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Within person predictors of physical activity and fatigue in Long Covid: findings from an ecological momentary assessment study.

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Abstract

Objective

We aimed to examine the extent to which current perceived demand for energy and affect predict subsequent physical activity and fatigue in people with Long Covid using an intensive longitudinal method (ecological momentary assessment).

Methods

Analysis of data from a study of 69 adults with self-reported Long Covid combining 3-hourly self-report data perceived energy, and fatigue, on a smartphone app with continuous physical activity recording. We tested three hypotheses derived from cognitive behavioural and neuroscientific models of fatigue. These related to expectation, current affect and recalled emotional demand. Analysis used linear mixed effects models with fatigue and physical activity as outcomes.

Results

Expectation of energy need for the next 3 hours was predictive of physical activity, fatigue and recalled demandingness of the period. (p-values 0.005 to <0.0001). Currently feeling positive was predictive of slightly more subsequent physical activity and less fatigue 3 hours later (p=0.01). Feeling negative was not predictive of physical activity or subsequent fatigue but was predictive of subsequent recall of the period being emotionally demanding. Feeling more anxious was predictive of greater fatigue 3 hours later (p=.001) but not of reduced physical activity. Absolute effects were small: a one-point increase in anticipated demand (on a scale of 1-7) was associated with an extra 2.2 minutes of moderate or vigorous physical activity and a one standard deviation increase in anxiety was associated with a one-point increase in fatigue (0-100 scale).

Conclusion

In the day-to-day experience of Long Covid expectation and affect have little detectable effect on subsequent physical activity or fatigue.

Keywords

Long covid, post covid-19 condition, fatigue, physical activity, ecological momentary assessment, anxiety

Introduction

Long Covid (also known as post COVID-19 condition) is a heterogeneous illness which follows acute infection with the SARS-COV-2 virus, persists for several months and cannot be better explained by an alternative diagnosis[1]. Common symptoms of Long Covid include fatigue, cognitive dysfunction, and breathlessness, but a wide range of other symptoms are commonly present and may predominate in some patients[2,3]. The prevalence of Long Covid remains uncertain: estimates of 10% of adults following infection are common [3] and a recent large meta-analysis estimated the prevalence of at least one cluster of Long Covid symptoms as 6% at 3 months and approximately 1% at 12 months after infection[4]. Evidence exists for multiple pathophysiologic mechanisms in Long Covid[5,6]. There is evidence of altered muscle function[7,8] and low-grade inflammation[9]. Neurological features are well recognised after SARS-COV-2 infection including changes in grey matter [10] altered smell and taste and cognitive difficulties[11].

Fatigue is a major component of Long Covid. Fatigue can have both peripheral (e.g. muscle) and central (brain) component in both health and disease[12]. Altered muscle structure and function has been demonstrated in recent studies of Long Covid [7,8] indicating likely involvement of peripheral factors. However central factors are also likely to be important in pathological fatigue [13] and are the focus of this analysis. In particular we considered two models, the cognitive behavioural[14] and a neuroscientific model[15].

The cognitive behavioural model of fatigue [14] has been widely used to understand the central component of fatigue. It has been applied to understanding fatigue in association with well-defined medical conditions such as multiple sclerosis[16] and cancer[17] and in myalgic encephalomyelitis / chronic fatigue syndrome[14]. The model focuses on conscious thoughts (cognitions) and behaviours. These include regarding fatigue as negative and aversive; attentional focus on symptoms; and negative beliefs about the relationship between exercise and fatigue[18]. These factors are present in cross sectional data and, over the long term, appear to diminish in those who improve with treatment[16,19,20]. However, there is substantial variation between individuals [21]and a recent study in ME/CFS found no consistent patterns linking fatigue to psychological factors using a within-person approach. [22]

Current neuroscientific models of fatigue view it as a consequence of neural processing to optimise use of brain and body resources [15]. There is evidence that this involves predictive processing of interoceptive signals from the body[12] in which the prefrontal cortex playing an important role in allocating neural resources[15]. Interoceptive signals from the body which indicate effort have a negative effect on the perception of pleasure during effortful activity which in turn affects cerebral haemodynamics and cardiac autonomic control [15] . In addition, imposing cognitive demand during exercise leads to greater regulatory activity in the prefrontal cortex and inhibition of descending spinal motor signals[23].

