ABSTRACT

Title of dissertation: EXPERIMENTAL MEASUREMENT OF BEHAVIORAL APPROACH MOTIVATION IN MAJOR DEPRESSIVE DISORDER

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Major Depressive Disorder (MDD) presents a significant public health challenge. Given the symptoms heterogeneity and widespread changes in brain structure and function in MDD, there may be several subtypes of depression not sufficiently distinguished by current diagnostic criteria but important to recognize to improve clinical outcomes. One of the two core symptoms of MDD is 'markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day' and is often referred to as anhedonia (DSM-IV, V). Anhedonia may have a variety of underlying causes such as not finding previously enjoyed   activities appealing, lacking motivation to engage or reluctance to put forth necessary effort, and these processes may be quite unique and not differentiated by current assessment methods (Treadway & Zald, 2011). It has been long recognized that depression is associated with insufficient environmental reinforcement (Lewinsohn & Graf, 1973) and treatments   were developed to address this deficiency (Lewinsohn, Sullivan, & Grosscup, 1980).   Clinical studies of effectiveness of the Behavioral

Activation Treatment for Depression (BATD), (Hopko, Lejuez, LePage, Hopko, & McNeil, 2003), suggest that an increase in the engagement in reinforcing activities may be helpful in treatment of depression. However, a crucial aspect of activity related behavior, the initial approach and engagement which necessarily precede potential experience of enjoyment, has not been sufficiently characterized.

In the current work, we present the development of an experimental behavioral approach motivation paradigm (BAMP) to study approach motivation to engage in liked activities, and relate experimental results to the symptoms of depression and anhedonia to better characterize approach behavior in MDD.

We sought to establish a valid behavioral measure of approach motivation in major depression that will be suitable for behavioral and neuroimaging studies of anhedonia. In the BAMP study, subjects rated activity words for the appetitive value, and later 'approached' and 'avoided' the stimuli in an implicit joystick task.

The findings indicated reduced range of activities rated as liked by depressed patients versus healthy controls, but no difference on an approach measure of liked activities. The depressed group showed a stronger approach rather than avoidance of *disliked* activities. Thus, 'lack of interest or pleasure' may be partially related to excessive approach of mood-maintaining negative experiences, and inadequate avoidance of disliked situations. Further study of altered approach and avoidance behavior could shed additional light on processes underlying anhedonia in Major Depressive Disorder.

EXPERIMENTAL MEASUREMENT OF APPROACH MOTIVATION IN
MAJOR DEPRESSIVE DISORDER

by

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Chapter 1: Introduction

Major Depression and its Impact

The word 'depression', originating from Latin 'deprimere', refers to pressure down, a decrease in force, value or position. Often used in everyday language, the word primarily refers to a negative emotional state that may include feelings of despondency, dejection, hopelessness, inadequacy and lack of interest in life (Merriam Webster Online). If such feelings are present for an extended period of time and have a detrimental impact on individual's function, they may be considered symptomatic of Major Depressive Episode (MDE), as opposed to transient negative emotional state that could be due to life events (APA, 2001). An MDE can occur in the course of either Major Depressive Disorder (MDD), or Bipolar Disorder. A formal diagnosis of depression is made by a clinician based on reported symptoms, their duration, and impact on individual's life. Throughout this manuscript the word 'depression' will be used interchangeably with Major Depressive Disorder (MDD), and refer to depressive state in the course of the unipolar depression.

Despite decades of progress in research and treatment, depression remains a very serious public health issue. Long predicted to become the second leading cause of death and disability in the United States by 2020 (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Murray, Lopez, Harvard School of Public, World Health, & World, 1996), MDD is currently the leading cause of disability for people ages 15-44 (World Health Organization, 2008). The burden of disease measured by years lived with

disability for unipolar depression alone constitutes 11% of all disability (Greden, 2001). MDD affects people of all ages, including children and the elderly. Lifetime prevalence of MDD in the US is 17%, which means that 17 out of 100 Americans will experience an episode of depressive illness in their lifetime. In any given 12 month period, 6.7% of US population met criteria for MDD (Kessler, Berglund, Demler, & et al., 2003; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). World-wide point prevalence figures based on recent meta-analysis of epidemiological data estimated that 4.7% of the global population is currently depressed, a staggering number of over 341 million individuals (Ferrari et al., 2013). Studies indicate that depression affects all ethnicities and all socioeconomic levels, although the odds ratio of developing MDD is higher in less educated and lower income groups (Lorant et al., 2003). MDD is often chronic with relapsing course, and in some individuals it may be treatment resistant and lifelong (Kessler et al., 2003). Because of the impact on individual quality of life, the staggering cost and increasing prevalence, treating depression should be a priority worldwide (Moussavi et al.)

Challenges in Treatment and Research on MDD

The staggering prevalence numbers and depression related disability statistics pose an urgent challenge to researchers and clinicians in the mood disorders field. Depression is underdiagnosed and undertreated (only about 50% seek treatment) and the standard treatment guidelines for depression may not be adequately informed by

the current research findings on depression (Luyten, Blatt, Van Houdenhove, & Corveleyn, 2006). Only about 40% of patients achieve remission after initial treatment for depression (B. N. Gaynes et al., 2009; P. E. Holtzheimer & Mayberg, 2011), warranting a question: Why is major depression so difficult to treat?   The purpose of this chapter is to identify the challenges in the current treatment of depression, while at the same time to summarize the remarkable progress in understanding depression resulting, in part, from novel research tools and interdisciplinary approaches. Ways in which research in neurobiology and behavioral science could contribute to improvements in the clinical outcomes will be highlighted.

