The temporal dynamics of emotion and reward related brain activity – relations to health, well-being and psychopathology

By

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Abstract

The experience of positive emotions can promote health and act as a buffer against the development of psychopathology. However, the underlying the role of positive affect in health and psychopathology has been understudied. Investigators have primarily explored positive emotion as a unitary, static phenomenon despite the fact that emotions unfold over time. Across several studies, we found that the temporal dynamics of reward-related brain activity predicts self-reported positive affect in both untreated and treated depressed patients. Additionally, the temporal dynamics of reward-related brain activity predict well-being and stress hormone output in a community sample. Lastly, we used cell-phone based experience sampling (via text messaging) to examine the neurobiological substrates of sustained positive affect experienced in the real world. Further exploring these temporal dynamics are critical to better understand individual differences in positive emotion, health, and potentially developing novel treatments for affect-related psychopathology.

Chapter 1

Introduction & Background

Since Darwin's initial publication on The Expression of Emotions in Man and Animals (Darwin, 1872/1998), theories of emotion have posited a functional role for emotions. This led to the idea that at the most basic level, organisms seek to either approach or withdraw from stimuli (Schneirla, 1959), and that the experience of emotions is to promote a state of readiness in the organism to act in the face of these appetitive or aversive contexts (Ekman, 1992; Frijda, 1992; Lang, 1995; Levenson, 1999). From this framework, one popular theory is that emotion can be broken down along valence (positive—negative) and arousal (high—low arousal) dimensions (Lang, 1995; Rolls, 2000). It is suggested that one's current location in this valence—arousal plane predicts the extent to which approach or withdrawal actions are readied. Taken to its philosophical extreme is the notion of embodiment (Nunez and Freeman, 1999), but is not discussed further in this dissertation. In humans, the experience of emotion takes on additional complexity with an enlarged brain and, in particular, an elaborated prefrontal cortex. While approach and withdrawal may continue to be the foundational building blocks and function of emotion, feelings such as awe and savoring, rumination and self-hate add nuance to our emotional experience and are in part likely to be by-products of our elaborated pre frontal cortex.

At various points of western civilization, depending on cultural and societal norms, emotion and psychopathology have thought to arise supernaturally and were not biologically based (Porter, 2002).Yet as early as Hippocrates, the Ancient Greeks were well aware of the relationship between the brain, emotion and psychopathology:

> Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter, and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant. . . It is the same thing which makes us mad or delirious, inspires us with dread and fear, whether by night or by day, brings sleeplessness, inopportune

> mistakes, aimless anxieties, absentmindedness, and acts that are contrary to habit (cited in: Porter, 2002).

Despite this early enlightenment, in the fifteenth to seventeen centuries, melancholia and madness were thought to be a result of weakness towards the seductions of Satan and bewitchment. Following the rise of the scientific method and materialism, the theory that experience is biologically based has become dominant. Thus, as tools for studying the brain have improved, so has our understanding and acceptance of the role of the brain in emotion and psychopathology.

To witness the current prevailing belief that positive and negative emotions are central to psychopathology, one need look no further than the Diagnostic and Statistical Manual (DSM; American Psychiatric Association., 2000) for mental illness. The diagnosis of depression, for example, requires an individual to be experiencing persistent sad mood or a reduction in pleasure. Despite equal weight given to increased negative affect and decreased positive affect in the DSM definition of depression, research investigating reduced positive affect in depression has lagged behind research on increased negative affect. This asymmetric focus on negative affect is mirrored in basic research of positive and negative emotion in healthy samples whereby there is more research on negative affect as compared with positive affect. Clinically, this asymmetry is all the more interesting as research suggests that depressed patients themselves conceptualize remission from depression as increased positive affect more than reduced negative affect (Zimmerman et al., 2012). For example, when asked to select the most important factors in determining remission, depressed patients identified “presence of positive mental health, a return to one’s usual self, a general sense of well-being, as well as the absence of symptoms of depression” (Zimmerman et al., 2006).

Similar to a depressed patient's conceptualization that remission from depression grows out of increased positive affect, positive emotions are critical in the promotion of well-being – defined as a sense of purpose, meaningful and positive engagement with life (also referred to as "flourishing", Ryff, 1989; Ryff and Keyes, 1995; Fredrickson and Losada, 2005). Aristotle termed this type of well-being as eudaimonia (see also, Diener, 1984; Diener and Lucas, 1999). Importantly, research has begun to suggest a link between well-being and measures of health (Pressman and Cohen, 2005). Individual differences in multiple types of well-being have been found to predict a variety of objective indices of health including, cardiovascular (Boehm and Kubzansky, 2012), levels of stress (as measured by the stress hormone cortisol; Ryff et al., 2004) and peripheral inflammation (Dockray and Steptoe, 2010). This research suggesting a connection between mental and physical health is further complimented by a growing body of evidence that individuals suffering from depression have increased levels of peripheral inflammatory biomarkers (Miller et al., 2009; Raison and Miller, 2011). However, it is currently unknown whether increased negative affect or decreased positive affect better predict increased inflammation in depression.

As described in the foregoing, over the last forty years, there has been a growth of research suggesting a connection between the brain, emotion and psychopathology. However emotion does not have a single, unitary dimension, nor is it static – emotion unfolds over time in a dynamic, changing environment. Within an individual, experiences may differ in the magnitude of emotional response, the speed at which the maximal response is reached, the length of time that emotion is experienced, and the magnitude of emotional response to a subsequent affective event (Solomon and Corbit, 1974; Davidson, 1998, 2003). *Individuals* also differ on these dimensions in their response to identical stimuli which allow researchers to examine the

relationship between individual differences in these affect variables and health. Much of the work to date examining the relationship between individual differences in emotion and health has focused on the magnitude of emotional response. Yet, attention to these additional variables, particularly individual differences in the length of time an emotion is experienced (ie., "savoring" for sustained positive affect, and "rumination" for sustained negative affect), and the magnitude of emotional response to repeated affective events may improve our understanding of health, psychopathology and may account for additional variance in the neurobiology underlying emotional experience.

Before discussing the potential importance of the temporal dynamics of emotion and the neurobiology underlying such temporal dynamics further, a digression regarding the definitions of emotion and emotion regulation is required. Research has distinguished between emotion and its regulation (Gross, 1998a; Davidson et al., 2002b). In particular, recent theories of several types of mental illness have suggested that it is not emotion per se, but the inability or maladaptive regulation of emotion that underlies psychopathology (Cicchetti et al., 1995; Davidson et al., 2002a; Kring and Werner, 2004). The distinction between emotion and emotion regulation is indeed an important one and presents a conceptual challenge when examining the temporal dynamics of emotion. The regulation of emotion can occur in anticipation of, or in response to an emotional stimulus (Gross, 1998b). Such regulation will necessarily alter the magnitude and time-course of emotion and thus impact on the temporal dynamics of affect. Though emotion regulation is classically thought of as a conscious, volitional process, it need not be – emotion regulation can occur automatically and without conscious awareness. This is akin to unconscious, automatic processes involved in homeostasis (Craig, 2003, 2004; Chow et al., 2005). As such, even in paradigms where emotion regulation is not specified, the regulation of

such emotion can nonetheless be occurring. This possibility is confounded with the temporal dynamics of emotion per se, as we cannot separate individual differences in temporal dynamics resulting from the emotional response versus temporal dynamics resulting from the regulation of such emotion. While findings relating the temporal dynamics of emotion and brain activity to individual differences in health will not be able to specify whether this is due to reverberant brain activity within a single brain region or due to top-down regulation (automatic or otherwise), it does not diminish such a relationship. Future work may be able to address these mechanistic questions, but for the purposes of this dissertation, the term "temporal dynamics of emotion" encompasses both of these possible situations: It will encompass the temporal dynamics of emotion without the impact of emotion regulation, in addition to the temporal dynamics of emotion where regulation is impacting directly on the emotional and neurological response. The term "emotion regulation" will be reserved for use in paradigms where the volitional, cognitive regulation of emotion is required.

Importance of temporal dynamics

Highlighting the centrality of temporal dynamics of emotion, the DSM explicitly highlights the necessary nature of time for diagnosis of depression stating, "The essential feature of a Major Depressive Episode is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities" (American Psychiatric Association., 2000). Sustained, acute increases in negative or decreases in positive affect are thus core to the concept of depression.

It is important to highlight that despite the phrase above, increased negative or decreased positive affect are not synonyms. As noted earlier, depressed patients appear to value increased positive affect and greater well-being over reducing negative affect and sadness in the treatment

of their illness (Zimmerman et al., 2012). From neuroscience, we know that while there is substantial overlap in the systems governing emotion generally, there are also important differences in the networks responsible for processing valence (see below). Sustained positive and negative affect also likely have distinct downstream effects on facial musculature – with sustained positive and negative affect engaging the zygomatic and corrugator muscles of the face, respectively (Cacioppo and Tassinary, 1990). And of course, sustained positive affect and negative affect are phenomenologically distinct phenomena and thus must have distinct neurobiological substrates. How emotion is sustained is unknown, though it is likely that engagement of the prefrontal cortex is highly relevant to the sustainment of affect (Miller and Cohen, 2001). However, the degree to which similar or distinct prefrontal regions may serve to support sustained positive and negative emotion is yet unknown. For the purposes of this chapter, because so little work has been done in the area of temporal dynamics of emotion, when highlighting the importance of these dynamics generally, I will occasionally use a phrase including both sustained negative *and* positive affect.

A core feature of early models of the etiology of depression implicitly assumed the importance of the emotional response across time. One of the most influential theories regarding the etiology of depression is Abramson and colleagues' reformulated Helplessness Theory (Abramson et al., 1978). This theory posits that "when highly desired outcomes are believed improbable, or highly aversive outcomes are believed probable, and the individual expects that no response in his repertoire will change their likelihood, (helplessness) depression results" (Abramson et al., 1978). Nearly all research investigating this phenomenon examines individuals' response to aversive outcomes across time. It is assumed that consecutive, unavoidable outcomes will result in a specific cognitive, motivational and affective state that is a

model of depression. Thus, an individual's susceptibility or resilience to these manipulations is directly related to the dynamics of negative emotion across time (ie., across multiple stressful episodes). An individual unable to adaptively habituate the negative emotional response across time will be more likely to succumb to helplessness depression than an individual more adept at effectively engaging such habituation.

Indeed, animal models of learned helplessness bear this point out (see, Duman and Monteggia, 2006 for review). For example, acute doses of an antidepressant increases the amount of time a rodent spends actively struggling when placed in a beaker of water (forced swim test), suspended by their tail (tail-suspension test), or the amount of sucrose the rodent consumes (sucrose preference test). These animal models use time spent active or amount consumed as the primary dependent measure. While these animal models are certainly not perfect models of depression, it is telling that the central variable for these models reflects a specific temporal dynamic.

Further, research on resilience – the ability of an individual to adapt to acute or chronic forms of stress (Feder et al., 2009; Russo et al., 2012) – implicates the importance of examining emotion across *time* to health (and conversely, to pathology). Indeed, researchers from various laboratories have suggested that a critical factor to reduce stress and improve coping is the ability of individuals to sustain positive emotion or rapidly decrease negative emotion (Folkman and Moskowitz, 2000; Southwick et al., 2005). Rodent models of resilience suggest that resilience may be subserved by glutamatergic interactions between the prefrontal cortex (PFC) and ventral striatum (VS, including the Nucleus Accumbens [NAcc]), complimented by ascending dopaminergic pathways from the ventral tegmental area (VTA) to the VS and PFC (see below for more on neuroanatomy of positive affect; Russo et al., 2012). Optogenetic studies have

recently suggested that more sustained activity in the mPFC (roughly analogous to the vmPFC in humans – with direct projections to the VS) promotes resilience in a rodent model of resilience (Russo et al., 2012).

It has also been argued that sustained positive emotions can serve to replenish depleted emotional regulation resources (Folkman and Moskowitz, 2000) such that emotion regulation capacity may be restored following sustained positive emotion. This provides support for a hypothesis that sustained positive emotion can be protective and lead to resiliency. Sustaining hope and a positive outlook is central to Viktor Frankl's experience of survival and growth during his time in the Nazi concentration camps, and is elaborated in Man's Search for Meaning (Frankl, 1959). Similarly, Fredrickson's "broaden and build theory of positive emotions" posits that positive emotions serve to build personal resources by broadening one's thoughts and actions (Fredrickson and Losada, 2005; Tugade and Fredrickson, 2007). Thus, the ability to maintain positive emotion and amidst stressful experiences – across time – may be promote well-being and resilience.

One of the most influential theories of stress related pathology, considers that the inability to decrease negative emotion, or maintain positive emotion across time to be fundamental to the development of allostatic load and stress related pathology (McEwen, 1998; McEwen and Seeman, 1999). From a health promotion perspective, McEwen has argued that cumulative exposures to stressful events can lead to an array of health impairments including coronary artery disease, chronic pulmonary disease, cancer, alcoholism, depression, and drug abuse (Shonkoff et al., 2009). Not only does this highlight the connection between mental and physical health, but this suggests that individuals better able to sustain positive or decrease

negative emotion across time in response to stressful events, may subsequently be less likely to suffer from stress-related pathology.

As researchers have become more attentive to the relevance of the temporal dynamics of affect to understanding individual differences in health and pathology, animal models explicitly designed to examine such dynamics have slowly followed suit. LeDoux and colleagues have begun to explicitly investigate the temporal dynamics of emotion using a rodent model of behavior (Bush et al., 2007). Using outbred Sprague-Dawley rats, LeDoux and colleagues found stable, trait-like differences among rats displaying high and low reactivity to a shock during fear conditioning (as measured by freezing level). Perhaps more importantly, they also were able to identify rodents displaying either rapid or slow recovery during extinction trials. While they have not yet reported any biological differences separating the two rodent groups, they do highlight the potential impact of using these specific measures of temporal dynamics to better understand the biological mechanisms underlying rodent models of mood disorders.

The relevance and potential of sustained positive affect in combating psychopathology has become a recent focus for several researchers. The notion of "savoring" – as sustained positive affect has been referred to – has been in the psychological literature for some time (Bryant, 1989), but has become a focus of more research in recent years. The notion of savoring has been exploited in the development of a novel psychotherapeutic intervention by Fava and colleagues. In this therapeutic intervention, patients are trained to sustain positive affect with the intention of enhancing and reducing well-being and depression, respectively (Fava and Tomba, 2009). Other recent therapies have also explicitly attempted to increase patients capacity to sustain positive emotion (McMakin et al., 2010). This notion was also inherent in Lewinsohn's seminal idea of behavioral treatments for depression (Lewinsohn, 1974). Thus sustaining

positive emotion and positive emotion regulation appears to be relevant for psychotherapeutic intervention.

That sustained negative affect can be detrimental to mental health is inherent in the notion of rumination (Nolen-Hoeksema et al., 2008). Rumination is a mode of responding to distress that involves repetitively focusing on symptoms of distress (Nolen-Hoeksema et al., 2008). These would be considered to be automatic thoughts in Beck's model of depression (Beck, 1970). Not surprisingly, individual differences in rumination predict depressive symptoms (Nolen-Hoeksema, 2000). Such temporal dynamics have also been referred to as emotional inertia (Kuppens et al., 2010a; Kuppens et al., 2010b). Thus, sustained negative affect, particularly as critical judgments and statements directed towards the self increases the likelihood for development of depression.

The notion that the temporal dynamics of emotion are relevant for individual differences in health and psychopathology grows out of theoretical work on The Opponent Process Theory of Motivation and Emotion (Solomon and Corbit, 1974) and Affective Chronometry (Davidson, 1998). The evidence presented suggests a potentially important role for examining the temporal dynamics of affect. It also suggests that neuroscience research examining the temporal dynamics of brain activity underlying such emotion may reveal relationships not known to this point. Because positive affect has been less studied than negative affect and is so central to mood disorders and well-being this dissertation focuses primarily on the temporal dynamics of positive affect and reward-related brain activity. What follows is a brief review of the neuroanatomy of positive affect.

Neuroanatomy of Positive Affect

Since Olds and Milner discovered that animals are driven to excessive self-stimulation when electrodes are implanted into the Ventral Striatum (VS), researchers have examined the role this area has in reward (Olds and Milner, 1954). Recent years have seen an increase in research attempting to elucidate the neural processes involved in reward and positive affect (Haber and Knutson, 2010; Lalumiere and Kalivas, 2012). The VS is primarily composed of medium spiny GABAergic projection neurons (95% of neurons within the VS) as well as fast spiking interneurons (Gerfen and Bolam, 2010). The medium spiny projection neurons of the VS primarily target the Hypothalamus, Bed Nucleus of Stria Terminalis (BNST), Ventral Pallidum, Ventral Tegmental Area (VTA), medial Substantia Nigra, Nucleus Basalis and Pedunculopontine nucleus (See Figure 1, Haber and Knutson, 2010; Lalumiere and Kalivas, 2012). Conversely, the VS receives glutamatergic afferents from the medial PFC, hippocampus, amygdala, and lateral hypothalamus. These projections primarily target VS GABAergic interneurons which modulate the excitability of the GABAergic medium spiny projection neurons. Lastly, the VS receives well-known dopaminergic input from the VTA.

The ascending dopaminergic projections from the VTA to the VS has received considerable attention for its role in reward processing and the so-called "prediction error" (Schultz, 1998; Haber and Knutson, 2010). These dopamine signals display short-latency, phasic reward properties that distinguish between actual and predicted rewards (Schultz, 2002). Once a conditioned stimulus reliably predicts a reward, ascending dopaminergic projections respond to the conditioned stimulus in anticipation of the reward but not to the reward itself. If a conditioned stimulus associated with a reward is followed by no reward, there is a depression in dopaminergic firing. This has led to the suggestion that the dopamine may act in part as a reward learning signal (Schultz, 2002). The effect of the dopamine signaling onto the VS is as a

neuromodulator via modulation of voltage-gated sodium, potassium and calcium channels in spiny projection neurons. This modulation leads to complex and state-dependent changes in striatal neuronal excitability (Oorschot, 2010).

In addition to ascending dopaminergic neurotransmission appearing to be a reward prediction signal, the VS is also involved in the hedonic response to affective stimuli. Within the VS, studies have primarily targeted the Nucleus Accumbens (NAcc) as well as the adjacent ventral pallidum. Seminal work by Kent Berridge in rodent models has distinguished two separable functions of the NAcc with regards to reward processing (see: Berridge and Kringelbach, 2008; Kringelbach and Berridge, 2009 for reviews). The first, primarily governed by dopaminergic and opioid transmission, occurs within the entire NAcc and is associated with "wanting" – the motivation or "incentive salience" to work for a reward. The second, primarily governed by opioid transmission (and not dopaminergic transmission), occurs within the NAcc 'shell' as well as the ventral pallidum and is associated with "liking" – the actual hedonic impact of a rewarding stimulus. A recent publication by Berridge's group highlights the potential for investigating temporal dynamics of reward related activity (Smith et al., 2011). As can be seen (Figure 2), while recording from the ventral pallidum, an area adjacent to the NAcc, there is substantial variability in the time-course of reward related firing. The authors did not examine this systematically, nor did they quantify the temporal dynamics of affective facial responses in the rats. However, the variability in the reward related firing may be meaningful and could eventually be exploited to examine individual differences. One difficulty with extending this important distinction into human work is that the NAcc core, shell subregions, as well as the ventral pallidum are relatively small and adjacent to one another (Kringelbach and Berridge, 2009). Given the native spatial resolution of fMRI (~4mm), imperfection in spatial normalization

procedures to compare across individual brains, and the need to spatially smooth functional data (often between 4-8mm) delineation of these specific subregions will be difficult.

Other subcortical regions have also been dissociated along this "wanting/liking" axis. Subcortical areas in addition to the NAcc involved in "wanting" include the Ventral Tegmental Area (VTA), and hypothalamus. In contrast, subcortical areas in addition to the NAcc 'shell' involved in "liking" include the Ventral Pallidum (VP), Periacqueductal Grey (PAG) and amygdala. For example, microinjection of mu-opioid agonists into rodent NAcc shell or VP increases hedonic facial reactions such as tongue protrusions when the rat receives sucrose stimulation (Smith and Berridge, 2007).

Human neuroimaging work examining the cortical circuits involved in reward and positive affect have by and large not dissociated between "wanting" and "liking". However, recent meta-analyses of positive emotion have suggested that positive emotion engages (Kober et al., 2008) various portions of the limbic system including the ventral and dorsal portions of the striatum, Anterior Cingulate Cortex (ACC), Orbitofrontal Cortex (OFC) and the Inusla (Delgado, 2007; Kringelbach and Berridge, 2009). Work by Rolls and colleagues in both human and nonhuman primates, has highlighted the vmPFC as an important component in the hedonic processing circuit (Kringelbach and Rolls, 2004). In recent studies with humans as well as non-human primates, the vmPFC has been found to track the value of a stimulus across several reward types (Behrens et al., 2008; Hare et al., 2009; Smith et al., 2010; Grabenhorst and Rolls, 2011). Further, neuroimaging studies have also found that subjective value is coded within subcortical regions including the basal ganglia (Porcelli and Delgado, 2009; Haber and Knutson, 2010).

Overview of empirical work

My work thus far has attempted to examine the relationship between the temporal dynamics of emotion and brain activity with individual differences in reduced positive affect in depression and well-being. We have principally used functional Magnetic Resonance Imaging (fMRI) to examine individual differences in the repeated engagement of brain circuits thought to be relevant in the processing of rewards and positive affect, namely, the VS. In particular, we have examined temporal dynamics of brain activity in two ways. Looking at individual differences in rates of habituation across time – that is, how reward related circuitry responds to the repeated occurrence of positive stimuli makes up the first three empirical chapters of this dissertation (Heller et al., 2009; Heller et al., In Press; Heller et al., Under Review). This is examined with reduced positive affect in depression as well as in individual differences in well-being in a representative community sample. The last empirical chapter uses experience sampling (also termed Ecological Momentary Assessment; Shiffman et al., 2008) via text messaging to examine sustained positive and negative affect over time in participant's native environment. This last study had several differences from the previous three. First it used financial rewards instead affective images. Altering the rewarding stimulus (from affective images to financial incentives) tests the generalizability of the previous findings to a new stimulus domain, but no work to this point has directly compared the temporal dynamics of BOLD activity in response to visual vs. financial rewards. As a result, there may be some divergences in the findings which are due simply to stimulus type than to individual differences in the temporal dynamics of affect and brain activity. Second it used undergraduate students instead of a community or psychiatric sample. The advantages of utilizing undergraduate students are that they are easy to recruit and could be used to collect data for multiple studies rapidly. An important disadvantage is the potential for reduced variability in trait measures of

well-being or positive affect. A restriction of range could impact our ability to find relationships between on temporal dynamics of state-induced positive affect and brain activity. Third, instead of examining rates of habituation across trials it primarily was concerned with sustained brain activity and sustained positive affect within trials. It is unknown the relationship between these two measures of the temporal dynamics of positive affect and whether one is more predictive of health and well-being than the other.

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Chapter 2

Reduced capacity to sustain positive emotion in major depression reflects diminished maintenance of fronto-striatal brain activation.

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Abstract

Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a core feature of major depression. While theorists have argued that anhedonia reflects a reduced capacity to experience pleasure, evidence is mixed as to whether anhedonia is caused by a reduction in hedonic capacity. An alternative explanation is that anhedonia is due to the inability to sustain positive affect across time. Using positive images, we employed an emotion regulation task to test whether individuals with depression are unable to sustain activation in neural circuits underlying positive affect and reward. While upregulating positive affect, depressed individuals failed to sustain nucleus accumbens activity over time as compared to controls. This decreased capacity was related to individual differences in self-reported positive affect. Connectivity analyses further implicated the fronto-striatal network in anhedonia. These findings support the hypothesis that anhedonia in depressed patients reflects the inability to sustain engagement of structures involved in positive affect and reward.

Introduction

Anhedonia, the loss of pleasure or interest in previously rewarding stimuli, is a hallmark of clinical depression (American Psychiatric Association., 2000). Anhedonia and/or a persistently depressed mood are required by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for the diagnosis of Major Depressive Disorder (MDD). While the exact biological bases of anhedonia are not known, research suggests that anhedonia may result, in part, from disruption of systems implicated in reward and motivation, which likely include the Nucleus Accumbens (NAcc) (Nestler et al., 2002; Tremblay et al., 2005; Nestler and Carlezon, 2006) and the frontostriatal network (Del Arco and Mora, 2008). Furthermore, human and nonhuman work suggest that the prefrontal cortex (PFC) influences activity in the striatum and can modulate reward-related firing in the NAcc in a top-down manner (Grace et al., 2007; Kim and Hamann, 2007; Del Arco and Mora, 2008; Wager et al., 2008). Indeed, a recent review of the rodent literature by DelArco and Mora (Del Arco and Mora, 2008), makes a strong case for modulation of NAcc activity by efferent PFC neurons. This network has been proposed as one pathway by which anhedonia is instantiated (Nestler et al., 2002; Nestler and Carlezon, 2006).

One hypothesis regarding the etiology of anhedonia is that depressed patients suffer from reduced hedonic capacity, defined as the total amount of positive affect that is possible for one to experience (Myerson, 1922; Meehl, 1975). While many current depression researchers subscribe to the notion of reduced hedonic capacity, behavioral and physiological studies of individuals with anhedonia have been mixed as to whether anhedonic individuals actually show a reduction in their capacity to experience pleasure.

Many studies have shown that individuals with depression or non-depressed individuals with the trait of anhedonia have decreased facial EMG zygomatic responses (Sloan et al., 2002), reduced startle attenuation (Larson et al., 2007), and reduced self-reported experience of positive affect to positive stimuli (Fiorito and Simons, 1994). Other studies, however, have been unable to replicate these findings (Berlin, 1998; Germans, 2000; Kaviani et al., 2004). Neuroimaging studies of individuals with anhedonia are also inconclusive. For instance, some studies show that depressed individuals or those with trait-like anhedonia display a lack of increase in NAcc activity when presented with pleasurable stimuli (Keedwell et al., 2005; Epstein et al., 2006). Yet, other studies have not found group differences in NAcc activity in MDD (Mitterschiffthaler et al., 2003; Schaefer et al., 2006; Harvey et al., 2007; Knutson et al., 2008).

Such inconsistencies suggest the possibility that MDD reflects more than just a simple reduction in the capacity to experience pleasure. As was proposed by Myerson (Myerson, 1922), anhedonia may not be solely due to a tonic reduction in the capacity to experience pleasure, but an inability to sustain positive affect and reward responsiveness over time. The notion of sustainability of positive affect was more recently discussed by Tomarken & Keener (Tomarken, 1998) who hypothesized that in depression the inability to sustain positive affect may result from disordered positive emotion regulation. They suggested that effective up- and down-regulation of positive emotion is necessary to experience positive affect over time. Indeed, in healthy individuals there is evidence suggesting that the regulation of positive affect involves biasing signals directed from PFC to the NAcc (Kim and Hamann, 2007; Wager et al., 2008). Collectively, this

suggests the hypothesis that depressed individuals will exhibit difficulties using PFC to sustain NAcc activity over time, particularly when that activity occurs in the context of attempts to up-regulate or *enhance* positive affect.