Two important differences exist between newer neuroscientific models of fatigue and the cognitive behavioural model. The first is that the newer models operate at a neural level which is not accessible to awareness or conscious thought. The second is that the newer models actively link interoception with allostasis[24], the automatic regulation of the body by the brain to anticipate and adapt to the internal and external environment. In Long Covid, it is plausible that interoceptive signalling and processing within the brain are affected by other pathophysiologic mechanisms such as neuroinflammation or altered cellular metabolism.

The mechanisms of fatigue in Long Covid are still not fully understood hence this represents an important knowledge gap. We recently reported an intensive longitudinal study in which adults with self-reported Long Covid recorded symptoms and physical activity every 3 hours over 14 days[25]. Data showed marked variability in symptoms over short timescales and heterogeneity between individuals in correlations between symptoms. It also showed weak and inconsistent relationships between physical activity and symptoms. In this analysis we examine the short-term relationship in the data between outcomes (subjective fatigue, objective physical activity, and recalled physical and emotional demand in the preceding three hours) and predictors (expectations of how much energy would be needed, feeling positive or negative about the next three hours and current anxiety). We aimed to examine the strengths of these relationships by testing three hypotheses: (1) that expectations of effort and feeling positive or negative about the next few hours at one time point would predict physical activity over that period and fatigue at the next time point; (2) that anxiety at one time point would predict physical activity during the time to the next time point and fatigue at that next time point; and (3) that recall of greater recent emotional and mental demand would be associated with less physical activity in the last few hours and greater current fatigue. The first two hypotheses relate to the cognitive behavioural model of fatigue while the third relates to the neuroscientific model of fatigue.

Methods

Study design.

We carried out an intensive longitudinal study (also known as ecological momentary assessment) [26]using self-report data collected through a custom smartphone app supplemented by activity data from a wrist worn accelerometer. The methods have been reported in detail elsewhere[25]. To briefly recap, the study took place in the UK between July and October 2021 and was delivered remotely. Intensive data collection took place over 14 days. During these days, participants were prompted to enter data 5 times per day (at 3-hour intervals) while wearing the accelerometer continuously. The 14-day intensive data collection period was preceded by a 7-day run-in period during which participants completed the app twice daily. Ethical approval for the study was granted by Sheffield Hallam University Research Ethics Committee (reference number: ER27968999).

The smartphone app was custom-built for the project and ran on participants' own smartphones (both iOS and Android platforms). Data was regularly uploaded from the app to a secure server at Sheffield Hallam University. The app was designed to send an audible reminder up to three times at pre-specified times during the day (08.00, 11.00, 14.00, 17.00 and 20.00). Data entry was by touchscreen and involved a mix of Likert and visual analogue scale (VAS). Participants wore an Axivity AX3 triaxial accelerometer on their non-dominant wrist and were encouraged to wear it at all times except when bathing. Devices were calibrated prior to use and set to start automatically at the beginning of the scheduled 14-day period. Data was collected at 100Hz and stored in epochs of 5 seconds.

Participants

Participants were primarily recruited from the RICOVR [27] database established by Sheffield Hallam University for people living with symptoms of Long Covid. Inclusion criteria were the presence of ongoing physical symptoms which the individual attributed to Long Covid and which followed (by at least 3 months) a recognisable acute infection during the Covid-19 pandemic. These criteria were applied irrespective of whether they had undertaken a PCR test for SARS-CoV-2 or what the result of any test was. Enrolment, including informed consent was carried out remotely by email and online survey. Participants received no financial or other reward for taking part.

Data collected

The smartphone app collected data on physical symptoms, including fatigue, which have been reported previously. For this analysis we used the following additional items from the app.

Physical Activity

Data from the activity sensor was aggregated into 30 second epochs. Acceleration was estimated using the Euclidian norm minus one (ENMO) algorithm [28] in the *GGIR* package for R [29] and reported as the time (in minutes) spent in moderate or vigorous physical activity (MVPA), using a threshold of 40 milligravitational units or above, for each 3-hour period between app data entry points.

Fatigue and Anxiety

These were collected as single item visual analog scales in a series of symptoms headed "Please rate your symptoms just now" and labelled "Fatigue" and "Feeling anxious or worried". End anchors labels were "None" and "Severe". Touch points on the screen were converted to a numeric scale from 0 to 100. Within the limitations posed by the EMA format we did not attempt to be more specific about anxiety (general or situational versus health anxiety or concern about symptoms). In developing the data collection we found participants preferred the generic term.

