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Positive affect predicts cerebral glucose metabolism in late middle-aged adults

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Abstract

Positive affect is associated with a number of health benefits; however, few studies have examined the relationship between positive affect and cerebral glucose metabolism, a key energy source for neuronal function and a possible index of brain health. We sought to determine if positive affect was associated with cerebral glucose metabolism in late middle-aged adults ($n = 133$). Participants completed the positive affect subscale of the Center for Epidemiological Studies Depression Scale at two time points over a two-year period and underwent 18F-fluorodeoxyglucose-positron emission tomography scanning. After controlling for age, sex, perceived health status, depressive symptoms, anti-depressant use, family history of Alzheimer's disease, *APOE* ε4 status and interval between visits, positive affect was associated with greater cerebral glucose metabolism across para-/limbic, frontal, temporal and parietal regions. Our findings provide evidence that positive affect in late midlife is associated with greater brain health in regions involved in affective processing and also known to be susceptible to early neuropathological processes. The current findings may have implications for interventions aimed at increasing positive affect to attenuate early neuropathological changes in at-risk individuals.

Key words: positive affect; cerebral glucose metabolism; well-being; FDG-PET; health; neuroimaging

Introduction

Positive affect refers to pleasant emotional and mood states, broadly experienced as happiness, enthusiasm, contentment, coping, well-being and optimism (Folkman and Moskowitz, 2000; Lyubomirsky *et al.*, 2005; Pressman and Cohen, 2005). Over the past few decades research has provided evidence of the association between positive affect and beneficial outcomes across many important psychosocial (Connolly and Viswesvaran, 2000; Fredrickson *et al.*, 2003; Kashdan and Roberts, 2004; Lyubomirsky *et al.*, 2005; Ruvolo, 1998; Wright and Staw, 1999) and health domains (Boehm and Kubzansky, 2012; Davidson *et al.*, 2010; Ostir *et al.*, 2001; Steptoe *et al.*, 2005). Furthermore, studies have demonstrated that positive affect and related measures of happiness and well-being are associated with healthy aging and reduced mortality (Danner *et al.*,

2001; Diener and Chan, 2011; Krijthe *et al.*, 2011; Levy *et al.*, 2002; Moskowitz, 2003; Ostir *et al.*, 2000; Steptoe *et al.*, 2015; but see Liu *et al.*, 2016). While the direction of causality between positive affect and beneficial outcomes, particularly within the domains of health and longevity (Liu *et al.*, 2016; Lyubomirsky *et al.*, 2005), requires further evaluation, it is reasonable to postulate that positive affect may also be associated with brain health.

Cerebral glucose metabolism, indexed by positron emission tomography (PET) tracer 18F-fluorodeoxyglucose (18F-FDG), is an *in vivo* measure that is widely used as a marker of brain health and function in normal aging and disease. In normal aging, decreases in cerebral metabolism have been observed in anterior brain regions (Kalpouzos *et al.*, 2009; Pardo *et al.*, 2007; Petit-Taboue *et al.*, 1998) with more pronounced disruption of metabolic processes within temporoparietal regions in neurodegenerative diseases such as Alzheimer's disease (AD) (Dukart *et al.*, 2013; Kalpouzos *et al.*, 2009; Yoshizawa *et al.*, 2014). Abnormal cerebral glucose metabolism has also been consistently observed within fronto-limbic regions in depression (Drevets *et al.*, 1997; Seminowicz *et al.*, 2004), a disorder often characterized by low levels of positive affect and high levels of negative affect (Watson and Clark, 1997; Wichers *et al.*, 2012).

Given the above evidence of age and disease-specific changes in cerebral glucose metabolism as well as the beneficial health outcomes associated with positive affect, it is possible that levels of positive affect will also have an association with cerebral glucose metabolism. To date, little is known about the relationship between positive affect and brain health, particularly in midlife when interventions aimed at modifying risk factors for pathological aging may be most effective. In the current study, we examined the relationship between positive affect and cerebral glucose metabolism in 133 healthy late middle-aged adults who provided ratings of positive affect twice over a two-year period and then underwent FDG-PET scanning. We hypothesized that greater positive affect would be positively associated with cerebral glucose metabolism, a marker of brain health.

Materials and methods

Participants

This study used data from the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort (Table 1), a longitudinal registry of > 1500 cognitively healthy adults recruited in middle-age and enriched for AD risk factors of *APOE* ε4 carriage and parental family history of AD (Sager *et al.*, 2005). Determination of *APOE* ε4 and FH status in this sample has been previously described (Jonaitis *et al.*, 2013; Koscik *et al.*, 2014).