Accordingly, we used functional magnetic resonance imaging (fMRI) data acquired from a sample of depressed (n=27) and control (n=19) individuals during an instructed emotion regulation paradigm to test whether depression reflects a deficit in the ability to sustain activity in structures involved in reward, motivation and positive affect over a 37 minute scan session. Participants were instructed to use cognitive appraisal to "enhance" or "suppress" their emotional response to positive and negative images, or to simply "attend" to the stimuli in the absence of cognitive reappraisal. To investigate changes across the scan session, we modeled time in two ways. In our primary analyses, we split the 37 minute scan session into two halves and examined the change in activation across those two halves. We additionally treated time continuously across the six scan runs and examined the slope of change in activity across time. Thus, we were able to test several specific predictions. We first predicted that depressed patients will fail to sustain activity in the striatum (including the NAcc) when upregulating affect in response to positive stimuli. To this end, we examined the weighted Group x Time interaction for the "enhance" vs. "suppress" contrast. Our initial analysis contrasted the "enhance" vs. "suppress" conditions for two reasons. First, this contrast compares changes in activity across time in the condition which putatively causes the most positive affect with the condition which causes the least positive affect. Second, contrasting the two active regulatory conditions accounts for the cognitive load produced by volitional emotion regulation (Urry et al., 2009). In our second prediction, we tested the hypothesis

that the deficit in sustaining engagement of the NAcc will be more pronounced when depressed patients were required to repeatedly regulate (or increase) their positive affect. To do this, we conducted a similar Group x Time analysis using the "enhance" vs. "attend" contrast. The third prediction was that individual differences in the ability to sustain activity in reward related regions would predict overall self-reported positive affect acquired outside the scanner. The fourth prediction was that the inability to sustain engagement of the NAcc would be related to attenuated connectivity between the NAcc and PFC.

Materials and Methods

Participants. We examined a group of 27 medication-free, right handed adults satisfying the DSM-IV (American Psychiatric Association., 2000) criteria for unipolar major depressive disorder (age range, 19-53; mean age, 31.48 years; SD, 11.58; 12 males). These depressed individuals were compared with an age and sex-matched group of 19 right-handed controls (age range, 20-60 years; mean age, 31.84 years; SD, 14.65; 9 males; age difference between groups not significant; $F<1$). All subjects were recruited via the use of flyers posted in public places around the Madison, WI area. Depressed participants had depressive symptoms for at least 1 month prior to their screening visit and a score of at least 18 on the Hamilton Rating Scale for Depression (Hamilton, 1960) (HAM-D) at screen and the fMRI scan (mean HAM-D ± SD depressed, 20.6 ± 2.39; controls, 1.2 ± 1.6). In addition to standard MRI compatibility criteria, subjects were screened for and excluded if they met DSM-IV criteria for alcohol or drug abuse or dependence, other DSM-IV Axis I or Axis II diagnoses, had a personal or family history of bipolar disorder or were using any medications that affect CNS function. Participants

were also excluded if they had an anxiety disorder, ensuring that the sample represent a relatively "pure" MDD group. In addition to the HAM-D, both before and after the scan session, all participants except one depressed subject completed the extended version (48 total items) of the Positive Affect/Negative Affect scales (Watson et al., 1988) (PANAS-X) and was therefore removed from the analysis. The pre- and post-scan PANAS scores were then averaged to ensure reliable self-reported affect scores. Subjects participating in this study are the same as those who participated in (Johnstone et al., 2007). This research was approved by the University of Wisconsin–Madison Health Sciences Institutional Review Board, and all participants provided written informed consent. Because depression is a heterogeneous disorder (e.g., Drevets et al., 2008), we over-recruited the MDD group in an attempt to ensure sufficient power to address the underlying neural abnormalities subserving the binary category of MDD.

Task. The experimental task was a variant of that used previously in our laboratory with normal subjects (Urry et al., 2006) and similar to the tasks used in other recent studies (Jackson et al., 2000; Schaefer et al., 2002; Ochsner et al., 2004). Subjects were scanned while viewing a sequence of 72 emotionally positive and 72 negative pictures taken from the International Affective Picture System (IAPS) (Lang PJ, 2005). A 1s fixation cross coupled with a tone oriented subjects to the upcoming trial, after which each image was presented for 10s, followed by a 6 s blank screen. To ensure participants remained attentive to the task, at the onset of each picture, subjects had to judge whether the image was positive or negative and respond with an appropriate button press on a two-button response pad. Four seconds into the presentation of each picture, an audio prompt instructed the participant to either increase ("enhance") or decrease ("suppress") their

emotional response to the picture or to continue to "attend" to the picture. Participants were trained during a previous session while positioned inside a mock scanner on the use of cognitive re-appraisal strategies to re-evaluate the images as more or less emotional (Jackson et al., 2000; Urry et al., 2006). For the enhance condition, participants were trained to either imagine themselves or a loved one experiencing the situation being depicted or imagine a more extreme outcome than the one depicted (e.g., in response to a picture of a stunning natural scene, a participant might imagine being in that scene or one of their own choosing). Conversely, for the suppress condition, individuals were trained to either view the situation as fake or unreal or imagine that the situation being depicted had a different outcome than the one suggested (e.g., a couple in love were just actors and did not feel the way depicted in the image). Alternatively, on attend trials, participants were instructed to maintain their attention to the picture without changing their affective experience. Simulated scanner sounds and task instructions were presented using earbud headphones during this training session. The training was succeeded by follow-up queries to ensure that participants were using the strategies as instructed and reported being able to perform the task. Negative pictures were selected according to the IAPS norms to be both unpleasant (1, most unpleasant, to 9, most pleasant; $M = 2.95$; SD, 0.87) and arousing (1, least arousing, to 9, most arousing; $M = 5.44$; SD, 0.80), whereas positive images were pleasant ($M = 7.13$; SD, 0.62) and arousing ($M = 5.28$; SD, 0.58) Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA) via a fiber-optic goggle system (Avotec, Stuart, FL) with a screen resolution of 800 x 600 pixels. In the fMRI session, there were 24 repetitions of each regulation condition and 12 repetitions of the attend condition for each picture valence, evenly distributed over six

scans, each lasting 380s. The order of positive and negative images and the three regulation instructions was pseudorandomized such that each scan run contained at least one trial of each condition type. With regard to order of positive and negative trials: positive trials were preceded by other positive trials approximately as often as by negative trials (42% of the positive trials were preceded by a positive trial and 57% of the positive trials were preceded by a negative trial; χ^2=1.37; p=.241), suggesting that the results are not due to the lingering effects of negative stimuli on BOLD response to positive stimuli.

Behavioral measures. Reaction time to image onset, as well as pupil dilation measures were acquired. Assessing pupil dilation provides an unobtrusive measure of autonomic arousal (Loewenfeld, 1993) with pupil constriction driven primarily by the parasympathetic branch of the autonomic nervous system (ANS), and pupil dilation primarily reflecting activity of the sympathetic branch. Pupil dilation is thus an indicator of increased cognitive and attentional load during effortful top-down regulation (Kahneman and Beatty, 1966; Siegle et al., 2003; Ohira et al., 2006). To assess autonomic arousal associated with effortful reappraisal, we measured the extent to which the pupil dilated during the active reappraisal period of each stimulus trial. Based on our previous research showing pupil dilation to be a sensitive index of the cognitive effort during reappraisal in healthy individuals (Urry et al., 2006; van Reekum et al., 2007), we examined whether pupil dilation changed across the scan session for either of the groups.

Pupil data acquisition and analysis. Horizontal pupil diameter data were acquired continuously at 60 Hz using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments, Teltow, Germany), which was interfaced with the

fiber optic goggle system. Pupil data from four controls and six depressed individuals were not usable because of technical problems. Pupil dilation data were processed using algorithms written by Siegle et al. (2002) (unpublished MatLab code) with MatLab software (MathWorks, Natick, MA), modified in our laboratory. Blinks were identified and eliminated using local regression slopes and amplitude thresholds. Data were smoothed with a five-sample rolling average and linearly detrended over each scan run. For successive 500 ms bins in each trial, the proportion of time that the eye was open and mean pupil diameter were calculated. Pupil values were then range-corrected to standardize according to the pretrial maximally dilated pupil diameter and the maximally constricted pupil diameter in the 2 s after picture onset [(current pupil diameter – minimum pupil diameter)/(maximum pupil diameter – minimum pupil diameter)]. Data were averaged across a 5 s interval starting 1 s after instruction and continuing until picture offset (the reappraisal period). Data were then analyzed using mixed model GLM (subject as a random factor nested within the fixed factor group, and reappraisal as a within subject fixed factor).

Image acquisition. Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems, Waukesha, WI) equipped with a standard clinical whole-head transmit-receive quadrature head coil. Functional images were acquired using a T2*-weighted gradient-echo, echo planar imaging (EPI) pulse sequence [33 sagittal slices, 4 mm thickness, 1 mm interslice gap; 64 × 64 matrix; 240 mm field of view (FOV); repetition time (TR)/echo time (TE)/Flip, 2000 ms/30 ms/60°; 190 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion

recovery fast gradient echo; 256 × 256 in-plane resolution; 240 mm FOV; 124 × 1.1 mm axial slices).

Image analysis. Individual subject data were slice-time corrected, motion corrected, and analyzed in AFNI (Cox, 1996). Our GLM included covariates intended to model each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction), and for both the early and late phases of the scanning session (early: runs 1-3; late: runs 4-6) as well as six motion estimate covariates (Johnstone et al., 2006). We also included a second-order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of five sine basis functions to produce separate estimated hemodynamic response functions (HRFs) for each trial type. The estimated HRFs were converted to percentage signal change values, and within-subjects contrasts were calculated between the enhance and suppress conditions for positive pictures (i.e., positive enhance – positive suppress; 1st Half, 2nd Half), averaged across time points corresponding to the peak hemodynamic response during the regulation period (8–14 s after stimulus onset). Contrasts were normalized to Talairach space and smoothed using a 5 mm full-width at half-maximum Gaussian filter.

These smoothed contrast maps were then entered into a multiple linear regression analysis, in which contrasts were weighted to yield those brain areas that displayed a depressed group-specific decrease in activation across time. Specifically, our weights were as follows: 1st Half-Control (+1); 2nd Half-Control (+1); 1st Half-Depressed (+1); 2nd Half-Depressed (-3). The outcome of this analysis is essentially a weighted Group x Time interaction for the positive "enhance" vs. positive "suppress" as well as the "enhance" vs. "attend" condition contrast. In order to examine time as a continuous variable, we

performed a second analysis in which we modulated the amplitude of each run in a linear fashion. Following single subject GLM analysis, we normalized and smoothed the maps identically to the parameters above and subsequently contrasted the "enhance" and "suppress", as well as the "enhance" vs. "attend" brain maps for each subject prior to performing random effects group analyses. We elected not to use the amplitude modulator for all analyses because the time course plots as well as the connectivity analyses required splitting the scan session into discrete sections. We also performed the same analysis for negative stimuli in order to compare the group differences in neural activity to positive vs. negative slides. Connectivity analyses were performed using the beta series correlation method described in (Rissman et al., 2004), which is a variant of the PPI approach. More details on this method can be found in Appendix I.

Univariate statistical maps were thresholded at $p < 0.05$, corrected for multiple comparisons using cluster-size thresholding based ($k > 50$ voxels) on Monte Carlo simulation (the AlphaSim program in AFNI) using a whole-brain mask. The connectivity statistical maps were thresholded at $p < 0.05$, small volume corrected for multiple comparisons using a PFC mask which included clusters found to be significant in a recent meta-analysis of fMRI studies of emotion regulation (Kalisch, 2009) and resulted in clusters exceeding a minimum of $k = 15$ voxels. For further details see Appendix I.

Results

Depressed individuals fail to sustain NAcc activation when amplifying positive emotion

We first examined whether individuals with depression showed an inability to sustain activity in reward-related regions across the scan session when attempting to upregulate positive affect. Supporting the failure to sustain positive affect hypothesis of

depression, we observed a significant weighted group–by-time interaction ($p < .05$, corrected for multiple comparisons) in the NAcc (Figure 1a; peak x,y,z: -9, 12, 0), such that the depressed group showed a decrease in the "enhance" vs. "suppress" contrast during the second half of the scan session only; the control group showed sustained activity in this region (Figure 1c; timecourses: Figure 2). Follow-up pairwise contrasts supported this. The groups differed during the 2nd half ($t_{(43)} = 4.22$; $p<.001$), but not during the first half ($t_{(43)} = .717$; $p=.48$). In addition, the depressed group showed a reduction in activity from 1st to 2nd Half ($t_{(25)} = 3.09$; $p=.005$), whereas the controls showed no change ($t_{(18)} = -1.37$; $p=.18$). Other regions showing an effect included the left Insula/Transverse temporal gyrus and right Thalamus (see Table 1)[1].

Second, we examined the hypothesis that the deficit in sustaining engagement of the NAcc will be more pronounced when depressed patients were required to repeatedly up-regulate their positive affect. To do this, we assessed whether changes in the NAcc cluster found in the first step showed a similar weighted Group x Time effect for the more conventional "enhance" vs. "attend" contrast. Indeed, this test was significant ($F_{(1,88)} = 8.56$; $p=.004$), and follow up tests indicated a trend for the groups differing during the 2nd half ($t_{(43)} = 1.74$; $p=.089$), but not during the first half ($t_{(43)} = .324$; $p=.747$). In addition, the depressed group showed a reduction in activity from 1st to 2nd Half ($t_{(25)} = 2.60$; $p=.015$), whereas the controls showed no change ($t_{(18)} = 4.64$; $p=.65$). This indicates that this result was not specific to our choice of control condition. We also performed this contrast in a map-wise fashion; for other significant regions, see Table 1 in Appendix I. We also performed the above two analyses in which time was modeled continuously (as a

[1] Moreover, each of these analyses regarding positive stimuli remained significant after controlling for activity in the NAcc cluster on the negative trials.

function of run) with an amplitude modulator. Within the NAcc cluster found in the first step and using the "enhance" vs. "suppress" contrast, the depressed group showed a significantly greater linear reduction across time than the controls (at $p<.005$) in the NAcc, providing further evidence that NAcc activity habituates in a linear fashion across time in depressed patients. In an analysis using the "enhance" vs. "attend" contrast, a similar pattern emerged, albeit at a lower threshold ($p<.025$). These results corroborate our findings when splitting the session into halves and suggest that the decreased engagement of NAcc by the depressed patients occurred in a linear fashion.

As a way of integrating these results, we performed a follow-up trend analysis using the NAcc cluster from the first analysis to examine whether the reduction in NAcc activity across time was linearly related to the amount of positive affect putatively produced by condition (defined as the greatest decrease across scan session for the "enhance", followed by the "attend" condition, and the least decrease during the "suppress" condition). Using change in activity from 1st Half to 2nd Half as the dependant variable, the Group x Condition ("enhance", "attend", "suppress") interaction was significant ($F_{(2,42)}=5.01$;$p=.01$). Simple effects tests showed that for the MDD group, change in NAcc activity was linearly related to regulation instruction ($F_{(1,76)}=6.77$;$p=.01$) such that the greatest change in NAcc activity occurred in the condition which putatively engendered the most positive affect; for the control group, change in NAcc activity was not linearly related to regulation instruction ($F_{(1,55)}<1$;$p=.54$; see Figure 3).

To examine change in NAcc activity across time in a more neutral context (i.e. without effortful emotion regulation), we investigated whether the mean activity in the NAcc cluster defined in the first analysis also evinced a significant Group x Half (1st and

2nd Half) interaction in the "attend" vs. baseline contrast. The NAcc cluster did show a significant interaction ($F_{(1,43)} = 6.71$; p=.013) and follow up t-tests showed that the depressed group showed a specific reduction in NAcc activity in the second half of the experiment ($t_{(25)} = 3.325$; p = .003); controls showed no change ($t_{(18)} = -.63$; p = .536; see Table 2 in Appendix I for whole brain effects).

We further tested the hypothesis that sustainability of activity in the NAcc during the enhance condition can reliably differentiate between depressed patients and healthy controls. Given recent discussions in the neuroimaging literature (e.g., Kriegeskorte et al., 2009), we wish to emphasize that this analysis is meant to be descriptive in nature, with the intention of quantifying the consistency of this finding across participants, and *not* as a separate and novel test. To do this, we performed a linear discriminant analysis to show that the ability to sustain NAcc activation was able to significantly classify depressed patients (81% of MDD group, and 68% of controls were correctly classified; $F_{(1,44)} = 13.22$; $p = .001$). Critically, by contrast, NAcc activation averaged across time was not predictive of group, ($F_{(1,44)} < 1$; $p = .434$).

Deficits in sustaining activity in the NAcc is specific to positive emotion

We further examined whether the changes in NAcc activity in the depressed group were specific to trials on which positive stimuli were presented. To test this, we created an "enhance" vs. "suppress" and "enhance" vs. "attend" contrast map for each subject (for both the 1st and 2nd half of the scan session) for trials on which negative stimuli were presented. We then performed a weighted ANOVA to examine whether decreased NAcc activity in the second half of the scan session occurred only during upregulation of positive and not negative affect in the MDD group. As predicted, a

cluster in the NAcc, overlapping the cluster found in the previous analysis was significant at $p < .005$, indicating that reductions found in NAcc across the scan session are specific to positive stimuli.

In addition, taking the mean percent signal change across the entire NAcc cluster found in the first analysis, we tested whether changes in NAcc activity across the scan session during the positive "attend" condition was also present during the "attend" condition when negative stimuli were presented. For the MDD group only, there was a significant Valence x Half (1st and 2nd Half) interaction $F_{(1,25)} = 6.55$ (p=.017). Follow up paired t-tests revealed that NAcc activity decreased across the scan session during the positive "attend" ($t_{(25)} = 3.325$; p = .003), but not the negative "attend" ($t_{(25)} = 0.597$; p = .57) condition.

Patients who fail to sustain NAcc activity report less intense positive emotion

We next used a highly reliable and well-validated measure of self-reported positive affect to assess whether the failure to sustain ventral striatal activity in depression is related to the conscious experience of positive emotion. To do this, we examined relations between overall, self-reported positive affect (as assessed by the PANAS (Watson et al., 1988)) with activity changes from the NAcc cluster across time. For the depressed group only, less decrease in NAcc activity across time in the enhance condition predicted greater overall self-reported positive affect (r=-0.46; p=.019; Figure 1b). In the positive "enhance" condition, those depressed individuals with a sharper decline of activity in the NAcc across the two scan session halves reported experiencing less overall positive affect. This relationship was not driven by any outliers as confirmed by a Spearman's RHO test (rho= –.538; p=.005). These relations were valence-specific,

as similar relations were not found for self-reported negative affect (r=.05; *p*=.81). These relations were also specific to the sustainability of activity in the NAcc, as aggregated activity across the scan session to the positive enhance condition was not related to self-reported positive affect (r=.05; *p*=.82). In fact, the correlation between self-reported positive affect and sustainability of NAcc activity was significantly greater than the correlation between self-reported positive affect and aggregated NAcc activity ($t_{(25)}$=-2.095; *p*=.047). This provides further evidence that it is the specific ability to sustain activity in the NAcc across time which is related to general levels of self-reported positive affect.

Difficulties sustaining NAcc activation reflect reduced prefrontal connectivity

We then tested whether depressed individuals' inability to sustain NAcc activity during the positive enhance condition reflected a failure to engage regions of PFC implicated in emotion regulation. To this end, we performed a connectivity analysis using the significant cluster in left NAcc as the seed region. Consistent with our prediction, a prefrontal cluster (BA 8; peak x,y,z: -37, 13, 59; in the left middle frontal gyrus (MFG; Figure 4; see Table 1 in Appendix I) showed a significant Group x Time interaction (*p* <.05; small volume corrected), such that a reduction in connectivity with the NAcc across time was specific to the depressed group. This suggests that the reductions in activity in the NAcc may be driven, in part, by disordered connectivity with the left MFG.

Analyses controlling for task engagement

It was possible that depressed individuals' inability to sustain positive affect simply reflects nonspecific group differences in task engagement or motivation to regulate. If so, depressed individuals would be expected to show parallel differences in

measures sensitive to motivation and workload, such as reaction time (RT) or pupil dilation. In particular, over the scan session, one would predict that depressed individuals would be slower to indicate the valence of the image, reflecting their diminished engagement or greater fatigue. A 2-way Group x Time (1st vs. 2nd Half) ANOVA of RT to the positive images revealed no significant interaction ($F<1$). There was also no Group x Time interaction when RT to all images was used ($F<1$). Another objective measure of motivation is that of changes in pupil dilation, which reflect total cognitive effort (Kahneman and Beatty, 1966; Urry et al., 2006). A 2-way Group x Time (1st vs. 2nd Half) ANOVA of pupil dilation occurring during the enhance condition revealed no significant interaction ($F<1$), suggesting that changes in NAcc activity in the depressed group are specific to affect and not to motivation or attention.

Discussion

Anhedonia is a hallmark symptom of MDD and elucidating the core neural signatures and processes of anhedonia is necessary for a more complete understanding and treatment of the disorder (Pizzagalli et al., 2008). Given that the NAcc and fronto-striatal network have been implicated in reward processing (Wise, 2002; Knutson and Cooper, 2005; Knutson and Wimmer, 2007) and positive emotion regulation (Kim and Hamann, 2007), we hypothesized these networks to be involved in the disordered regulation of positive affect characteristic of anhedonia. In addition, due to inconsistencies in the anhnedonia literature, we tested a novel hypothesis, namely, that anhedonia reflects, in part, an inability to sustain positive affect across time.

FMRI results supported our hypotheses: First, while attempting to upregulate positive emotion, individuals with MDD showed a specific decrease in activation in the

NAcc across time, while control subjects maintained their level of activation. Depressed participants were also unable to sustain elicitation of NAcc engagement when simply attending to their emotional response to positive images. Furthermore, depressed patients displayed the greatest decreases in NAcc activity across time in those conditions which putatively engendered the most positive affect. The implication of this finding is that it is more difficult for depressed patients to sustain NAcc engagement in contexts during which the maintenance and/or upregulation of positive affect is expected. Second, we demonstrated that the amount of decrease in NAcc activity across time predicted overall self-reported positive affect. Lastly, a connectivity analysis revealed that the inability to sustain activity of NAcc may result from a breakdown in connectivity with left MFG. Collectively, these results suggest that disordered positive emotion regulation may result from an inability to sustain activity in the fronto-striatal network which leads to abnormalities in reward processing and reductions in positive affect.

Our lab previously published data from these same patients examining the neural correlates of cognitive emotion regulation in response to negatively valenced stimuli (Johnstone et al., 2007). In comparison to controls, the MDD patients displayed abnormalities in distinct networks when regulating negative as opposed to positive affect. However, both studies found abnormalities in the PFC. The fact that in depression, the PFC appears to be abnormally engaged in both positive and negative emotion regulation contributes to a growing body of work which suggests that depressed patients may have difficulty recruiting prefrontal resources to regulate subcortical structures involved in affect.

Researchers working at the nonhuman level work have found that the NAcc responds differentially to the anticipation vs. consumption of reward (Berridge and Robinson, 1998), suggesting that differentiating these phases of reward processing in depression is theoretically important. A recent publication by Pizzagalli and colleagues (Pizzagalli et al., 2009) sheds light on this issue. Patients engaged in a monetary incentive delay task in which they pressed a button in response to a target stimulus. Group differences in basal ganglia activity were weak during the anticipation period, but robust group differences were found in the Caudate and Nucleus Accumbens during the consummatory phase of the trial. While a rich non-human literature underscores the complexity of the NAcc in reward processing (Berridge and Robinson, 1998), the findings of Pizzagalli and colleagues suggest that the inability to sustain NAcc activity found here may result from specific deficits in the consummatory phase of reward processing – which rely heavily on the ventral striatum. Indeed, previous research suggests that NAcc activity tracks the hedonic value of outcomes (O'Doherty et al., 2004; Tricomi et al., 2004). It may be the case, therefore, that depressed patients have difficulty sustaining the engagement of the NAcc in response to tasks which require both the effortful heightening, and maintaining of positive affect. However, while this study suggests that the ability to continue to elicit NAcc engagement covaries with self-reported positive affect in general, future work should endeavor to track both NAcc activity and changes in self-reported positive affect with higher temporal resolution.

The clinical implications of our findings suggest that a treatment regimen which attempts to increase the depressed patient's ability to sustain engagement of the NAcc may ameliorate anhedonic symptoms. Because NAcc activation has been linked to

reward and motivation, training depressed individuals to sustain engagement with tasks which may activate the NAcc might be able to be used in clinical practice. Indeed, the behavioral therapy model for depression explicitly instructs depressed patients to increase the length of time spent performing rewarding activities (Lewinsohn, 1974). Because outcome studies have supported the clinical efficacy of the behavioral model (Hoberman, 1985), we would predict that one component of recovery from depression may be the ability to sustain engagement of the brain circuits implicated in reward and motivation.

Additionally, because both positive and negative stimuli were presented, it is important to be clear about the implications of these findings. Our study examines the ability of depressed patients to sustain engagement of the NAcc while enhancing positive affect in response to positive images *embedded* within a stream of stimuli that included both positive and negative images. This is a very important point, particularly with regard to the ecological validity of these findings. Namely, in everyday life, individuals do not generally encounter uninterrupted positive stimuli. Negative experiences often intermix with positive ones, and the ability of individuals to heighten and maintain positive affect in the face of negative stimuli is vitally important for health and well-being.

Lastly, an important issue that requires further delineation is distinguishing the neural substrates underlying the symptoms of anhedonia versus those of decreased motivation and psychomotor retardation seen in depression. A large nonhuman literature has suggested that the NAcc is involved in motivated, goal-directed behavior in addition to its contribution to reward processing (Salamone et al., 2003; Salamone et al., 2007). Yet it is not entirely clear to what degree disordered firing in the NAcc could also be relevant to other MDD symptoms of psychomotor retardation and reduced motivation.

An important challenge for future work will be to disentangle the role of the NAcc in specific symptomatology associated with MDD including anhedonia, psychomotor retardation, and decreased motivation.

In conclusion, our findings suggest that individuals with depression suffer from an inability to sustain reward-related activity that is reflected in the fronto-striatal network across time, and that this deficit is associated with reduced positive affect. These findings are consistent with the hypothesis that the hallmark symptoms of anhedonia in MDD are based on an inability to sustain positive affect. These data offer a novel interpretation for the symptom of anhedonia in depression. The findings also underscore the need for future studies to investigate the temporal dynamics of positive affect in depression and underscore the important role of affective chronometry in understanding the mechanistic bases of affective style (Davidson, 2003).

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Figure Legends

Figure 1: Activation in Nucleus Accumbens shows specific decrease for individuals with depression. (a) Depressed show a specific decrease from 1st to 2nd half of scan session (P<.05 corrected; k>50 voxels) in the Nucleus Accumbens. (b) For Depressed, less change in left NAcc activity is associated with greater self-reported positive affect. (c) Depressed patients show a decrease in NAcc activity, across time, in the Enhance vs. Suppress contrast. (d) Depressed patients show a decrease in NAcc activity, across time, in the Enhance vs. Attend contrast (error bars = Standard error of mean).

