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Harold H. Lee

Jessica A. Emerson

See next page for additional authors

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Affective Response to Physical Activity as an Intermediate Phenotype

Harold H. Lee[1], Jessica A. Emerson[1], Lauren Connell Bohlen[2], and David M. Williams[1]

[1]*Department of Behavioral and Social Sciences, Brown University School of Public Health, Providence, RI, USA*

[2]*Department of Kinesiology, University of Rhode Island, Kingston, RI, USA*

Address for Correspondence:

Harold Lee

Department of Behavioral and Social Sciences

Brown University School of Public Health

Box G-S121-3, Providence, RI 02912

Tel +1 (951) 818-4246

Fax +1 (401) 863-6697

Email: harold_lee@brown.edu

Abstract

Over the past seventy years, biomedical and epidemiological research has shown that regular physical activity (PA) is critical for physical and mental health. Despite this knowledge, physical inactivity is the fourth leading risk factor for global mortality, accounting for 9% (5.3 million) of premature deaths annually. We suggest this mismatch between knowing about the risks of PA and engaging in regular PA can be reconciled by focusing less on expected health benefits of PA and more on how people feel during PA. Specifically, in this position paper, we argue that affective response (feeling good versus bad) to PA is an intermediate phenotype that can explain significant variance in PA behavior and is, in turn, a function of genetic variability. In making this argument, we first review empirical evidence showing that affective response to PA predicts future physical activity behavior. Second, we systematically review research on single nucleotide morphisms (SNPs) that are associated with affective response to PA. Investigating affective response to PA as an intermediate phenotype will allow future researchers to move beyond asking "*What* SNPs are associated with PA?", and begin asking "*How* do these SNPs influence PA?", thus ultimately optimizing the translation of knowledge gained from genomic data to intervention development.

Key words: Affect; exercise; intermediate phenotype; physical activity; motivation; mechanism

1. Introduction

Over the past seventy years, biomedical and epidemiological research has shown that regular physical activity (PA) is critical for physical and mental health (Garber et al., 2011; Haskell et al., 2007; Horstmann, 1950; Schuch et al., 2011; Wennesland et al., 1959). Despite this knowledge, physical inactivity is the fourth leading risk factor for global mortality, accounting for 9% (5.3 million) of premature deaths globally (Lee et al., 2012).

The low rates of PA are a function of a wide range of environmental factors, but a substantial proportion (48–71%) of variance in habitual PA can also be attributed to genomic variability (Aaltonen et al., 2010; Bouchard & Perusse, 1994; Cai et al., 2006; Carlsson et al., 2006; Eriksson et al., 2006; Fisher et al., 2010; Franks et al., 2005; Joosen et al., 2005; Maia et al., 2002; B. D. Mitchell et al., 2003; Simonen et al., 2002; Stubbe et al., 2006). Research identifying the specific genetic variants, or single nucleotide polymorphisms (SNPs), has been stagnant in the past decade (chiefly due to small sample sizes). However, large-scale genomic data collection efforts, such as NIH's precision medicine initiative cohort (i.e., "All of Us": (https://allofus.nih.gov/), may identify what SNPs are associated with PA (Collins & Varmus, 2015).

To optimize the translation of discoveries from large-scale genomic data to behavioral intervention development, it is necessary to identify intermediate phenotypes—i.e., traits that mediate the effects of the genome on the behavioral phenotype, in this case PA. Accordingly, the goal of this paper is to examine affective response to PA (i.e., how one feels during PA) as a potential intermediate phenotype. Similar intermediate phenotypes have been hypothesized and received empirical support in the context of other health behaviors, including subjective and affective responses to the consumption of alcohol (Ray & Hutchison, 2004; Ray et al., 2010),

caffeine (Alsene et al., 2003; Dlugos et al., 2007; Kendler & Prescott, 1999; Loke, 1988), amphetamines (Hart et al., 2011; Lott et al., 2005; Lott et al., 2006), and nicotine (Hoft et al., 2011; Hutchison et al., 2007; Sherva et al., 2008; Zeiger et al., 2007). If affective response to PA proves to be a viable intermediate phenotype, it can advance understanding of PA behavior and potentially provide new opportunities for PA promotion intervention.