A total of 133 out of 178 asymptomatic late middle-aged adults (mean age 59.29 years, SD = 6.11, range = 46.58–71.07, 71.4% female) were included in the current analyses if they had completed a comprehensive neuropsychological battery, self-report ratings of affect as indexed by the Center for Epidemiologic Studies Depression Scale (CES-D), magnetic resonance imaging (MRI), FDG-PET; and were determined by neuropsychological evaluation and consensus review to be cognitively normal, and absent of a major psychiatric diagnosis, history of neurological disease and head trauma. Forty-five participants were not included in the analyses for the following reasons: 14 declined the FDG-PET scan, 11 were lost to follow-up, nine had CES-D measurements that followed the FDG-PET scan (see section labeled 'Design'), four were MRI ineligible, four had an abnormal FDG-PET scan and three were missing CES-D

Table 1. Participant characteristics

Variable	Participants ($N = 133$)
Age at initial CES-D	59.29 (6.11)
Age at FDG-PET scan	63.22 (5.99)
Female, %	71.4
Caucasian, %	97
Education (years)	16.97 (2.97)
Initial MMSE	29.47 (0.87)
FH positive, %	66.9
APOE ε4 positive, %	40.6
Perceived health status[a]	3.81 (0.71)
Anti-depressant use, %	30.8
CES-D total[a]	5.89 (4.95)
CES-D positive affect[a]	10.64 (1.61)
CES-D-16 depressive symptoms[a]	4.52 (4.01)

[a]Calculated as the mean across two visits.
CES-D, Center for the Epidemiologic Studies Depression; FDG-PET, fluorodeoxyglucose positron emission tomography; FH, parental family history of Alzheimer's disease; *APOE* ε4, Apolipoprotein Epsilon-4; MMSE, Mini-Mental Status Examination. Non-percentage values are sample means with standard deviations in parentheses.

data. The University of Wisconsin Institutional Review Board approved all study procedures and each participant signed informed consent prior to participation.

Design

Participants completed the CES-D on two different visits scheduled approximately two years apart (mean visit 1 to visit 2 interval = 26.63 months, SD = 3.47) prior to the FDG-PET scan. Participants then underwent FDG-PET scanning ∼20 months after their second visit (mean visit 1 to FDG-PET scan interval = 47.23 months; SD = 15.46 and mean visit 2 to FDG-PET scan interval = 20.60 months; SD = 15.85).

Self-report measures

The CES-D, a well-validated questionnaire composed of 20-items designed to measure frequency of depressive symptoms experienced over the past week (Radloff, 1977) was used to assess affect. Factor analytic research on the internal structure of the CES-D typically yields a four-factor structure (Positive Affect, Negative Affect, Somatic Symptoms and Interpersonal Problems) (Shafer, 2006). This structure was tested and confirmed in the current study sample. The four statements comprising the positive affect subscale ('I felt that I was just as good as other people'; 'I felt hopeful about the future'; 'I was happy'; 'I enjoyed life') have previously been shown to be associated with beneficial health outcomes (Ostir 2000; Moskowitz, 2003) and were used to assess positive affect in the current study. For each item, participants were asked to use a four-point Likert scale (e.g. rarely/none, some/little, occasionally/moderate, most/all of the time; scored 0–3, respectively) to indicate how often they experienced a particular statement. Scores ranged from 0 to 12, with higher scores equating to a greater frequency and/or level of positive affect. A mean positive affect score based on their ratings at the two visits was calculated for each participant as a measure of characteristic positive affect (Dotson *et al.*, 2009a,b). We included the remaining 16-items of the CES-D (CES-D-16) to control for depressive symptoms (Stansbury *et al.*, 2006). Scores ranged from 0 to 48, with higher scores equating to more depressive symptoms. For each

participant, scores collected at each of the two visits were used to calculate mean depressive symptoms. To assess perceived health status at each visit participants were asked, 'How would you rate your current health?' on a five-point Likert scale ranging from 'Poor' to 'Excellent', with higher scores equating to greater perceived health. A mean score of perceived health status over the two visits was calculated and included to control for potential confounding effects of ill health on positive affect (Liu *et al.*, 2016).