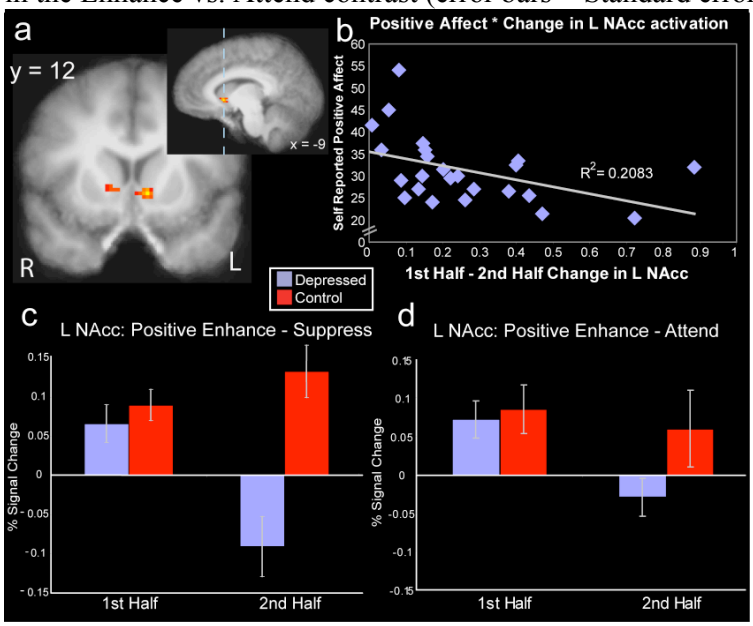

Figure 2: Time courses of activation in Nucleus Accumbens ROI for controls & depressed, 1st and 2nd half of scan session for the "enhance", "attend", and "suppress" conditions. Gray box denotes regulation period.

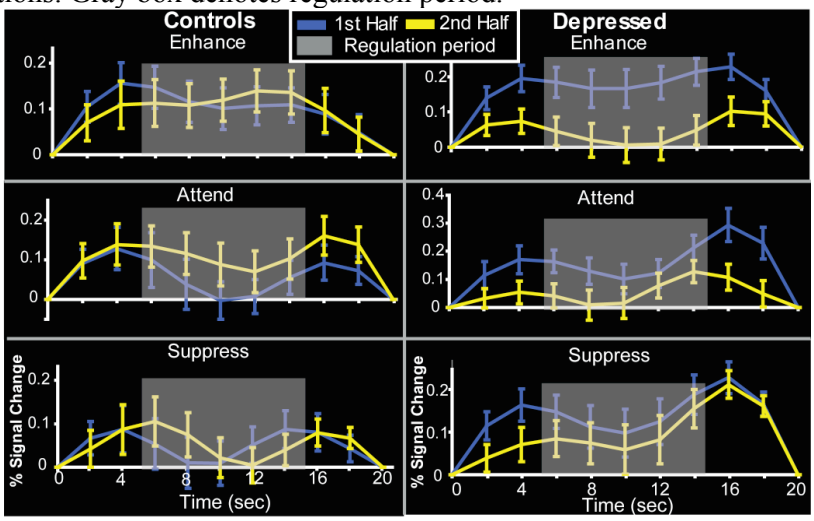

Figure 3: For depressed patients, the greatest decrease in NAcc activity across time occurs to the enhance condition. Greater values indicate a greater decrase in activation from 1st to 2nd half. Across the three conditions, the Group x Condition interaction was significant (F(2,42)=5.01;p=.01); the MDD group also showed a significant linear trend across conditions (F(1,76)=6.77;p=.01); controls did not (F<1). Pairwise t-tests for the MDD group were significant in the Enhance vs. Attend (t(25) = 2.60; p = .015) and Enhance vs. Suppress (t(25) = 3.09; p = .005) contrasts, there were no significant pairwise conrasts for the controls. Significant group differences were also found in the Enhance (t(43) = -3.86; p < .001) and Attend (t(43) = -2.59; p = .01) conditions such that the MDD group showed a greater decrease in NAcc activity from 1st to 2nd Half than controls. Error bars = standard error of mean. * = p < .05; ** = p < .01.

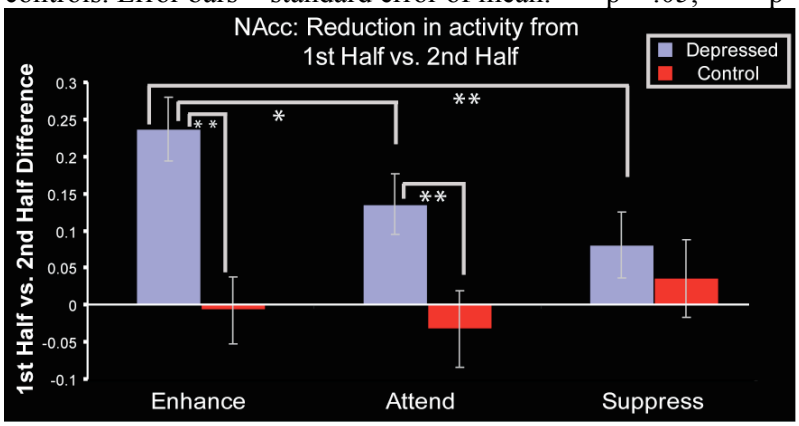

Figure 4: (a,b) Connectivity analysis indicating breakdown of LNAcc/L MFG connectivity as a function of time ($p < .05$, small volume corrected; $k>15$ voxels); error bars = SEM.

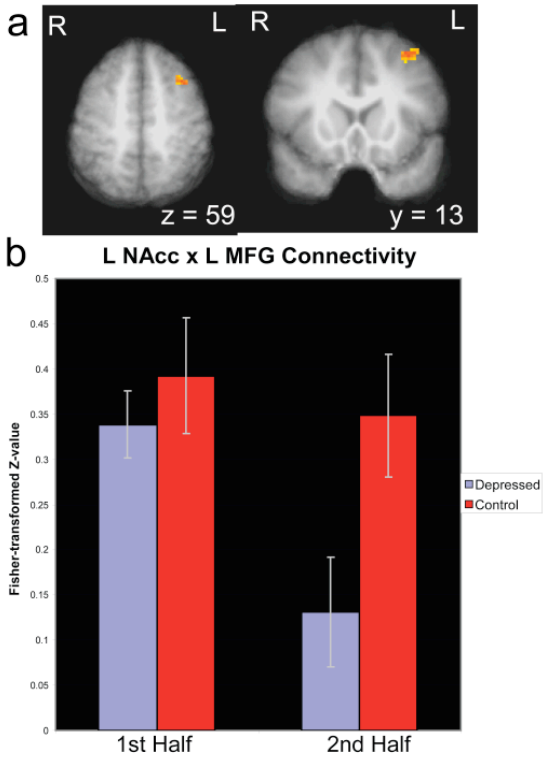

Table 1: Significant activations at $p<.05$ (corrected) for the weighted Group x Time interaction for enhance vs. suppress

	Cluster Maximum						
Location	x	y	z	# Voxels	Cluster Volume (mm^3)	F-Value	p-value
L Insula/Transverse Temporal Gyrus	-53	-17	14	99	792	16.62	9.8×10^{-5}
R Thalamus	1	-13	9	70	560	17.31	7.2×10^{-5}
L Nucleus Accumbens	-9	12	0	65	520	18.78	3.8×10^{-5}

Corresponding to p threshold: 0.005 (k > 50 voxels). L: left, R: right. Brackets: Brodmann areas. Coordinates: Talaraich System. F- and p-values correspond to the peak.

Chapter 3

Changes in sustained fronto-striatal circuitry resulting from antidepressant treatment correlates with changes in positive affect in major depression

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Abstract

Objective: Deficits in positive affect and their neural bases have been associated with major depression. However, whether reductions in positive affect result solely from an overall reduction in nucleus accumbens activity and fronto-striatal connectivity or the additional inability to sustain engagement over time of this network is unknown. Accordingly, we sought to determine whether treatment-induced changes in the ability to sustain nucleus accumbens activity and fronto-striatal connectivity during the regulation of positive affect are associated with gains in positive affect.

Method: Using fMRI, we assessed the ability to sustain activity in reward-related networks when attempting to increase positive emotion during performance of an emotion regulation paradigm in 21 depressed patients prior to, and after 2 months of antidepressant treatment. 14 healthy control subjects were scanned over the same interval.

Results: After 2 months of treatment, self-reported positive affect increased. Those patients demonstrating the largest increases in sustained nucleus accumbens activity over the 2 months were those demonstrating the largest increases in positive affect. In addition, those patients demonstrating the largest increases in sustained fronto-striatal connectivity were also those demonstrating the largest increases in positive affect when controlling for negative affect. Healthy controls showed none of these associations.

Conclusions: Treatment induced changes in the sustained engagement of fronto-striatal circuitry tracks the experience of positive emotion in daily life. Studies examining reduced positive affect in a variety of psychiatric disorders might benefit from examining

the temporal dynamics of brain activity when attempting to understand changes in daily positive affect.

Introduction

Reductions in the ability to experience positive affect is a hallmark of Major Depressive Disorder (American Psychiatric Association., 2000). Reduced positive affect is central to the concept of anhedonia; and symptoms of anhedonia or depressed mood are required by the DSM-IV for a depression diagnosis (American Psychiatric Association., 2000). Despite the importance of reduced positive affect to depression, research has only recently begun to focus on this aspect of the disorder. In particular, there is evidence that depressed patients show reduced electrophysiological reactivity to positive stimuli (Sloan et al., 2002; Larson et al., 2007) and reduced striatal hemodynamic activity to monetary or visual rewards (Keedwell et al., 2005a; Epstein et al., 2006; Pizzagalli et al., 2009; Gotlib et al., 2010). However, these findings have not consistently replicated (Gehricke and Shapiro, 2000; Mitterschiffthaler et al., 2003; Dichter et al., 2004; Forbes and Dahl, 2005; Keedwell et al., 2005a, b; Surguladze et al., 2005; Tremeau et al., 2005; Schaefer et al., 2006; Harvey et al., 2007; Knutson et al., 2008; Dichter et al., 2010), suggesting that alternative models may be needed.

One possibility is that the attenuated positive affect characteristic of depression stems from difficulties sustaining affective responses to positive stimuli, rather than an attenuation of the overall, affective response (Myerson, 1922). Broadly consistent with this possibility, there is evidence that depression patients are impaired at integrating reward reinforcement history over consecutive trials (Pizzagalli et al., 2008), fail to sustain normative response bias toward reward-predicting cues (Liu et al., 2011), and that mothers experiencing postpartum depression demonstrate a lack of sustained ventral striatal activity within-trials to financial rewards (Moses-Kolko et al., 2011). More direct

evidence comes from work showing that patients, but not controls, fail to repeatedly engage nucleus accumbens activity and fronto-striatal connectivity across trials when instructed to cognitively enhance their response to positive emotional images (Heller et al., 2009; note that in this manuscript we refer to "sustained" activity as the examination of the temporal dynamics across trials. For more, see Appendix II). Notably, individual differences in the ability to sustain nucleus accumbens activity correlated with ratings of daily positive affect among patients, suggesting that sustained activity in this circuitry could generally support the experience of positive affect among patients. Theoretically speaking, these studies and the study presented here have generally examined the consummatory aspects of reward processing as opposed to the anticipatory aspects of reward (but see, Treadway and Zald, 2011).

The present study extends this line of work by testing whether treatment with antidepressants (Fluoxetine or Venlafaxine Extended Release) strengthens activity in this circuitry and whether treatment-induced changes in sustained activity accounts for treatment-related improvements in daily positive affect. Patients were randomly assigned to receive Fluoxetine or Venlafaxine Extended Release (hereafter referred to simply as Venlafaxine) in a double-blind design and followed for 6 months. The central circuitry underlying the ability to sustain positive affect was assayed at baseline and 2 months in patients and controls using a well-validated emotion regulation paradigm (Jackson et al., 2000). We predicted that, 1) positive affect and negative affect would increase and decrease, respectively, over 2 months of treatment, and 2) changes in sustained nucleus accumbens activity and fronto-striatal connectivity resulting from treatment would correlate with changes in daily positive affect.

Method:

Subjects

At the baseline, 29 medication-free, right-handed adults satisfying DSM-IV (American Psychiatric Association., 2000) criteria for unipolar major depressive disorder and 19 matched controls were examined. Subjects were recruited through community advertisements. At enrollment, subjects were screened for standard MRI compatibility criteria, CNS medications, comorbid substance abuse/dependence, other comorbid DSM-IV Axis I (including Anxiety) or Axis II diagnoses, and a personal or familial history of bipolar disorder. Patients were required to have had depressive symptoms for at least 1 month prior to enrollment and scores >17 on the 21-item Hamilton Depression Rating Scale (HAMD; Hamilton, 1960) at enrollment and baseline fMRI assessment (mean HAMD ± SD depressed, 20.6 ± 2.39). The HAMD assessment interview was completed on the day of the scan session. All subjects completed the 38-item version of the extended Positive Affect/Negative Affect scales (PANAS-X; Watson et al., 1988) and all depressed subjects save one completed the 90-item Mood and Anxiety symptom questionnaire (MASQ; Watson et al., 1995). The PANAS-X was acquired at both baseline and 2-month follow-up on the day of the scan session. On this day, the participants completed the PANAS measure twice – both immediately prior to, and immediately following the scan. To create a reliable measure of current affective functioning, we computed the mean PA and NA for that participant across the pre- and post-scan PANAS on that day. Subjects participating in this study are the same as those who participated in (Johnstone et al., 2007; Heller et al., 2009; Light et al., 2011). This

study was approved by the Institutional Review Board and subjects provided informed written consent.

Following baseline assessment, patients were randomized to six months of either Venlafaxine or Fluoxetine treatment. For the first 2 months of treatment, patients had seven weekly medication visits with a doctor associated with the study. In week 1, patients received 37.5mg or 20mg of Venlafaxine or Fluoxetine, respectively. In week 2, patients received 75mg or 20mg of Venlafaxine or Fluoxetine, respectively; these dosing levels were the minimum dosing levels for the study. Further titration was based on clinical response (side effects and antidepressant effect). Maximum dosing was Venlafaxine of 300mg or Fluoxetine of 80mg. During the first 2 months of treatment, the average dosage for those depressed patients randomized to receive Fluoxetine was 37mg/day (SD=8.7mg/day); the average dosage for those patients receiving Venlafaxine was 118mg/day (SD=36.6mg/day). At 2 months, subjects returned for a second fMRI assessment. Eight patients and 5 controls discontinued participation, leaving 21 patients and 14 controls. These remaining depressed and control participants did not differ in age ($p=0.97$), sex ($p=0.73$), initial positive affect ($p=0.45$), or negative affect ($p=0.41$) scores from those who discontinued. There was a marginally significant difference in initial HAMD score between those patients completing the trial and those not completing the trial ($t(27) = 1.93$, $p=0.06$), such that those completing the trial had lower initial HAMD scores. After unblinding, it was revealed that twelve patients had begun a trial of venlafaxine and nine patients had begun a trial of fluoxetine. Analyses incorporated medication “responders” and “non-responders.”

Design

Subjects were scanned while viewing a sequence of 72 positive and 72 negative images from the International Affective Picture System (IAPS; Lang PJ, 2005). The same images were used at both scan sessions; however, the order of image presentation was randomized across the two scans. Trials began with a 1s fixation cross and auditory tone. Then, an image was presented for 10s, followed by a 6s blank screen. To ensure compliance, at the onset of each image, subjects used a button response pad to judge whether the image was positive or negative. Four seconds following image onset, an auditory prompt instructed subjects to increase ("enhance") or decrease ("suppress") their emotional response to the image or to continue to "attend" to the picture. Participants were trained during a previous session while positioned inside a mock scanner on the use of cognitive re-appraisal strategies to re-evaluate the images as more or less emotional. For the enhance condition, participants were trained to either imagine themselves or a loved one experiencing the situation being depicted or imagine a more extreme outcome than the one depicted (e.g., in response to a picture of a stunning natural scene, a participant might imagine being in that scene or one of their own choosing). Conversely, for the suppress condition, individuals were trained to either view the situation as fake or unreal or imagine that the situation being depicted had a different outcome than the one suggested (e.g., victims of a car accident survived and healed well). Alternatively, on attend trials, participants were instructed to maintain their attention to the picture without changing their affective experience. Simulated scanner sounds and task instructions were presented using earbud headphones during this training session. The training was succeeded by follow-up queries to ensure that participants were using the strategies as instructed and reported being able to perform the task. Across 6 380-sec scans, there were

24 trials of the regulation conditions and 12 trials of the attend condition for each valence (order pseudorandomized).

Negative pictures were selected according to the International Affective Picture System (IAPS) norms to be both unpleasant (1, most unpleasant, to 9, most pleasant; M = 2.95; SD, 0.87) and arousing (1, least arousing, to 9, most arousing; M = 5.44; SD, 0.80), whereas positive images were pleasant (M = 7.13; SD, 0.62) and arousing (M = 5.28; SD, 0.58). Arousal ratings did not differ significantly across positive and negative images ($t<1$), thus allowing us to manipulate valence while controlling for stimulus intensity. Stimuli were presented using E-Prime software (Psychology Software Tools, Pittsburgh, PA) via a fiber-optic goggle system (Avotec, Stuart, FL) with a screen resolution of 800 x 600 pixels.

Image acquisition.

Images were collected on a General Electric 3 Tesla scanner (GE Medical Systems, Waukesha, WI) equipped with a standard clinical whole-head transmit-receive quadrature head coil. Functional images were acquired using a T2*-weighted gradient-echo, echo planar imaging (EPI) pulse sequence [33 sagittal slices, 4 mm thickness, 1 mm interslice gap; 64 × 64 matrix; 240 mm field of view (FOV); repetition time (TR)/echo time (TE)/Flip, 2000 ms/30 ms/60°; 190 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 × 256 in-plane resolution; 240 mm FOV; 124 × 1.1 mm axial slices).

Behavioral measures.

Reaction time to image onset, as well as pupil dilation measures were acquired. Reaction time from two participants was lost due to hardware error. Assessing pupil dilation provides an unobtrusive measure of autonomic arousal (Loewenfeld, 1993) with pupil constriction driven primarily by the parasympathetic branch of the autonomic nervous system (ANS), and pupil dilation primarily reflecting activity of the sympathetic branch. Pupil dilation is thus an indicator of increased cognitive and attentional load during effortful top-down regulation (Kahneman and Beatty, 1966; Siegle et al., 2003; Ohira et al., 2006). To assess autonomic arousal associated with effortful reappraisal, we measured the extent to which the pupil dilated during the active reappraisal period of each stimulus trial. Based on our previous research showing pupil dilation to be a sensitive index of the cognitive effort during reappraisal in healthy individuals (Urry et al., 2006; van Reekum et al., 2007), we examined whether pupil dilation changed across the scan session for either of the groups.

Pupil data acquisition and analysis.

Horizontal pupil diameter data were acquired continuously at 60 Hz using an iView X system (v. 1.3.31) with a remote eye-tracking device (SensoMotoric Instruments, Teltow, Germany), which was interfaced with the fiber optic goggle system. Pupil data from four controls and six depressed individuals were not usable because of technical problems. Pupil dilation data were processed using algorithms written by Siegle et al. (2002) (unpublished MatLab code) with MatLab software (MathWorks, Natick, MA), modified in our laboratory. Blinks were identified and eliminated using local regression slopes and amplitude thresholds. Data were

smoothed with a five-sample rolling average and linearly detrended over each scan run. For successive 500 ms bins in each trial, the proportion of time that the eye was open and

mean pupil diameter were calculated. Pupil values were then range-corrected to standardize according to the pretrial maximally dilated pupil diameter and the maximally constricted pupil diameter in the 2 s after picture onset [(current pupil diameter – minimum pupil diameter)/(maximum pupil diameter – minimum pupil diameter)]. Data were averaged across a 5 s interval starting 1 s after instruction and continuing until picture offset (the reappraisal period). Data were then analyzed using mixed model GLM (subject as a random factor nested within the fixed factor group, and reappraisal as a within subject fixed factor).

Image analysis.

Analytic techniques were identical to those in our prior report (Heller et al., 2009). Briefly, data were slice-time and motion corrected using Analysis of Functional NeuroImages (commonly referred to as AFNI). Single-subject general linear models modeled each of the six trial types (positive/negative stimulus; enhance, attend, and suppress reappraisal instruction) separately, and for both the early (runs 1–3; denoted as 1st Half from here on) and late phases (runs 4–6; denoted as 2nd Half from here on) of the scanning session as well as six motion nuisance covariates. We also included a second-order polynomial used to model the baseline and slow signal drift. Regressors consisted of a set of five sine basis functions to produce separate estimated hemodynamic response functions for each trial type. The estimated hemodynamic response functions were converted to percentage signal change values and averaged across time points

corresponding to the peak hemodynamic response during the regulation period (8–14s after stimulus onset). As the process of sustaining nucleus accumbens activity during the increasing of positive affect was central to our previous report, contrasts for analyses presented here were the positive enhance(2^{nd} Half) – positive enhance (1^{st} Half) unless otherwise noted (see supplement). For analyses examining treatment response, contrasts were: enhance: 2-month$_{(2nd\ Half - 1st\ Half)}$ − enhance: Baseline$_{(2nd\ Half - 1st\ Half)}$. Single-subject contrasts were normalized to the 2mm MNI152 template and smoothed (5-mm full-width at half-maximum).

For analyses specifically examining nucleus accumbens function, we used an a priori region of interest from the Harvard-Oxford subcortical atlas implemented by FSL with a probability of 25% that all voxels were within the nucleus accumbens (Kennedy et al., 1998; Makris et al., 1999). Subsequently, we used Analysis of Functional NeuroImages's (AFNI) program AlphaSim to calculate the required small volume corrected cluster-size threshold for $p<.05$. Single-voxel and connectivity analyses were similarly thresholded at $p < 0.05$, corrected for multiple comparisons using cluster-size thresholding based ($k > 18$ voxels for small volume correction with the apriori nucleus accumbens region of interest in the univariate analyses, and $k > 54$ voxels for whole brain masked) on Monte Carlo simulation (the AlphaSim program in Analysis of Functional NeuroImages).

Analyses examining sustained nucleus accumbens activity and nucleus accumbens-prefrontal cortex connectivity from baseline to the 2-month assessment, used the following contrast: 2-month$_{(2nd\ Half - 1st\ Half)}$ –Baseline$_{(2nd\ Half - 1st\ Half)}$ (see Supplement). The resulting value was regressed on positive affect as well as negative affect. For

control analyses examining reaction time (reaction time was successfully acquired on 19 of the 21 depressed patients) or pupil dilation (pupil data was successfully acquired on 15 of the 21 MDD patients at both time points), we performed the same analysis 2-month$_{(2nd\ Half - 1st\ Half)}$ –Baseline$_{(2nd\ Half - 1st\ Half)}$.

In addition to using the difference metric described above in which the scan session is broken into halves (2nd half vs. 1st half), we performed a more traditional fMRI analysis in which fMRI signal is aggregated across the experimental session and treated uniformly. For each participant, we extracted the mean beta value across the significant nucleus accumbens cluster from the difference metric (2nd half vs. 1st half) as well as from the traditional, aggregated metric. Using multiple regression, we then examined whether the difference metric continued to be associated with gains in positive affect while including the aggregated metric as an additional independent variable. This also allowed us to examine whether the aggregated metric, on its own, correlated with gains in positive affect.

Connectivity Analysis

Connectivity analyses were performed using the beta series correlation method described in Rissman et al., (Rissman et al., 2004). Briefly, this approach requires that separate parameter estimates (beta values) be computed for each trial. Trials were modeled as having two components: one component occurring at the onset of the image presentation – before regulation instruction; the second component being placed six seconds after image onset, modeling the neural response to the regulation of emotion. BOLD responses during stimulus onset and regulation periods were modeled as brief epochs of neural activity convolved with an in-house canonical hemodynamic response

function, obtained by averaging empirically derived hemodynamic response functions (Rissman et al., 2004). The onsets of temporally adjacent covariates were spaced at least 4 s apart (Zarahn et al., 1997) to minimize the contamination of the regulation period covariate by residual stimulus onset period activity. This approach has been used to successfully model separate components of a trial in numerous published studies (Postle et al., 2000; Curtis et al., 2004; Ranganath et al., 2004). The least squares solution of the general linear model yielded a set of 236 beta values of interest (2 trial components x 2 picture valences x 3 regulation instructions [24 enhance, suppress trials; 12 attend trials). Nuisance covariates included the second-order polynomial used to model the baseline and slow signal drift, as well as six motion estimate covariates. Beta values were sorted by trial type so that a series of betas exist for each component of each condition. The extent to which brain regions interact during a particular task stage is quantified by the extent to which their respective beta series from that condition are correlated. See main text for results. See Appendix II for additional methods, results and discussion.

Results

Changes in symptom severity:

At 2-months, mean HAMD scores were reduced (Figure 1; $t(20) = -10.72$; $p < .001$, $p\eta^2=0.85$). At 2-months nine patients (43%) had "remitted" (HAMD score ≤ 7) and of the remaining twelve patients, six patients (50%) were "responders" (≥ 50% decrease), leaving six non-responders. There was no difference in HAMD change (two-sample t-tests: $t(19) = 0.59$, $p = 0.56$, $p\eta^2=0.02$), among patients receiving fluoxetine vs. venlafaxine.

Controls and depressed patients provided ratings of positive affect and negative affect at both assessments. We entered the change in positive affect and negative affect as dependent measures and performed a repeated-measures ANOVA (change in negative affect was multiplied by -1 so that both scales were coded in the same direction. Results revealed that the Group x Scale (positive affect, negative affect) interaction was significant ($F_{(1,33)} = 18.36$, $p<.001$, $p\eta^2 = 0.36$). There was also a main effect of Group on change in affect ($F_{(1,33)} = 6.19$, $p=.02$, $p\eta^2 = 0.16$), suggesting that affect changed in patients more than in controls. Follow up tests revealed that, among patients, positive affect increased ($p\eta^2=0.22$) and negative affect decreased ($p\eta^2=0.66$) across assessments, ($ps < .03$). Among controls, positive affect increased ($p = 0.03$, $p\eta^2 = 0.30$), whereas there was no change in negative affect ($p = 0.34$, $p\eta^2 = 0.07$). Groups did not differ in the magnitude of the change in positive affect ($p = 0.91$, $p\eta^2 < .001$). By contrast, patients showed a steeper decrease in negative affect ($p<.001$, $p\eta^2 = .44$). Within the depressed group, change in positive affect ($t(19) = 1.19$, $p=0.25$, $p\eta^2 = 0.07$), and negative affect ($t(19) = -0.03$, $p = 0.98$, $p\eta^2 < 0.01$) did not differ between patients receiving fluoxetine or venlafaxine .

We next examined the correlations between positive affect and negative affect measures. Among patients, change in positive affect and negative affect scores from baseline to 2 months were significantly inversely correlated ($r = -0.61$, $N = 21$, $p = .004$; see Supplemental Table 1), and in the control group, they were also inversely though not significantly correlated ($r=-0.45$, $N = 14$, $p=0.10$). Among patients, changes in the MASQ Anhedonia subscale was also significantly correlated with changes in PA (see supplementary Table 1; $r=-0.68$, $t(18)=-3.91$, $p=.001$)

Replication of previous findings with the same sample

In these same patients, we previously reported that sustained nucleus accumbens activity correlated with positive affect ratings prior to treatment. After two months of treatment, we found that individual differences in sustained nucleus accumbens activity correlated with patient ratings of positive affect in daily life (peak x,y,z: [-12 18, -6]; B(2-month positive affect) = 0.01, t(17) = 2.50, p=.02; controlling for baseline positive affect and sustained nucleus accumbens activity at baseline, small volume corrected for multiple comparisons; Table 1). This effect remained significant after controlling for drug type (B = 0.01, t(16) = 2.38, p = .03).