In proposing affective response to PA as an intermediate phenotype, we will first explicate the general concept of an intermediate phenotype and introduce its criteria. We will then examine whether affective response to PA is a conceptually plausible intermediate phenotype for understanding the effects of genes on PA behavior. Specifically, we will summarize findings from a recent systematic review that examined the effect of affective response to PA on future PA behavior. We will then conduct our own systematic review to examine genetic variants that are associated with affective response to PA. Finally, we will discuss strengths and limitations of the literature and implications of applying an intermediate phenotype approach to affective response to PA.

2. Definition of intermediate phenotype

An intermediate phenotype is a phenotype that is posited to mediate the effects of the genotype on a more distal phenotype such as an outcome or behavior of interest. For a variable to be considered an intermediate phenotype, the variable should be predictive of the distal phenotype of interest, and the variable should be influenced by genetic variation.

The term *intermediate phenotype* is often interchangeably used with *endophenotype*—i.e., "measurable components unseen by the unaided eye along the pathway between disease and distal genotype"—which originated from genetic research in schizophrenia (Gottesman & Gould, 2003). There are subtle differences between the two concepts (for further discussion of this

distinction see (Goldman & Ducci, 2007)), but the pragmatic utility of both approaches for public health research is that they shift the focus away from the clinical outcome—e.g., disease or behavioral outcome proximal to the disease—and toward psychobiological variables that are mechanistically closer to the genotype. By way of analogy, knowledge regarding psychobiological mediators between genetic variation and health behaviors may provide additional insights into the causes of negative health behaviors (e.g., PA, smoking, drinking, and drug abuse) in the same way that knowledge regarding psychosocial mediators between socioeconomic status and health behaviors provide insights into alleviation of health disparities. In other words, knowledge regarding intermediary mechanistic processes between genome and behaviors are crucial as they allow researchers to move beyond *predicting* behaviors based on genomic profile and start investigating *how to change* behaviors.

3. Affective response to physical activity as a potential intermediate phenotype

Affective response to PA is a conceptually plausible intermediate phenotype because it may have a causal influence on PA behavior. Consistent with the ancient principle of psychological hedonism, people tend to repeat behaviors that feel good and avoid behaviors that feel bad (Bentham, 1789/2007; Hobbes, 1789/2008; Kahneman et al., 1997; Mill, 1861/2012; Usener, 1887/2010; Williams, 2018). When applied to PA behavior, those who experience a more positive affective response to PA are more likely to repeat it in the future, and thus more likely to engage in regular PA (Williams, 2008).

Affective response to PA is defined herein as the shift in core affective valence, ranging from good/pleasure to bad/displeasure (Russell, 1980), from immediately *prior to* PA to *during* PA. We focus on *core affective valence* rather than discreet moods or emotions because core affective valence is pervasive in human experience, both within and outside the context of

various moods and emotions, and has a strong theoretical basis regarding its relationship to behavior—i.e., psychological hedonism. We focus on affective response *during PA* (i.e., change in affect from prior to PA to during PA) rather than affective response following PA (i.e., change in affect from prior to PA to after PA), because the proximal consequences of a behavior more robustly predict future behavior compared to more distal consequences (Hall, 1976). Moreover, affective response following PA may be better conceptualized as how one feels as a result of completing a session of PA, rather than affective response to PA behavior itself.