FDG-PET imaging

Each participant underwent FDG-PET imaging using the Alzheimer's Disease NeuroImaging Initiative protocol (Jagust *et al.*, 2010) including five mCi FDG injection with a 30-min uptake period followed by a 30 min acquisition. To reduce intersubject variability participants abstained from food, caffeine, tobacco and medication for a minimum of 4 h prior to scanning. Post-processing involved frame-to-frame realignment and summation of the 30 min emission scans. Images were co-registered to the T1-weighted image, spatially normalized to the ICBM 152 atlas and smoothed to 8 mm using SPM12 (www.fil.ion.ucl.ac.uk/spm). Intensity normalization was achieved by calculating the mean signal over the pons and cerebellar vermis (Jagust and Landau, 2012; Knopman *et al.*, 2013) producing scaled images for each participant that were used in second level analyses.

MRI

T1-weighted images were acquired for the purpose of coregisteration of FDG-PET scans. Participants underwent scanning on a General Electric 3.0 Tesla Discovery MR750 MRI system with an eight-channel head coil (Excite HD Brain Coil, GE Healthcare). T1-weighted images were acquired in the axial plane with a 3D fast spoiled gradient-echo sequence using the following parameters: inversion time (TI) = 450 ms; repetition time (TR) = 8.1 ms; echo time (TE) = 3.2 ms; flip angle = 12°; acquisition matrix = 256 mm × 256 mm, field of view (FOV) = 256 mm; slice thickness = 1.0 mm.

Family history and *APOE* ϵ4 status

To verify the diagnosis of AD in the parent, parental medical records, autopsy reports or results of the dementia questionnaire (Kawas *et al.*, 1994) were obtained and reviewed by a multidisciplinary diagnostic consensus conference (Jonaitis *et al.*, 2013; Koscik *et al.*, 2014; Sager *et al.*, 2005). Absence of FH of AD was verified through detailed medical history surveys and phone interview with the participants. Genotyping for *APOE* ϵ4 status was done previously in WRAP and described elsewhere (Johnson *et al.*, 2011).

Statistical analyses

Associations between positive affect and glucose metabolism were assessed using multiple regression analyses conducted in SPM12. The model included positive affect as the main continuous predictor variable with FDG-PET as the dependent measure. Age at visit 1, sex, depressive symptoms, anti-depressant use at visit 1 and/or visit 2, perceived health status, family history of AD, *APOE* ϵ4 status, and interval between visit 1 CES-D and scanning were treated as covariates (Table 1). No covariate exceeded a Pearson product correlation of 0.5. Voxel-wise analyses were restricted to gray matter using an explicit mask made by thresholding the International Consortium for Brain Mapping

Tissue Probabilistic Atlases gray matter map at 0.20. This was done to minimize type 1 errors, ensuring that voxels with less than a 20% likelihood of being gray matter were not included in analyses. Statistical parametric maps were thresholded at $P \leq 0.001$ (uncorrected) with a cluster extent threshold of > 100 contiguous voxels. Resulting clusters were considered significant if they surpassed a threshold of $P = 0.05$, cluster-level Family Wise Error (FWE) correction.

Results

Table 1 provides information on the participant characteristics and self-report measures. Whole brain voxel-wise analysis revealed a significant main effect of positive affect on cerebral glucose metabolism ($P < 0.05$ FWE cluster-corrected) in the bilateral posterior cingulate gyrus/precuneus; left angular/suparmarginal gyrus; left middle/inferior temporal gyrus and left middle/frontal gyrus where greater positive affect was associated with higher cerebral glucose metabolism in these regions (See Figure 1 and Table 2 for maxima and submaxima within each cluster).

Discussion

The current study examined the novel association between positive affect and cerebral glucose metabolism in a healthy late middle-aged sample. Consistent with our hypothesis, whole-brain voxel-wise analyses revealed a significant association between positive affect and cerebral glucose metabolism, such that greater positive affect was positively associated with relatively greater cerebral glucose metabolism within para-/limbic, frontal, temporal and parietal regions. Broadly, these regions have been implicated in functional neuroimaging studies of affective processing (Blood *et al.*, 1999; Damasio *et al.*, 2000; Davidson and Irwin, 1999; Duerden *et al.*, 2013; Hofer *et al.*, 2007; Maddock *et al.*, 2003; Phillips *et al.*, 2008) and show changes in glucose metabolism in depression (Fitzgerald *et al.*, 2008; Su *et al.*, 2014), a disorder often characterized by low levels of positive affect (Watson and Clark, 1997; Wichers *et al.*, 2012). In addition, regional grey matter volume in the precuneus, parahippocampus, medial prefrontal cortex and insula correlate with models of well-being (Kong *et al.*, 2015; Lewis *et al.*, 2014); which are constructs related to positive affect and often found to be associated with beneficial health outcomes (Boehm and Kubzansky, 2012; Ryan and Deci, 2001).

