the work bout, is selected.

The example also illustrates the fact that specific acute variables are interrelated (e.g., acute density, acute duration, and intensity of work and rest intervals). (b) Schematic illustration of the difference between frequency and chronic density in the context of chronic physical activity. The visualization shows that the same frequency (3x physical activity bouts per week) can be distributed differently over a week resulting in a different chronic density and, in turn, dose. The asterisk (*) indicates that other acute (i.e., type of physical activity, intensity, and acute duration) and chronic variables (i.e., chronic duration) that characterize the bout(s) of physical activity are assumed to be constant. Please note that we used sedentary behavior as an example for the rest bout(s). With regard to acute and chronic physical activity, physical activity at a lower intensity than that of the work bout(s), standing, and sleep can be also encompassed by the rest bout(s), depending on the context. Furthermore, the operationalization of chronic density depends on the period of interest (e.g., day, week, month, year).

3. Operationalization of acute and chronic density

In the following sections, we propose different approaches to operationalize and analyze density considering the temporal context of PA, the availability and accessibility of population-based datasets, and recent advances in technology to assess PA (i.e., miniaturized wearables to track activities within the 24-hour activity cycle).

3.1 Acute density

As illustrated in Figure 1a, acute density can be operationalized by the duration of the rest bout(s) between the successive work bouts (i.e., in seconds or minutes or relative to the duration of the work bout) within a single session of PA. Thus, a modification of acute density can be achieved by decreasing or increasing the duration of the rest bout(s), resulting in a higher acute work-rest ratio (i.e., higher density) or a lower acute work-rest ratio (i.e., lower density), respectively.

3.2 Chronic density – Simple analysis approaches

The operationalization of chronic density depends on the period of interest (e.g., day, week, month, year). Although chronic density can be operationalized in minutes or hours when several isolated work bouts are performed throughout the day, the operationalization of chronic density is more challenging when longer periods are considered (e.g., week, month, year), especially for unplanned and unstructured forms of PA. To illustrate chronic density in terms of a micro-cycle of one week, consider the following example: if a person is physically active on Monday, Wednesday, and Friday or Monday, Tuesday, and Wednesday, this will result in the same frequency but not the same chronic density within a micro-cycle of one week (see also Figure 1b). More specifically, in the first example shown in Figure 1b, the person is physically active on non-consecutive days (i.e., work bouts spread over a week), whereas in the second example, the person is physically active on consecutive days (i.e., work bouts performed on three consecutive days).

Accordingly, a simple approach to studying the influence of different chronic density patterns on brain health is to characterize different groups of individuals based on their chronic density patterns (e.g., a low chronic density group in which individuals performed PA on non-consecutive days versus a high chronic density group in which individuals performed PA on consecutive days – see also Figure 1). For chronic physical exercise, the influence of chronic density on specific measures of brain health can be studied by comparing intervention groups that were instructed to perform physical exercise sessions with different chronic densities (e.g., a low chronic density group performing physical exercise sessions on non-consecutive days versus a high chronic density group performing physical exercise sessions on consecutive days).

3.3 Chronic density – Sophisticated analysis approaches

Comparable to other studies analyzing the influence of PA patterns (e.g., intensity, and duration of the acute PA bouts) on health-related outcomes (e.g., cognitive performance or cardiometabolic health), the application of more sophisticated approaches using distributional data analysis [109] or machine learning (e.g., via K-means clustering) [110–113] holds some promise for identifying groups of individuals with distinct chronic density patterns. Despite some limitations and challenges (e.g. the need for large sample sizes and, high-dimensional data, the time-consuming nature of training algorithms, and the lack of benchmark data), machine learning-based approaches provide several advantages for the purpose of profiling PA patterns (e.g., more accurate classification and prediction, the possibility of a hypothesis-free/generating approach) [114–118]. Another advantage of machine learning-based approaches is their capacity to handle large, complex, and high-dimensional datasets [114]. The ability and flexibility to handle such datasets make machine learning-based approaches well-suited for analyzing the influence of density on specific markers of brain health because density is a more complex variable than other PA variables (e.g. duration). This assumption is supported by the fact that these approaches have already been successfully applied to elucidate the influence of “micropatterns” of PA including intensity and duration (also referred to as bout length) on health-related outcomes such as mortality [119, 120] and cancer incidence [121]. Thus, extending machine learning-based approaches to density is a promising area for future research to elucidate the influence of different chronic density patterns on measures of health in general and brain health in particular.

In the context of brain health, the application of such sophisticated classification and analysis techniques may enable the investigation of specific research questions (e.g., *is a low density of moderate-intensity PA in older adults more, less, or equally beneficial for brain health than having a high density of moderate-intensity PA?)* or to study the association of specific density-related PA patterns, such as the stability of density, with measures of brain health. In this context, we propose that the stability of density is characterized by the periodicity and the fluctuations (variability) that are reflected by the degree of randomness of the duration of the rest bouts between successive work bouts within a given time interval (e.g., day, week, month, year). We suggest that, among other approaches [122], the stability of density can be operationalized by measures used to assess fractal dynamics.