Recalled physical, emotional and mental demand over the preceding 3 hours

These were presented as a four-point Likert Scale in a sequence of three matching statements differing only by the type of demand: "Thinking about what you have been doing in the last few hours how [physically, emotionally, mentally] demanding was it?". Anchor labels were "not at all" and "very"). Likert scales for demand were converted to numeric scales (range 0-3) and the emotional and mental scores were summed to give a measure of combined emotional and mental demand.

Expected energy demand over the next 3 hours and affective valence

These were presented as 7-item numeric rating scales in a sequence of statements beginning "Thinking ahead for today …". For expected energy demand, this was followed by "How much energy do you think you will need?" and for affective valence this was "Are you feeling positive or negative about what you will be doing?". These items had anchor labels of "Very little energy…. A large amount of energy" and "Very negative … Very positive". For analysis the affective valence data was reduced to 3 categories: negative, neutral and positive, with neutral (a score of 4 out of 7) as the reference category.

Statistical analysis

Before conducting analyses, we centred and standardised continuous variables (fatigue, anxiety, time in MVPA) at the individual mean level such that for each participant and variable there was both an absolute value and a z-score for that value (with mean of 0 and standard deviation of 1).

We carried out a series of comparisons in which the outcome variable was either fatigue or physical activity. Depending on the model these could be measured at the start of each 3-hour period (here described as t) or at the end (t_{+1}). This allowed us to examine the extent to which expectation, anxiety, or affective valence at one time point affected fatigue or physical activity at the next. We also examined the relationship between these predictors and recalled demand over the preceding 3 hours, both physical and emotional. Univariate models were shown visually, conditioned on affective valence.

As is recommended for analysis of intensive longitudinal data [26,30] we used linear mixed-effects regression to produce multilevel models in which observations were nested within participants. We included all complete sets of data related for 3 hour periods (i.e app data at t and t+1 and accelerometer data between the two time points. We did not add additional lagged values as previous analysis showed weak or absent autocorrelation. Fatigue and time in MVPA were separately analysed as outcomes, with the other features described above (and the preceding value of the outcome variable) included as predictors. Additionally we fitted models with recalled demand over the preceding three hours as the outcome. These multilevel models were fitted as random intercept models using the lmer package in R3.4.2 using Restricted Maximum Likelihood estimation. We attempted to fit random slope and intercept models but either these models did not converge on a solution or, when they did, there was minimal difference in fit from the random slope models. Estimation of the p-values of the fixed effects coefficient used t-tests with Satterthwaite's method for correction and we used Akaike Information Criterion (AIC) to select between models. We did not add participant level covariates such as age, gender or duration of illness.

Estimate of statistical power

The study design was dictated by feasibility and resources rather than an a priori calculation of statistical power. However, we carried out a post-hoc power calculation using the ema.powercurve package in R. This demonstrated that for a study with 70 participants, 70 possible data entries and 80% completion we had 90% power to detect a moderate standard effect size of 0.5 but only 40% power to detect a small standard effect size of 0.2.

Results

Participants

The study included 82 participants with self-reported Long Covid. For this analysis we used data from 69 individuals (84%) who had completed at least 35 of the possible 70 data entries and had accelerometer data for 12 or more days. Participants were aged between 21 and 64; the median age was 50, (IQR = 42 to 54). As previously reported over 80% were female and of White British ethnicity. Over half had been educated to university degree level. Most participants had had Long Covid for between 12 and 18 months at the time of data collection. Almost all participants had substantially impaired quality of life (median EQ-5D-5L Index 0.63, IQR 0.37 to 0.75); the median visual analogue scale for fatigue was 60/100.

Relationship between fatigue and physical activity

Figure 1 shows the relationship of physical activity with subsequent fatigue and of current fatigue on subsequent physical activity. The data is presented both as a single fit and conditioned on categories of affective valence. While the weak negative correlation between prior fatigue and subsequent physical activity (figures 1C and 1D) is intuitive, the equivalent negative correlation between prior activity and subsequent fatigue (figures 1A and 1B) may be initially surprising (most people's default assumption is that more effort will produce more fatigue). However, it is important to recognise that these represent multiple discretised sequences which are highly sensitive to confounding. For instance feeling more unwell is likely to lead to both less effort and more fatigue, while feeling better than usual may lead to both more effort and less fatigue.