Variation in sustained nucleus accumbens activity across time correlates with gains in positive affect.

Using the nucleus accumbens cluster described above, we next examined whether *changes* in sustained nucleus accumbens activity correlated with gains in positive affect across assessments. This analysis showed that patients displaying larger improvements in sustained nucleus accumbens activity showed larger gains in positive affect (Figure 2; B = 0.01, r = 0.54, t(19)=2.76, p=0.01, R^2=0.29; see Supplemental Table 2). This remained significant after controlling for drug type (B = 0.01, t(18)=2.42, p=.03).

We performed several control analyses to examine the specificity of this effect. First, we examined whether changes in nucleus accumbens activity aggregated across the scan session (as is most commonly done in fMRI analyses) was associated with increases in positive affect. In this analysis we contrasted nucleus accumbens activity (aggregated across the scan session) during the positive "enhance" condition at 2 months with aggregated nucleus accumbens activity during the same condition at baseline, and

correlated that activity with changes in positive affect. There was no relationship between increases in nucleus accumbens activity aggregated across the scan session over the course of treatment and increases in positive affect over this same time period (r=.04, N=21, p=0.87). Additionally, we tested whether including both changes in sustained nucleus accumbens activity and changes in aggregated activity in the same regression model was associated with changes in positive affect revealed. This revealed that changes in sustained nucleus accumbens activity was specifically associated with changes positive affect (B=24.01, t(18)=2.90, p=.01), whereas changes in aggregated nucleus accumbens activity was not associated with changes in positive affect (B=11.85, t(18)=0.93, p=.37). This provides further evidence that examination of changes in sustained activity over the scan session is important and uniquely associated with changes in positive affect.

Second, we examined whether this effect could be explained by changes in reaction time or pupil dilation across the two scan sessions to examine whether these effects may be due to changes in engagement or fatigue following treatment. For reaction time, in the depression group, there was no Time (pre-treatment vs. 2-month) x Half (2^{nd} Half vs. 1^{st} Half) interaction F(1,18) =.60, p=.45). Individual differences in change in reaction time also did not correlate with change in positive affect (r=-0.04, N=19, p=.85). For pupil dilation, in the depressed group, there was no Time (pre-treatment vs. 2-month) x Half (2^{nd} Half vs. 1^{st} Half) interaction F(1,14) =.06, p=.82). Individual differences in change in pupil dilation also did not correlate with change in positive affect (r=0.11, N=15, p=.69). These data suggest that the relationship between changes in sustained nucleus accumbens activity and positive affect is unlikely to be due to changes in engagement or fatigue.

Third, we examined whether the relationship between changes in sustained nucleus accumbens activity and positive affect remained significant after controlling for changes in negative affect. When controlling for changes in negative affect, the association between changes in positive affect and changes in nucleus accumbens was no longer significant ($\rho r = .27$, $t(19) = 1.24$, $p=0.23$), suggesting that increases in sustained nucleus accumbens activity are associated with both increases in positive affect and decreases in negative affect among patients. See supplemental materials for additional analyses addressing specificity.

Increases in sustained nucleus accumbens-middle frontal gyrus, nucleus accumbens-ventromedial prefrontal cortex connectivity correlates with increases in positive affect while controlling for changes in negative affect

We previously reported that untreated patients have difficulty sustaining connectivity between nucleus accumbens and dorsolateral prefrontal cortex when instructed to enhance positive emotion elicited by positive images (Heller et al., 2009). In addition, since the nucleus accumbens alone is involved in processes other than reward (Bromberg-Martin et al., 2010), and that treatment-related changes in sustained nucleus accumbens activity was associated with changes in both positive affect and negative affect, it may be that changes in nucleus accumbens-prefrontal cortex connectivity yield a more sensitive method for examining changes specific to positive affect. Thus, we conducted a connectivity analysis (Rissman et al., 2004) to examine whether treatment-related changes in nucleus accumbens-prefrontal cortex connectivity is associated with gains in positive affect while controlling for changes in negative affect. This revealed a region of left middle frontal gyrus (peak x, y, z: [-22 60 18]; BA 10/46) where variation

in sustained nucleus accumbens-middle frontal gyrus connectivity was associated with gains in positive affect (ρr=0.64, t(18)=3.61, p=.002; Figure 3; Table 2) when controlling for changes in negative affect, corrected for multiple comparisons across the whole brain. This relationship was also significant when not controlling for changes in negative affect (r=0.43, t(19)=2.13, p=.05). In addition, increases in sustained connectivity between the nucleus accumbens and ventromedial prefrontal cortex was associated with gains in positive affect while controlling for negative affect (ρr=0.78, t(18)=5.44, p<.001; Table 2). Similarly, this relationship was significant when not controlling for changes in negative affect (r=0.56, t(19)=2.94, p=.008).

As with the univariate analyses reported above, we performed a control analysis examining whether changes in sustained nucleus accumbens-middle frontal gyrus connectivity was uniquely associated with changes in positive affect or whether aggregated nucleus accumbens-middle frontal gyrus connectivity across the scan session was additionally associated with changes in positive affect (controlling for negative affect). Treatment-induced changes in aggregated nucleus accumbens-middle frontal gyrus connectivity was not associated with change in positive affect (controlling for negative affect, ρr=-0.03, N=21, p=.90). We additionally ran a regression model including both changes in sustained nucleus accumbens-middle frontal gyrus connectivity and changes in aggregated nucleus accumbens-middle frontal gyrus connectivity (in addition to changes in negative affect) in the same regression model to examine associations with changes in positive affect. This revealed that changes in sustained nucleus accumbens-middle frontal gyrus connectivity was uniquely associated with changes in positive affect when controlling for negative affect (B=6.25, t(17)=3.51,

p=.002), whereas changes in aggregated nucleus accumbens-middle frontal gyrus connectivity was not associated with changes in positive affect (B=1.34, t(17)=0.34, p=.74). Similarly, with the ventromedial prefrontal cortex cluster, changes in aggregated nucleus accumbens-ventromedial prefrontal cortex connectivity was not associated with change in positive affect controlling for negative affect (ρr=0.25, N=21, p=.27). We additionally included both changes in sustained nucleus accumbens-ventromedial prefrontal cortex connectivity and changes in aggregated nucleus accumbens-ventromedial prefrontal cortex connectivity (in addition to changes in negative affect) in the same regression model to examine associations with changes in positive affect. This revealed that changes in sustained nucleus accumbens-ventromedial prefrontal cortex connectivity was uniquely associated with changes in positive affect when controlling for negative affect (B=13.00, t(17)=5.47, p<.001), whereas changes in aggregated nucleus accumbens-middle frontal gyrus connectivity was not associated with changes in positive affect (B=4.76, t(17)=1.52, p=.15). This further supports the notion that examination of treatment induced changes sustained nucleus accumbens activity and connectivity capture unique variance in increases in positive affect.

Comparison of venlafaxine and fluoxetine

Next, we tested whether the effects we found were due to differences driven by either medication alone. The correlation between change in sustained nucleus accumbens activity and change in positive affect for Fluoxetine: r=0.48, N=9; and for Venlafaxine: r = 0.50, N=12. There was no difference between these correlations (z=.05, p=0.96). For the connectivity, the correlation between change in sustained nucleus accumbens-BA46 connectivity and change in positive affect (controlling for change in negative affect) for

Fluoxetine: r=0.68, N=9; and for Venlafaxine: r=0.54, N=12. There was no difference between these correlations (z=.43, p=0.67). And, the correlation between change in sustained nucleus accumbens-ventromedial prefrontal cortex connectivity and change in positive affect (controlling for change in negative affect) for Fluoxetine: r=0.72, N=9; and for Venlafaxine ER: r=0.79, N=12. There was no difference between these correlations (z=.31, p=0.76). As none of these correlations were significantly different from one another, it suggests that the mechanism of action of these two antidepressant medications on change in positive affect and change in sustained nucleus accumbens activity/fronto-striatal connectivity were not different.

Examination of anhedonic symptoms as measured by the MASQ

As the PANAS-now is an acute state measure of positive affect, we additional examined the anhedonic scale of the MASQ as a more traditional measure of anhedonia that asks participants to integrate their emotion over the previous week. The depressed sample showed a significant decrease in anhedonic symptoms from pre-treatment to 8-weeks ($t(20) = -2.41$, $p=0.026$), whereas the control sample showed no significant change in anhedonic symptoms over this timeframe ($t(13)= 0.94$, $p= 0.36$).

Within the depressed sample, there was a significant correlation between changes in anhedonic symptoms and changes in sustained nucleus accumbens activity (r=-0.46, N=20, p=.03) such that individuals showing increases in ability to sustain repeated engagement of nucleus accumbens activity were those with the largest decrease in anhedonic symptoms. However, there was no relationship between changes in sustained nucleus accumbens-BA46 connectivity during the positive enhance condition and anhedonic symptoms (r=-0.06, N=20, p=0.81). Further, including both changes in

anhedonic symptoms and changes in current positive affect, increases in current positive affect uniquely was uniquely associated with changes in nucleus accumbens-BA46 connectivity (B=0.055, t(18)=2.55, p= 0.02), while changes in anhedonic symptoms was not uniquely associated with changes in nucleus accumbens-BA46 connectivity (B=0.01, t(18)=1.35,p= 0.20). Similarly, there was no relationship between changes in nucleus accumbens-ventromedial prefrontal cortex connectivity during the positive "enhance" condition and changes in anhedonic symptoms (r=-0.19, N=20, p=0.42). In a simultaneous regression with changes in current positive affect and changes in anhedonic symptoms, changes in current positive affect was uniquely associated with changes in nucleus accumbens-ventromedial prefrontal cortex connectivity (B=0.034, t(18)=2.97, p=0.008), whereas changes in anhedonic symptoms was not (B=0.005, t(18)=1.05, p=0.31; See supplement).

Healthy controls demonstrate no association between changes in sustained nucleus accumbens activity and changes in positive affect

Using the same nucleus accumbens cluster found with the depressed patients, healthy controls showed no significant association between changes in sustained nucleus accumbens activity and positive affect (r=-0.36, N=14, p=0.21; R^2=0.13) – note that the relationship in controls was negative whereas the relationship was positive in depressed patients. Indeed, the strength of this relationship was greater in patients compared to controls in the nucleus accumbens (z = 2.54, p = .01). When performing this correlation voxelwise within the control group, no regions demonstrated a significant association between changes in sustained activity and changes in daily positive affect (after correcting for multiple comparisons).

With regard to the connectivity analyses presented above for the depressed sample, controls showed no significant relationship between changes in nucleus accumbens-middle frontal gyrus connectivity and changes in positive affect over the 2 months ($r=0.24$, $N=14$, $p=0.41$). Similarly, for nucleus accumbens-ventromedial prefrontal cortex connectivity, controls showed no relationship between changes in sustained connectivity over the 2 month period and changes in positive affect ($r=-0.34$, $N=14$, $p=0.24$). See Appendix II for additional methods, results and discussion.

Discussion

The present study provides novel evidence that improvements in daily positive affect due to 2 months of antidepressant treatment can be explained in part by increases in patients' ability to sustain activity in prefrontal-accumbens circuitry. In particular, we found that those individuals displaying the greatest improvement in sustained nucleus accumbens activity also showed the largest gains in self-reported positive affect. Interestingly, the relationship between increases in sustained nucleus accumbens activity and gains in self-reported positive affect was partially accounted for by decreases in negative affect. Thus, changes in sustained nucleus accumbens activity appears to be related to improvements in affect generally, and may not be specific to positive affect. However, using a connectivity analysis strategy, we found that increases in sustained nucleus accumbens-middle frontal gyrus and nucleus accumbens-ventromedial prefrontal cortex connectivity when attempting to enhance positive emotion was specific to gains in self-reported positive affect as this relationship was significant when controlling for changes in negative affect. In addition, changes in *sustained* nucleus accumbens activity and nucleus accumbens-middle frontal gyrus as well as nucleus accumbens-ventromedial

prefrontal cortex connectivity was associated with changes in positive affect above and beyond changes in *aggregated* nucleus accumbens activity and nucleus accumbens-middle frontal gyrus connectivity. In addition, that changes in anhedonic symptoms on the MASQ was associated with changes in sustained nucleus accumbens activity but not changes in sustained nucleus accumbens-prefrontal cortex connectivity suggests that changes in sustained nucleus accumbens activity may reflect both acute and longer-term state positive affect (as the MASQ asks participants to integrate their affect over the previous week), whereas the ability to sustain top-down modulation of the nucleus accumbens by prefrontal cortex structures is particularly relevant for changes in current, acute positive affect following treatment. This provides further evidence that examining the temporal dynamics of striatal activity and fronto-striatal connectivity is important for understanding positive affect in depression.

It is potentially informative that that when controlling for changes in negative affect, there was no unique relationship between increases in sustained nucleus accumbens activity and increases in positive affect. This suggests that changes in sustained nucleus accumbens activity may underlie alterations in both positive and negative affect (Haber and Knutson, 2010). Indeed, a wealth of preclinical research demonstrates that the nucleus accumbens is not engaged solely during reward-related behaviors. In both rodents (Roitman et al., 2005) and humans (Jensen et al., 2003), studies demonstrate the nucleus accumbens to be involved in the processing of aversive stimuli. For example, Berridge and colleagues reported that injection of a glutamate receptor antagonist in the shell of the nucleus accumbens can elicit either approach or avoidance behaviors based upon whether the injection is made in the rostral or caudal

portion of the nucleus accumbens shell, respectively (Reynolds and Berridge, 2003). Unfortunately, the spatial coarseness of fMRI precludes distinguishing subcomponents of the nucleus accumbens. Further, our findings suggest that the utilization of functional connectivity can provide additional sensitivity when examining changes in affect resulting from treatment (Mayberg, 2007) such that changes in sustained nucleus accumbens-prefrontal cortex connectivity underlie changes in positive affect in depression uniquely. These data suggest a role for connectivity analyses in helping to further uncover alterations in the pathophysiology of mood disorders with treatment.

Some of the densest direct connections between the ventral striatum and prefrontal cortex lie within the medial portion of the prefrontal cortex (Haber et al., 2006; Haber and Knutson, 2010), including both the ventromedial prefrontal cortex and the middle frontal gyrus cluster found in the connectivity analysis. These regions of prefrontal cortex provide glutamatergic innervation onto mostly GABAergic medium spiny neurons within the ventral striatum (Haber and Knutson, 2010). This suggests that it is the afferents of the prefrontal cortex which impact on the "top-down" regulation of affect. While given the task, we could not dissociate the relative contributions of the two prefrontal cortex clusters to changes in positive affect, speculation can be made based on the extant literature. Given the well-established role of the ventromedial prefrontal cortex in stimulus valuation and more dorsolateral areas of the prefrontal cortex in cognitive control, it may be that changes in sustained connectivity between nucleus accumbens-ventromedial prefrontal cortex relate to the changes in the evaluation of appetitive stimuli over time, whereas changes in sustained nucleus accumbens-middle frontal gyrus connectivity may underlie the effortful increasing of positive affect required in the

experimental paradigm. Further studies, both in humans and nonhuman animal models, however, would be required to elucidate the exact mechanisms by which interactions between the nucleus accumbens and prefrontal cortex underlie these phenomena.

One concern may be the existence of two separate drug treatments. However, controlling for drug treatment did not attenuate any of the effects, and the correlations were not significantly different from one another when run for both groups separately. Further, evidence suggests that Fluoxetine and Venlafaxine have similar striatal serotonin occupancy and mechanism of action (Meyer et al., 2004). Meyer and colleagues used PET imaging to assess 5-HT binding potential in the striatum in human subjects across five different antidepressants (Citalopram, Fluoxetine, Setraline, Paroxetine, and Venlafaxine). They found that at therapeutic doses, all antidepressants had similar 5-HT binding potential – specifically in the striatum. This suggests that there is a strong overlap in mechanism of action in these two treatments. Nonetheless, future work should seek to separate the distinct mechanism of action for all depression treatments (e.g., DeRubeis et al., 2008) and their effects on specific affective symptoms.

In conclusion, our findings suggest that sustained nucleus accumbens activity and fronto-striatal connectivity when attempting to enhance positive emotion track self-reported daily positive affect. Further, individual differences in the magnitude of change in sustained nucleus accumbens activity and fronto-striatal connectivity correlate with gains in positive affect following antidepressant treatment. These findings are consistent with the hypothesis that reductions in state positive affect associated with depression may in part result from a loss of the ability to sustain nucleus accumbens activity and fronto-striatal connectivity over time. These findings underscore the need for future studies to

examine the mechanisms underlying the temporal dynamics of positive and negative affect in depression (Davidson, 2003) and how these mechanisms are impacted by antidepressant treatment.

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Figure 1. Changes in HAMD, self-reported positive affect and negative affect from 0 – 2 months. * = p < .01; ** = p < .001. Solid lines: depressed patients, hatched lines, healthy controls. Note that HAMD for controls was not shown because mean HAMD for controls was 1.07 and 1.64 for baseline and 8 week assessment, respectively.

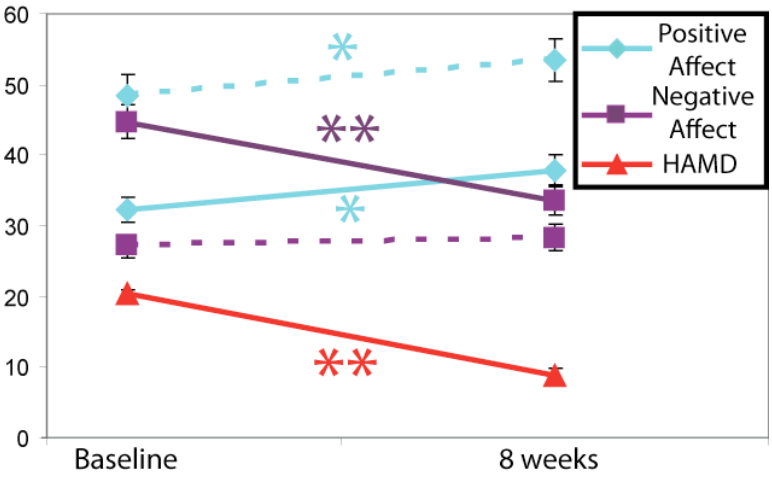

Figure 2. For those who completed the trial, those individuals displaying the greatest improvement in sustained nucleus accumbens activity also showed the largest gains in self-reported positive affect. X-axis reflects individual differences in changes in sustained nucleus accumbens activity from pre- to post-treatment (2 month post-treatment$_{(2nd\ Half - 1st\ Half)}$ − Pretreatment Baseline$_{(2nd\ Half - 1st\ Half)}$). Y-axis reflects gains in self-reported positive affect. Blue dots represent depressed patients on Venlafaxine, green dots represent patients on Fluoxetine.

Figure 2

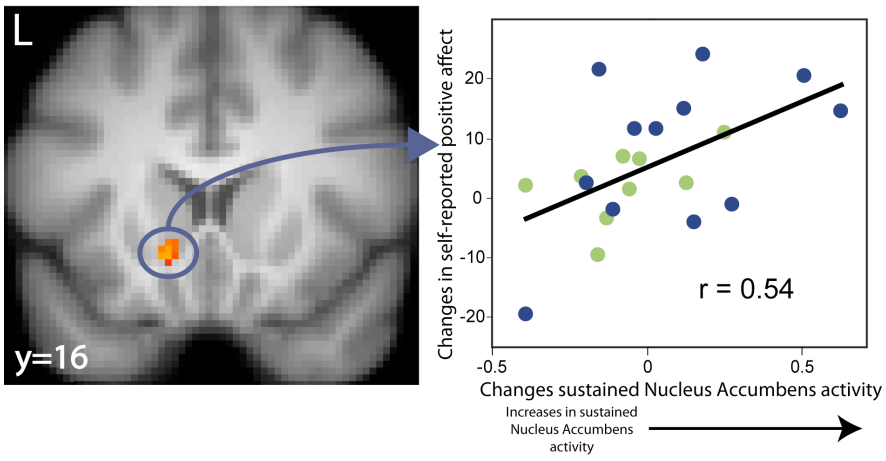

Figure 3. A) Increases in sustained nucleus accumbens-middle frontal gyrus (BA 10/46) connectivity is related to gains in self-reported positive affect after controlling for changes in self-reported negative affect. B) For scatter plot, X-axis reflects changes in

sustained nucleus accumbens-middle frontal gyrus connectivity from pre- to post-treatment (2 month post-treatment$_{(2nd\ Half - 1st\ Half)}$ – Pretreatment Baseline$_{(2nd\ Half - 1st\ Half)}$). Y-axis reflects gains in positive affect after controlling for changes in negative affect. Blue dots represent depressed patients on Venlafaxine, green dots represent patients on Fluoxetine.

Figure 3

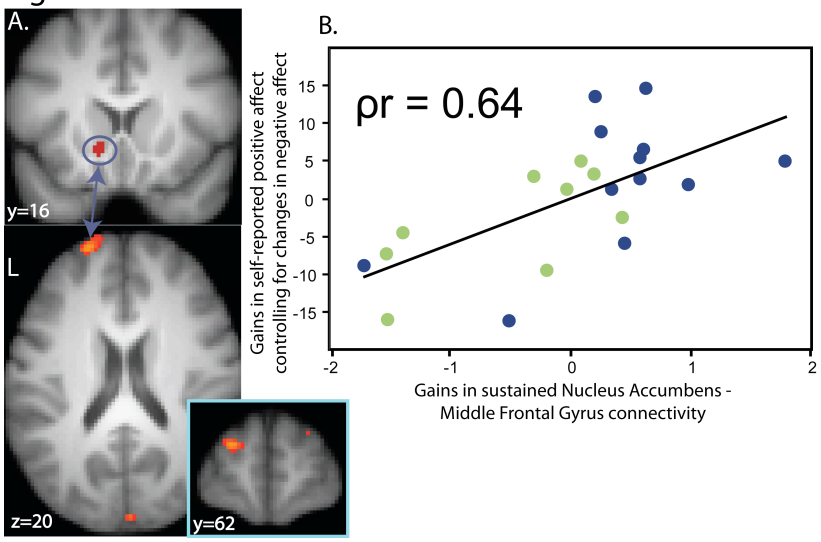

Table 1. Results from a voxelwise regression examining the relationship between sustained (2nd Half – 1st Half) brain activity at 2 months into treatment with self-reported positive affect at 2 months into treatment, controlling for pretreatment sustained brain activity and pretreatment self-reported positive affect.

Location (BA)	*x,y,z(mm)*	*cluster size (voxels)*	*max t-value*
R Insula (48)	60, 8, 4	605	4.33
R Superior Frontal Gyrus (45/46)	34, 34, 20	342	5.37
Supplementary Motor Area (6)	8, 0, 62	153	4.02
R Occipital Cortex	20, -56, 38	122	4.73
R Middle Temporal Gyrus	70, -42, -4	104	6.10
L Middle Frontal Gyrus (46/47)	-40, 54, -4	97	4.32
L Superior Temporal Gyrus (21)	-60, -50, 4	81	4.24
Superior Occipital Gyrus	-4, -96, 26	78	5.28

Table 2. Results from a voxelwise regression examining the relationship between changes in sustained nucleus accumbens connectivity 2-month$_{(2nd\ Half - 1st\ Half)}$ – Baseline$_{(2nd\ Half - 1st\ Half)}$ with changes in self-reported positive affect, controlling for changes in negative affect.

Location (BA)	*x,y,z(mm)*	*cluster size (voxels)*	*max t-value*
R Anterior Insula (47)	36, 22, 0	243	4.19
vmPFC (11)	-4, 32, -14	76	4.81
L Middle Frontal Gyrus (10/46)	-22, 60, 18	66	3.90

Chapter 4

Sustained ventral striatal activity predicts eudaimonic well-being and cortisol output

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Abstract

Eudaimonic well-being - a sense of purpose, meaning and engagement with life – is protective against psychopathology and predicts physical health, including lower levels of the stress hormone cortisol. While it has been suggested that the ability to engage reward circuitry may promote well-being and mediate the relationship between well-being and health, this hypothesis remains untested. Sustained engagement of reward circuitry is particularly compelling as the ability to continually engage reward circuitry when encountering positive events may be predictive of health and well-being. To test this hypothesis, participants viewed positive, neutral and negative images while fMRI data were collected. Individuals with sustained activity in the ventral striatum and dorsolateral prefrontal cortex to positive stimuli over the course of the scan session reported higher well-being and had lower cortisol output. This suggests that sustained engagement of reward circuitry when encountering positive events underlies well-being and adaptive regulation of the hypothalamic pituitary adrenal axis.

Introduction

The concept of well-being – a sense of purpose, meaningful and positive engagement with life (Ryff, 1989) – has been of interest to philosophers since at least Aristotle. Aristotle termed this type of well-being as eudaimonia and differentiated it from that of hedonic positive affect (PA), defined as the momentary experience of pleasure (see also, Diener and Lucas, 1999). Aristotle was fundamentally interested in how one may increase their own degree of eudaimonic well-being and at one point called eudaimonia the "highest of all goods achievable by human action" (Aristotle, 1925; translated by D. Ross). Supporting Aristotle's interest in eudaimonic well-being, research has begun to uncover a link between well-being and measures of health (Pressman and Cohen, 2005). Individual differences in multiple types of well-being has been found to predict a variety of objective indices of health including, cardiovascular (Boehm and Kubzansky, 2012), levels of stress (as measured by the stress hormone cortisol; Ryff et al., 2004) and peripheral inflammation (Dockray and Steptoe, 2010). However, while there appears to be an important relationship between eudaimonic well-being and physical health, the neurobiology mediating this link is not understood.

The link between brain function and various health outcomes, including regulation of stress hormones has been previously examined: Functional neuroimaging studies have suggested that a network including the hippocampus, amygdala, prefrontal cortex (PFC) and striatum may impact (or be impacted by) cortisol release (Urry et al., 2006; Dedovic et al., 2009; Pruessner et al., 2010; Strelzyk et al., 2012). These areas are also generally thought to be part of a circuit which is involved in the regulation of emotion (Ochsner and Gross, 2008). Therefore the fact that their function is tightly linked

with stress responses is not surprising. Of note, the ventral striatum (VS), amygdala and hippocampus may be particularly relevant for regulating cortisol release as they all directly connect to the paraventricular nucleus of the hypothalamus (Bubser and Deutch, 1999; Haber and Knutson, 2010), a key element of the hypothalamic-pituitary-adrenal axis.

In contrast, only recently have neuroscientists begun examining the other half of this association – the link between the brain and well-being. Two prior studies examining the neural correlates of eudaimonic well-being have found that surface electrophysiology measures of relative left anterior cortical activation at rest (Urry et al., 2004) and ventromedial prefrontal cortex (VMPFC) BOLD signal in response to negative affective stimuli (van Reekum et al., 2007) predict well-being. In recent commentaries, Kringelbach and Berridge (e.g., Kringelbach and Berridge, 2009) suggested that brain regions involved in basic reward processing such as the ventral striatum (VS) and prefrontal cortex (PFC) may play an important role in well-being. However, this compelling hypothesis remains untested. Moreover, these predictions do not incorporate the fact that variability in the temporal dynamics of emotion critically contributes to health and well-being (Solomon and Corbit, 1974; Siegle et al., 2002; Heller et al., 2009) nor do they make predictions regarding how these temporal dynamics may be encoded in the brain.