Fractal dynamics are characterized by the self-affinity (also referred to as self-similarity or scale invariance) of a given signal (e.g., derived from accelerometers) across time scales [123–127]. There is a strong case to be made that fractal dynamics can help to better understand the periodization of chronic physical exercise [128], and several studies have used this approach to analyze physiological data (e.g., frequently applied to heart rate variability data [129–146]) or PA patterns [147–150]. In the context of PA, a popular method for assessing fractal dynamics (e.g. of PA [147–150]) is detrended fluctuation analysis (DFA), which is a nonstationary time-series analysis of specific signals (e.g., accelerometer data) that reflects the correlative structure and fractal dimension of signal fluctuations across a range of time scales based on a modified root-mean-square analysis [126, 127, 151–153]. For instance, a study using data from 5097 middle-aged adults showed that greater fractal stability of daily PA (i.e., assessed via a thigh-mounted accelerometer over seven days and reflected in a higher DFA scaling exponent) was associated with better verbal fluency performance in males but not in females [150]. Such sex-specific differences are consistent with the evidence suggesting that sex is an important moderate in the relationship between PA and brain health [47, 48, 154–160]. However, whether such findings extend to the chronic density of PA remains a promising area for further investigations.

3.4 Recommendations regarding the assessment of chronic density

To quantify the chronic density of PA, we recommend the application of device-based assessments to complement subjective assessments (i.e., questionnaires) for the following reasons. First, popular questionnaires to assess chronic PA such as the International Physical Activity Questionnaire (IPAQ) only quantify the frequency but not the chronic PA density (i.e., neither the long form [161] nor the short form [162] of the IPAQ), although some recently developed questionnaires do collect such information (e.g., Daily Activity Behaviours Questionnaire [163–166]). Second, although subjective assessment tools (e.g., questionnaires) have several advantages (e.g., low burden for participants, cost-effective and convenient administration), they are prone to several sources of bias (e.g., recall bias or social desirability bias) that can confound the estimation of chronic PA patterns [95, 167–169]. Device-based assessment tools can circumvent the above-described limitations of subjective assessment tools, but it should be considered that (i) the applied device-based measurement tool needs to be valid and reliable [170–172], and (ii) there is not yet a fully established consensus on the application of device-based measurement tools (e.g., placement and sampling frequency of the device) or on the data processing procedures to obtain specific indices of PA (e.g., minimal length of the epochs, filter, cut-off points, non-wear-time definition) although some recommendations exist [173–175].

Furthermore, we recommend combining popular device-based tools such as accelerometers with other sensors (e.g., for environmental light, barometer/altimeter, or geolocation) and digital tools (e.g., smartphones) to allow for the recording of contextual information (e.g., weather via geolocation at specific time point [176] or type of activity conducted during rest bout(s) via an accelerometer-triggered e-diary [176–182]). The latter approach is also referred to as ambulatory assessment [81, 177, 183, 184]. In addition, regarding the analysis of chronic density in the context of chronic PA, future studies should consider SB and sleep to provide a more holistic understanding of the 24-hour activity cycle on health in general [185–189] and brain health in particular [81, 92, 190–193].

3.5 The potential of density to complement existing analysis approaches of the 24-hour activity cycle

Since density specifies the temporal distance between stimuli within or between successive bouts of PA, it can complement other approaches used to analyze the influence of PA patterns within the 24-hour activity cycle on health-related outcomes, namely (i) timing of PA (e.g., time of day on which the PA has been conducted such as in the morning, afternoon or evening [194–196]) and (ii) compositional data analysis (e.g., using the relative time spent in a specific activity [e.g., PA] in relation to the time spent in other activities [e.g., SB or sleep] instead of absolute times spent in a specific activity for analysis [197–204]).

In terms of the diurnal impact of PA, PA is an important “Zeitgeber” (time cue) for the human circadian system [205] and thus a critical factor in sleep health, a mediator of the effects of PA on brain health [5, 206]. In this regard, the findings of a recent systematic review suggest that there is currently no consistent evidence in adults as to whether PA conducted at one time of day (e.g., morning) is associated with more pronounced health benefits than PA performed at a different time of day (e.g., afternoon or evening) [194]. In general, PA is associated with better sleep health [207–212], but there is no compelling evidence that PA performed at any particular time of day is superior for promoting sleep health [209, 213, 214] because even acute PA conducted in the evening is not typically detrimental for sleep [215–217] if it is not performed too close before bedtime (≤1 hour) [215]. To the best of our knowledge, the timing of PA and its direct relationship with measures of brain health so far has received relatively little attention in empirical studies. The findings from one study suggest that, in adolescents, an acute bout of physical exercise in the morning is more effective in improving behavioral measures of brain health (e.g., global reaction time), compared with the afternoon [218]. However, currently (i) there is a lack of studies on the influence of the timing of PA on brain health, and (ii) the evidence on the timing of PA on sleep health, an important mediator of the effects of PA on measures of brain health [5, 206], is less clear. Thus, future research is needed to draw firm conclusions on whether the timing of PA can influence specific measures of brain health differentially [219]. Such future research on the timing of PA is likely to benefit from considering density, which specifies the temporal distance between stimuli within or between successive bouts of PA (e.g., the time between morning and/or evening bouts of PA).

