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REVIEW

Physical activity as a model for health neuroscience

Chelsea M. Stillman and Kirk I. Erickson

Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Address for correspondence: Chelsea M. Stillman, Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, 210 S Bouquet Street, Pittsburgh, PA 15260. cstillman@scivelo.pitt.edu

Health neuroscience is a new interdisciplinary field that combines theories and techniques from health psychology and cognitive and social–affective neuroscience in order to understand how the brain affects and is affected by health behaviors. Physical activity (PA) research can serve as a useful model for various ways in which the brain can be incorporated into health neuroscience studies to better understand variability in the adoption and maintenance of, as well as benefits gained from, health behaviors. Here, we summarize evidence linking PA to brain and cognitive performance from studies conceptualizing the brain as either an outcome or mediator of cognitive change. We then discuss an emerging body of studies using a brain as a predictor approach. We discuss how studies using this approach complement existing PA studies and provide insight into a major source of variability in the outcomes of PA interventions, above and beyond the variability accounted for by known biological and demographic moderators. A more complete understanding of the bidirectional relationships between brain and behaviors, such as PA, could provide valuable insight into how to tailor interventions to optimally affect individuals, identify key barriers, and inform the development of novel policies to promote public health.

Keywords: fMRI; physical activity; intervention; adherence

Introduction

Health neuroscience is an emerging interdisciplinary field that aims to assess and understand how the brain both affects and is affected by physical health. To accomplish this, the field of health neuroscience attempts to merge theories and techniques from health psychology and cognitive and social–affective neuroscience.[1] In this way, studies in health neuroscience consider the brain and body together as a dynamic system where the brain can be a determinant, mediator, or consequence of physical health status, depending on the research question.[1]

In the context of physical activity (PA) research, the brain has been most often treated as an outcome of interest or end point. However, there are several other ways to conceptualize the brain in relation to health behaviors and their cognitive health benefits. Here, we summarize the various ways that measures of brain health can be incorporated into studies of PA in order to further our understanding of the complex relationships among brain, behavior, and physical and cognitive health.

In the popular brain-as-outcome model, independent variables of interest are observed or manipulated (e.g., PA), and associations or effects on the brain—the dependent variable or outcome of interest—are measured. A related approach is to consider the brain as a mediator between PA and the behavioral changes resulting from PA (e.g., improved cognition). In the brain-as-mediator model, PA-induced changes in brain structure or function are an intermediary outcome for changes in behavior.[2] Although it is self-evident that the brain must be mediating behavioral changes, it is not self-evident that changes in brain structure and function, as assessed through neuroimaging approaches, act as mediators for behavioral changes. It is possible that the most important brain changes resulting from PA are happening on the molecular and cellular levels and that these effects are not being detected or revealed by current neuroimaging techniques. Finally, while these approaches provide valuable evidence about the effect of health behaviors, such as PA, on the brain and the potential

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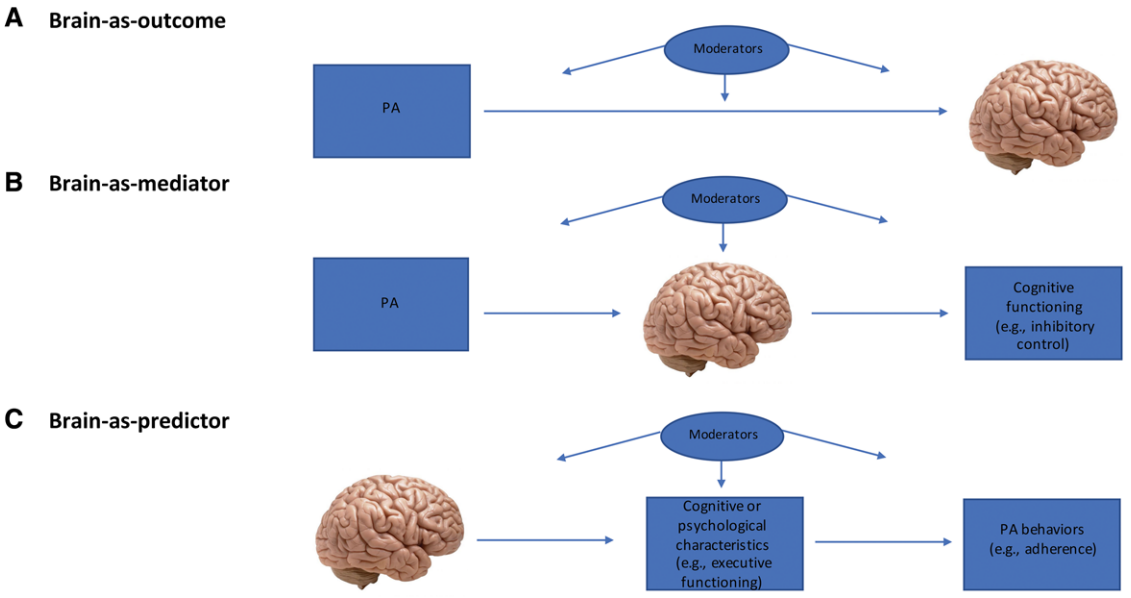