Despite frequent media messages that "exercise feels good" (Backhouse et al., 2007) and evidence suggesting that most people feel good after PA (Berger & Motl, 2000; Reed & Ones, 2006), numerous studies have shown that affective response *during* moderate intensity PA—the intensity of PA on which national recommendations are based (USDHHS, 2008)—varies greatly from person to person. Some people tend to feel bad during PA, other typically feel good, whereas others feel neither good nor bad (Backhouse et al., 2007; Ekkekakis et al., 2005; Parfitt et al., 2006; Rose & Parfitt, 2007; Van Landuyt et al., 2000; Welch et al., 2007). Some of the variance in affective response to moderate intensity PA may involve situational factors, such as the physical and/or social setting (Dunton et al., 2015; Gellert et al., 2011), or individual factors such as fitness level or overweight status (Ekkekakis et al., 2010; Ekkekakis et al., 2016). We posit that a significant proportion of the variability in affective response to moderate intensity PA may be a function of genetic variance, as is the case for affective response to the consumption of alcohol (Ray & Hutchison, 2004; Ray et al., 2010), caffeine (Alsene et al., 2003; Dlugos et al., 2007; Kendler & Prescott, 1999; Loke, 1988), amphetamines (Hart et al., 2011; Lott et al., 2005; Lott et al., 2006), and nicotine (Hoft et al., 2011; Hutchison et al., 2007; Sherva et al., 2008; Zeiger et al., 2007).

In the next two sections, we review the available empirical evidence that directly bears on affective response to PA as a potential intermediate phenotype: whether it is a function of genetic variability (Figure 1, A-path) and whether it has downstream causal effects on PA behavior (Figure 1, B-path). We examine the latter hypothesis first because there is a more robust literature on this topic.

4. Evidence for affective response to physical activity as a predictor of physical activity behavior

Rhodes and Kates (2015) performed a systematic review of evidence on affective response to PA as a potential predictor of PA behavior. The authors identified 24 studies that examined some version of this relationship based on literature published up to July 2014. Among the 24 studies, four specifically examined the relationship between affective response to PA and its association with PA behavior, of which three were longitudinal (Kwan & Bryan, 2010; Williams et al., 2008; Williams et al., 2012) and one was cross-sectional (Schneider et al., 2009).

All four studies examining affective response to PA were predictive of PA behavior, despite heterogeneity in study designs, intensity of PA, and assessments. For example, in a cross-sectional design, Schneider et al. (2009) assessed affective response to moderate (80 % of ventilatory threshold) and high intensity (above ventilatory threshold) cycling, and its association with accelerometry-measured moderate to vigorous PA among 124 adolescents of mixed PA status (i.e., inactive and physically active). Affective response was assessed before and during exercise at minutes 10, 20, and 40 using the Feeling Scale, a one-item measure of affective valence (i.e., feeling good versus bad; Hardy & Rejeski, 1989). In a longitudinal observational study, Kwan and Bryan (2010) assessed affective response to a 30-min session of PA at moderate intensity (i.e., 65 % of VO_{2max}) and its relationship with change in self-reported PA 3

months later among 127 adults. Affective response was assessed before and during exercise at minutes 5, 10, 20, and 30 using the Physical Activity Affect Scale, a 12-item questionnaire that measures four subscales: positive affect, negative affect, tranquility, and fatigue (Lox et al, 2000). In another longitudinal observational study, Williams et al. (2008) assessed affective response to moderate intensity PA (i.e., 64-76 % of maximum predicted heart rate) and its relationship with change in self-reported PA six and 12 months later among 31 sedentary adults. Affective response was assessed every two minutes during a 30-minute treadmill walk using the Feeling Scale. Finally, Williams et al. (2012) evaluated affective response to during a 10-min moderate intensity walking bout (i.e., 2.5-4.0 mph on a treadmill) and its relationship with change in self-reported PA 6 months later among 146 adults, again using the Feeling Scale to assess affective response before and during exercise at minutes 2, 5, and 8 during a 10-minute treadmill walk. Despite the heterogeneity in procedures (e.g., operationalization of moderate intensity) and assessment of PA, all four studies that examined the association between affective response to PA and future PA showed a positive association, ranging from r=.18 to r=.51. That is, participants who reported more positive shifts in affective response to PA tended to engage in more future PA.