Compositional data analysis has been used to investigate the relationship between PA and behavioral measures of brain health in preschoolers [220–222], middle-aged [223], and older adults [224] and has provided valuable insights into the complex relationship between PA and brain health. For example, compared to other activities of the 24-hour activity cycle (e.g., SB and sleep), a loss of time spent in moderate-to-vigorous PA appears to be relatively detrimental to cognitive performance (i.e., cognition composite score) in middle-aged adults, given its smaller relative amount in the 24-hour cycle [223]. Notably, in older adults, longer time spent in light-intensity PA was associated with better inhibitory control (i.e., operationalized by Stroop task performance), especially when accumulated in bouts longer than 10 minutes [224].

Comparable to compositional data analysis approaches, a promising area for further investigations is to operationalize density as the relative time spent in work bout(s) (e.g., PA in a specific intensity zone) in relation to the time spent in rest bout(s) (e.g., SB or sleep) to further our understanding of the temporal dynamics of PA and their influence on brain health. Such a better understanding of the temporal dynamics of PA is needed to better inform the individualization of PA interventions [225].

3.6 Interim summary

Taken together, chronic density captures information beyond that provided by frequency, because frequency only specifies the number of PA bouts in a given time interval (e.g., day, week, month, year) but not their distribution within that time interval. Given that the dose of PA, which is influenced by the external load and confounding factors in terms of the acute psychophysiological responses elicited [37, 40], is an important factor in inducing changes in measures of brain health, including cognition [22, 27], it seems reasonable to assume that acute and chronic PA performed at different densities might differentially influence measures of brain health. This latter assumption is also supported by the fact that density is also related to exercise intensity [80, 226, 227] and both acute and chronic density are variables that are important in inducing a specific level of overload and achieving progression [70], both of which are well-known and important factors and principles influencing the dose of PA and therefore the desired outcomes [40, 69]. In the next section, we will discuss the role of density in modifying the dose of PA in more detail.

4. Density and the dose of physical activity

Currently, neither the precise dose [6, 8, 22, 26, 27, 35, 36] nor the neurobiological mechanisms that drive the positive effects of acute and chronic PA on brain health are fully understood [5, 6, 23, 40, 228–230]. This knowledge gap extends to the empirical evidence on how density may influence the dose and neurobiological mechanisms that drive brain health. However, our assumption that accounting for density is crucial when aiming to elucidate the dose-response relationship between PA and brain health is supported by evidence from (i) acute PA studies on the temporal dynamics of specific markers of brain health and (ii) studies on glycemic control and brain health in adults with type 2 diabetes, although the latter cannot be readily generalized to healthy adults.

4.1 Temporal dynamics of acute physical activity for brain health

There is some evidence from a meta-analysis that the after-effects of acute physical exercise on cognitive performance are transient, depending on the characteristics of the physical exercises, such as type of physical exercise, intensity, and duration [25]. More specifically, according to this meta-analysis, the greatest effects of acute physical exercises on cognitive performance can be expected 11-20 minutes after the cessation of the acute bout of physical exercises and diminish with longer delays [25]. However, some studies provide evidence that the after-effects of acute physical exercises on specific behavioral measures of brain health (e.g., executive functions) can even persist for up to 30 minutes in healthy younger adults [231–234], 60 minutes in children [235] and younger adults [236], and 90 minutes in healthy younger adults, [237] or even that in healthy younger adults performing acute physical exercise four hours after learning is more beneficial for improving memory performance and hippocampal pattern similarity (i.e., assessed 48 hours later) as compared to performing acute physical exercise immediately after learning the task [238].

Based on the paucity of research in this area, the exact time course and moderators (e.g., acute PA-related factors such as type, intensity, duration, and non-PA-related factors such as age, sex, health status, and fitness level) of the after-effects of acute PA on specific measures of brain health remain somewhat elusive, at least in part due to methodological challenges (e.g., a limited number of follow-up assessments, confounding influence of activities performed between cessation of acute PA and cognitive test administration) [23]. However, based on the above-presented evidence, it is reasonable to assume that considering temporal dynamics of PA - conceptualized as density - has a great potential to add to our understanding of the dose-response relationship of acute PA on specific measures of brain health. More importantly, considering density in future research may help to elucidate the precise time point(s) at which the acute PA stimulus needs to be applied or repeated to prolong the acute PA-related benefits on specific measures of brain health. Such information on the appropriate timing to set a PA stimulus is thus crucial to inform an experimental design and to maximize the effectiveness of PA interventions (e.g., “just-in-time adaptive PA interventions” [239–241]).