Figure 1. Depiction of various ways in which the brain can be conceptualized in the context of physical activity (PA). (A) Brain as an outcome. (B) Brain as a mediator of PA-related cognitive change. (C) Brain as a predictor of PA behaviors via cognitive or psychological characteristics (as emergent properties of brain function). Moderators, such as sex, genetics, or baseline characteristics of participants (e.g., fitness), may moderate these relationships at any stage.

underlying mechanisms of cognitive or behavioral changes, we know that the brain is not a passive organ that simply accumulates the effects of health behaviors. Thus, in addition to treating the brain as an outcome variable, measures of brain health could also be treated as a predictor for engagement in and maintenance of health behaviors.

In this review, we briefly summarize the evidence linking PA to brain and cognitive performance from studies employing the more common brain-as-outcome and brain-as-mediator approaches, including a brief summary of known moderators of PA effects in these contexts. We will then discuss studies using the emerging brain-as-predictor approach and how studies using this approach can complement the results of existing PA studies. The brain-as-predictor approach highlights the bidirectional nature of the relationships among PA, the brain, and cognition. Thus, characteristics of brain structure and function are used for predicting PA behavior, as well as PA-related outcomes, such as enjoyment, fatigue, adherence to PA training, and long-term maintenance of a PA routine. Such information could provide valuable insight into tailoring interventions to enhance the impact of PA, identify key barriers, and inform the development of novel policies to promote health behaviors.

Brain as an outcome or mediator

Much of the PA research in humans to date considers the brain as either an outcome of PA or fitness or as a mediator of the effects of PA or fitness on changes in behavior (Fig. 1A). Numerous cross-sectional studies have demonstrated that those with higher levels of cardiorespiratory fitness (hereafter referred to as *fitness*) or habitual levels of PA perform better on various cognitive tasks, especially those measuring executive or memory functions.[3–10] Higher fitness has also been linked in cross-sectional work to better structural integrity (e.g., gray matter volume; Refs. 11–13) or function (e.g., activation) in regions of the brain that support executive and memory-related cognitive functions, including the hippocampus and prefrontal cortex (Ref. 14). Prospective epidemiological studies provide additional support for this idea (Refs. 15–17), suggesting that fitness confers a degree of protection against normal and pathological cognitive decline in aging. However, despite the promising cross-sectional and prospective evidence linking PA to improved cognitive and brain health,

neither of these study designs rule out the possibility that some unmeasured variable (i.e., other than fitness or PA levels) is responsible for the observed cognitive and brain improvements. This is because PA is not directly manipulated in these study designs.

Fortunately, the critical causal link between PA and cognitive and brain health has been established in a growing number of randomized clinical trials (RCTs). In the typical RCT design, inactive individuals (usually older adults) are randomly assigned to either an aerobic exercise training or a control group. Participants in the exercise group undergo an aerobic training (usually walking) program in which they meet for about 60 min 3–4 times per week for a period ranging from a few weeks to several (or more) months. The control group either receives no additional contact (e.g., a waitlist or usual-care control) or receives an intervention matched in terms of time commitment and social support/contact but differing in the intensity of the activity (e.g., stretching and toning at a light level). Brain and/or cognitive functioning are assessed before and after the intervention as the primary outcomes of interest. RCTs of aerobic PA lasting 6 months or longer have consistently demonstrated improvements in memory and executive functioning,[18] as well as in brain structure and function in specific brain regions.[19–23] In a seminal study on this topic, for example, 120 inactive older adults were randomly assigned to a 12-month aerobic walking (experimental) group or to a stretching and toning (control) group.[24] Following the intervention, the aerobic exercise group showed greater volume of the anterior hippocampus compared with the control group. Furthermore, changes in hippocampal volume in the exercising group correlated with improvements in spatial memory performance. These findings are the first experimental evidence directly linking changes in exercise to changes in both hippocampal volume and cognitive performance in aging humans in the context of a RCT. Most RCTs, however, assess either cognitive or brain changes resulting from exercise training.[2] This raises an important question regarding mechanisms of PA: are PA-related brain changes a necessary intermediary of PA-related cognitive changes or a meaningless byproduct of PA behavior? These questions can be answered via statistical mediation modeling.