Of note, all four studies were considered high quality research based on evaluation of the risk of bias by Rhodes and Kates (2015) using a modified version of the checklist created by Downs and Black (1998). For example, affect experienced prior to the PA session was controlled in all four studies, and three of the four studies controlled for past PA behavior (Kwan & Bryan, 2010; Williams et al., 2008; Williams et al., 2012).

Studies that examined the association between affective response after PA and future PA behavior had overall null effects (Rhodes & Kates, 2015). Taken together, the existing research

generally supports the overall premise that affective response to PA is predictive of PA behavior (B-path, Figure 1), although there are some limitations which we address below in the discussion. Next, though, we turn to the evidence for genetic influence on affective response to PA.

5. Evidence for genetic influence on affective response to physical activity

In order for affective response to PA to be an intermediate phenotype, genetic variation should explain differences in the putative intermediate phenotype. Schutte et al. (2016) estimated the heritability of affective response during and after PA among adolescents (n=226 twins and n=38 siblings) and found that genetic factors explained 15% of the between-person variance in affective response to PA during a graded exercise test. While this study suggests low to moderate heritability of affective response to PA, it does not provide insight into which particular gene loci account for the differences in affective response to PA.

To identify the specific genetic variants associated with affective response to PA, we conducted a systematic review. Specifically, in accordance with the PRISMA checklist (Moher et al., 2009), we searched PubMed and PsycINFO using search terms specific to genetic variants, affective response, and PA behavior. Consistent with a previous systematic review of genetic variants (Bruneau et al., 2016), search terms used for genetic variants were “genetic variants,” “genotype”, “single nucleotide polymorphism”, “allele”, and “polymorphism”. Consistent with a previous systematic review of affective response to PA (Rhodes & Kates, 2015), search terms used for affect included “affect”, “emotion”, “mood”, “activation”, “circumplex model”, “exercise induced feeling states”, “subjective exercise experience”, and “pleasant feeling state”. Consistent with a previous systematic review in the PA literature (Johnson et al., 2014), search terms used for PA were “physical activity”, “exercise”, “running”, “bicycle”, “treadmill”, “speed

training", "training duration", "training frequency", "training intensity", and "aerobic endurance".

To be eligible for review, studies must (i) assess genotype, (ii) include a measure of affective response to PA, and (iii) report an association between the two variables. We excluded articles that examined affect that was unrelated to PA (e.g., depressive symptoms), affective response after PA, and non-human studies. Finally, we only included peer-reviewed articles published in English.

The literature search included studies published between January 1, 1970 and November 1, 2017. Title and abstract screening was done by the lead author and selected papers (n=19) were reviewed by co-authors to determine the final articles included in the systematic review.

Out of 634 articles from PubMed and PsychInfo, 19 articles were relevant based on the title and abstract screening, and only two articles met inclusion criteria after full-text review (Figure 1). Among the 19 articles, three papers were excluded because they were non-human studies and 14 papers were excluded because they did not assess affective response to PA. Of note, three of the excluded studies examined pre to post changes in mood resulting from a 4-week PA intervention (Dotson et al., 2016; Gujral et al., 2014; Hopkins et al., 2012) but did not examine affective response during PA. The two included studies were Bryan et al. (2007) and Karoly et al. (2012).

Bryan et al. (2007) investigated the association between the SNP in brain derived neurotropic factor (BDNF) and affective response to treadmill walking. The human *BDNF* gene, located on chromosome 11p14.1, encodes a BDNF protein that is widely expressed in the mammalian adult brain and plays an essential role in the growth and survival of neuronal cells in the peripheral and central nervous system (Hofer et al., 1990; Murer et al., 2001). In the *BDNF*

SNP, rs6265, some people carry the G allele, while approximately 1% of African, 19%, of European Caucasians, 21% of Hispanic, and 62% of Asians are A-allele carriers (Sherry et al., 2001). Investigators asked 64 healthy participants (32 men and 32 women; mean age = 23.8 years) walk on a treadmill at moderate intensity (65% VO_{2max}) for 30 minutes and assessed affective response during the treadmill walk. Compared to A-allele-carriers (AG/AA), the GG-allele carriers for *BDNF* rs6265 showed a more negative affective response to PA.