Several studies support the notion that the density of the PA can be important in optimizing the effectiveness of PA interventions. For example, two studies in healthy younger adults investigated the effects of two repeated acute bouts of high-intensity interval exercise (HIIE, 4x 4-minute work bouts at 90% of $VO_{2\ peak}$ interspersed with 3-minute rest bouts at 60% $VO_{2\ peak}$) on inhibitory control (i.e., assessed by the Stroop task every 10 minutes after the cessation of each bout of physical exercise for 5x times) [242, 243]. In both studies, a recovery interval of 60 minutes separated the first bout of acute HIIE from the second bout of HIIE, in which the Stroop task performance was repeatedly assessed [242, 243]. These studies showed that inhibitory control (i.e., reverse Stroop interference score) improved immediately [242, 243] and 10 minutes [243] after exercise cessation after the first and second bout acute bouts of HIIE compared to the pretest. However, only after the first acute bout of HIIE the after-effect did persist up to 40 minutes after exercise cessation [242, 243]. In contrast, the executive performance assessed 10 minutes [242] or 20 minutes [243] after the second bout of HIIE was not significantly different from the pretest and was lower than that of the first bout of HIIE when assessments at 20 minutes [242], 30 minutes [242], and 40 minutes [242, 243] (but not 50 minutes [242, 243]) after exercise cessation were considered. Collectively, these observations suggest that the acute PA-related effects on inhibitory control were less pronounced in the second bout of HIIE compared to the first bout of HIIE. Hypothetically, such a diminished effect after the second bout of HIIE could be, among other factors, related to the relatively close temporal proximity between the two single bouts of HIIE (i.e., 60 minutes).

Based on the observation that the acute PA-induced performance improvements in inhibitory control correlated with changes in blood lactate concentration in both studies [242, 243] and that changes in peripheral blood lactate concentration were significantly lower during and after the second bout of HIIE [243], it seems reasonable to speculate that there is a neurobehavioral relationship between both measures [8, 40, 108, 244, 245]. This assumption is supported by the fact that peripheral blood lactate can cross the blood-brain barrier via monocarboxylate transporters and be utilized as “fuel” for cognitive processes [246–254], which may further explain the positive associations between acute PA-induced blood lactate increases and cognitive enhancement. Indeed, recent studies have reported that changes in peripheral blood lactate concentration are correlated with acute PA-related improvements in cognitive performance [255–257] although it remains somewhat unclear whether blood lactate changes are a mediator of acute PA-induced benefits on cognitive performance because only one study found evidence in favor of this idea [258] while another did not [259].

In addition, there is evidence that a change in peripheral blood lactate concentration (e.g., induced by acute physical exercise [260] or infusion at rest [261]) is associated with a change in the concentration of serum levels of the brain-derived neurotrophic factor (BDNF), an important neurotrophin involved in processes of PA-related neuroplasticity and brain health [7, 12, 15, 262–267]. Notably, in younger healthy adults BDNF changes in response to acute PA are correlated with cognitive improvements [268], lending credence to the hypothesis that BDNF is involved in acute PA-induced improvements in behavioral measures of brain health [269]. Such acute PA-triggered effects of BDNF on cognitive performance are likely to be transient, as several studies on the kinetics of BDNF have consistently shown that elevated BDNF levels return to baseline 15-60 minutes after exercise cessation (for review, see [9]), supporting the notion that temporal dynamics (e.g., density) should be considered when examining the effects of acute PA on brain health.

Regarding the functional brain level, alterations in cerebral blood flow (CBF) are hypothesized to mediate the acute effects of PA on behavioral measures of brain health [23]. Indeed, some studies provide evidence that acute PA-induced changes in cerebral blood velocity (CBV), a surrogate for CBF that can be operationalized by monitoring middle cerebral artery velocity via transcranial Doppler ultrasound [270–273], correlate with acute PA-induced improvements in behavioral measures of brain health (i.e., executive functioning operationalized by the antisaccade task) [274, 275]. The acute PA-induced increase in CBV can persist for up to 2 hours after exercise cessation depending on several factors (e.g., characteristics of the person and the acute bout of PA, methodological factors - for review see [270]) but typically returns to baseline levels relatively shortly after exercise cessation [270, 271] (e.g., 30 minutes - for review see [270]). Comparable to the transient effects of acute PA at the cellular and molecular level (e.g., BDNF), the transient nature of acute PA-related changes at the functional brain level (e.g., CBF) urges future research to consider density as a variable to facilitate our understanding of the neurobiological mechanisms mediating the effects of acute PA on brain health, which is currently relatively scant [5, 23, 229]. Such a better understanding of the temporal dynamics at different levels of analysis [5, 23, 40] (e.g., molecular and cellular levels, such as changes in the noradrenergic and dopaminergic systems [230] or functional levels, such as brain activity or connectivity changes [17, 18]) may yield a more robust understanding of the potential dose-response relationship, which in turn can help to inform future practical applications better.