Mediation models allow for the evaluation of several alternative causal mechanisms between the treatment (e.g., PA) and outcome variables (e.g., cognition) by examining the roles of several intermediate variables (e.g., brain) that lie in the causal path. An intermediate variable is considered a mediator if the coefficient describing the strength of the treatment–outcome relationship through the mediating variable (i.e., the indirect effect) is statistically significant.[25] In other words, the significance of the indirect effects determines whether the mediator is a viable mechanism by which the independent (treatment) variable influences the outcome. Statistical mediation can be used to test the plausibility of causal models not only in RCTs, but also in observational, longitudinal, or quasi-experimental designs in which random assignment did not occur and/or the treatment variable of interest was not directly manipulated.[26]

To date, few PA studies (RCTs or otherwise) have taken advantage of the capacity of mediation models to determine whether PA-related brain changes are a mechanism underlying PA-related cognitive changes (Fig. 1B). One possible reason for this is that mediation models tend to require larger sample sizes, which are often rare in RCTs. To get around the sample size dilemma, some RCTs have assessed associations between changes in the brain and changes in PA-related cognitive function as a way to suggest possible mediation without statistical mediation modeling.[24] A recent review of studies that have used statistical mediation models suggests that regional gray matter volume statistically mediates the relationship between cardiorespiratory fitness or PA and cognitive functioning, although most of these studies have been limited to cross-sectional designs.[22] In addition, white matter microstructure and functional brain activity may also be mediating associations between fitness or PA and cognition.[14,27] From this work, we can conclude that the effect of PA on brain morphology, including gray and white matter, is likely acting as an important mechanism for the salutary effect of PA on cognition.

Brain as a predictor

One exciting possibility that is now gaining research traction in the PA field is the idea that certain brain characteristics may be able to predict engagement in and maintenance of health behaviors (Fig. 1C). This approach has already proved informative in the fields of weight management and addiction.

For example, baseline levels of reward-related brain activity elicited by high-calorie food stimuli can be used to identify individuals who will gain weight up to 3 years later.[28,29] Similarly, brain reactivity in the medial prefrontal cortex (a region involved in self-control) to smoking-related cues predicts individual differences in future quitting success, even beyond self-report measures.[30] These predictive aspects of brain function are now being used to develop more effective interventions. In the realm of weight management, for example, teaching patients to reattribute their attention to the health aspects of rewarding food cues is effective at changing value signals in the medial prefrontal cortex, and this subsequently leads to healthier food choices in individuals identified to be at risk for weight gain.[31] These findings suggest that knowledge of the central neural networks underlying certain health behaviors (e.g., eating), along with knowledge of individual differences in the strength of such networks at baseline (i.e., before a treatment intervention), can be leveraged to identify individuals most likely to respond to a standard intervention versus those who may need additional support.

PA may be one health behavior where using the brain as a predictor may be a critical element for developing support strategies and understanding variability in adoption and adherence. This is because, while there is a wealth of evidence that PA benefits cognitive and brain health, less than 5% of American adults engage in the recommended amount of PA per week.[32] Moreover, PA trends are decreasing in developed counties compared with just a decade ago.[33,34] The utility of identifying such characteristics is that they could aid in predicting those most likely to adhere to a regular PA routine, as well as lead to the development of novel strategies to proactively encourage PA in those at high risk for a sedentary lifestyle.

There are several reasons to suspect that the brain is an important predictor of PA-related outcomes, such as study adherence, PA enjoyability, and likelihood of consistent PA engagement. First, there are social–cognitive aspects to engage in health-promoting behaviors, and social–cognitive theory provides a useful framework for understanding individual differences in PA behaviors.[35] Within this model, measures of exercise self-efficacy are the most consistent predictors of PA participation and adherence.[36–39] Additionally, other social–cognitive factors predict participation and adherence, including self-perceived health and fitness,[40–42] social support,[43–45] and outcome expectations related to fitness and exercise.[45] Neuroimaging evidence from social-affective neuroscience, cognitive neuroscience, and motivation neuroscience suggest that these social–cognitive predictors of adherence are supported by the medial and lateral prefrontal cortex (LPFC), cingulate cortex, and (albeit less consistently) temporal and parietal regions.[46–49] Given that sociocognitive and basic cognitive factors account for only a small fraction of the total variance in PA behavior observed in many of the studies cited above, understanding the neural predictors of PA participation and adherence may capture the collective variance in adherence explained by social–cognitive factors, as well as the nontrivial amount of unexplained variance in adherence (in many cases $>70\%$) after accounting for these social–cognitive factors.