As a variety of emotionally tinted events occur intermixed over time, it may be particularly important for an individual to maintain engagement of reward circuitry in response to positive events, even in the midst of negative ones. Our prior work suggests that the inability to *repeatedly* engage reward circuitry in a sustained manner when

presented with positive events intermixed with negative ones is associated with core clinical features of depression, such as reductions in positive affect (Heller et al., 2009). Thus, it is similarly possible that sustained engagement of reward circuits may be important for well-being and protective against life's stressors in healthy individuals without frank psychopathology. However, data linking sustained engagement of reward circuitry to well-being and objective measures of stress in healthy individuals is lacking.

Therefore, in a sample of adults of a wide age range (n=64; mean=58.20 years min=38, max=76), from the MIDUS-II study (midus.wisc.edu) we examined how individual differences in the sustained engagement of reward circuitry over the scan session in response to affective stimuli were related to health and well-being[1]. We used a linear trend analysis across the five scan runs to derive a statistic representing the rate of habituation of brain activity in response to positive, negative, and neutral pictures over the scan. Because the distinction between eudaimonic well-being, and hedonic PA has been of fundamental interest to philosophers since Aristotle (Aristotle, 1925) and modern researchers (Kringelbach and Berridge, 2009) alike, participants completed a highly reliable measure of eudaimonic well-being (Ryff, 1989) approximately 3 years prior to the scan session and a measure of trait, hedonic PA (Watson et al., 1988). These self-report measures were complemented with indicators of diurnal fluctuations of the stress hormone cortisol – a biomarker of well-being in daily life. Participants provided four saliva samples per day on four consecutive days while at home approximately 1.5 years prior to the scan session. Cortisol magnitude was extracted, and we calculated the Area Under the Curve with respect to ground (AUCg; Pruessner et al., 2003) as an indicator of

[1] While there are several timescales to examine the temporal dynamics of brain activity, for this report, the term "sustained" reflects the ability to engage brain activity across trials.

total hormonal output. Lower total cortisol output over the day has been found to predict higher levels of positive affect (Steptoe et al., 2005) and lower levels of morbidity (Dekker et al., 2008).

Method

Participants.

72 participants of a representative sample from the Midwestern United States were scanned in a General Electric 3 Tesla scanner. There were several "waves" of data collection for the MIDUS study, with the fMRI portion as the final wave. Therefore, there was some variability between assessments. Of the 72 participants, eight participants were excluded due to excessive motion. Four participants had several large spikes of more than 2 mm, two participants had drift and spikes > 2 mm, and two participants had severe drift (> 2.5 mm). Forty-five of the participants were female, with a mean age of 58.20 years (sd = 11.42; range = 38-79).

Self-report measurements.

Participants completed a measure of Psychological Well-Being (PWB; Ryff, 1989; Ryff and Keyes, 1995) the Positive Affect/Negative Affect-Now (measuring current PA) scale as well as the trait Positive Affect/Negative Affect-Gen scale (PANAS; Watson et al., 1988). The PWB measure contains six subscales (self-acceptance, positive relations with others, autonomy, environmental mastery, purpose in life, and personal growth) hypothesized to account for the primary dimensions encompassing the PWB construct. The PWB measure is a highly reliable measure of eudaimonic well-being (6-week test-retest reliability for the six scales > 0.8; Ryff, 1989). To calculate an overall PWB score, we calculated the mean of the six subscales. PWB was calculated during the

first wave of data collection and was collected an average of 1212 days prior to the fMRI session (SD=367 days, min=348, max=1669 days). In addition, the PANAS-Gen was acquired (the trait version of the scale). This asks participants to "Indicate to what extent you GENERALLY feel this way, that is how you feel ON AVERAGE"). The PANAS-Gen was acquired on average 393 days before the fMRI session (though note that the median number of days the PANAS-Gen was completed before the fMRI session was 1 day because while a few subjects were recruited back 3-4 years later, the majority were recruited back for the following day). For the PA-Now, see Appendix III.

Imaging Task.

Participants viewed 60 positive, 60 neutral and 60 negative images for four seconds over five functional scan runs with a 4-16s variable length ITI. Images were taken from the International Affective Picture System (IAPS) set (Lang PJ, 2005) and their presentation order was randomized. Participants saw each image once during the scan session. To maintain participants' alertness throughout the session, they made a forced-choice button press indicating the valence of the image upon image presentation. Following 120 of the trials, a neutral male face was presented (taken from the Surrey Set) for 500 msec. The face was presented either at 1 second or 3 seconds following offset of the IAPS slide. As our prediction regarding VS engagement and well-being pertains to the neural response to the affective slides, we restrict our analysis to the IAPS image presentation epoch.

Image Acquisition

During scanning, participants were equipped with a standard clinical whole-head quadrature head coil. Functional images were acquired using a T2*-weighted gradient-

echo, echo-planar images (EPI) pulse sequence [30 sagittal slices, 4 mm thickness with 1 mm gap; 3.75 x 3.75 mm in-plane (64 × 64 voxels); FOV = 240; repetition time (TR)/echo time (TE)/Flip, 2000 ms/30 ms/60°; 262 whole-brain volumes per run]. Five functional scan runs were acquired. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 × 256 in-plane resolution; 240 mm FOV; 124 × 1.1 mm axial slices).

Image Analysis.

FMRI data were slice-time and motion corrected using AFNI (Cox, 1996). Echo planar images (EPI) data were normalized to the 2mm MNI152 template using FSL's linear normalization algorithm FLIRT and smoothed (5mm FWHM). Individual subject GLMs modeled the three valenced conditions (i.e., positive, negative, neutral images), and included the six motion estimates as covariates of no-interest. Data were modeled using the canonical double gamma HRF provided by FSL's software (Smith et al., 2004; Woolrich et al., 2009). Using FSL's 3-level approach, a separate GLM was performed for each run of EPI data. Subsequently, a fixed effects GLM was performed to combine the parameter estimates of the 5 runs for each subject. Sustained neural response was measured as the ability of participants to repeatedly engage reward circuitry over the scan session. In order to examine such sustained brain activity over the 5 scan runs, we performed a linear trend analysis weighting scan run as [-2 -1 0 1 2]. This yielded a beta estimate corresponding to the slope of change in activity over the scan runs for the 3 conditions (positive, negative and neutral). Utilizing the linear contrast approach allowed for a greater sensitivity to individual differences in sustained brain activity by assigning a weight to all the scan runs. The product of this fixed-effects analysis was used in the

group analysis. At the group level, we performed a multiple regression examining the relationship between sustained brain activity (i.e., the beta value obtained in the fixed-effects analysis) and mean PWB. Voxelwise data were thresholded at $p<.005$, $k>60$ voxels, corresponding to $p<.05$ corrected for multiple comparisons based on Monte Carlo simulation (AFNI's AlphaSim program) across the whole-brain. Clusters found to be significant in the group analysis examining the relationship between PWB and sustained brain activity in response to positive images were used in subsequent analyses testing specificity as well as relationships with cortisol. Following the initial group analysis, we performed several follow up analyses examining the specificity of the finding of sustained brain activity in response to positive images and PWB. We extracted the mean sustained activity in the cluster in response to the valenced image and used these cluster summary statistics in follow up analyses which were all performed in R. To examine specificity with regard to valence, we performed simultaneous regression analyses including both sustained activity in response to positive as well as negative (or neutral) stimuli to predict PWB. To examine specificity with regard to sustained activity, we extracted mean, aggregated signal across the entire scan session (as is commonly done in fMRI studies) and included both sustained and aggregated measures in simultaneous regression analyses to test which measure accounted for greater variance in PWB or cortisol.

Cortisol acquisition and analysis

Saliva samples were collected at waking (before getting out of bed), 30 minutes after getting out of bed, before lunch, and before bed for four consecutive days. Participants were instructed to collect samples before eating, drinking, or brushing their

teeth. Participants were asked not to consume any caffeinated products (coffee, tea, soda, chocolate) before collecting samples. Data on the exact time respondents provide each saliva sample was obtained from the nightly telephone interviews *and* from a paper-pencil log sent with the collection kit to ensure accuracy. Participants indicated how many blood pressure, cholesterol, depression and corticosteroid medications they were currently prescribed and these metrics were controlled for in the regressions. When all 16 saliva tubes were ready to be sent, participants used a pre-addressed, paid courier package for return mailing. The enclosed salivettes were shipped to the MIDUS Biological Core at the University of Wisconsin, where they were stored in a freezer at -60^{o} C. For analysis, the salivettes were thawed and centrifuged at 3000 rpm for 5 minutes. Cortisol concentrations were quantified with a commercially available luminescence immunoassay (IBL, Hamburg, Germany), with intra-assay and inter-assay coefficients of variation below 5%. AUC was calculated according to the method described by Pruessner (Pruessner et al., 2003). Cortisol values are nanomoles per liter (nmol/l). Minimum cortisol value over the day was 3.50 nmol/L and the maximum was 38.45 nmol/L. Fifty-one of the participants provided sufficient samples. Cortisol was assessed on average of 530 days prior to the fMRI session, although cortisol for some participants was acquired following the scan session – which contributes to the large standard deviation (SD=674 days, min=505 days following to the scan, max=1491 days prior to the scan). One participant's AUCg metric was a significant outlier (z=5.56) and was excluded from analysis.

Mediation Analysis

To assess whether sustained brain activity mediated the relationship between eudaimonic well-being and cortisol and whether the VS mediated the relationship of the DLPFC and PWB, we used bootstrapping procedures developed by Preacher and others (MacKinnon et al., 2002; Preacher and Hayes, 2008) recommended for smaller samples. In our analyses we used 5,000 bootstrap resamples of the data with replacement. Statistical significance with alpha at .05 is indicated by the 95% confidence intervals not crossing zero.

Results

Increased well-being was associated with sustained engagement of brain activity in response to positive images in two regions (whole-brain corrected for multiple comparisons): the VS ($r=0.45$, $p<.001$) and the right dorsolateral prefrontal cortex (DLPFC; $r=0.47$, $p < .001$; Table 1). The relationship between sustained engagement of the VS and well-being increased after controlling for individual differences in days between well-being assessment and fMRI scan session ($B=0.42$, $t(61)=3.91$, $p<.001$). The relationship between sustained engagement of the VS and well-being remained after controlling for sustained activity in response to neutral images ($B=0.35$, $t(61)=2.91$, $p<.005$). To further examine the valence-specificity of the effect, we tested whether sustained VS activity over the scan session in response to negative images predicted well-being. It did not ($r=0.15$, $p=0.23$), suggesting specificity of sustained VS activity in response to positive stimuli predicting well-being. Indeed, the correlation of sustained VS activity over the scan session to negative images is significantly lower than the r-value for the correlation of sustained VS activity over the scan session to positive images ($t(61)=2.38$, $p=0.02$). Because our sample included a wide age range, we verified that

controlling for age did not attenuate this relationship (B=0.39, t(61)=3.61, p<.001). We also tested whether VS activity in response to the positive images aggregated across the scan session (as is customarily done in imaging studies) predicted well-being; in a simultaneous regression including measures of *sustained* and *aggregated* VS activity to predict well-being, only *sustained* VS activity did predict well-being (B=0.42, t(61)=3.94, p<.001); while *aggregated* VS activity did not (B=0.001, t(61)=0.04, p=.97).

To assess the specificity of the relationship between sustained engagement of the VS and eudaimonic well-being, we also assessed the relationship between trait hedonic PA and sustained engagement of the VS in response to positive stimuli. There was a significant zero-order correlation between the PA-Gen and sustained VS activity (r=0.31, t(62) = 2.58, p=.01). However, when including both PA Gen and PWB into a simultaneous regression predicting sustained striatal activity, PWB uniquely predicted sustained VS activity (B=0.50, t(61)=2.85, p=0.006), while PA-Gen did not (B=0.24, t(61)=0.143, p=0.89; results for current hedonic PA were identical, see Appendix III). This suggests that sustained engagement of the VS in response to positive stimuli across trials is specifically related to eudaimonic well-being as opposed to hedonic PA per se.

Extending the implications of sustained VS activity in response to positive stimuli to the health domain, we tested whether sustained VS activity predicted cortisol output over the day. Because certain medications have been found to affect cortisol output, we additionally controlled for the number of blood pressure, cholesterol, depression, and corticosteroid medications participants were currently prescribed (Kirschbaum et al., 1995). Sustained VS activity in response to positive stimuli significantly predicted cortisol output (B=-2.43, t(44) =-2.23, p=.03) such that individuals with greater sustained

VS activity had lower daily cortisol output (Figure 2). This effect was not attenuated by controlling for age (p=.02), nor was it attenuated by controlling for days between cortisol assessment and fMRI session (B=-2.46, t(43) =-2.31, p=.03). Further suggesting specificity to positive stimuli, sustained VS activity in response to negative stimuli did not predict cortisol output (B=-0.04, t(44) =-1.61, p=.11). Critically, sustained VS activity in response to positive stimuli significantly mediated the relationship between well-being and cortisol (95% confidence interval: -2.90, -0.10, p<.05) suggesting that sustained engagement of VS activity may act as a protective factor in reducing daily cortisol output[2].

With regard to the significant association between sustained engagement of the DLPFC in response to positive images and well-being, the relationship remained after controlling for sustained activity in response to neutral images (B=0.55, t(61)=4.40, p<.001), while sustained activity in response to neutral images did not predict well-being (B=-0.16, t(61)= -1.31, p=0.19). Controlling for days between well-being assessment and fMRI session did not attenuate the relationship (B=0.50, t(61)=4.11, p<.001). To examine specificity with regard to valence, we tested whether sustained DLPFC activity over the scan session in response to negative images predicted well-being. It was marginally non-significant (r=0.24, p=0.06). We tested whether DLPFC activity in response to the positive images aggregated across the scan session predicted well-being; it did not (r=-0.008, p=0.95). A simultaneous regression including measures of both *sustained* and *aggregated* DLPFC activity to predict well-being showed that it was only *sustained* engagement of DLPFC activity that predicted well-being (B=0.53, t(61)=4.26, p<.001)

[2] There was not a significant correlation between well-being and cortisol (B=-0.02, t(44)= -1.21, p=0.23), though it was in the expected direction.

and not *aggregated* DLPFC activity (B=0.03, t(61)=0.87, p=.39). Controlling for age did not attenuate the relationship between sustained DLPFC activity and well-being (B=0.47, t(61)=3.87, p<.001).

To assess the specificity of the relationship between sustained DLPFC activity and well-being, we assessed the relationship between trait PA and sustained DLPFC activity in response to positive stimuli. There was a significant zero-order correlation between the PA-Gen and sustained DLPFC activity (r=0.32, t(62) = 2.69, p=.009) As with the VS, when including well-being and trait PA in a simultaneous regression to predict sustained DLPFC activity, well-being uniquely predicted sustained DLPFC activity (B=0.42, t(61)=3.00, p=.004, while PA did not (B=0.20, t(61)=.14, p=.89). This suggests that sustained engagement of the DLPFC in response to positive stimuli is specifically related to eudaimonic well-being. To examine total variance accounted for in well-being, we performed a simultaneous regression in which we included both sustained VS and sustained DLPFC activity to predict well-being. The multiple R^2 was 0.29 suggesting that 29% of the variance in well-being was accounted for by sustained VS and DLPFC activity in response to positive images.

Sustained DLPFC activity in response to positive stimuli significantly predicted cortisol output over the day (B=-2.50, t(44) =-2.04, p=.05) when controlling for the medications known to affect cortisol output such that individuals with greater sustained DLPFC activity had lower daily cortisol output. This effect was not attenuated by controlling for age (p=.04). This effect was also not attenuated when controlling for days between cortisol assessment and fMRI scan session (B=-2.71, t(43) =-2.25, p=.03). Again suggesting specificity to positive stimuli, sustained DLPFC activity in response to

negative stimuli did not predict cortisol output (B=-0.91, t(44) =-0.84, p=.40). Using the same bootstrapping method as done for the VS cluster, sustained DLPFC activity also mediated the relationship between well-being and cortisol (95% confidence interval: -2.85, -.05, $p<.05$).

Lastly, as it may be the case that subcortical activity mediates the relationship by which prefrontal engagement and impacts upon behavior (Ochsner and Gross, 2008; Wager et al., 2008), we tested whether the sustained activity in the VS cluster found in the group analysis would mediate the relationship between sustained DLPFC activity and well-being. Indeed it did (95% confidence interval: 0.02, 0.31, $p<.05$), suggesting that sustained DLPFC engagement may only promote well-being to the degree that it effectively influences VS activity for that individual.

Discussion

Nearly four decades ago Solomon and Corbit (1974) suggested that examining the temporal dynamics of emotion could yield a more complete and nuanced understanding of affect. It is only recently, however, that researchers have begun to empirically test this prediction. Specifically, how the brain responds to the repeated occurrence of positive stimuli have been successfully examined to explain affective differences between depression or at risk individuals and healthy controls (Siegle et al., 2002; Heller et al., 2009). Whether similar dynamics may account for individual differences in well-being in healthy individuals had not been previously examined, and our findings suggest that it does. It is worth noting that, this paradigm contained positive images embedded within a stream of stimuli that included neutral and negative images. In our view, this enhances the ecological validity of these findings as in everyday life individuals do not often

encounter uninterrupted positive stimuli. Negative experiences intermix with positive ones, and the ability of individuals to repeatedly engage circuitry involved in reward and positive affect in the face of negative stimuli may be important for health and well-being.

Our data demonstrate that sustained engagement of reward circuitry in response to positive stimuli is associated with increased eudaimonic well-being measured several years previously. The import of this relation is amplified by the finding that sustained VS and DLPFC activity both predicted levels of the stress hormone cortisol such that more sustained activity in response to positive stimuli predicted lower levels of cortisol output – also measured on a different date. Critically, sustained activity in both these regions mediated the relationship between cortisol and well-being suggesting a possible neurobiological mechanism through which well-being may influence health. In addition, that well-being and cortisol were measured on different days than the fMRI session likely strengthens the associations with sustained brain activity as it suggests that these associations reflect stable interindividual differences lasting over years.

The VS is an area known to be involved in the anticipation and processing of reward as well as reinforcement learning (Kringelbach and Berridge, 2009; Haber and Knutson, 2010). However, research also supports a role for the VS in coding punishment and negative affect (e.g., Roitman et al., 2005). The VS has dense dopaminergic projections from the ventral tegmental area, as well as efferents from amygdala, the hippocampus and the medial PFC which make it well situated to assist in the assignment of salience to stimuli (Berridge and Robinson, 1998). Until now, habituation in the VS has mostly been examined with reference to addiction processes (Di Chiara, 2002) – whereby a lack of VS habituation to drug cues is interpreted as part of the addiction

process. However, whether in certain contexts, sustained engagement of the VS to appetitive cues may also represent an adaptive and healthy process has not been widely discussed. The mediation analyses presented here, that sustained VS activity significantly mediated the relationship between sustained DLPFC activity and well-being, in addition to the work by Wager and others (Ochsner and Gross, 2008; Wager et al., 2008) provide initial evidence towards this hypothesis. For example, sustained connectivity between the VS and distinct structures in the PFC or other limbic regions may predict whether such sustained VS activity is adaptive (e.g., promoting well-being) or not (e.g., promoting addiction/craving processes). Our results suggest a more nuanced view of the how the VS responds to the repeated occurrence of positive stimuli is needed.

The area of DLPFC (BA 8/9) found in the current study is not typically thought to be part of the affective network. In general, these regions of DLPFC are more commonly found to be involved in studies of working memory (Owen et al., 2005) and attention (Corbetta et al., 2008). Nonetheless, this region is likely important in facilitating affect-cognition interactions: a meta-analysis shows that DLPFC is reliably engaged when regulating emotion (Kalisch, 2009). In addition, this analysis could be conceptualized from a repetition suppression perspective. Repetition suppression is an experimental method whereby stimuli or classes of stimuli are repeated and researchers examine changes in brain activity following such repetition (Grill-Spector et al., 2006). As both repetition suppression and our analysis strategy looked at rates of habituation of brain activity over time, it is not surprising that studies of repetition suppression have found suppression effects across the PFC (Rainer and Miller, 2000).

Both the VS and the DLPFC are also well positioned to influence cortisol output. The VS has GABAergic projections directly to the hypothalamus (Haber and Knutson, 2010) and it could impact hypothalamic activity indirectly via its projections to the bed nucleus of the stria terminalis, amygdala and hippocampus (Davis et al., 2010; Haber and Knutson, 2010). As a result, sustained engagement of the VS may be one pathway by which cortisol output over the day is regulated. Further work examining how the VS responds to the repeated occurrence of positive stimuli in relation to cortisol output are required to test this hypothesis. The DLPFC, on the other hand, has no direct outputs to the hypothalamus, however, several studies have demonstrated a modulatory role for the DLPFC on cortisol (Dedovic et al., 2009; Pruessner et al., 2010) and relations between PFC activity and diurnal cortisol output (Urry et al., 2006). As a result, the DLPFC may affect cortisol indirectly via its connections to limbic structures.

Examining the temporal dynamics of emotion and brain activity may yield a refined view of how emotion unfolds over time and the individual differences which relate to such variation. A recent example where temporal dynamics were exploited was in the facilitation of extinction following fear conditioning (Schiller et al., 2010). The authors showed that following fear conditioning, extinction can be facilitated if preceded by a re-presentation of the conditioned-unconditioned stimulus association. Clinically, this finding suggests that understanding temporal dynamics may aid in the treatment of psychopathology. Our work adds additional evidence to this view by demonstrating that sustained VS and DLPFC activity in response to positive stimuli – in the midst of negative and neutral stimuli – predicts well-being. Critically, sustained activity in these regions mediated the relationship between daily cortisol output and well-being. This

suggests a neurobiological mechanism by which psychological constructs such as eudaimonia may ultimately lead to improved physical health and improve the quality of life.

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Figure 1. Ability to sustain VS activity to positive stimuli predicts psychological well-being (corrected for multiple comparisons, p<.005, k>60).

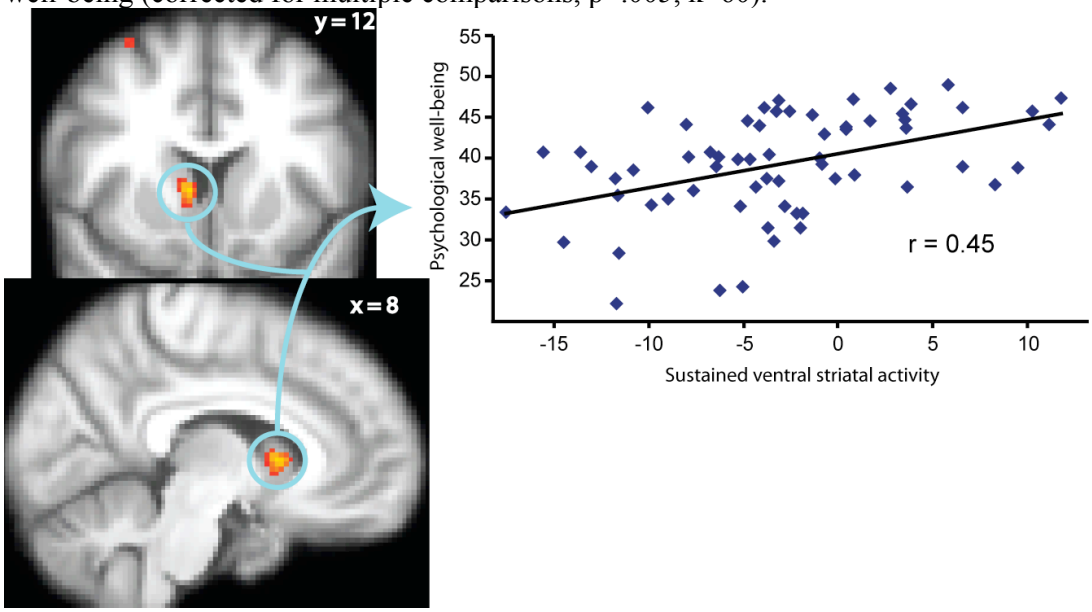

Figure 2. Sustained VS activity (left) and DLPFC activity (right) to positive stimuli predicts total cortisol output over the day such that more sustained VS activity in response to positive pictures predicts lower cortisol output – when controlling for medications currently prescribed. The analytic strategy utilized continuous distribution of sustained BOLD signal, but for illustrative purposes here, we split the data into quartiles. Error bars indicate SEM.

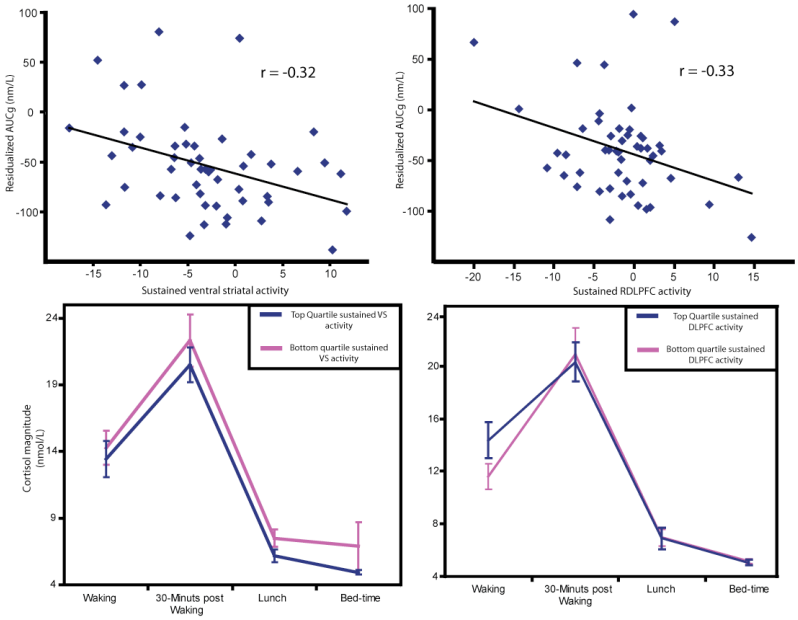

Figure 3. Ability to sustain DLPFC activity to positive stimuli predicts psychological well-being (corrected for multiple comparisons, p<.005, k>60).

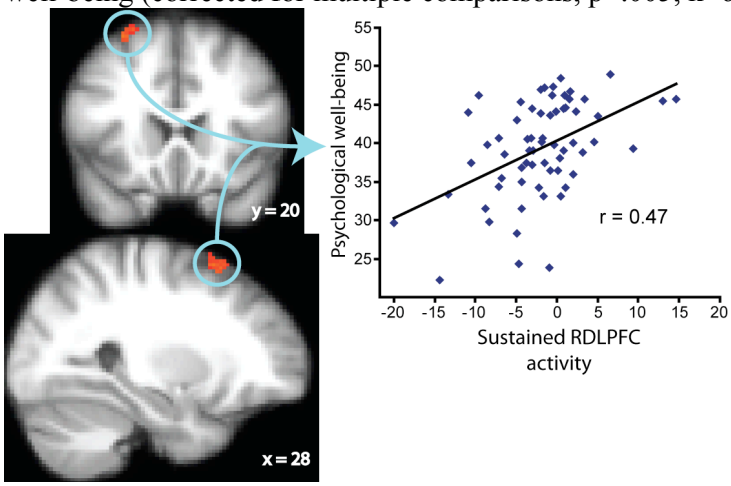

Table 1. Result of voxelwise correlation between sustained brain activity and level of eudaimonic well-being.