A recent study provided direct evidence that acute density can influence the acute PA-related effects on specific behavioral measures of brain health. In particular, this study used a within-subject crossover design with a pretest-posttest comparison to investigate in healthy younger adults whether the use of different inter-set rest intervals (i.e., 1 minute versus 3 minutes, representing higher and lower acute densities) during an acute bout of low-load resistance exercise (i.e., 40% of a one-repetition maximum, 6x sets of 10x repetitions) can influence acute exercise-induced changes in inhibitory control (i.e., operationalized with the Stroop test) [276].

In this study, it was observed that shorter inter-set rest intervals (i.e., 1 minute - high density) improved inhibitory control (i.e., operationalized by a reverse Stroop interference score) immediately, 10 minutes, 20 minutes, and 30 minutes after exercise cessation, whereas such effects were absent for longer inter-set rest intervals (i.e., 3 minutes - lower acute density). Moreover, the improvement in executive functions was greater at 20 and 30 minutes after exercise cessation in the shorter inter-set rest interval condition (i.e., higher acute density) compared with the longer inter-set rest interval condition (i.e., lower acute density) [276]. Thus, the findings of the above-presented study provide strong support for the importance of considering acute density when investigating the dose-response relationship of acute PA with specific measures of brain health.

4.2 Glycemic control and brain health

There is growing evidence that type 2 diabetes, which is characterized by impaired glucose control [277] and poses a public health burden due to its high and still growing worldwide prevalence and related health complications [277–280], is associated with significantly poorer brain health [281–284]. For instance, there is accumulating evidence that type 2 diabetes is associated with reduced structural and functional brain integrity [285–288], lower cognitive performance [285–293], and an increased risk of dementia [294–297]. Given that impaired homeostasis of glucose control is the key feature of type 2 diabetes [277], maintaining “normal” glucose control across the lifespan (e.g., by reducing sedentary behavior and engaging in PA) seems to be an important factor in maintaining brain health, especially in later life stages [298]. Indeed, some systematic reviews provide evidence that PA in adults with type 2 diabetes is associated with a positive but weak influence on specific measures of brain health such as cognitive performance, [299–302] although such evidence is not universal, probably due to the heterogeneity of intervention studies in terms of the exercise and training variables characterizing the physical exercise interventions [303].

Notably, two small-scaled studies (n = 12 in both studies) in adults with type 2 diabetes showed that interrupting 7 hours of sitting with 3 minutes of light-intensity walking every 15 minutes (i.e., high acute density) was more beneficial for specific measures of glucose control (e.g., fasting glucose and duration of the dawn phenomenon [304] or post-breakfast and 21-hour glucose control [305]) than interrupting sitting every 30 or 60 minutes (i.e., low acute density) [304, 305]. During the rest periods, the participants had access to a personal computer, internet, and books [304, 305]. Thus, these two small studies in adults with type 2 diabetes provide preliminary evidence that density can influence neurobiological processes (i.e., glucose control) relevant to brain health [298] which, in turn, supports our idea that considering density is crucial for a more nuanced understanding of the dose-response relationship between PA and measures of brain health. However, the higher density in the above-described studies

[304, 305] is also related to a higher frequency of physical exercise bouts, and thus future high-quality studies are needed to (i) disentangle the unique influence of frequency and density on (brain) health-related measures, and (ii) investigate whether different acute and chronic densities of PA might differentially influence specific levels of brain health (e.g., at the molecular and cellular levels such as the release of brain-derived neurotrophic factor).

4.3 Interim summary

Taken together, the evidence on temporal dynamics of specific markers of brain health in response to acute PA and the glucose control - brain health association corroborates our assumption that density is important for advancing our understanding of the dose-response relationship between PA and measures of brain health because it provides crucial information on temporal distribution of PA. More specifically, studying density plays an important role in understanding the minimal and optimal dose by providing information on the minimal and optimal time interval (i.e., rest bout) between PA stimuli within a single bout of PA or successive bouts of PA (i.e., work bouts) being required to maintain or improve specific measures of brain health. Such information on the minimal and optimal time intervals for the delivery of a PA stimulus holds great potential to inform and optimize intervention approaches aimed at promoting PA, such as “just-in-time adaptive PA interventions” [239–241] (e.g., in the context of breaking up prolonged sitting with acute breaks of PA including physical exercise [306–309]).

5. Density in relation to other activities of the 24-hour cycle

There is an increasing interest in the scientific community to develop a more holistic understanding of the influence of the 24-hour activity cycle including PA, standing, sedentary behavior (SB), and sleep on health status [185–189] and brain health [81, 92, 190–193].
Regarding density, rest bouts are a key construct and may be considered synonymous with, or primary to, time spent in SB when considering waking hours. Epidemiological and experimental evidence shows that sedentary time may influence the relationship between participation in PA and its well-established cardiometabolic health benefits (i.e. highly sedentary individuals may need to do more than the recommended levels of PA to offset the detrimental effects of sedentary behavior) [99–101, 310]. Experimental evidence provides compelling insights into the potential for “exercise resistance” [100]. Coyle and colleagues showed that when acute physical exercise was preceded by a prolonged period of SB, postprandial metabolic responses and metabolic benefits were significantly attenuated [311–313]. More specifically for brain health, the effect of physical exercise on cognitive function is altered by subsequent exposure to prolonged sitting versus breaks in sitting [306], and

emerging evidence shows that different types of SB, namely passive and mentally active SB, could be differentially associated with brain health [81, 103, 314]. For instance, previous studies have indicated that mentally active SB (e.g., reading or using a computer) can benefit measures of brain health (for review see [81, 103, 314]). A growing body of evidence suggests that the consequences of too much time spent in SB are distinct from those of too little PA with respect to cardiometabolic health [100] and brain health [81, 101, 105]. This reinforces the utility of considering SB as a mechanism for the importance of density as a key new element to complement the FITT-VP principle.