Relationship of fatigue or physical activity with other variables

Figure 2 shows the relationships of fatigue and physical activity with recalled demand, and prior anxiety and anticipated demand. Again, each relationship is shown conditioned on categories of affective valence. Figures 2A and 2C show there is little or no relationship between fatigue and either recalled physical demand or prior expected demand, particularly when affective valence is negative or neutral. Figure 2B shows that there is a weak correlation between recalled demand and physical activity which does not vary by affective valence. Figure 2D suggests that there is a relationship between expected demand and subsequent activity when an individual is feeling positive or neutral about the upcoming time period, but not when feeling negative. Figures 2E and 2F show a weak relationship between anxiety and subsequent fatigue and physical activity. Finally figures 2G and 2H show little relationship between fatigue or recent physical activity and recalled emotional demand over the preceding 3 hours.

Linear mixed-effects regression

Table 1 summarises the linear mixed effects regression with fatigue and time in moderate and vigorous physical activity as outcomes. Neither model showed strong predictive ability: the marginal r-squared, which represents the proportion of variance explained by the fixed effects of the predictors was 0.05 for fatigue and 0.07 for physical activity. Intraclass correlation coefficients were large for both models (for fatigue 0.50 and for physical activity 0.32), even after standardising [25] the fixed effect variables. As expected from figure 1, fatigue at t was associated with fatigue at t_{+1} and with less physical activity between these time points. Additionally fatigue at t_{+1} was associated with anxiety and anticipated demand at t, but not with negative affective valence. Time in moderate and vigorous physical activity in the period t: t_{+1} was associated with anticipated demand and weakly with anxiety and positive affective valence.

All observed effects were small: a one standard deviation increase in anxiety was associated with a one-point increase in fatigue (0-100 scale) and a one point increase in anticipated demand (on a scale of 1-7) was associated with an extra 2.2 minutes of moderate or vigorous physical activity.

Table 2 summarises the linear mixed effects regression with physical and emotional demand in the period t:t_{+1} and recalled at t_{+1} as outcomes. Recalled physical demand was significantly associated with fatigue at t_{+1}, physical activity in the period t:t_{+1}, and anticipated demand at t. It was weakly related to prior positive affective valence but not anxiety. In contrast recalled emotional demand, while still associated with fatigue, was only weakly associated with physical activity but was strongly associated with anxiety, anticipated demand, and negative affective valence at t. The marginal r-squared for the model with recalled physical demand as the outcome variable was 0.25 and for recalled emotional demand was 0.14. Recalled mental demand (not shown in the table) was also associated with fatigue at t_{+1}, anticipated demand at t and weakly with anxiety at t.

Table 3 summarises the data in tables 1 and 2 to show the contrasting effects on outcomes for three predictors at the start of each 3 hour period: anticipated demand, anxiety, and affective valence towards the upcoming period. These are reported as p-values so as to be common across analyses, however in the orginal tables they are shown in terms of the absolute effect of standardised predictors.

Discussion

Summary of main findings

This study tested three hypotheses. We found that (1) while expectations of effort were associated with both physical activity over the next three hours and fatigue at the next time point, feeling positive or negative had weak or no effects on these; (2) that anxiety was weakly associated with fatigue at the next point but had no effect on physical activity during the time to the next time point; and (3) that current emotional and mental demand was associated with subsequent fatigue and recalled physical demand (adjusted for observed physical activity).

Strengths and limitations

The main limitation of this study is that the psychological measures we included were non-specific (anxiety and feeling positive or negative about the upcoming 3 hour period) rather than specific to a cognitive behavioural model of fatigue. Nonetheless the generic construct of anxiety should be capable of capturing some aspects of fatigue-related processes such as symptom focus and catastrophisation. Similarly, fears or concerns relating to activity should be reflected in negative affective valence to the upcoming period if the anticipated demand is high. In practice, “anxiety” commonly figures in explanations of Long Covid given by practitioners to patients so in that regard our inclusion of anxiety has face validity. Our sample was largely white, female, middle-aged and well-educated. This reflects the opportunistic sample taken from an online panel of research volunteers promoted by peer-support groups, however this has been seen in other studies of Long Covid [31]. It means that if any differential effects due to demographic variables could not be meaningfully estimated from our data. Approximately one third of participants had their initial illness before the widespread availability of PCR testing for SARS-Cov-2 and another third reported that their PCR test had been negative. This raises the possibility that not all participants’ symptoms were sequelae of covid infection [32] however we were unable to test serology in this study nor check records for prior symptoms. A challenge to analysis was the scatter of points at each level of demand. This scatter represents the “noise” in perceptions of physical activity. Whether this is a feature of Long Covid or simply a reflection that perception of activity is part of interoception[12] and is therefore more or less hidden from consciousness is not clear.