Region (BA)	*x, y, z (mm)*	*Cluster size*	*Max t-value*
R DLPFC (8/9)	30, 14, 60	75	3.71
R Ventral Striatum	8, 12, 4	61	4.16

Chapter 5

Temporal dynamics of affect experienced in one's own environment and its relationship to sustained brain activity

Introduction

In the previous studies we examined the association of across-trial temporal dynamics with self-reported positive affect measured in the lab. However emotions are episodic experiences and unfold over time. As self-reported positive affect was not measured repeatedly, our measures of self-reported affect were unable to assess the temporal dynamics of individuals' experienced emotion (ie., how long does someone experience positive affect on average?). A question raised by the previous studies is whether the temporal dynamics of experienced emotion maps on to the temporal dynamics of such reward-related brain activity.

A second question raised by the previous studies has to do with whether self-reported positive and negative affect measured in the lab maps on to positive and negative affect reported in individuals' own environment. The previous chapters used measures of self-reported positive affect assessed in the laboratory. For instance, Kahneman has suggested that humans experience life in chunks, which he refers to as "moments". He proposes that each of these "moments" last for approximately 3 seconds (Kahneman and Riis, 2005), such that people may experience roughly 10.5 million waking moments in a single year. Ultimately, this point is made to argue that when faced with the task of processing and storing all of these experiences, the brain resorts to several conservation mechanisms and the vast majority of experienced moments simply disappear. Much of the previous research on emotion has focused on an individual's memory of their aggregated life experience. This is the case for research assessing positive and negative affect in "healthy" populations but is particularly the case when assessing for psychopathology. Psychiatric samples are often asked to aggregate over a

two week period. Such retrospective evaluation of past episodes has been referred to as remembered utility (Kahneman and Tversky, 2000). On the other hand, momentary utility refers to the valance and intensity of current affective experience. Momentary utilities can be measured using techniques such as Ecological Momentary Assessment (also referred to as experience sampling methods; Hektner et al., 2007; Shiffman et al., 2008) and then aggregated to form a measure of experienced utility.

Several studies have shown that remembered utility does not always accurately reflect the mean of experienced utility. Redelmeier and Kahneman (Redelmeier and Kahneman, 1996) showed that when remembering painful medical procedures, patients use the Peak/End Rule, which states that remembered utility only accounts for the most extreme (peak) and final (end) moment utilities, while the rest of the experience is largely unrepresented in memory. In this study, they recorded both experienced pain and remembered pain in patients undergoing colonoscopy or lithotripsy procedures. Patients' experienced pain was measured by prompting them to rate their current intensity of pain every 60 seconds. Their momentary pain was then used to calculate a measure of total pain, average pain and peak/end pain. They also provided retrospective evaluations one hour and one month after the procedure. Patients' retrospective evaluations of pain were correlated with the peak pain experienced and the pain experienced in the last three minutes of the procedure, but not with the total pain experienced during the procedure. Thus the duration of the procedure had no significant effect on the retrospective measure of pain. This last finding has been called duration neglect. These results indicate that remembered utility does not reflect the average or total experience, leading to the notion

that a separate measure of experienced utility is necessary to obtain a comprehensive view of the experience.

In a follow-up study, (Redelmeier et al., 2003) they investigated whether they could utilize their understanding of the Peak/End Rule to alter patients' memories of painful medical procedures and thus improve return rates for subsequent colonoscopy procedures. In order to reduce patients remembered pain, a modified procedure was designed in which the colonoscope was allowed to rest in the rectum for 3 minutes prior to removal. This caused the final moments of the colonoscopy to be less painful. Approximately half of the patients were randomized to receive this modified procedure. A similar method of recording both experienced utility and remembered utility was utilized as in the previously described study (Redelmeier and Kahneman, 1996). In the moment reports suggested that there was no significant difference between the 2 groups in the level of pain experienced during the beginning, middle, or worst part of the procedure, but the modified care group experienced less pain during the final part of the procedure. Despite their equivalent experienced pain, patients who received the modified procedure remembered less total pain than those receiving the conventional procedure. Patients receiving the modified procedure were also 18% more likely to return for their next colonoscopy. Other studies using auditory stimuli have found similar results (Schreiber and Kahneman, 2000).

Recent research has found that acute, state measures (ie., moment utility measures) of positive affect predict rates of survival (Steptoe and Wardle, 2011). Importantly, these acute state measures often do a better job at predicting health and morbidity than more traditional self-report measures which ask participants to report their

average affect for the previous one or two weeks (e.g., Steptoe et al., 2007). These biases also have been shown to vary across diagnoses, such that patients with MDD weight different factors than do psychiatrically healthy individuals when filling out more traditional, trait-like questionnaires (Peeters et al., 2003; Bylsma et al., 2011). This is not to say that retrospective self-report measures of affect or psychopathology are invalid. However, it is likely that in the moment ratings of emotion and retrospective self-reports measure distinct phenomena (Robinson and Clore, 2002). In particular, while momentary utility may more accurately capture in the moment levels of positive and negative affect, retrospective self-reports likely rely on cognitions, and in particular, memory or semantic processes about the self in determining the way individuals interpret and report their emotion (Robinson and Clore, 2002). For example, the longer the time interval between the in-the-moment and retrospective self-report, the larger the discrepancy between the two (Ebner-Priemer & Trull, 2009), and in-the-moment measures of affect often show relatively poor overlap with retrospective self-reports (Shiffman et al., 2008)

Accordingly, despite converging evidence from the previous three studies, important questions regarding the relationship between affect and temporal dynamics of brain activity remain. First, how do individual differences in the temporal dynamics of emotion – experienced in the real-world and assessed at the time of emotional experience actually map on to the temporal dynamics of brain activity in similar affective states? Do individual differences in the temporal dynamics of emotion correlate with the temporal dynamics of reward-related brain activity? For this final chapter, we set out to use fMRI and experience sampling to measure brain activity of participants after they provided in-the-moment assessments of their affect. In addition, to gain some experimental control

while subjects participated in their own environment, we developed a method so that participants would play a game to win or not win money. This would putatively induce an emotion after which we could measure sustained positive and negative affect.

MATERIALS & METHODS

Participants

A sample of 105 participants (62 Females) completed the experience sampling portion of the experiment. Ages ranged from 18-36 years (M= 20.49, SD= 2.76). During the initial and follow-up visits, all participants were run individually. No participants dropped out of the study or failed to come to the follow-up laboratory visit. Participants were made aware of the study through flyers which were posted on bulletin boards in UW-Madison buildings and other campus locations, as well as the surrounding area. At this point, interested participants were placed on a waiting list where they were randomly selected to be contacted, via email, to schedule their initial visit. Forty participants were recruited to return to the lab for the fMRI portion of the study. These participants were randomly selected, with the requirement that they had responded to at least 75% of the text messages within the allotted time of ten minutes. This was done to ensure that those participants who were scanned had provided sufficient experience sampling data.

Procedures

Experience Sampling. This study consisted of three parts: an initial laboratory visit, a 10-day ecological data collection period, and a follow-up laboratory visit. Participants received $20 for completing the study, and had the opportunity to earn extra money during the data collection period. The initial visit took place at our laboratory, where participants were run in individual sessions that lasted 45-60 minutes. During this

visit, participants read and signed the study consent form, completed a battery of paper-and-pencil assessments, and were given all necessary study information; this information included detailed instructions on how to complete the ecological data collection portion of the study and how monetary compensation would be awarded. Also at this visit, research staff collected the participants' cell-phone numbers as well as the dates and time periods the participants would be available to receive and respond to text messages. Starting with the day after the initial visit and continuing until ten days were selected, participants were asked to provide a continuous 10-12 hour time period during which they would be able to receive and send text messages. Participants were allowed to skip a day if they desired, but never more than three days in a row. Also, participants were allowed to select different 10-12 hour blocks for different days, but were not allowed to break up a daily 10-12 hour block into separate components. This information was recorded into in-house designed software.

During each of the ten days and 10-12 hour time periods selected by participants, ecological data was obtained via text messaging between participants' personal cellular devices and Tropo (https://www.tropo.com/), a text messaging data acquisition service. Participants were told that they would receive $4 for each day they responded to at least 90% of text messages within seven minutes, for a total possible bonus of $40 over the 10-day study. All text messages, both sent and received, were time-stamped electronically. Participants received up to thirty text messages a day, and these messages were of two types; messages either assessed the current emotional state of participants or implemented the daily game played by participants.

Messages which assessed the current emotional state of participants were all identical, and read: “Enter how much positive emotion (1-9) and negative emotion (1-9) you are feeling right now.” Participants were instructed to respond to these text messages by sending back, in a single text message, two digits between one and nine separated by a space, representing their positive and negative emotion, respectively. Participants were instructed that a “9” rating indicated the participant was feeling a very high amount of that particular kind of emotion, while a “1” rating indicated the participant was feeling a very low amount of that type of emotion. If participants did not respond to these text messages within seven minutes, their response was discarded and not included in analysis. These text messages were sent at 60 to 90 minute intervals throughout the day in order to collect baseline levels of emotion from participants, and were also sent at fixed intervals during and following the game in order to assess the emotional response the game produced.

A series of text messages were used to implement the game. At a random point in the 10-12 hour block, participants received a text message reading: “Are you ready to play a game and answer more text messages for the next two hours? (y/n)”. This message allowed participants the option of playing the game now (by responding “y”) or postponing the game until later in the day (by responding “n”) when they would receive this prompt again. Participants were previously informed that for two hours following the game, they would receive text messages assessing their emotional state at a greater frequency than normal. Participants were also told to postpone the game if they were not in a situation enabling them to respond to text messages at this rate. When participants elected to not play the game, they were put back into the baseline state where they would

receive text messages assessing their current emotional state every 60 to 90 minutes until being prompted to play the game again. When participants opted to play the game, they were sent a text message stating: "We generated a number between 1 and 9. Guess if it's lower or higher than 5. (low/high)". After providing their guess, participants then received a standard emotional assessment text message. After supplying this information, participants were told if they guessed correctly ("The number was [1-9]. You guessed right! $15 has been added to your account.") or incorrectly ("The number was [1-9]. You guessed wrong. No additional money has been added to your account."). Participants won $15 every time they won the game, and did not gain or lose any money when losing the game. Immediately after being informed of the game's outcome, participants began receiving text messages assessing their emotional state. These texts were sent once every ten minutes for the first hour, and then at an incrementally decreasing pace for the second hour following the game.

After completion of the ten day ecological data collection period, participants were contacted via email to come back to the laboratory for a follow-up visit. At this visit, participants filled out a post-study questionnaire which included the retrospective assessments and various paper-and-pencil assessments. They also were informed of the total amount of monetary compensation earned (out of a possible $210) and filled out payment forms. Participants were then debriefed and thanked for their participation. Experience sampling measures of emotion were attained from participants during baseline and post-game periods. In total, eleven EMA measures were obtained: Baseline PA, Baseline NA, PA Reactivity (Win), PA Reactivity (Loss), PA Regulation (Win), PA Regulation (Loss), NA Reactivity (Win), NA Reactivity (Loss), NA Regulation (Win),

NA Regulation (Loss). Baseline PA and baseline NA were obtained by averaging all responses received from participants during the baseline period. "PA reactivity" and "NA reactivity" were measured separately for wins and losses, and calculated by taking the difference between the participant's average baseline emotional level (i.e. baseline PA or baseline NA) and the emotional level reported in the experience sample which directly followed the game outcome text message. "PA regulation" and "NA regulation" were measured temporally and in minutes. We calculated a confidence interval surrounding each participant's baseline PA and NA scores (2* the standard error[1]), and for each participant assessed the average amount of time (in minutes) required for PA or NA to return to baseline levels following notification of game outcome.

fMRI Portion

Participants.

As stated above, 40 participants were recruited to return to the lab for an additional fMRI portion. These participants were randomly selected of those who responded to more than 80% of the text messages during the experience sampling portion. The fMRI portion of the study was designed to examine the temporal dynamics of brain activity when performing a task which putatively induces positive and negative affect.

Imaging Task

Instead of using an explicit emotion regulation paradigm or a more passive affective image viewing task as we did in previous studies, to maximize similarity across the experience sampling and fMRI portions, we elected to use a monetary gambling task

[1] The standard error for baseline PA and NA was calculated as: Standard Deviation / square root(number of samples)

that is relatively similar in structure to the experience sampling study, and has been shown to activate the Ventral Striatum (VS) in several studies (Delgado et al., 2000; Delgado et al., 2003; Delgado et al., 2008). In this "card guessing" task, each trial was worth $1. Individuals were presented with a cue number 5 and asked to indicate whether the next, target number is above or below the cue number. Participants were given a 2 second window to respond to this initial cue image and register their guess. This was followed by a variable 3.5-5.5 second anticipation period after which participants were presented with the number the computer had generated and either an upward or downward point arrow indicating they had guessed correctly and won $1 or guessed incorrectly and not won any money, respectively. There was a variable ITI of 10±4 sec. The design and organization of the fMRI paradigm was done to parallel the fMRI and experience sampling studies as closely as possible. Each scan run contained 20 trials and there were 6 scan runs, comprising of a total of 120 trials with 60 win and 60 no-win trials.

Image Acquisition

Echo-Planar Images (EPI) with a native resolution of 4x3.75x3.75mm and 40 slices through the sagittal plane were acquired on a 3 Tesla GE scanner. During scanning, participants were equipped with a standard clinical whole-head quadrature head coil. Functional images were acquired using a T2*-weighted gradient-echo, EPI pulse sequence; FOV = 240; repetition time (TR)/echo time (TE)/Flip, 2000 ms/25 ms/60°; 173 whole-brain volumes per run]. A high-resolution T1-weighted anatomical image was also acquired (T1-weighted inversion recovery fast gradient echo; 256 × 256 [1.0 mm x 1.0 mm] in-plane resolution; 256 mm FOV; 156 × 1.0 mm axial slices).

Image Analysis.

FMRI data were slice-time and motion corrected using AFNI (Cox, 1996). A study specific template was created using ANTS (Klein et al., 2009) and EPI data were normalized to it at 1mm isotropic using ANTS' nonlinear registration algorithm and smoothed (6mm FWHM). Individual subject GLMs modeled the two outcome conditions (i.e., win or no-win). Data were modeled in two approaches. The first approach was the more traditional, canonical approach. The outcome phase of the trial was modeled using the canonical double gamma HRF provided by FSL's software (Smith et al., 2004; Woolrich et al., 2009). Using FSL's 3-level approach, a separate GLM was performed for each run of EPI data. Subsequently, a fixed effects GLM was performed to combine the parameter estimates of the 6 runs for each subject. In addition to the main effects analysis, sustained neural response across trials (sometimes referred to as across trial rates of habituation, or repetition suppression) was measured as the ability of participants to repeatedly engage reward circuitry over the scan session. In order to examine such across trial sustained brain activity over the 6 scan runs, we performed a linear trend analysis weighting scan run as [-2.5 -1.5 -0.5 0.5 1.5 2.5]. This yielded a beta estimate corresponding to the slope of change in activity over the scan runs for the 2 conditions (win or no-win).

The second approach was intended to examine within trial temporal dynamics (ie., on average, how long activity was sustained over a win or a no-win trial). To do this, we performed a Finite Impulse Response (FIR) GLM for each run in FSL. Instead of using a canonical HRF to acquire a single Beta estimate corresponding to the mean BOLD amplitude for that temporal epoch, a FIR model assumes no canonical shape and

estimates the mean BOLD activity for each time point of interest. Because the TR was 2s and we were interested in the 14 seconds following participants finding out whether they won or did not win. We thus modeled each of the 7 TRs following notification of game outcome. To examine within-trial temporal dynamics, we located the maximal response within TRs 2-4 and from that point, performed a regression analysis in which we calculated the slope of BOLD activity from that maximal point to the end of the trial for "win" and "non-win" trials on a voxelwise basis. This yielded voxelwise beta estimates for "win" and "no-win" trials corresponding to an estimate of within trial sustained activity for win and no-win trials for each subject.

Group Analyses

Main effect analyses examined brain areas which were significantly active during the win, no-win and win vs. no-win conditions. We performed several analyses to examine the relationships between sustained activity brain activity across trials and positive affect. We tested the association between individual differences in rates of habituation in the win vs. no-win conditions (fMRI) and sustained positive affect following a win vs. sustained negative affect following a no-win as measured via experience sampling. As in previous studies we found associations between rates of habituation and self-reported positive affect and/or well-being, we also tested whether rates of habituation in the win condition was correlated with current self-reported positive affect as measured on the PANAS-Now (Watson et al., 1988) as well as with a measure of Psychological Well-Being (Ryff and Keyes, 1995).

We next examined within trial dynamics. We examined the association between the within trial temporal dynamics of brain activity after winning money and within trial

temporal dynamics of self-reported positive affect after winning money in the real-world. Accordingly, we tested the association between individual differences in within trial sustained brain activity in the win vs. no-win conditions (fMRI) and sustained positive affect following a win vs. sustained negative affect following a no-win as measured via experience sampling. All fMRI analyses were corrected for multiple comparisons using cluster based thresholding.

Results

Experience Sampling: Baseline Estimates

Again, Baseline estimates of PA and NA were those text messages which were sampled outside of the game period. Mean baseline PA and NA were 6.00 and 2.90, respectively (SDs: 1.28, 1.17). Across participants, baseline PA was significantly higher than baseline NA ($t(104)=16.04$, $p<.001$). There was a trend towards a significant difference in the standard deviation of affect estimates such that individual subjects had more variance in their baseline NA than baseline PA ($t(104)=1.75$, $p=.08$).

Experience Sampling: Affect Induction

The amount of change in PA or NA following notification of game outcome is referred to as "reactivity". Immediately following a win condition in which participants were informed they had won $15 increased PA (mean=1.33 points above baseline PA, $t(103) = 13.99$, $p<.001$). Immediately following a no-win condition, participants' PA dropped (mean = –0.94 points below baseline PA, $t(104) = -8.59$, $p<.001$). NA dropped immediately following a win, (mean = – 0.72 points below baseline NA, $t(103) = -7.94$, $p<.001$) and increased following a loss (mean = 1.03 points above baseline NA, $t(104) = 7.90$, $p<.001$). After computing the absolute value of the PA reactivity in the loss

condition and NA reactivity in the win condition so amounts are on the same scale, we performed a 2x2 repeated measures ANOVA to test whether there were significant differences in amount of affect change in the game. There was a significant Affect (PA, NA) x Outcome (Win, No-win) interaction ($F(1,103) = 7.74$, $p=.006$, Figure 1) such that PA changed more in the win condition than NA ($t(103)=5.60$, $p<.001$), but PA and NA changed equally in the no-win condition ($t(104)=0.50$, $p=.62$). There was also a significant main effect of affect ($F(1,103)=16.18$, $p<.001$ such that PA was more reactive overall than NA. There was not a significant main effect of game outcome ($p=.81$).

The assessment of sustained PA and NA following notification of game outcome was measured in minutes (see Methods). On average following a win, participants' PA stayed beyond the confidence interval of their baseline PA for 49.21 minutes (SD=23.53), and for 54.53 minutes (SD=24.02) following a no-win. Whereas following a win, participants' NA stayed beyond the confidence interval for 62.36 minutes (SD=24.53) and for 28.57 minutes following a no-win (SD=19.35). We performed a similar 2x2 repeated measures ANOVA for the measure of sustained affect following game outcome. There was a significant Affect (PA, NA) x Outcome (Win, No-win) interaction ($F(1,103) = 78.39$, $p<.001$), such that amount of time NA remained beyond baseline NA varied more across win and no- win conditions than did PA (see Figure 2). Note that this interaction could be due to a ceiling effect on PA such that mean baseline PA was 6.00, and mean PA reactivity following a win was approximately 1.4, whereas mean baseline NA was 2.90 and therefore had further to increase in a no-win condition (for more detail, see Figure 3). There was a main effect of affect such that following the game PA remained above baseline PA longer than NA remained below baseline NA

($F(1,103)=31.79$, $p<.001$). There was also a main effect of outcome ($F(1,103)=16.63$, $p<.001$) such that the win condition caused significantly longer change in affect than did the no-win condition.

Inter-relationships between experience sampling metrics and self-report measures

We present a correlation matrix of the relationships between several of the experience sampling metrics and the PANAS as well as the PWB – as these were measures used in our previous studies (see Table 1). Notably, both PA and NA baseline standard deviation metrics were significantly correlated with PA reactivity following a win as well as negatively correlated with NA reactivity following a win. Also, sustained PA following a win was significantly correlated with PA reactivity following a win. Similar relationships were apparent for PA reactivity following a loss with sustained PA following a loss, NA reactivity following a loss with sustained NA following a loss and NA reactivity following a win with sustained NA following a win.

We also examined the correlations between the variety of experience sampling measures with the PA and NA as measured on the PANAS-Gen (Watson et al., 1988) as well as psychological well-being (Ryff and Keyes, 1995). Interestingly, the strongest relationships between experience sampling measures and the retrospective self-reports were with the experience sampling PA:NA baseline ratio. PA:NA baseline ratio measured with experience sampling was positively correlated with Psychological Well-being (PWB) and PANAS-PA, and inversely correlated with PANAS-NA. Baseline NA standard deviation was also correlated with PANAS-NA. It is telling that while mean baseline PA and mean baseline NA were significantly correlated with PANAS-PA and PANAS-NA, respectively, the correlations ranged from 0.3 – 0.47 leaving nearly 80% of

unshared variance between these two putatively similar measures of positive and negative affect.

fMRI: Main Effects Analyses

To examine the main effects, we used FSLs double gamma function for the period at and immediately following notification of game outcome (see Methods for more detail). When examining areas showing a main effect of game outcome (win vs. baseline), several areas emerged, including the VS, PFC and visual cortex (see Figure 4, Table 2). Surprisingly, when examining the win vs. no-win conditions there were no brain areas which survived multiple comparison correction. For example, Figure 5 (taken from using the FIR model analysis) provides support that both conditions – winning and not winning the game equally activated this part of the VS.

fMRI: Individual differences in baseline positive affect

To examine the relationship between baseline positive affect and individual differences in sustained BOLD response to a win, we performed a voxelwise regression examining the brain areas – where sustained BOLD activity following a win were significantly associated with PA at baseline. One brain area survived multiple comparison correction: the left prefrontal cortex in Broadmann's Area 10 (Figure 6; cluster size = 52; max coordinate= [-14, 64, -2]; $r=0.54$, $p<.001$; spearman rho=0.41, $p=.008$).

fMRI: Individual Differences in Emotional Reactivity

To examine individual differences in emotional reactivity to winning the game, we performed a voxelwise regression examining the relationship between brain activity in response to winning the game with individual differences in emotional reactivity as assessed by change in PA from baseline. As our hypothesis specifically included the VS,

we applied a brain mask to the VS using the HarvardOxford mask (Kennedy et al., 1998; Makris et al., 1999). In addition, because there was a significant correlation between individual differences in baseline PA and PA reactivity following a win (Table 1), we controlled for PA baseline. When controlling for PA baseline, there was a significant relationship between BOLD signal in the VS and PA reactivity following a win such that those individuals showing greater increase in PA following a win (controlling for baseline PA), had higher activity in the VS following win trials (Figure 7, cluster size=36).

fMRI: Individual Differences of within-trial sustained activity

To examine individual differences in within-trial sustained brain activity with sustained positive affect following a win vs. a no-win, we performed a voxelwise regression examining brain areas which demonstrated within-trial sustained activity in a win vs. a no-win trial with sustained PA following a win vs. sustained NA following a no-win (see Figure 8 and Table 3). Two areas of particular interest emerged including the dorsal Caudate Nucleus and vmPFC. In both of these areas, more sustained brain activity following a win vs. a no-win was positively associated with longer positive affect following a win ("savoring") as compared with sustained negative affect following a no-win ("ruminating"). We also tested whether these associations were significant after controlling for reactivity as well as when controlling for mean PA following a win and mean NA following a no-win. First when controlling for reactivity: For the dorsal Caudate, this relationship was significant when controlling for PA reactivity following a win vs. NA reactivity following a no-win (B=.000027, t(37)=2.88, p=0.007). For the vmPFC this association also remained significant when controlling for reactivity

(B=.0001, t(37)=3.80, p<.001). In both of these tests, reactivity did not significantly predict either sustained dorsal Caudate or sustained vmPFC activity. Second, we controlled for mean PA following a win vs. mean NA following a loss to test whether the sustained slope measure accounts for variance above and beyond a simpler, aggregate measure. We found that sustained dorsal caudate activity following the win vs. no-win condition continued to predict sustained PA following a win vs. sustained NA following a no-win when controlling for mean PA following a win vs. mean NA following a no-win (B=.000025, t(37)= 2.76,p=0.009). Similarly, when controlling for mean affect change following the game, the relationship between sustained vmPFC activity and sustained affect following the game remained significant (B=.0001, t(37)=3.80, p<0.001). In both of these tests, mean PA following a win vs. mean NA following a no-win did not significantly predict either sustained dorsal Caudate or sustained vmPFC activity.

fMRI: Individual Differences of across-trial sustained activity

To compare the results from this study with our previous ones (Heller et al., 2009; Heller et al., In Press; Heller et al., Under Review), we examined the association between individual differences in sustained brain activity across trials in the winning condition with self-reported PA as well as psychological well-being. Interestingly, when examining the association between PA and sustained brain activity across trials, there were no areas which survived multiple comparison correction. The same was true for associations between psychological well-being and sustained brain activity across trials. At a more liberal threshold, and using small volume correction, we also examined whether there were associations between self-reported PA, well-being and three brain areas: the VS and

the two regions found above (the vmPFC and dorsal caudate). However, none of these relationships were significant (all ps > 0.3).

Discussion

To examine the neurobiological underpinnings of the temporal dynamics of emotion, we developed a paradigm to study affect in the real world via experience sampling and recruited a sample of participants back to the lab to be scanned. To facilitate experimental control over the timing of an emotion, participants played a game in which they could win money. The outcome of this game (winning or not winning money) was included as an experimentally controlled affect induction after which we could assess individual differences in sustained positive and negative affect. This approach was complimented by a fMRI session in which subjects participated in a similar game where they could win or not win money.

The affect induction of the experience sampling phase of the study was indeed successful. Winning and not winning money increased self-reported positive and negative affect, respectively. The fMRI paradigm also induced activity in a set of brain areas including the ventral striatum. There were also individual differences in emotional reactivity such that individuals showing greater increase in PA following a win (controlling for baseline PA), had higher activity in the VS following win trials. Examining within-trial temporal dynamics also revealed interesting individual differences. In both the vmPFC and dorsal striatum, more sustained brain activity following a win vs. a no-win was positively associated with longer positive affect following a win (ie., “savoring”) vs. sustained negative affect following a loss (ie., “ruminating”). There were also some findings which did not concord with our

predictions. First, surprisingly, while there was a main effect of outcome (e.g., win vs. no-win) in self-reported PA and NA in the experience sampling portion, there was not a significant main effect of outcome in the fMRI data. Second, in contrast with our previous findings (Heller et al., 2009; Heller et al., In Press; Heller et al., Under Review) we did not see a relationship between across-trial sustained brain activity and self-reported PA or psychological well-being.