Given that the duration and the characteristics of the rest bout(s) are the key elements in defining density, considering sleep is important in understanding how the temporal distance between successive bouts of PA can influence measures of brain health, especially when tracking and analyzing free-living PA over longer periods (e.g., a week, month, or year). There is growing evidence that sleep (i.e., often operationalized as time in bed) can mediate and/ or moderate the effect of PA on brain health [193, 219, 315, 316]. For example, several cross-sectional studies provide evidence that (i) older adults with poor sleep efficiency (i.e., percent of the time in bed spent asleep) benefit most from PA in terms of global cognition [317], (ii) sleep efficiency mediates the relationship between PA and working memory, task switching, verbal ability and fluency, and memory recall in a mixed sample of younger and older adults [21], (iii) better subjective sleep quality mediates the relationship between PA and verbal fluency, immediate recall, and delayed recall [318] or working memory [319] in middle-aged and older adults, and (iv) subjective sleep quality and sleep efficiency mediate the relationship between PA level and inhibitory control in younger adults [320]. A 6-month intervention study, in which cognitively healthy older adults performed moderate- or high-intensity interval exercise twice a week, reported that participants in the moderate-intensity group, who had poorer sleep efficiency at baseline, showed greater exercise-induced improvements in episodic memory and global cognition [321].

Collectively, the above-presented evidence supports the idea that consideration of all activities in the 24-hour activity cycle [81, 92, 190–193, 316] is necessary to improve our understanding of the influence of specific lifestyle-related factors on brain health. This assumption is reinforced by emerging evidence suggesting that (i) other activities of the 24-hour cycle that can contribute to or constitute the rest bout(s), such as free-living standing activity [322] and light-intensity PA [29], are positively associated with behavioral measures of brain health, and (ii) activities such as SB and sleep, which are typical activities of a rest bout(s), interact with each other with respect to brain health, as an observational study showed that sleep problems mediated the detrimental associations of passive SB with depression [323]. To this end, complementing the 24-hour activity cycle approach with density may enable even more nuanced insights into its health effects by improving the characterization and thus our understanding of the dose of PA.

6. The current state of evidence and future directions

The role of density as an important variable can be considered helpful when investigating dose-response relationships of PA with key health-related outcomes (e.g., brain health). For brain health, the current evidence indicates that (i) acute density is typically not considered when analyzing the influence of acute bouts of PA on cognitive performance (e.g., as a moderator variable) [23, 25, 324–326], (ii) chronic density is often not reported in studies investigating the influence of chronic PA on brain health [8, 327], (iii) chronic density is absent in moderator analyses in recent systematic reviews and meta-analyses investigating the influence of chronic PA on cognitive performance [22, 26], and (iv) chronic density is typically not mentioned in recommendations (e.g. from the World Health Organization) and policies aimed at reducing the risk of cognitive decline and dementia by lifestyle changes (e.g., via PA) [328]. Such an absence of density in the literature, analyses of the dose-response-relationships, and recommendations of official bodies could lead to the assumption that (i) acute and chronic density are unimportant variables or (ii) that researchers studying the effects of PA on measures of brain health are unaware of the importance of density.

Given that other fields of research have begun to recognize the influence of the distribution of PA across a week (e.g., the “weekend warrior” pattern characterized by ≤2x bouts [329–336] or 1x bout [337] of PA per week) and the interrelated impacts of PA, sleep, and SB [81, 92, 100, 101, 186–189, 191–193, 316], density is an excellent candidate determinant of brain health effects that should not be overlooked when analyzing the dose-response relationship within the context of PA-related benefits on measures of brain health. To simulate future research, we highlight in the following two sections further directions for observational and intervention studies on the influence of PA density on measures of brain health.

6.1 Observational studies

Other research fields have started to analyze observational and population-based data in adults regarding the influence of achieving the amount of PA recommended by the World Health Organization (i.e., ≥150 minutes of moderate- or ≥75 minutes of vigorous-intensity PA per week [88, 89]) in ≤2x bouts per week (i.e., denoted as “weekend warrior”) or ≥3x bouts per week on health-related outcomes such as the risk of mortality [329–331], risk of cardiovascular events [336], prevalence and health aspects associated with the metabolic syndrome (e.g., adiposity, hypertension) [332, 334], or risk of mental disorders [333]. Although none of the above-mentioned studies considered chronic density, because they did not account for the temporal distance between the successive bouts of PA into account, all provided evidence that achieving the recommended amount of PA in ≤2x bouts per week has a comparable influence on health-related outcomes as achieving this amount in ≥3x bouts per week [329–334, 336].