Implications

Our findings suggest that, even though statistically significant, at the within day lived experience level, any effects of conscious expectation, negative affect or non-specific anxiety on subsequent physical activity and fatigue appear small. In terms of the hypotheses and underlying mechanisms these findings tend to favour a resource optimisation model for fatigue [15] over one in which conscious expectation plays a leading role. This is important because cognitive behavioural models which include perception and anticipation are commonly used with patients to explain their experience of fatigue and are often challenged by patients.This suggests a need for further research in order to better understand the relationship between symptoms such as fatigue and psychological mechanisms and also to provide explanations which are in keeping with the science and are acceptable to patients. In this context, neuroscientific explanations for central components of fatigue which include the brain's allocation of internal resources, competition between emotional, mental and physical demands, and involuntary errors in predictive coding due to altered interoception[12] become both plausible and potentially useful. In Long Covid it is further possible that this brain processing is impaired by neuroinflammatory or mitochondrial changes as well as by impairment of interoception and body-sensing[25]. Taking this approach does not exclude a role for emotions and cognitions in affecting symptoms or wellbeing but it places them as a consequence of interoceptive and allostatic processes rather than the root cause. Further research should attempt to replicate these findings, ideally in a more diverse patient population, and seek better understanding of the mechanisms which drive fatigue and symptoms in Long Covid.

Conclusion

In the day-to-day experience of Long Covid expectation and affect have little detectable effect on subsequent physical activity or fatigue.

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Table 1 Results of linear mixed effects regression with standardised values of continuous predictor variables

	Outcome					
	Fatigue (t_{+1})[a]			Time in MVPA ($t : t_{+1}$) (minutes)		
Predictor	Coeff.	95%CI	p-value	Coeff.	95%CI	p-value
Fatigue (t) [b]	3.93	3.34 to 4.53	<.0001	-0.48	-0.95 to -0.02	0.04
Time in MVPA (t : t+1) [b]	-0.99	-1.59 to -0.4	0.001			
Time in MVPA (t_{-1} : t) [b]				-0.01	-0.44 to 0.43	0.98
Anticipated demand (t) [c]	0.37	-0.18 to 0.91	0.18	2.24	1.83 to 2.65	<.0001
Anxiety (t) [b]	0.81	0.2 to 1.42	0.01	0.56	0.09 to 1.04	0.02
Negative about next 3 hrs (t)	-0.65	-2.55 to 1.25	0.50	-1.28	-2.76 to 0.2	0.09
Positive about next 3 hrs (t)	-2.09	-3.65 to -0.54	0.01	1.53	0.33 to 2.74	0.01
Recalled mental and emotional demand (t+1)	1.22	0.75 to 1.68	<.0001	-0.05	-0.41 to 0.31	.80

MVPA: Moderate or Vigorous Physical Activity (time measured in minutes); Coeff: coefficient; PA: Physical Activity; (t), (t_{+1}) etc refer to time points in the data collection.

[a] Measured on a 0-100 point scale

[b] indicates individually standardised value (z-score) used in regression model,

[c] in view of linear relationship seen in figure 2, analysed as continuous variable rather than categorical.

Table 2 Fixed effects from linear mixed effects regression with standardised continuous predictor variables