There are several possibilities for the lack of concordance between this final study and the previous ones. First is the use of financial rewards as opposed to visual stimuli. While it has been suggested primary and secondary rewards act more or less similarly on the brain, this may not always be the case – particularly when examining temporal dynamics. Second, previous studies using this financial game paradigm have indeed found activity in both the win and no-win conditions (Delgado et al., 2000; Delgado et al., 2003). This is not entirely surprising as a growing literature suggests a role for the VS in processing both appetitive and aversive stimuli (Jensen et al., 2003; Roitman et al., 2005; Haber and Knutson, 2010), although it is unclear how aversive the no-win condition indeed was. It also appears that amount of money won or lost modulates the degree of reward-related activity (Delgado, 2007). The relatively low amount to be won on each trial for the fMRI portion was $1 (whereas in the experience sampling portion the amount was $15), may have added to the lack of a main effect. Experimentally, we anticipated that this might occur and attempted to circumvent this potential issue by telling participants that while each trial was only worth $1, there were many more trials in the fMRI than in the ESM portion, so the potential for winning a large sum of money

was indeed present. However, this may have not been a sufficient enticement for participants.

A third possible important difference between this and the previous chapters regards the sample. While the depressed sample examined in the first two studies (Heller et al., 2009; Heller et al., In Press) is a clearly distinct group, the large representative sample from the MIDUS study (Heller et al., Under Review) may be more comparable to this one (despite the age difference). When comparing self-reported PA and NA from the PANAS, between this sample and the MIDUS sample, PA from the MIDUS sample was significantly higher than PA from this sample (mean MIDUS PA=34.81, mean undergraduate PA=28.49, $t(101)=4.91$, $p<.001$), while there was no difference in NA (mean MIDUS NA=12.48, mean undergraduate NA=13.25, $t(101)=-1.24$, $p=0.22$). Strikingly, and in contrast to PA, undergraduate well-being was substantially higher than well-being in the MIDUS sample (mean MIDUS well-being=39.31, mean undergraduate well-being=64.93, $t(102)=18.89$, $p<.001$). As a result of these differences, the two samples may have processed rewards in different ways. For example, with higher hedonic PA but lower well-being, the MIDUS sample may have evidenced higher initial reward-related reactivity, but that this reward-reactivity did not last. If true, this would have yielded greater variability in reward-related activity across-trials. This discrepancy suggests substantial differences in the sample which may have additionally affected temporal dynamics.

The lack of a significant main effect aside, the finding that reactivity of the VS predicts individual differences in PA reactivity above and beyond baseline PA extends previous work of the role of the VS in positive emotion. Nonhuman animal research has

strongly suggested that distinct areas of the VS have been involved in both liking and incentive salience (Berridge and Robinson, 1998). Studies have found a relationship between self-reported positive affect and activity in the VS in response to winning money (Forbes et al., 2009), but the association that degree of emotional reactivity predicts VS activity provides new evidence regarding the role of the VS in affective responding – particularly with regard to the individual differences in consummatory reward processing.

In addition, the finding that sustained vmPFC and dorsal caudate activity when winning vs. not-winning predict sustained PA following a win vs. NA following a no-win provide initial evidence for a circuitry underlying individual differences in what we've referred to as "savoring". Research suggests that such sustained PA may be adaptive and promote resilience (Folkman and Moskowitz, 2000). Delgado's previous work using this paradigm (Delgado et al., 2000; Delgado et al., 2003; Delgado, 2007) has indeed found dorsal caudate activity during periods of wins. The dorsal caudate is structurally connected to motor and dorsolateral prefrontal regions (Gerfen and Bolam, 2010). This has led researchers to suggest a role in motor learning and reinforcement processing (Delgado, 2007). On the other hand, it has been found that the vmPFC is involved both in emotion regulation (Quirk, 2007) as well as stimulus valuation (Hare et al., 2009; Grabenhorst and Rolls, 2011). The vmPFC has strong excitatory afferents to the VS (Haber and Knutson, 2010). It is still unclear how the vmPFC may subserve these two apparently distinct roles of emotion regulation and stimulus evaluation. It is also unknown exactly how the VS and vmPFC interact to encode rewards and influence behavior that results from such stimuli. Nonetheless, these data suggest that the vmPFC may underlie some of the functions of sustained affect (which could be construed as

emotional regulation) while in parallel being involved in a circuit which assess the current value of the same stimulus. It will be interesting for future research to attempt to tease apart the stimulus valuation and emotional regulation capacities of the vmPFC. These data suggest that examination of within-trial temporal dynamics may help to elucidate these functions.

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Figure 1. Emotional Reactivity. Following notification of outcome, participants responded with their level of positive (PA) and negative (NA) affect. There was a significant 2x2 interaction between outcome and affect.

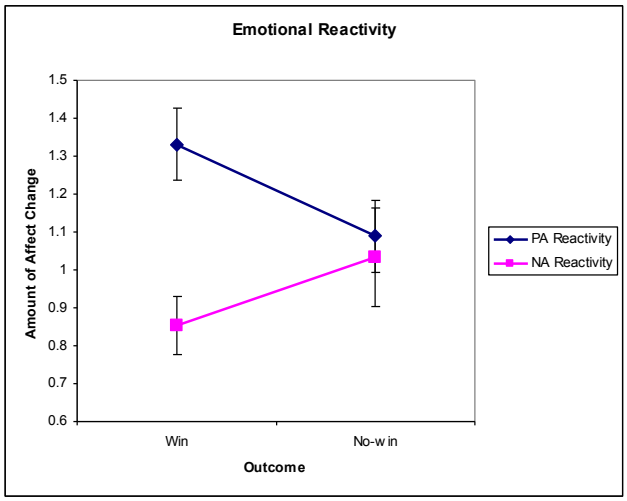


Figure 2. Emotional Sustainment. Amount of time subjects' PA and NA remained outside the confidence interval of their baseline (in minutes). There was a significant 2x2 interaction between outcome and affect.

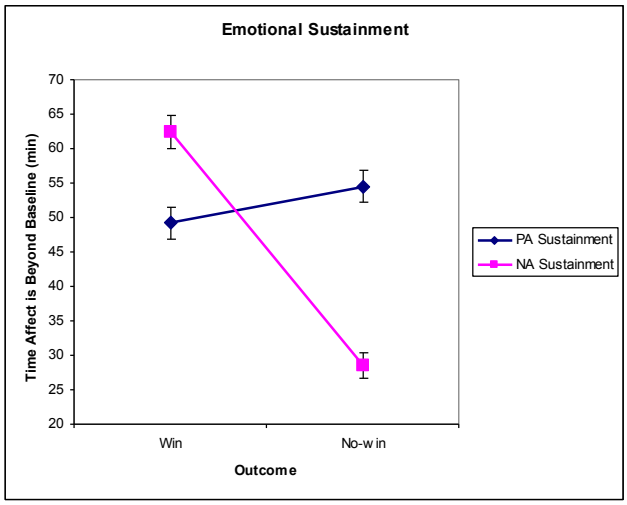
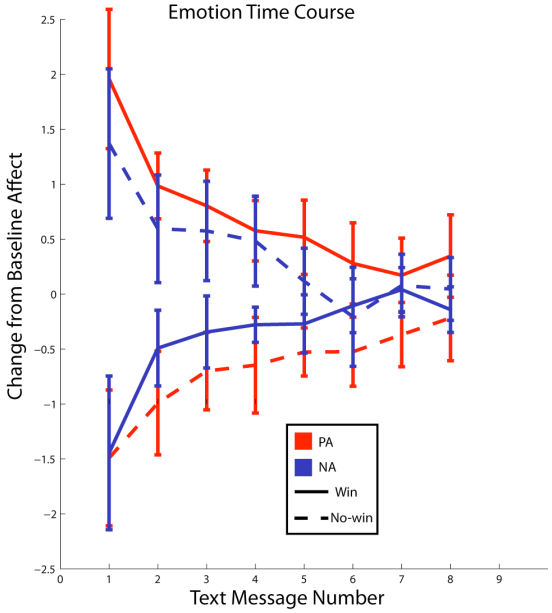


Figure 3. Emotion Time course displaying the time course of affect following a win and no-win trial.



Note that Text Message #1 is the first affect rating following outcome. Zero point on y-axis represents mean PA or mean NA

Figure 4. Significant clusters resulting from the win condition.

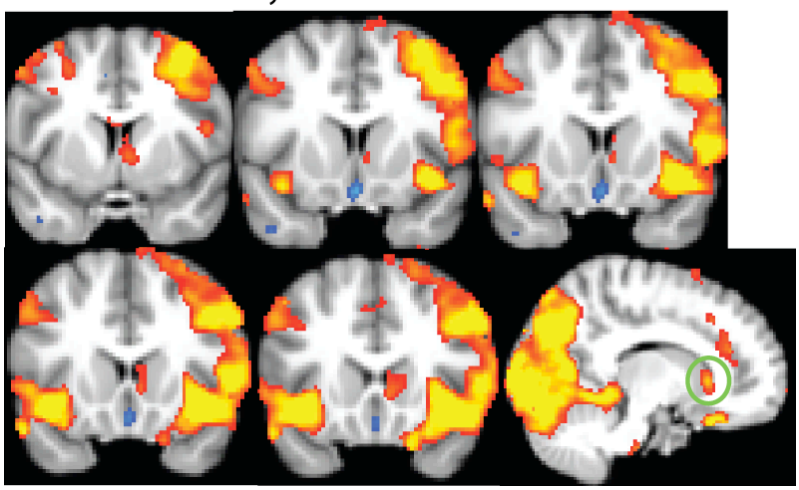


Figure 5. Time course of brain activity in the VS (region circled in green above) in response to win and no-win conditions. Note the lack of difference between the conditions. (A.U. = arbitrary units).

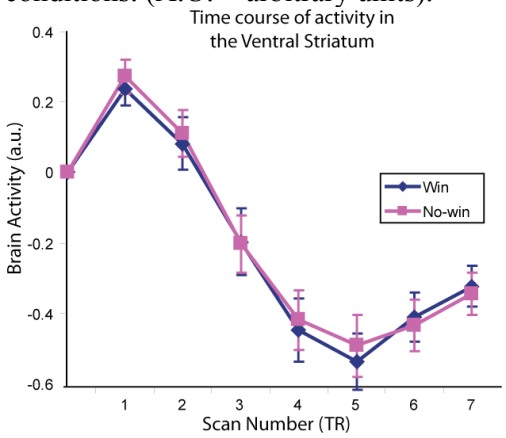


Figure 6. Sustained activity in BA10 following a win predicts higher baseline PA. This relationship remained significant when performing a spearman's rho analysis suggesting the two apparent outliers on the x-axis are not causing a false positive result.

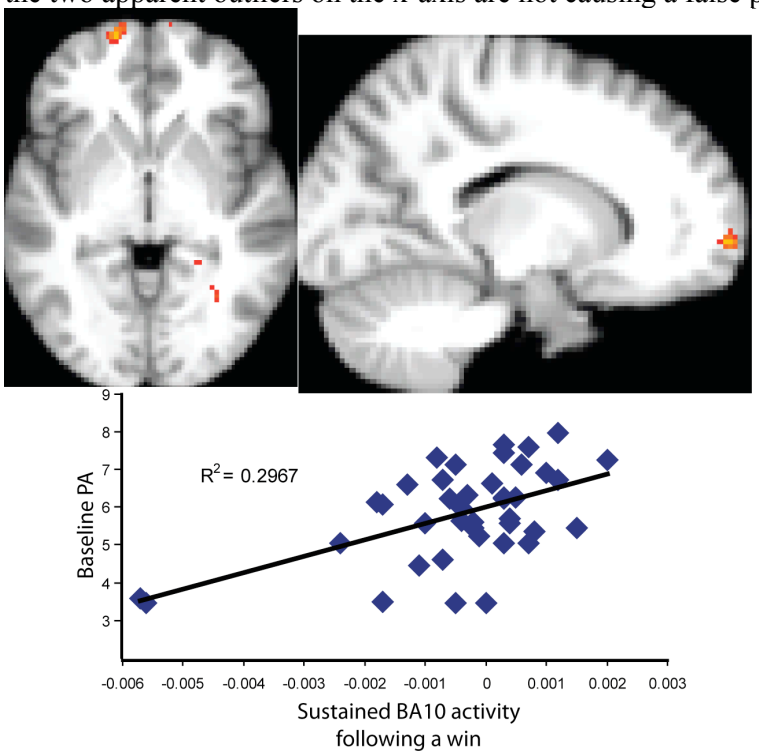


Figure 7. PA reactivity following a win predicts VS activity following a win.

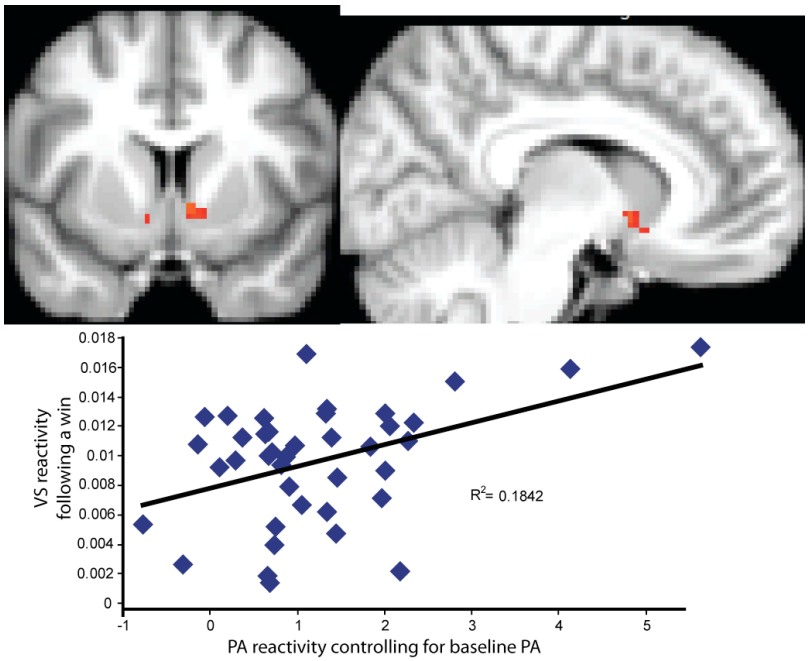


Figure 8. Sustained brain activity (as measured by slope) in the win vs. no-win trial predicts sustained PA following a win vs. sustained NA following a loss.

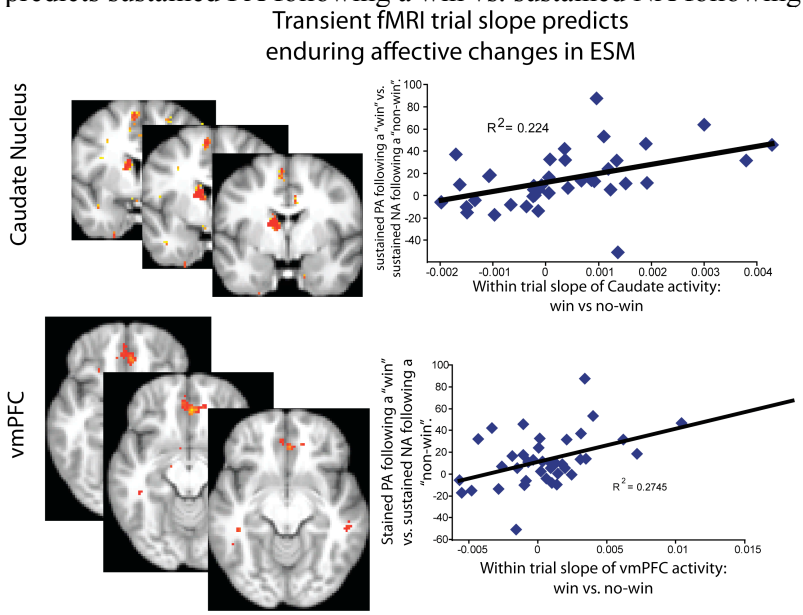


Table 1. Correlation among experience sampling measures (* = p<.05, ** = p<.01, **BOLD** indicates p<.05 adjusted for multiple comparisons using Holm's method)[2]

	PA_baseline	NA_baseline	PA:NA_baseline	PA_baseline_std	NA_baseline_std	PA_Sustain_win	PA_Sustain_loss
PA_baseline	1						
NA_baseline	-0.32**	1					
PA:NA_baseline	**0.64****	**-0.81****	1				
PA_baseline_std	**-0.5****	**0.38****	**-0.33****	1			
NA_baseline_std	**-0.4****	**0.59****	**-0.46****	**0.75****	1		
PA_Sustain_win	0.06	0.01	0.01	0.08	-0.01	1	
PA_Sustain_loss	-0.18	0.04	-0.18	-0.08	-0.09	-0.14	1
PA_Reactivity_win	**-0.54****	**0.35****	**-0.37****	**0.63****	**0.52****	**0.36****	0.12
PA_Reactivity_loss	0.03	-0.05	0.12	-0.04	0.01	-0.18	**-0.46****
NA_Sustain_win	0.05	-0.06	0.08	0.07	-0.06	**0.41****	0.05
NA_Sustain_loss	-0.22*	0.29**	**-0.35****	0.08	0.2*	0.23*	0.15
NA_Reactivity_win	0.09	**-0.59****	0.32**	**-0.39****	**-0.52****	-0.21*	0.01
NA_Reactivity_loss	-0.1	0.08	-0.15	0.05	0.12	0.12	0.27**
Pre_PWB_Total	0.17	-0.29**	**0.35****	-0.15	-0.19*	0.18	-0.06
PANAS_PA	0.3**	-0.31**	**0.4****	-0.1	-0.13	0.19	-0.22*
PANAS_NA	-0.19	**0.47****	**-0.4****	0.24*	**0.37****	-0.08	-0.01

Table 1 continued.

	PA_Reactivity_win	PA_Reactivity_loss	NA_Sustain_win	NA_Sustain_loss	NA_Reactivity_win	NA_Reactivity_loss
PA_Reactivity_win	1					
PA_Reactivity_loss	-0.18	1				
NA_Sustain_win	0.18	-0.04	1			
NA_Sustain_loss	0.3**	**-0.37****	-0.09	1		
NA_Reactivity_win	**-0.53****	0.1	**-0.4****	-0.26**	1	
NA_Reactivity_loss	0.27**	**-0.73****	0.05	**0.57****	-0.14	1
Pre_PWB_Total	0	0.04	0.12	0.07	-0.02	0.09
PANAS_PA	0	-0.06	0.04	-0.07	-0.03	0.14
PANAS_NA	0.11	0.03	-0.06	-0.1	-0.12	-0.06

[2] Note that Baseline PA and NA are those samples which were assessed outside of the game window.

Table 2. Main effect of win vs. baseline (BA=Broadmann's Area).

Region (BA)	x,y,z (mm)	Cluster size	Max T-value
Visual Cortex	[22 -94 10]	49577	14.40
IFG (38)	[-38 16 -12]	9088	12.18
Dorsal ACC (32)	[-6 34 32]	1269	8.33
R Insula/R IFG (48)	[40 18 -10]	1102	11.16
vmPFC (11)	[24 64 -16]	697	8.47
R Hippocampus	[26 -30 -4]	154	7.28
Fusiform Gyrus	[46 -50 -22]	82	6.07
Ventral Striatum	[-12 22 2]	65	6.26
Parahippocampal Gyrus	[-24 2 -36]	63	6.38

Table 3. Slope of fMRI BOLD activity in the win vs. no-win condition significantly predicts sustained PA following a win vs. sustained NA following a no-win.

Region	Coordinates (x,y,z in mm)	Cluster Size	max t-value
Dorsal Caudate	12,-4,20	59	3.53
vmPFC (11)	-2, 38, -12	51	4.2

Chapter 6

Summary & General Discussion

Positive affect is a core human experience. It is central to a variety of mental illnesses including depression, but it is also critically important to the promotion of psychological well-being; it is related to mental and physical health. Understanding the neurobiological mechanisms underlying such positive emotions is thus extremely relevant to promoting health and ameliorating mental illness. Yet, research investigating the mechanisms underlying the association between positive affect and health is still in its infancy. Nearly four decades ago Solomon and Corbit (Solomon and Corbit, 1974) suggested that examining the temporal dynamics of emotion could yield a more complete and nuanced understanding of affect. It is only recently, however, that researchers have begun to empirically investigate these phenomena.

Temporal Dynamics of Reward-Related Brain Activity Predicts Positive Affect and Well-Being

Non-human animal work has suggested a role for the ventral striatum (VS; including the Nucleus Accumbens) and ventromedial prefrontal cortex (vmPFC) as central nodes in a circuit responsible for processing reward and pleasure (Berridge and Kringelbach, 2008). Non-human animal models of anhedonia and human imaging of depressed patients have built on this foundation to examine whether reward-related processing in these networks is predictive of reduced positive affect. Although reduced positive affect is a core symptom of depression, it has been relatively understudied. In particular, research has focused less on the impact of treatments specifically enhancing positive affect as compared with treatments decreasing depressive symptoms despite their equal weight in the DSM. While some studies have indeed found attenuated activity in reward-related regions in depressed patients, these findings have not consistently

replicated suggesting that more nuanced models may be needed. Because a critical feature of emotions is that they unfold over time, we hypothesized that attenuated positive affect in depression may stem from difficulties sustaining affective responses to positive stimuli, rather than simply an attenuated emotional response. In a first study (Chapter 2), we thus examined whether untreated depressed patients demonstrated a lack of *sustained* activity in reward related regions compared with healthy controls. Indeed they did. Across trials, depressed patients demonstrated faster habituation of activity in the VS in response to positive images as compared with healthy controls. Importantly, we found that individual differences in sustained VS activity predicted self-reported positive affect such that those patients with the most sustained VS activity reported the higher levels of positive affect. We also found that the depressed group showed a lack of sustained VS-PFC connectivity over the scan as compared with healthy controls suggesting this deficit may result from abnormal interactions between the PFC and VS. These findings suggested that reduced positive affect in depression result from a lack of sustained reward related activity as opposed to simply reduced overall activity.

In a second study (Chapter 3), those untreated depressed patients from the previous study were randomized to receive either Fluoxetine or Venlafaxine, followed for 2 months, and scanned again with the same paradigm. To further examine the prediction that the temporal dynamics of reward-related activity captures important and unique variance in positive affect, we tested whether changes in sustained VS activity and VS-PFC connectivity predicted changes in positive affect. Indeed it did. Those depressed patients making the greatest gains in positive affect over two months demonstrated the largest increases in sustained VS activity and sustained VS-PFC connectivity. This was

irrespective of treatment type and again captured more variance in changes in positive affect than using the traditional measures of mean brain activity. This further suggests the import and utility of examining such temporal dynamics metrics.

In a third study (Chapter 4), a large, representative sample from the MIDUS-II project, were scanned using a similar paradigm in which affective images were presented to the subjects. Participants completed a measure of psychological well-being which putatively taps an individual's level of eudaimonia – a sense of purpose, meaningful and positive engagement with life. Eudaimonic well-being has been found to be protective against psychopathology and predicts physical health, including lower levels of stress hormones. Thus, in addition to imaging measures of sustained brain activity and self-reported well-being, a substantial portion of the participants (n=50) also provided salivary samples for assessment of the stress hormone cortisol. In this large, representative sample, a similar finding as that of the previous studies emerged – individual differences in sustained activity in the VS and PFC predicted higher levels of well-being. Once again, the sustained metric captured a greater percentage of the variance than did the aggregated, mean metrics. In addition, the sustained metric in the VS predicted cortisol level over the day such that those individuals with more sustained VS activity had lower levels of total cortisol output. We also found that sustained VS activity mediated the relationship between well-being and cortisol, suggesting a specific pathway by which reward-related activity can connect the hypothalamic pituitary adrenal (HPA) axis and psychological well-being.

In a fourth study (Chpater 5), we sought to use novel experience sampling methodologies to assess the temporal dynamics of emotion in undergraduate students

using more ecologically relevant methods. Participants responded to text messages assessing their current level of positive and negative affect. To induce an affective incentive, they also played a game in which they could win additional money which allowed us to measure individual differences in real-world sustained positive affect. We then recruited a portion of those participants back to the lab for scanning. Results found that individual differences in sustained real-world positive affect predicts sustained activity in the vmPFC – an area thought to be involved in stimulus valuation – as well as the dorsal striatum. This suggests that individual differences in the temporal dynamics of positive affect experienced in the real world relate to sustained brain activity and is an initial step in using experience sampling to further our understanding of the relevance of sustained positive affect for mood disorders as well as well-being.

Temporal dynamics are ubiquitous to life. While basic research examining the temporal dynamics of positive and negative affect is still in its infancy, there is great potential for understanding of such temporal dynamics to impact upon treatment of psychopathology. One domain in which this may be exploited is the treatment of mood and anxiety disorders. For example, in the treatment of phobias and PTSD, a common effective treatment is through exposure and behavioral interventions (Barlow, 2002) done in the real world. The use of experience sampling for a therapist to monitor and intervene while the patient is participating in such exposures may increase the time a patient maintains engagement in such an exposure and hence its effectiveness. Perhaps more hypothetically, at certain points of a major depressive episode patient's affects and cognitions may be most plastic and amenable to intervention. For example, when a depressed patient is experiencing increased positive affect, this may be a time in which an

ambulatory intervention to assist the patient to sustain that positive affect may be particularly effective in treating the disorder. This idea is an extension of Fava's recent well-being therapy (Fava and Tomba, 2009) and has connections to Lewinsohn's original Behavioral Activation therapy for depression (Lewinsohn, 1974). Similarly, when rumination or self-criticism becomes particularly pronounced or when specific negative "schema" are enacted (Beck, 1970), therapeutic intervention may be most effective in creating lasting, generalizable change.

Another example is from the literature on epigenetics. For example, Meaney and colleagues have found in rats that affiliative behavior of liking and grooming between mother rats and their offspring can alter the stress reactivity and future parenting style of the offspring. However, malleability of the trait of stress reactivity and future parenting style is only plastic for approximately the first week post-natal (Meaney, 2010). Epigenetic processes, in particular methylation of genes which activate glucocorticoid receptors in the hippocampus, appear to be critical in the mechanism underlying plasticity of stress reactivity and future parenting behavior. These findings have implications for understanding of "critical periods" and the temporal course of human development. Undoubtedly, the successes of federal programs such as "Head Start" are exemplars of such dynamics and critical periods (Hackman et al., 2010).

It is unclear whether such within-trial or across-trial temporal dynamics may be the result of adaptation of modulatory neurotransmitters such as dopamine and mu-opioid or the result of changes in GABAergic signaling within the VS via medium spiny neurons, or glutamatergic efferents of the PFC. Studies in addiction (Di Chiara, 2002) suggest that lack of across-trial habituation of dopaminergic activity within the VS

represents a maladaptive process as part of addictive behaviors in rodent models. However, whether in certain contexts in response to appetitive cues sustained engagement of the VS via sustained activity of dopamine or other neurotransmitters may also represent an adaptive and healthy process has not been widely discussed. It could be the result of top-down modulation via the glutamatergic efferents of the PFC, but could also be resultant from mu-opioid signaling as per recent reports by Berridge (Smith and Berridge, 2007; Smith et al., 2011).

There are several avenues for future work. First is how such temporal dynamics differ across distinct stimuli types. Chapter 5 which used financial rewards indeed differed in several respects from the previous chapters which used visual stimuli. It also appeared, however, that there may have been important differences between the samples. Mapping the within- and across-trial temporal dynamics of distinct appetitive stimuli (e.g., gustatory, visual, financial) is one avenue for research. In healthy populations, do these dynamics overlap in important ways, or do they differ?