Whether such observation extends to measures of brain health, given the moderating role of the acute and chronic density of PA is considered, is a promising area for further investigations. In this regard, we would like to acknowledge that all activities of the 24-hour activity cycle (i.e., PA, sedentary behavior, and sleep) should be considered for a more nuanced understanding of the dose-response relationship between PA and health in general [185, 186] and brain health in particular [81, 92, 191, 192]. In the context of acute and chronic density, we reiterate that the characteristics that define the work bout(s) and rest bout(s) must be considered when analyzing density (i.e., type of activity, intensity, and duration). This assumption is supported by emerging evidence showing that the characteristics of activities that are primarily involved in the rest bout(s) can influence brain health differentially. More specifically, there is evidence that the type of SB can moderate the effects of SB on brain health because cognitively active SB (e.g., reading) is positively associated with brain health, whereas cognitively passive SB (e.g., watching TV) did not confer such benefits [81, 103, 314, 338].

In addition, from a public health perspective, a key distinction is made between active and passive (sedentary) occupations [339]. In this context, analyzing the influence of acute and chronic density on measures of brain health might be especially relevant for health-related research in individuals with professions that require performing substantial occupational PA at higher intensities in relatively short time intervals (e.g., construction workers, or farmers) versus desk-based workers. Considering density in addition to traditional exercise variables (e.g., FITT-VP principle) may enhance our understanding of the “physical activity paradox” (i.e., occupational PA has less clear or no health benefits compared to leisure-time PA) [340–344] and the identification of “sweet spots” (e.g., individualizing leisure time PA recommendations by considering occupational PA levels) [187] which in turn can help to better inform future public health interventions. The latter assumption is reinforced by the fact that individuals with a lower socioeconomic position (i.e., lower educational qualifications, occupational class, income, or living in a deprived area), as compared to those with a higher socioeconomic position, showed different characteristics concerning their 24-hour activity cycle since they spent more time standing, moving, and walking but less time sitting during weekdays while on weekends these patterns were reversed [345]. Notably, those with higher socioeconomic positions engaged in higher levels of physical exercise-like activities (i.e., running, cycling, and inclined walking) and less time lying regardless of the day of the week. These findings suggest that socioeconomic disadvantages are mirrored in 24-hour activity cycle patterns [345]. Such an observation is of particular relevance for future studies on PA and brain health given that in adults a lower socioeconomic position is negatively associated with different markers of brain health (e.g., lower cognitive function and higher cognitive decline [346–356], higher dementia risk [355, 357–360], less favorable brain structure outcomes [353, 354, 360, 361]). Future well-designed research is needed for more robust conclusions in this direction [362, 363] and may benefit from considering the 24-hour activity cycle [191] including the density of PA.

6.2 Intervention studies

In addition to the examination of density in observational studies, we also recommend that acute and chronic density should be considered in the prescription of PA intervention studies to improve the standardization of reporting, the determination of the dose, and the comparability across studies. Although there is evidence that a higher frequency (i.e., 5-7 PA sessions per week), which is probably also mirrored in a higher chronic density, is more beneficial for improving cognitive performance in adults older than 50 years (i.e., double the effect size; 0.69 vs 0.32) than a lower frequency (i.e., 1-2 PA sessions per week) [27], providing information on acute and chronic density can be especially relevant for interventions with lower levels of direct supervision (e.g., home- and technology-based interventions using exergames). For example, in home-based studies using exergames and providing only general supervision, partial direct supervision, or even no supervision (for more information on supervision please see [364, 365]), older adults are typically instructed to achieve a certain duration of physical exercise over a week but are often allowed to self-select the frequency of the acute PA bouts [366–373]. Such studies have documented that older participants who are highly motivated can exceed the recommended training frequency and/or perform multiple acute PA bouts throughout the day [368, 373–375]. This may result in insufficient rest time, which is perhaps less than optimal for the materialization of adaptation processes (i.e., consolidation). The above theoretical assumption is supported by (i) an experimental study showing that in younger adults too much consecutive computer-based training can be detrimental to learning performance (i.e., accuracy of motion discrimination) [376] and (ii) a systematic review observing that cognitive performance declines when endurance athletes are overreached or overtrained [377]. These latter findings support the assumption that acute and chronic density should be considered when prescribing and monitoring physical exercise interventions aimed at promoting brain health.