	Outcome					
	Recalled Physical Demand (t_{+1})[a]			Recalled emotional & mental demand (t_{+1}) [a]		
Predictor	Coeff.	95%CI	p-value	Coeff.	95%CI	p-value
Fatigue (t_{+1}) [b]	0.09	0.06 to 0.12	<.0001	0.11	0.06 to 0.16	<.0001
Time in MVPA (t : t_{+1}) [b]	0.26	0.23 to 0.29	<.0001	-0.08	-0.13 to -0.03	0.0003
Anticipated demand (t) [c]	0.17	0.14 to 0.2	<.0001	0.24	0.2 to 0.29	<.0001
Anxiety (t) [b]	-0.01	-0.04 to 0.02	0.51	0.13	0.08 to 0.19	<.0001
Negative about next 3 hrs (t)	-0.04	-0.14 to 0.05	0.35	0.29	0.13 to 0.45	0.0003
Positive about next 3 hrs (t)	0.09	0.02 to 0.17	0.01	0.01	-0.12 to 0.14	0.87
Recalled emotional and mental demand (t+1)	0.13	0.11 to 0.16	<.0001			
Recalled Physical demand				0.39	0.32 to 0.46	<.0001

MVPA: Moderate or Vigorous Physical Activity (time measured in minutes); Coeff: coefficient; PA: Physical Activity; (t), (t+1) etc refer to time points in the data collection.

[a] Measured on a 4 point Likert scale, analysed as continuous variable.

[b] indicates individually standardised value (z-score) used in regression model,

[c] in view of linear relationship seen in figure 2, analysed as continuous variable rather than categorical.

Table 3: Summary of effects of predictors on outcomes three hours later (from multiple linear mixed effects regression – detailed data is in tables 1 & 2)

	Outcome at time t+1			
	Fatigue	**Physical Activity**	**Recalled Demand**	
Predictor (at time t)			**Physical**	**Emotional & Mental**
Anticipated Demand	++	+++	++	+++
Anxiety	++	+		+++
Negative about next 3 hrs*				++
Positive about next 3 hrs	-	+	+	
Recalled Physical Demand				+++
Emotional & Mental Demand	+++		+++	

+++: strong positive association ($p<0.0001$); ++: positive association ($0.0001 \leq p<0.01$);
+: borderline positive association ($0.01 \leq p<0.05$) -: negative association ($0.01 \leq p<0.05$);
blank cells.: $p \geq 0.05$.

* Association shown as positive when positive affect was associated with outcome and negative when negative affect associated with outcome.