There are also some broader, nonsocial–cognitive and affective aspects to engage in health behaviors. For example, individuals who are better able to hold long-term health goals in working memory and inhibit more enticing immediate goals (such as eating unhealthy food or lounging on the couch) are more likely to engage in PA.[38,50–52] In addition, happier individuals (i.e., those able to maintain a more positive affect) before and after PA bouts are more likely to continue a PA routine.[53] Cognitive processes, such as mood regulation, inhibition of negative health behaviors, and delay of gratification in service of long-term goals, fall under a category of cognitive processes known as executive functions.

Executive functioning is also associated with better attendance in PA interventions, as well as with continuation of a PA routine after the conclusion of an intervention.[51,54] For example, in a prospective study of 4,555 older adults collected as part of the English Longitudinal Study of Aging, Daly *et al.*[51] demonstrated that lower levels of PA predicted declines in executive functioning over time. In addition, poor executive functioning predicted declines in PA over time. Moreover, the latter association was 50% larger in magnitude than the contribution of PA to changes in executive function. Thus, the relationship between PA and executive functioning is a virtuous cycle; PA not only leads to better executive functioning (as discussed in the previous section), but better executive functioning also leads

to engagement in or maintenance of PA. Further, executive functioning may explain more variance in PA behavior than vice versa.

As with the social–cognitive characteristics described above, executive functions are supported by a network of brain regions, including the medial, orbital, and lateral prefrontal cortices. These regions consistently show changes in function and structure following PA interventions. However, the question that emerges from the bidirectional behavioral findings described in the previous paragraph is whether preexisting structural or functional characteristics of these brain regions can predict future PA (perhaps via cognitive functioning). In other words, do aspects of the brain predict PA engagement and adherence?

Several recent studies examined this question. In secondary analyses, Jonassen *et al.*[55] observed that participants in a 6-month aerobic PA (walking) intervention who had larger hippocampal volumes at baseline showed greater changes in cardiorespiratory fitness in response to the intervention. Similarly, using preexisting data from two clinical trials of PA, Best *et al.*[56] found that gray matter volume of the LPFC, a region supporting executive control, could predict exercise class attendance in 122 older women. Moreover, this effect remained significant after controlling for other potentially moderating factors, including baseline physical functioning, mood, and cognitive functioning. These results suggest that individual differences in brain structure hold predictive value for determining future engagement in PA, above and beyond the predictive utility of psychological and physical factors.

A recently published multimodal neuroimaging study extended these previous findings by examining whether brain structure, as measured by both gray matter volume and white matter microstructure, predicted attendance to a 12-month randomized PA intervention.[46] Supporting their hypothesis, greater gray matter volume in several frontal, temporal, and parietal regions predicted better adherence to the intervention, even after controlling for adherence-related psychological variables (e.g., exercise self-efficacy). In addition to volume, greater white matter integrity in a variety of tracts connecting regions supporting executive functions also predicted intervention adherence. Interestingly, both associations were independent of the intervention group assignment, suggesting that objective measures of neural integrity at baseline are not specific to aerobic forms of exercise alone, but rather to PA behaviors more broadly. These metrics of brain integrity may therefore be useful for predicting adherence to various positive health behaviors (in this case, aerobic PA and stretching/toning).

Moderators of PA

Even if PA adherence could increase using knowledge of brain (or other) predictors, there is still significant interindividual variability both within and between studies regarding the extent to which any one individual benefits from PA.[24,57] This suggests that there may be important moderators that influence PA outcomes. Moderating factors are those that act to either attenuate or amplify the effects of PA on cognitive and brain outcomes. While various potential moderators (e.g., demographics, genetics) have been reviewed elsewhere,[58] other important potential moderators of PA remain poorly understood. This is because many potential moderating variables are more often considered noise in the data and are therefore controlled for as nuisance variables or ignored rather than examined as moderators. In addition, sample sizes in many intervention studies are insufficient to test for moderation effects. Despite these challenges, several important potential moderators of PA are discussed below.