The positive association between positive affect and glucose metabolism across para-/limbic, frontal, temporal and parietal regions may be informed by a constructionist perspective, in which a variety of more 'basic psychological operations' from a complex array of distributed brain networks (Lindquist *et al.*, 2012) are involved in the monitoring, processing and generation of affect (Damasio *et al.*, 2000; Davidson, 2004; Lindquist *et al.*, 2015). As part of the paralimbic cortex, the PCC/precuneus, parahippocampus and insula each play a role as integrative hubs for a variety of functional processes (Buckner *et al.*, 2009) and are involved in affective processing (Blood *et al.*, 1999; Damasio *et al.*, 2000; Davidson and Irwin, 1999; Duerden *et al.*, 2013; Maddock *et al.*, 2003; Phillips *et al.*, 2008). The PCC/precuneus is a highly active metabolic region (Raichle *et al.*, 2001) involved in facilitating the integration of interoceptive and exteroceptive stimuli across a spectrum of attention (Leech and Sharp, 2014). The core underlying function of the parahippocampus is to bind contextual features (e.g. emotional content of a situation or experience) and link these features to a larger network of relevant

Table 2. Brain regions that showed a significant main effect of positive affect on glucose metabolism using voxel-wise analyses

Cluster location	Hemisphere	k	x	y	z	Peak t	P (FWE)
Posterior cingulate gyrus (23, 29, 31), precuneus (7)	B	1832	−6	−60	16	4.76	0.001
Angular/supramarginal gyrus (39, 40), insula (13), transverse temporal gyrus (41)	L	1320	−38	−54	30	4.63	0.003
Middle temporal gyrus (21, 22), para-hippocampal gyrus, hippocampal gyrus, inferior temporal gyrus (20)	L	738	−54	−42	−6	4.43	0.031
Middle frontal gyrus (10), superior frontal gyrus (10/11), anterior cingulate gyrus (32)	L	652	−30	50	0	4.38	0.044

X, Y, Z coordinates of the peak voxel of each cluster are presented in Montreal Neurological Institute (MNI) space. Corresponding Brodmann areas are in parentheses.
B = Bilateral; L, Left; k, number of contiguous voxels in cluster.
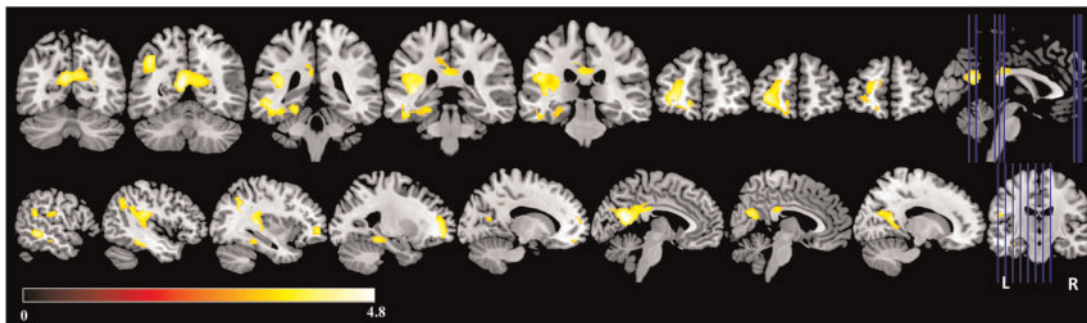
Fig. 1. Statistical parametric maps were thresholded at an uncorrected voxelwise threshold of P<0.001 with a cluster extent threshold of > 100 contiguous voxels. Resulting clusters were considered significant if they surpassed cluster-level threshold of P<0.05 with a Family Wise Error correction for multiple comparisons. Sagittal and coronal slices were derived from a normalized T1 anatomical image.

memories in the association cortex (Aminoff *et al*., 2013; Eichenbaum *et al*., 2007). The insula is positioned amidst these regions with specific connections to the parahippocampus, where it is involved in integrating internal homeostatic, visceral and sensory signals (Craig, 2009, 2010; Nagai *et al*., 2007; Suzuki, 2009). The frontal regions spanning the middle and superior frontal gyrus, and anterior cingulate gyrus, have extensive connections to the para-/limbic system and subcortical structures (Öngür and Price, 2000), and support range of cognitive functions relevant to affective processing including integration of sensory and visceral information, evaluation and attribution of affective stimuli and decision-making and self-regulation (Bechara *et al*., 2000; Ochsner and Gross, 2005; Phillips *et al*., 2008). Lastly, the left angular/supramarginal gyri are also involved in emotional processing (Hofer *et al*., 2007) and considered a heteromodal convergence zone supporting the integration and conceptualization of information from sensory, language and memory subsystems (Binder and Desai, 2011; Ciaramelli *et al*., 2008; Seghier, 2013). Taken together, we broadly suggest, that affect emerges when integrated representations (e.g. PCC/precuneus; angular/supramarginal gyrus; insula) of internal and external sensory stimuli based on contextual information from memories (e.g. para-/hippocampal gyrus) are deemed relevant and meaningful to the individual (e.g. prefrontal/frontal cortices). Of course, this is only a partial account based on our findings, thus evidence of additional regions (e.g. amygdala) and models of affective processing (e.g. lateralization; localist) (Davidson and Irwin, 1999; Rohr *et al*., 2013) deserve consideration.