An additional outstanding question regards how the temporal dynamics of positive affect and reward-related brain activity converge or diverge across disorders for which anhedonia is a core symptom. While categorical approaches to clinical science have been widely successful in creating a descriptive understanding of psychopathology, using these dimensional approaches across previous categories may uncover novel nosologies that could improve treatment. This dimensional approach would also encompass disorders in which positive affect is thought to be excessive and unregulated (e.g., bipolar disorder).

Emotion unfolds over time. The ability of researchers to understand the psychological and neurobiological properties of these dynamics and how they relate to individual differences in health, well-being and psychopathology may indeed carry import for the treatment of psychopathology as well as the enhancement of well-being for the population as a whole.

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Appendix I

Supplemental Materials for Chapter 2

Methods

Connectivity Analysis Connectivity analyses were performed using the beta series correlation method described in (Rissman et al., 2004). Briefly, this approach requires that separate parameter estimates (beta values) be computed for each trial. Trials were modeled as having two components: one component occurring at the onset of the image presentation – before regulation instruction; the second component being placed six seconds after image onset, modeling the neural response to the regulation of emotion. BOLD responses during stimulus onset and regulation periods were modeled as brief epochs of neural activity convolved with an in-house canonical hemodynamic response function (HRF), obtained by averaging empirically derived HRFs (Rissman et al., 2004). The onsets of temporally adjacent covariates were spaced at least 4 s apart (Zarahn et al., 1997) to minimize the contamination of the regulation period covariate by residual stimulus onset period activity. This approach has been used to successfully model separate components of a trial in numerous published studies (Postle et al., 2000; Curtis et al., 2004; Ranganath et al., 2004). The least squares solution of the GLM yielded a set of 236 beta values of interest (2 trial components x 2 picture valences x 3 regulation instructions [24 enhance, suppress trials; 12 attend trials). Nuisance covariates included the second-order polynomial used to model the baseline and slow signal drift, as well as six motion estimate covariates. Beta values were sorted by trial type so that a series of betas exist for each component of each condition. The extent to which brain regions

interact during a particular task stage is quantified by the extent to which their respective beta series from that condition are correlated.

Image analysis. With the AlphaSim clustering technique, the overall family-wise error rate (FWE) is controlled by simulating null data sets with the same spatial autocorrelation as found in the residual images and creating a frequency distribution of different cluster sizes. Clusters with a size that exceeds the minimum cluster size corresponding to the a priori chosen FWE are retained for additional analysis. This cluster-based method of thresholding, analogous to cluster-based thresholding using Gaussian Random Field Theory (Friston KJ, 1993), is an alternative to voxel-based correction and is often more sensitive to activation when one can reasonably expect multiple contiguous activated voxels (Forman et al., 1995; Petersson et al., 1999).

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Appendix II

Supplemental Materials for Chapter 3

Methods

Image Analysis.

In addition to using a difference metric (2nd half vs. 1st half), in which time is arbitrarily categorized into two chunks, we treated time continuously (as a function of run) by using a linear regressor (amplitude modulation in Analysis of Functional NeuroImages). This analysis yields a beta estimate for each subject which corresponds to the rate of change of nucleus accumbens activity over time. Using this beta estimate, we tested whether nucleus accumbens activity, when treated continuously correlated with gains in positive affect.

Results

Correlations between self-report measures

We examined the correlations between the various self-report measures. In the depressed sample, negative affect at baseline was correlated with negative affect at 8 weeks (r=0.66, p=.001); positive affect at baseline was not correlated with positive affect at 8 weeks (r=0.30, p=0.18). Positive affect and negative affect were not correlated at baseline (r=-0.29, p=0.20), nor were they correlated at 8 weeks (r=-0.34, p=0.14). Change in positive affect and negative affect scores from baseline to 8 weeks were significantly inversely correlated (r = -0.61, p = .004). Otherwise, assessments of HAMD, positive affect, and negative affect at both baseline and 8 weeks in the depressed sample were not significantly correlated (see table 1). In the control sample, negative affect at baseline was correlated with negative affect at 8 weeks (r=0.76, p=.002); positive affect at

baseline was correlated with positive affect at 8 weeks (r=0.75, p=.002). Positive affect and negative affect were not correlated at baseline (r=-0.28, p=0.33), nor were they correlated at 8 weeks (r=-0.40, p=0.16). In addition, in the control sample, change in positive affect and negative affect from 0 to 8 weeks were not significantly correlated (r=-0.45, p=0.10). Given that the control group demonstrated a significant correlation between positive affect sampled at baseline and positive affect sampled at 8 weeks (r=0.75), while the depressed group did not (r=0.30), we examined whether the magnitude of these correlations were significantly different between the groups. This test of the difference in correlations was at trend level (z=1.75, p=.08).

Concerns regarding dual-task

One concern could be that participants are performing two tasks – one involving a button response and one involving the regulation of emotion. However, the mean RT to the valence of the image at pretreatment was 1380 ms and 1238 ms at 8-weeks into treatment for depressed patients and 1252ms and 1433ms for controls at the same two time points. Because the regulation instruction did not occur until 4000 ms into image presentation, and it was time points related to the emotion regulation instruction that were specifically analyzed. Therefore, it is highly unlikely that engaging in a button response affected the brain activity when regulating emotion.

Supplemental fMRI analyses

We examined whether the relationship between changes in sustained nucleus accumbens activity across time when attempting to enhance positive emotion and gains in self-reported positive affect was specific to the enhancement of positive affect, or to the enhancement of affect more generally. Accordingly, we simultaneously included both

changes in sustained nucleus accumbens activity when attempting to enhance positive emotion (in response to positive IAPS slides) and when attempting to enhance negative emotion (in response to negative IAPS slides) to examine associations with gains in positive affect. Increases in sustained nucleus accumbens activity when enhancing positive affect was uniquely associated with gains in positive affect ($B = 19.96$, $t(18) = 2.34$, $p = .03$), while changes in sustained nucleus accumbens activity when enhancing negative affect was not uniquely associated with gains in positive affect ($B = 5.14$, $t(18) = 0.76$, $p = .45$). This suggests that the relationship between increases in sustained nucleus accumbens activity and gains in self-reported positive emotion is specific to the enhancement of positive affect and not related to the process of enhancement of affect more generally.

When controlling for changes in sustained nucleus accumbens activity when decreasing a positive affective response to a positively valenced image (ie., the "positive suppress" condition) from 0 – 8 weeks, a trend level relationship remained between sustained nucleus accumbens activity when increasing positive emotion and gains in positive affect ($B=15.94$, $t(18)=1.45$,$p=0.08$ [one-tailed]). In this regression model, there was no relationship between changes in sustained nucleus accumbens activity in the "suppress" condition and gains in positive affect ($B=4.993$, $t(18)=0.817$, $p=0.42$).

In order to examine whether the relationship between changes in sustained nucleus accumbens activity and gains in self-reported positive affect follow a linear function, we treated time continuously by using a linear regressor (ie., amplitude modulation, see supplemental methods) and examined the relationship between changes in sustained nucleus accumbens activity and gains in positive affect. Interestingly, when

time was treated continuously using a linear regressor, individual differences in sustained nucleus accumbens activity was not correlated with gains in positive affect ($r = 0.19$, $t(19) = 0.86$, $p=0.40$). This suggests that the best function to relate change in brain activity over time with gains in positive affect may not be linear, and may be more sigmoidal in shape.

Given the findings between changes in anhedonia as assessed by the MASQ and changes in sustained nucleus accumbens activity when upregulating positive affect, we ran a voxel-wise regression looking to see whether changes in sustained nucleus accumbens-connectivity resulting from treatment was associated with changes in MASQ assessed anhedonia. Interestingly, no area survived multiple comparison correction when correlating with changes in MASQ, suggesting a relatively specific effect of changes in sustained nucleus accumbens-prefrontal cortex connectivity and state positive affect.

Mean effects among depressed patients

Among patients, the mean level of sustained nucleus accumbens activity did not change across two months of treatment ($t(20) = 0.28$, $p = .78$). Likewise, there was no change in the mean level of sustained nucleus accumbens-MFG connectivity ($t(20) = -0.14$, $p = 0.99$), nor was there a significant change in mean level of sustained nucleus accumbens-ventromedial prefrontal cortex connectivity ($t(20) = -1.70$, $p = 0.11$). In our view, these null effects underscore the potential utility of exploiting individual differences to unmask and understand the brain bases of heterogeneity in treatment response.

The relation between affective responding on different time scales and psychopathology is not yet known (e.g., within vs. across trials). In this study, we aimed

to specifically examine one slice of this relationship (temporal dynamics across trials), but it is unknown the degree to which it is related to other time scales. However, to address the relationship between these two time-scales, we extracted the fitted time course from the nucleus accumbens cluster in the positive enhance condition (aggregated across the scan session) for both pre-treatment and 8-weeks into treatment for each subject. With the time course, we calculated a slope for the time points which corresponded to the maximal BOLD response to the regulation instruction (8 sec – 14 sec). This slope corresponds to the rate of change in of nucleus accumbens activity when regulating positive emotion. This is one method for examining variability in sustained activity within trials. For each depressed patient we subtracted the pretreatment within-trial slope measures from the 8-weeks within-trial slope measure and correlated that with changes in positive affect. Change in within-trial slope of nucleus accumbens activity in the positive enhance condition (from pretreatment to 8-weeks) was not correlated with change in positive affect ($r=0.16$, $p=0.47$). There was not a significant correlation between changes in the within trial slope (calculated here) and changes in the across trial (presented originally in the manuscript) effect ($r=-0.05$, $p=0.82$) either. We performed the same analysis for the positive "attend" condition because we thought the effect of cognitive regulation might mask a relationship between changes in within-trial dynamics and positive affect. There was again, no significant relationship ($r=0.23$, $p=0.32$). There was not a significant correlation between changes in the within trial slope (calculated here) and changes in the across trial (presented originally in the manuscript) effect ($r=0.12$, $p=0.61$). This suggests that the across trial and within trial effects are at least somewhat orthogonal in this sample with this paradigm.

Discussion

In our previous report, in addition to examining sustained nucleus accumbens activity using a difference metric (2nd half vs. 1st half, as we did in this report), we also examined the relationship using a linear regressor (ie., amplitude modulation) to assess change of nucleus accumbens activity over time. Using this linear regressor in the initial finding, we similarly found that depressed patients evidenced a lack of sustained nucleus accumbens activity, whereas healthy control participants showed sustained nucleus accumbens activity. In this initial finding, however, we did not examine whether individual differences in the beta-value for the linear regressor correlated with self-reported positive affect; we solely demonstrated that the difference metric (Pretreatment: 2nd half vs. 1st half) was related to self-reported positive affect. This is consistent with what we found, that at 8-weeks post treatment using the 2nd half vs. 1st half difference metric, changes in sustained nucleus accumbens activity correlated with gains in self-reported positive affect across that same time. These results suggest that the function best fitting the relationship between changes in positive affect and sustained nucleus accumbens activity may not be linear and be more step-wise, although future work should examine this issue further.

This report contributes to our previous findings with this sample by examining change in the neural correlates underlying depressed using an ecologically valid, emotion regulation paradigm. Our previous findings (Johnstone et al., 2007; Heller et al., 2009; Light et al., 2011) solely examined the brain at baseline, whereas this report examined changes resulting from treatment. However, it is clear from the previous findings that engagement of ventrolateral prefrontal cortex appears to be important when down-

regulating both negative emotion (Johnstone et al., 2007) and is associated with changes in trait anhedonia when down-regulating positive affect (Light et al., 2011). Given distinct cognitive processes required when down-regulating, as opposed to up-regulating emotion, it is not surprising that we find a distinct set of prefrontal cortical regions involved in the up-regulation of positive emotion as opposed to the down-regulation of both negative and positive emotion.

We have primarily examined one time scale – that of the ability to continually engage reward-related circuitry across trials. However, the temporal dynamics of affective responses within trials as has been examined as well (Siegle et al., 2002; Dichter and Tomarken, 2008; McMakin et al., 2009) and likely carries equal import for understanding the dynamics of affect and psychopathology. The ability to repeatedly engage reward circuitry across trials when presented with positive events may be important for health and well-being because positive and negative events occur intermixed in life over time. As a result, it may be particularly important for an individual to be able to continue to engage reward circuitry when a positive event occurs even in the midst of negative ones. On the other hand, the ability to sustain affective responses to an individual positive event more closely mimics the notion of "savoring", which has recently been exploited to develop novel psychotherapeutic treatments for depression (Fava and Tomba, 2009; McMakin et al., 2011). It is likely that both effects are of significance for understanding and treating psychopathology. Perhaps most importantly, the variance shared in these two separate time scales has not been examined in detail and work to this effect is required to disentangle the unique contribution of these effects on individual differences and psychopathology.

Researchers working at the nonhuman level work have found that the nucleus accumbens responds differentially to the anticipation vs. consumption of reward (Berridge and Robinson, 1998), suggesting that differentiating these phases of reward processing in depression is theoretically important (Treadway and Zald, 2011). A recent publication by Pizzagalli and colleagues (Pizzagalli et al., 2009) sheds light on this issue. Patients engaged in a monetary incentive delay task in which they pressed a button in response to a target stimulus. Group differences in basal ganglia activity were weak during the anticipation period, but robust group differences were found in the Caudate and Nucleus Accumbens during the consummatory phase of the trial. While a rich non-human literature underscores the complexity of the nucleus accumbens in reward processing (Berridge and Robinson, 1998), the findings of Pizzagalli and colleagues suggest that the inability to sustain nucleus accumbens activity found here may result from specific deficits in the consummatory phase of reward processing – which rely heavily on the ventral striatum. Indeed, previous research suggests that nucleus accumbens activity tracks the hedonic value of outcomes (O'Doherty et al., 2004; Tricomi et al., 2004). As there was no anticipation period of our task, we specifically examined the brain's response to onset of an appetitive stimulus. Therefore, it is likely that our findings relate more strongly to the consummatory component of reward processing, as opposed to the anticipatory component. It is also relevant that the use of an emotion regulation paradigm where individuals are attempting to increase their positive affect using **cognitive** strategies may be better suited to uncover interactions between the prefrontal cortex and ventral striatum than studies examining reward responsiveness or executive function alone. However, it will be important for future studies to separate the

components of reward in fronto-striatal networks in tasks requiring more or less executive function invovlement.

These findings may also provide a conceptual framework for understanding the mechanisms through which various psychological interventions that explicitly attempt to improve depressed patients' ability to sustain positive affect operate. For example, Behavioral Activation treatment (Lewinsohn, 1974), an empirically supported psychological intervention with similar rates of efficacy as Cognitive Therapy and antidepressant medications (Dimidjian et al., 2006) emphasizes sustained engagement with rewarding and pleasurable activities as one of the key ingredients in treating depressed. More recently, Fava (Fava and Tomba, 2009), and McMakin (McMakin et al., 2011) have shown that treatments specifically designed to increase a depressed patient's ability to sustain positive affect (ie., "savoring") appear to be successful in the treatment of major depression.

While some have argued that Cognitive Therapy is not particularly effective at increasing positive affect in depressed (Cornwall and Scott, 1997), Behavioral Activiation, Well-being therapy, and other psychotherapies may be more effective in increasing positive affect in depression (Lewinsohn, 1974; Seligman et al., 2006; Fava and Tomba, 2009). Therefore, it would be helpful for future studies to examine whether the changes in sustained nucleus accumbens activity when enhancing positive emotion correlates with gains in positive affect when treated with various psychotherapeutic techniques. Relatedly, it will be important to determine if these newer interventions explicitly designed to enhance aspects of positive affect produce a more robust and/or

more rapid change in fronto-striatal circuitry than more traditional psychotherapeutic or pharmacological interventions.

One concern could be the degree to which brain responses to negative stimuli impacted on subsequent responses to positive stimuli. Despite the fact that this analysis would be grossly underpowered with this design, we do not think this issue strongly affects interpretation of our findings. If positive trials were preceded by other positive trials approximately as often as by negative trials, we believe that lingering effects of the negative stimuli on positive trials would likely average out. We performed a χ^2 test to examine this and found that there were no significant differences in the valence of trials preceding a positive trial (42% of the positive trials were preceded by a positive trial and 57% of the positive trials were preceded by a negative trial; χ^2=1.37; p=.241).

It is unclear why positive affect changed in the control sample. We believe that the change in positive affect in the control sample may have been due to random variation and unlikely due to more fundamental change in affective symptoms or functioning (HAMD scores for controls were at baseline and did not change). Several lines of evidence support this. First, there was a significant Group x Affect interaction suggesting that depressed patients showed changes in both positive affect and negative affect in response to treatment, whereas controls only showed changes in positive affect. There was also a significant main effect of Group on change, suggesting that depressed patients affect changed more than controls overall. There was also a very significant main effect of Group on positive affect ($F(1,33)=26.92$, $p<.001$) such that controls had significantly higher positive affect than depressed patients. In addition, while the

depressed patients showed a significant drop of anhedonic symptoms (as assessed by the MASQ), healthy controls did not.

The failure to find an overall treatment effect on sustained nucleus accumbens activity and fronto-striatal connectivity, in conjunction with the finding of individual differences in the magnitude of change in these neural measures correlating with treatment response on measures of positive affect, underscores the value of an individual differences approach. The lack of a main effect of treatment may reflect variability in treatment response and it is precisely such situations that call for analyses of individual differences. It also may be the case that a treatment modality that more explicitly targets positive affect such as Behavioral Activation therapy or well-being therapy (Lewinsohn, 1974; Fava and Tomba, 2009), may produce a larger gain in positive affect as well as on the measures of sustained nucleus accumbens activation and fronto-striatal connectivity that are featured in this report.

We should note several limitations of the study. First, as the sample was made up of individuals with "pure" depression (i.e., with no comorbidity), it is unclear whether these findings would extend to depressed populations containing a comorbid anxiety, substance abuse, or Axis II diagnosis. While having a relatively "pure" depressed sample can be helpful in terms of minimizing unwanted variability due to concurrent psychiatric diagnoses, comorbidity is the norm, as opposed to the exception in depression (Kessler et al., 2003). Another limitation of the study is the sole use of antidepressants. A noted shortcoming of antidepressants in the treatment of depression is their relative lack of effectiveness in increasing positive affect (Fava and Tomba, 2009). Thus, it would be helpful for future studies to examine whether the changes in sustained nucleus accumbens

activity when enhancing positive emotion correlates with gains in positive affect when treated with various psychotherapeutic techniques.

Given the frequency of scanning and assessment of affect (twice over an 8 week period), the reviewer is correct that we are unable to address temporal directionality. It could be that affect is changing prior to changes in the brain, vice-versa, or they could be changing in tandem. To assess such questions, participants would need to be assessed (with both a fMRI scan and affect assessment) much more frequently. Unfortunately, this dataset did not contain such temporal resolution – burden upon depressed patients would be significant as well. Nonetheless, this is a very important point and future work should assess depressed patients much more frequently in order to address issues related to temporal directionality.

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Supplemental Table 1. Correlation matrix between HAMD, PANAS Negative Affect, PANAS Positive Affect for control subjects (above the diagonal and in italics) and depressed patients (below the diagonal). Note that control subjects did not complete the MASQ Anhedonia scale. *=p<.05, **=p<.01

	HAMD baseline	HAMD 8 weeks	Negative Affect baseline	Negative Affect 8 weeks	Positive Affect baseline	Positive Affect 8 weeks
HAMD baseline	1.00					
HAMD 8 weeks	0.11	1.00				
Negative Affect baseline	0.03	0.27	1.00	*0.76***	*-0.28*	*-0.29*
Negative Affect 8 weeks	0.02	0.59**	0.66**	1.00	*-0.18*	*-0.40*
Positive Affect baseline	0.08	0.23	-0.29	-0.04	1.00	*0.76***
Positive Affect 8 weeks	-0.23	-0.21	0.01	-0.34	0.30	1.00
MASQ Anhedonia baseline	0.28	0.27	0.65**	0.26	-0.31	0.01
MASQ Anhedonia 8 weeks	0.22	0.72**	0.42	0.67**	0.10	-0.48*

	HAMD Time 2 vs. Time 1	Negative Affect Time 2 vs. Time 1	Positive Affect Time 2 vs. Time 1
HAMD Time2 vs. Time 1	1.00		
Negative Affect Time2 vs. Time 1	0.28	1.00	*-0.45*
Positive Affect Time2 vs. Time 1	-0.22	-0.61**	1.00
MASQ Anhedonia Time 2 vs. Time 1	0.49*	-0.68**	0.56*

Supplemental Table 2: Results from a voxelwise regression examining the relationship between changes in sustained brain activity 2-month$_{(2nd\ Half - 1st\ Half)}$ –Baseline$_{(2nd\ Half - 1st\ Half)}$ with changes in self-reported PA

Location (BA)	*x,y,z(mm)*	*cluster size (voxels)*	*max t-value*
R Inferior Frontal Gyrus (46)	28, 42, 18	323	4.46
Precuneus	-6, -60, 52	249	4.17
R Middle Temporal Gyrus	68, -40, -4	195	5.22
R Middle Temporal Gyrus	66, -12, -12	181	4.64
L Middle Temporal Gyrus	-50, -12, -18	154	4.35
Precuneus	-10, -70, 36	145	4.50
R Inferior Frontal Sulcus (45)	54, 30, 28	133	4.55
L Middle Frontal Gyrus(46)	-38, 42, 30	80	3.99

Appendix III

Supplemental Materials for Chapter 4

Materials & Methods

Self-Report Measurements

The PANAS-Now, which asks participants to rate their current positive affect, was acquired twice on the day of the scan session – immediately prior to and immediately following the scan. To calculate positive affect (PA) scores from the PANAS we summed the ratings of the ten positively valenced adjectives and calculated the mean PA score of the pre- and post scan measurements. Two individuals did not complete the PANAS-Now.

Image Analyses:

To examine the association between sustained brain activity in response to negative stimuli and self-reported negative affect (NA), we performed a voxelwise correlation to test this relationship. See Supplemental Table 2 for the significant clusters.

Appendix III: Results

We examined the relationship between the PANAS PA-Now collected prior to the scan session vs. the PANAS PA-Now collected following the scan session. The correlation of the pre- vs. post-scan PANAS PA was significant: $r = 0.49$, $t=4.4$, $p<.001$. However, there was no systematic PANAS PA change from pre- to post-scan (ie., increasing or decreasing from beginning to end of scan) as a paired t-test was not significant: $t(61) = -0.20$, $p=0.84$.

To assess the specificity of the relationship between sustained engagement of the VS and eudaimonic well-being, we also assessed the relationship between current

hedonic PA and sustained engagement of the VS in response to positive stimuli. The zero-order correlation between well-being and PA from the PANAS-Now was significant (r=0.40, p=.001), as was the relationship between sustained VS activity and PA (r=0.26, p=.04). However, when including both well-being and PA in a simultaneous regression to predict sustained VS activity, well-being uniquely predicted sustained VS activity (B=0.45, t(60)=3.33, p=.001), while PA did not (B=0.10, t(60)=0.78, p=.44). When controlling for days since well-being was measured, we found similar results such that well-being uniquely predicted sustained VS activity (B=0.45, t(59)=3.31, p=.002) while PA did not (B=0.91, t(59)=0.67, p=.50).

To assess the specificity of the relationship between sustained DLPFC activity and well-being, we assessed the relationship between current PA and sustained DLPFC activity in response to positive stimuli. The zero-order correlation between sustained DLPFC activity and PA (r=0.34, p=.006) was significant. However, as with the VS, when including both well-being and PA in a simultaneous regression to predict sustained DLPFC activity, well-being uniquely predicted sustained DLPFC activity (B=0.36, t(60)=3.17, p=.002), while PA did not (B=0.17, t(60)=1.54, p=.13). Controlling for days between well-being assessment and fMRI session did not alter the relationship: well-being uniquely predicted sustained DLPFC activity (B=0.36, t(59)=3.15, p=.003), while PA did not (B=0.16, t(59)=1.42, p=.16). This suggests that sustained engagement of the DLPFC in response to positive stimuli is specifically related to eudaimonic well-being.

Appendix III: Figures and Tables

Figure 1. Association of PWB and sustained VS activity in response to positive images at three different thresholds (p<.005 in yellow, p<.01 in blue, and p<.05 in green) demonstrating that the cluster extends ventrally into the Nucleus Accumbens.

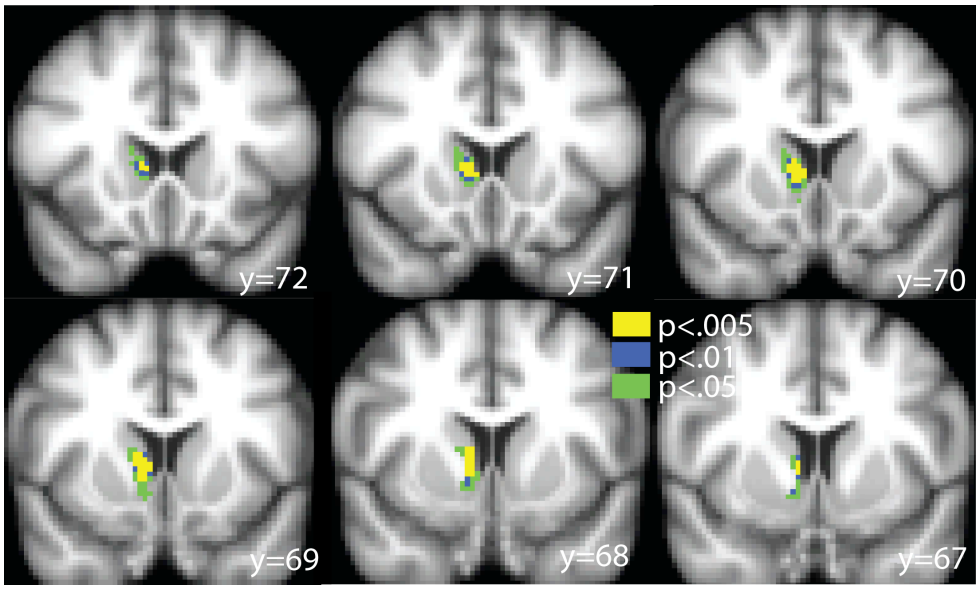

Table 1. Correlations between the six subscales of the PWB measure:

	Autonomy	Environmental Mastery	Personal Growth	Positive Relations	Purpose in Life
Environmental Mastery	0.52	1.0			
Personal Growth	0.53	0.50	1.0		
Positive Relations	0.41	0.66	0.62	1.0	
Purpose in Life	0.59	0.61	0.68	0.66	1.0
Self Acceptance	0.64	0.79	0.66	0.67	0.76

Table 2. Relationship between sustained brain activity in response to negative stimuli and self-reported negative affect as measured by the PANAS-Now.

Brain Area (BA)	x,y,z	Max T	Cluster size
Ventromedial PFC (11)	[4, 34 -16]	4.07	226
Parahippocampal gyrus	[-14 -2 -36]	4.35	121
Inferior temporal gyurs	[36 0 -42]	4.79	113

Cerebellum	[10 -46 -22]	3.87	66
Middle frontal Gyrus (9)	[-49 16 44]	4.34	63
Parietooccipital fissure	[20 -50 12]	4.86	61