Physical or psychological moderators

Other often-overlooked—yet likely important—moderators of PA behavior include physical and psychosocial baseline characteristics of study participants. For example, individual differences in baseline cardiorespiratory fitness, cognitive performance, mental health status, and even neighborhood walkability may influence the effectiveness of health interventions (e.g., see Ref. 59).

Baseline characteristics of participants have long been considered as moderators in other fields, such as weight management and addiction. For example, individual differences in physiological reactivity to food cues (e.g., salivation) predict future overeating,[60,61] and this effect is particularly exacerbated in individuals who are frequent dieters or "restrained eaters."[61] However, the use of baseline characteristics to predict behavior is much rarer in the context of PA. Nonetheless, several recent studies provide evidence that baseline

characteristics of individuals may be just as relevant for forecasting PA behaviors as they are to dietary and addictive behaviors. For example, higher depressive symptoms and perceived barriers to PA has been linked with both lower habitual PA levels over time[62] and smaller effects on PA levels during the intervention.[59,63] Depressive symptoms are also associated with poorer cognitive performance, particularly in the domains of memory and executive functioning.[64–67] In fact, depression-related cognitive impairment has been shown to persist, particularly for executive functions, even after successful treatment and remission of the affective symptoms.[65,68] Because executive functions are among the functions most consistently improved by PA, it is plausible that depression-related decreases in PA levels mediate long-lasting cognitive dysfunction following remitted depression. This literature suggests that it may be essential to take both physiological and psychological baseline characteristics into account when designing and interpreting the effects of PA interventions.

Despite the promising evidence that certain physical or psychological health characteristics modulate the effects of PA, to date only a handful of PA studies have tested for moderation effects[50] (but see Ref. 55). In fact, few studies even control for them. This makes it possible (even likely) that these characteristics contribute to the variability in the effect of PA and may even help explain why some studies fail to find significant effects of PA on cognitive and brain functioning (Ref. 69).

Conclusions

As evidenced by the number of reviews and meta-analyses cited above, there is an abundance of research demonstrating that PA positively influences the brain and cognitive functioning. However, this information is not maximally useful for preserving and enhancing public health if the factors underlying engagement in PA are not well understood. Fortunately, there is emerging evidence that the brain is an important predictor of health behaviors as well. These apparent virtuous relationships between the brain and mental and physical health are consistent with the view in health neuroscience that the brain and body are not separate entities, as the traditionally distinct neuroscience and health psychology literatures often treat them. The examples of health neuroscience studies discussed here highlight this point and serve as good models for future work in this nascent field, which will help disentangle the reciprocal relationships between health behaviors and brain health.

Of course, rather than simply describing the bidirectionalities between brain, mind, and body, one central goal of health neuroscience is to use this knowledge to change and improve health outcomes. In the era of personalized medicine, the utility of understanding how the brain can serve as a predictor of positive health behaviors is that individuals at risk for poor health can be identified early and directed into interventions that are likely to be successful. One possible application of this knowledge is that certain neural biomarkers could be used to predict future health behaviors and/or treatment outcomes at the level of individuals. Thus, interventionists and clinicians may eventually be able to predict those most likely to respond to certain types of treatments over others and better align resources (e.g., social support, informational resources of possible side effects) to maximize effectiveness and minimize adverse events. Thus, applying a health neuroscience perspective to the study of PA will help translate our knowledge of brain–body–mind mechanisms into health-promoting action.

Directions for future research

The more we learn about neural predictors of behavior, the more we can leverage this information in the development of future technologies to promote health. The brain-as-predictor literature is still in its infancy, and there are several immediate directions for future research, several of which are highlighted below. These next steps will enable us to begin to harness the brain's full predictive power.

There is a need to increase the number of studies using current neuroimaging techniques that examine the brain as a predictor of health behaviors, including PA and others (e.g., diet). Elucidating the extent to which the brain predicts engagement in health behaviors above and beyond traditional behavioral measures (e.g., questionnaires, surveys) could have important implications for understanding biological processes and for promoting precision medicine approaches for certain therapeutics.

There is a need for RCTs that have larger sample sizes and measures to allow an assessment of potential mediators for the behavioral benefits obtained through PA as well as a better appreciation for the

sociodemographic, physical, and psychosocial characteristics that moderate the benefits of PA on brain and cognition.

Competing interests

The authors declare no competing interests.

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