Karoly et al. (2012) investigated 14 SNPs and their associations with physiological and subjective responses to aerobic PA among 238 sedentary adults. Investigators assessed affective response to treadmill walking at moderate intensity (65% VO_{2max}) for 30 minutes. Among the 14 SNPs assessed, two SNPs (rs8044769 and rs3751812) in the *Fat Mass and Obesity-associated gene* (FTO) were associated with affective response to PA. Specifically, C-allele-carriers (relative to TT-allele-carriers) of rs8044769 and T-allele-carriers (relative to GG-allele-carriers) of rs3751812 had greater increase in positive affect over the course of the 30-minute treadmill walk. The other 12 SNPs were not associated with affective response to PA.

Taken together, findings from our systematic review generally support the premise that affective response to PA is a function of genetic variability (Figure 1, a-path). However, as with affective response to PA as a predictor of PA behavior, there are some limitations to the existing research, which we address below.

6. Discussion

We examined whether affective response to PA is a conceptually plausible intermediate phenotype that mediates genetic effects on PA behavior. Specifically, we summarized a recent systematic review that examined the effect of affective response to PA on PA behavior (Rhodes & Kates, 2015), and we conducted our own systematic review to examine genetic variants that

are associated with affective response to PA.

The systematic review that examined the relationship between affective response to PA and its impact on future PA (B-path, Figure 1) (Rhodes & Kates, 2015) revealed four studies showing relationships between affective response and PA behavior (Kwan & Bryan, 2010; Schneider et al., 2009; Williams et al., 2008; Williams et al., 2012) in the small to large effect size. More research is needed, however. Specifically, it will be important to examine whether the same association exists among diverse populations in terms of age, ethnicity, culture, and health status. Additionally, in the previous studies, affective response to PA was measured in the laboratory by research assistants, which may bias participants' responses due to factors such as social desirability (Paulhus, 1991). To improve the ecological validity—i.e., the extent to which the outcome of a trial can be generalized to real-world contexts—affective response to PA should be studied in a more natural setting (e.g., outdoors, gym, or park), which can be achieved through the use of ecological momentary assessment. Since the systematic review by Rhodes and Kates (2015), at least one study has used ecological momentary assessment to investigate the effect of affective response to PA on future PA, again showing support for the hypothesized association (Williams et al., 2016). Finally, it should be noted that the aforementioned research does not allow us to infer causality. That is, even when researchers control for prior PA, an unmeasured third variable could confound the findings by influencing both affective response to PA and future PA level.

Regarding the genetic influence on PA behavior, the present systematic review revealed two studies that investigated genetic variants associated with affective response to PA (Figure 1, A-path). n one study, the G allele of *BDNF* rs6265 was associated with negative affective response to PA (Bryan et al., 2007). In previous research the G allele of rs6265 was also

associated with low intrinsic motivation for PA (Hooper et al., 2014), lower adherence in response to a PA promotion intervention (Bryan et al., 2013), and obesity (Gong et al., 2013; Gunstad et al., 2006; León-Mimila et al., 2013; J. A. Mitchell et al., 2013; Shugart et al., 2009; Thorleifsson et al., 2009; Wen et al., 2012; Wu et al., 2010; Xi et al., 2013; Zhao et al., 2009). Further, PA can increase serum BDNF, which may create a feedback loop (*BDNF*↔PA) that could magnify the genetic effects of the *BDNF* phenotype on the PA behavior phenotype (Currie et al., 2009; J. Zoladz et al., 2008; J. A. Zoladz et al., 1998). However, more research is needed to study the *BDNF* genetic variant given the relatively small sample size (n<100) of the Bryan et al (2007) study.