In particular, acute and chronic density are important variables in the organization of physical exercise, namely the periodization and programming of physical exercise sessions, because they characterize the dose by defining the duration of rest bout(s) within a single bout of physical exercise or between successive bouts of physical exercise (i.e., work bouts). Whereas periodization is the temporal organization (i.e., macro-management) of the characteristics of physical exercise sessions (e.g., purposeful adjustment of variables such as exercise intensity and volume for progression) and application of training principles [37, 40, 128, 378–380], programming is defined as the micro-management of physical exercise that includes, but is not limited to, the organization of exercise and training variables (e.g., type of physical exercise, exercise intensity, exercise duration, and acute and chronic density) [40, 378, 380]. Thus, acute density is especially relevant for programming acute physical exercise sessions in which the physical exercises are performed in interval mode or a set structure because acute density defines the rest duration between the work bouts (e.g., also referred to as intervals or repetitions), between interval series or sets, or between different physical exercises [80, 227, 379]. As shown in Figure 1, acute density can be manipulated to alter the acute PA stimulus by decreasing or increasing the duration of rest between successive work bouts.

From the perspective of PA promotion, density can also complement newer approaches to foster PA, such as “vigorous intermittent lifestyle physical activity” (VILPA) [381, 382] and “exercise snacks” [381–384]. While VILPA has been empirically defined as vigorous bouts of incidental PA lasting up to 1 or 2 minutes [119, 121], the term “exercise snacks” has been more loosely defined as single planned bouts of physical exercise that typically (i) lasts ≤ 1 minute, (ii) occur multiple times throughout the day, and (iii) are performed at a vigorous intensity [382–384]. Regarding the VILPA and “exercise snacks” concepts, the variable density as a characteristic defining the dose can help to more precisely elucidate the influence of different rest durations between the short work bouts (e.g., performed at the vigorous intensity and conceptualized in the VILPA and “exercise snacks” approach or at other intensities in the context of free-living PA such as light- or moderate-intensity PA) on health-related parameters (e.g., brain health). However, it is worth noting that for a purposeful modification of density, the interrelation with other exercise variables needs to be considered (e.g., implementation of passive or active rest periods, exercise intensity, and duration of work and rest bouts) [37, 38, 40, 71, 80].

7. Limitations

In this article, we advocate the extension of the FITT-VP principle from a physiological perspective by proposing density as an additional variable that allows for a more fine-grained characterization of the dose of PA. However, the following limitations need to be acknowledged. First, it should be noted that others have already advocated for complementing FITT from a psychological perspective by integrating an additional “F” representing “fun” as an umbrella term for psychological factors such as affective valence and enjoyment of PA [385] to reflect that these factors are important determinants of engagement and adherence to PA [386–391]. Second, although we provide in this article a strong theoretical rationale that complementing FITT-VP by the variable density will improve our understanding of the dose-response relationship between PA and health-related outcomes, we wish to emphasize that the precise characterization or prescription of a specific PA dose will remain a considerable challenge because of the myriad of (i) non-modifiable factors (e.g., age, sex, genetics), (ii) potentially modifiable non-PA-related factors (e.g., diet, sleep, stress, environmental conditions), and (iii) modifiable PA-related factors (e.g., type of PA, intensity, duration, movement frequency), which include but are not limited to setting (e.g., home-based or center-based, and indoor or outdoor), method of delivery (e.g., in-person or online), level of supervision (e.g., no supervision, general supervision, direct supervision) and social interaction (e.g., individual or group-based), that can influence the dose and individual psychophysiological response(s) to PA [37, 38, 40, 45, 54, 71, 364]. In other words, adding density to FITT-VP is another piece of the puzzle to better characterize the dose of PA and, in turn, disentangle its influence on specific health-related outcomes.

8. Conclusions

In summary, we have provided an overview of the implications and the potential of addressing the density of PA as a variable that has been under-recognized when studying the relationship between PA and health-related outcomes, using the field of brain health as an example. In view of an increasing interest in understanding the dose of PA including but not limited to “micropatterns” assessed using high-resolution wearable data [119, 120, 392], density is a variable that can complement the traditional concept (i.e., the FITT-VP principle) by considering an additional element - the temporal distribution of PA stimuli within a single bout of PA or between successive bouts of PA relative to the time spent resting. We propose a definition for density and approaches for operationalizing it which, in turn, may allow for a more precise determination of the dose of PA for improved health effects and the prevention and treatment of chronic disease. Considering that an explicit focus on the density variable has been largely absent from research to date, investing greater effort in understanding it will add fruitful nuance to identifying the dose-response relationship between PA and health-related outcomes (e.g., brain health), and thus has the potential to provide important information on the optimal and minimal beneficial doses of PA.

Declarations

Authors' Contributions

F.H.: conceptualization, writing – original draft, visualization; L.Z., P.T., P.M., R.F., Q.Y., T.L.-A., C.H., A.F.K., K.E., B.C., Y.C., M.H., Z.Z., T.I., K.K., S.A., Y.G., J.C., M.H., M.H., Z.C., D.M., V.F., D.R., E.S., M.W. N.O., S.L., H.B.: writing – review & editing. T.G.: writing – review & editing, supervision. All authors read and approved the final version of the manuscript.

Acknowledgments

The authors have nothing to acknowledge.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interests

The authors declare no conflict of interest or competing interests.

Funding

Not applicable.

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