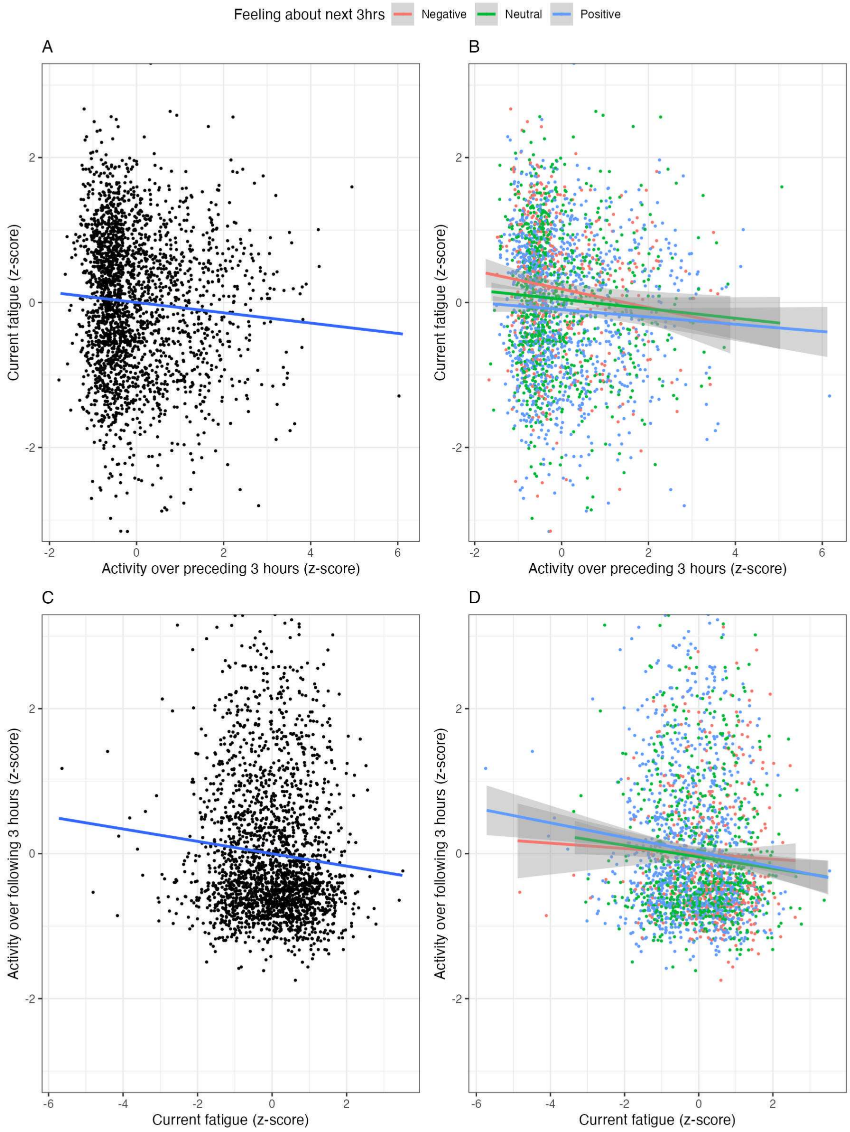

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Figure 1 Relationship between moderated and vigorous physical activity and fatigue, showing all data (A &C) and with data split by feeling about the next three hours (B&D)

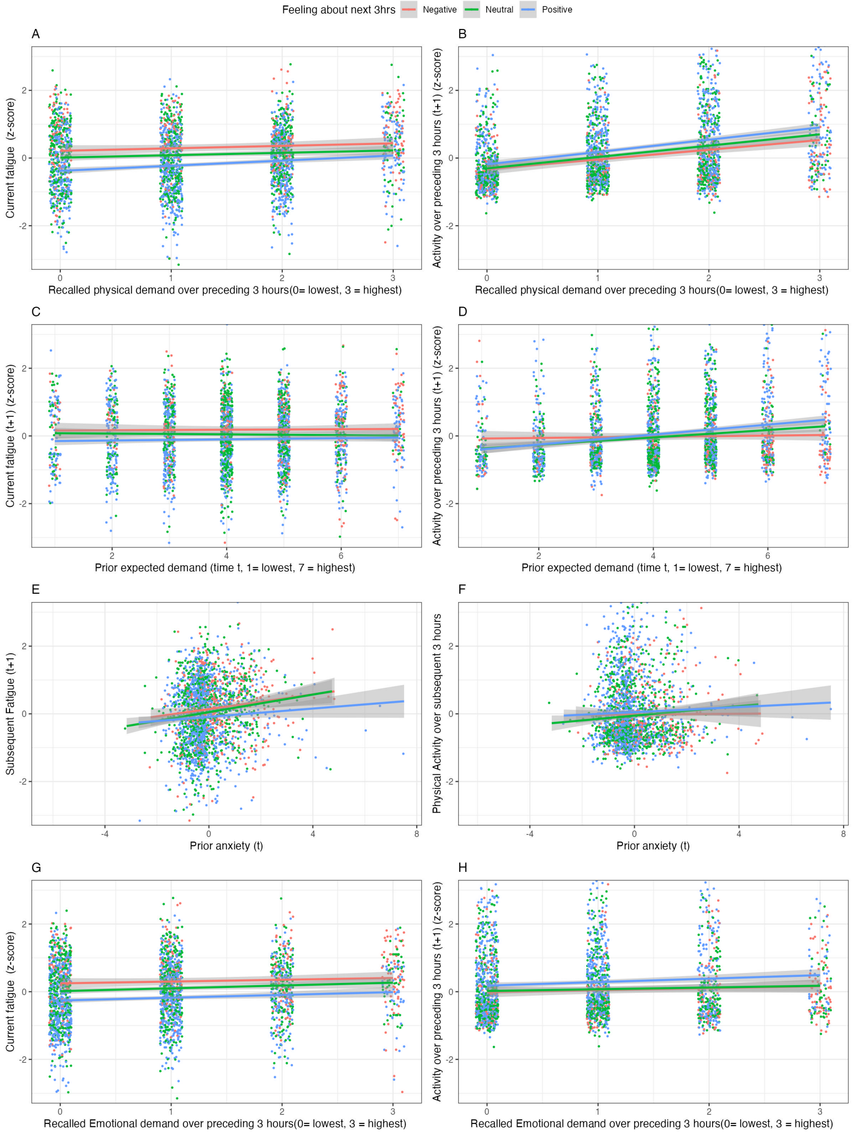

Figure 2: Relationship of fatigue and physical activity with recalled demand, anticipated demand and anxiety. All plots are conditioned on prior feeling about the next 3 hours.