In the study by Karoly et al (2012), people who are C-allele-carriers of rs8044769 and T-allele-carriers of rs3751812 on the *FTO* gene had a more positive affective response to PA. Prior studies have shown that C-allele-carriers of rs8044769 and T-allele-carriers of rs3751812 have higher body mass index (Hassanein et al., 2010; Thorleifsson et al., 2009; Wing et al., 2009). The specific molecular-physiological mechanism by which the FTO gene might affect brain function and adiposity remains the object of intense scientific investigation.

Overall, the quantity of studies supporting genetic influence on PA is much lower than emerging human genetic research examining subjective responses to alcohol (Ray & Hutchison, 2004; Ray et al., 2010), caffeine (Alsene et al., 2003; Dlugos et al., 2007; Kendler & Prescott, 1999; Loke, 1988), amphetamine (Hart et al., 2011; Lott et al., 2005; Lott et al., 2006), and nicotine (Hoft et al., 2011; Hutchison et al., 2007; Sherva et al., 2008; Zeiger et al., 2007) consumption.

In sum, there is preliminary evidence supporting affective response to PA as an intermediate phenotype; however, more research is needed. The advantage of the intermediate

phenotype when applied to affective response to PA can be best illustrated when considering the interaction between genetic and environmental determinants of PA behavior. Indeed, the depiction in Figure 1 is simplified because it does not account for gene-environment interactions. While the genetic predispositions of modern humans do not differ significantly from recent ancestors (e.g., grandparents and great-grandparents), their environments differ substantially. For example, before modern conveniences like motor vehicles, washing machines, and televisions, a genetic predisposition for a more negative response to PA was less likely to lead to an overall inactive lifestyle because most people had to engage in a significant amount of PA to function in society and in occupational contexts. On the other hand, a predisposition for a negative affective response to PA may be more likely to lead to low rates of PA in modern environments, which allow for sedentary lifestyles. Gene-environment interactions may be even more pronounced when considering variability in socio-economic factors such as unsafe sidewalks, low neighborhood attractiveness, and lack of access to parks, playgrounds, and fitness clubs. In sum, the effects of affective response to PA on PA behavior are moderated by various environmental factors.

The investigation of the genetic underpinnings of affective response to PA has the potential to accelerate optimal translation of discoveries from large-scale genomic data to behavioral intervention development. Genome wide association (GWA) studies examining PA will likely increase (e.g., NIH's precision medicine initiative cohort, "All of Us"), and a large number of PA-related SNPs will be identified soon. However, without a theoretical context, GWA studies reveal little about the mechanisms of genetic effects on behavior that may serve as intervention targets. To realize this translation, we need to understand *how* genetic variation influences PA among humans.

An intermediate phenotype is, relative to the target behavior, a more proximal and malleable variable that can be targeted by the health promotion intervention. For example, if genetic influences on PA behavior are mediated by variation in affective response to PA, this may point towards the need for targeting and tailoring interventions that consider differences in affective response. Specifically, those who respond more negatively to PA due to genomic profile may be encouraged to exercise at a self-paced intensity rather than prescribed moderate intensity (Williams et al, 2015). While no studies to date have used such an approach, the conceptual plausibility of affective response to PA as an intermediate phenotype for intervention development has gained significant traction among researchers in recent years (Bryan et al., 2017; Yanovski & Yanovski, 2018).

7. Conclusion

With recent advancements in technology for ecological momentary assessment devices (e.g., smartphones), objective assessments of PA (e.g., accelerometers) and the decreasing cost of genotyping, the investigation of the genetic underpinnings of the affective response to PA is timely and feasible. Investigating intermediate phenotypes will allows researchers to move from *predicting* PA based on genomic information to *understanding how* SNPs influence PA behavior, thus ultimately optimizing the translation of knowledge gained from genomic data to intervention development.

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