Within our late middle-aged sample, the association between positive affect and cerebral glucose metabolism was observed in a number of brain regions that are known to exhibit progressive reductions in metabolism in prodromal stages of AD, including the PCC, precuneus, para-/hippocampus and temporal/parietal (Buckner *et al*., 2005; Chetelat *et al*., 2003; Minoshima *et al*., 1997; Mosconi, 2005; Mosconi *et al*., 2009; Protas *et al*., 2013). Affective changes associated with depressive symptoms may be an important predictor of cognitive decline and dementia (da Silva *et al*., 2013; Ownby *et al*., 2006; Stepaniuk *et al*., 2008), and have been shown to correspond to alterations in brain volume and cerebral blood flow in vulnerable brain regions of older adults (Dotson *et al*., 2009a,b; Ries *et al*., 2009). Given that we controlled for depressive symptoms, the relationship between positive affect and cerebral glucose metabolism, notably in brain regions that support integrative functions involved in affective processing, suggests positive affect may be an important factor associated with brain health in late midlife, when neuropathological processes are only beginning to emerge and may still be modifiable (Jessen *et al*., 2014; Sperling *et al*., 2011).

This may have implications for interventions aimed at increasing and/or maintaining positive affect (Layous *et al*., 2011; Proyer *et al*., 2014; Seligman *et al*., 2005; Sin and Lyubomirsky, 2009). Specifically, the 'broaden and build' theory posits that positive affect expands the scope of 'thought-action repertoires' (e.g. exploration, creative problem solving, cognitive flexibility, broadening of attention), leading to a building of resources and beneficial outcomes (Fredrickson, 2001, 2013; Fredrickson *et al*., 2008). Consistent with this theory, positive affect is associated with reduced morbidity for a variety of known risk factors (e.g. cardiovascular; chronic stress) for AD (Boehm and Kubzansky, 2012; Pressman and Cohen, 2005; Steptoe *et al*., 2005), enhanced cognitive functioning (Ashby *et al*., 1999; Carpenter *et al*., 2013; Yang *et al*., 2013), and as our work suggests, relatively higher levels of cerebral glucose metabolism in regions vulnerable to early neuropathological changes. Thus,

interventions targeting positive affect could have potential in mitigating pathological processes associated with cognitive and functional decline through increasing flexible and adaptive responses (e.g. thought-action repertoires) to environmental demands and/or optimizing cerebral glucose metabolism within these particular brain regions. Of course, this is highly speculative, and warrants examination with more sophisticated modeling techniques and measures to further clarify the causal relationships between these variables.

There are potential limitations of our study that deserve mentioning. First, because over half the participants in this study have a family history of AD (66.9%), were late middle-aged ($m = 59.29$ yrs-old), highly educated ($m = 16.97$ yrs) and predominantly Caucasian (97.0%), the generalizability of our results is limited and would benefit from replication in more diverse samples. Second, while we included a measure of perceived health, which has been shown to attenuate the association between happiness and all-cause mortality (Liu *et al.*, 2016), we did not examine a variety of specific psychological (e.g. personality, coping style), health (e.g. cardiovascular, endocrine, exercise) and social factors (e.g. social stress and support, income) that may be associated with positive affect (Lyubomirsky *et al.*, 2005). Lastly, we speculate based on the literature regarding possible connectivity between regions, thus future analyses employing connectivity methods for FDG-PET data would be useful.

In conclusion, this study provides initial evidence that positive affect is associated with cerebral glucose metabolism in brain regions that support a variety of integrative functions involved in affective processing. A number of these regions are also known to be vulnerable to early progressive neurodegenerative changes, and therefore lay the foundation for future studies investigating the longitudinal relationship between positive affect and factors associated with pathological aging and brain health. Additionally, our findings highlight the potential for interventions aimed at increasing and/or maintaining positive affect, particularly in late-middle aged adults when early preclinical neuropathological processes may still be modifiable.

Acknowledgements

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