Treatment of MDD. There is a variety of treatments options for those who do seek help with depression. Both psychological and pharmacological approaches have been shown to be successful, at least partially, in a majority of patients (Kupfer, Frank, & Phillips). For the vast majority of depressed patients treatment will be initiated with a first line antidepressant medication, typically an SSRI (selective serotonin reuptake inhibitor). Unfortunately, an adequate trial of a first line antidepressant requires several weeks before its effectiveness can be evaluated, and there are no objective biomarkers to guide the choice of agent. Hence, the 'trial and error' approach, sequential use of medications to find an effective one, currently dominates psychiatric treatment. For the patient, this may delay relief from symptoms for weeks or months (Insel & Wang, 2009).

Psychological treatment is as effective as drug treatment in a similar percentage of patients with MDD (P. E. Holtzheimer & Mayberg, 2011). Of the existing psychotherapeutic approaches to the treatment of depression, the cognitive

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and behavioral therapies have been most extensively studied (S. D. Hollon, Stewart, & Strunk, 2006; Steven D. Hollon, Thase, & Markowitz, 2002). The early approaches were based on the behavioral principles of Skinner (Skinner, 1957) and a theory and practical treatment guidelines were developed by Ferster (Ferster, 1973). The emphasis in the behavioral therapy for depression was on changing depression maintaining behaviors by implementing strategies to increase behaviors likely to improve mood via reinforcement strategies. Functional analysis of patients' behavior allowed the therapist to identify targets of intervention, addressing avoidance and increasing reinforcement. Cognitive therapies based on Beck's theory of depression (Beck, 1964) conceptualized depression as a thought disorder and focused on cognitive processes which produce and maintain depressed mood, such as distortions, maladaptive thoughts and errors in reasoning. Contemporary therapeutic approaches combine aspects of both theories and address behaviors as well as cognitions of depressed patients and are efficacious, improve long term symptom relief (Dobson et al., 2008), and show promise in relapse prevention (S. D. Hollon et al., 2006). Behavioral Activation (BA) (Jacobson et al., 1996) is a therapeutic approach that shares features with cognitive therapy, but the emphasis in on an increase in active engagement in reinforcing activities that are individually relevant to goals and values more so than correcting maladaptive cognitive patterns. In this therapeutic approach, the focus is on engagement in health promoting, enjoyable activities, and subsequent positive reinforcement over time is thought to lead to a corresponding reduction in depressive symptoms, as well as an increase in positive affect (Hopko, Lejuez, LePage, Hopko, & McNeil, 2003). Of note, this approach directly addresses one

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central deficit of depression, loss of engagement in previously enjoyed activities. In one randomized study directly comparing medication, cognitive therapy and BA, behavioral activation was more efficacious than antidepressant medication as well as cognitive therapy (Dimidjian et al., 2006).

A unique group of interventions to relieve depression is represented by the somatic treatments, seeking to relieve symptoms by disrupting hypothesized abnormal biological processes. Those include invasive procedures such as electroconvulsive shock (ECT), deep brain stimulation (DBT) or vagal nerve stimulation (VNS) and have a reasonable success rate (Cusin & Dougherty, 2012; P. E. Holtzheimer & Mayberg, 2011). Due to side effects and the invasive nature of these interventions, they are applied mostly in severely ill patients who have failed multiple trials of standard treatments. Non-invasive somatic treatment approaches include sleep deprivation (Kundermann, Hemmeter-Spernal, Huber, Krieg, & Lautenbacher, 2008), and transcranial stimulation (TMS) methods (P. E. Holtzheimer, 3rd, Russo, & Avery, 2001). These various methods are effective for some patients and bring at least temporary relief, yet a remarkable variability in the treatment response remains a challenge. Of note, placebo response in treatment of depression is also high and may even reach 30% (Walsh B, 2002). With many types of intervention ranging from brain surgery to behavior modification, varying success rates and time needed to assess whether a chosen therapy actually works, the question remains how to swiftly find the right intervention for the individual patient, when to switch to another approach, and what is the best sequence of trials.

As the first line approaches to depression treatment most often include both pharmacological and psychological interventions, an attempt to structure and normalize treatment, a STAR-D (sequenced treatment alternatives to relieve depression) program of NIMH was initiated with guidelines to provide adequate trials of medication and suggest subsequent steps, including psychotherapy, if needed. According to STAR-D, failure to respond to the first level drug was to be followed by switching to other drugs and/or psychotherapy (S. C. Williams, 2006). STAR*D was the largest depression study ever done outside the pharmaceutical industry. The 2012 update of the study (Bradley N. Gaynes et al., 2012), reported the results from a representative sample of the US population in both psychiatric and primary care settings. The STAR*D employed up to four successive treatment steps, including a switch to and augmentation with additional drug or cognitive therapy in an equipoise randomization design. Remission rather than response was evaluated, and its rates in steps one to four were 36·8%, 30·6%, 13·7%, and 13·0%, respectively, with a cumulative remission rate of 67% after all four steps. The study confirmed that most patients need several sequential treatment steps to achieve remission, and demonstrated no clear advantage of one strategy of drug over another for patients who did not achieve remission after one or more acute treatments. Given that placebo controls were not employed, and sufficient numbers of patients were not enrolled in psychological treatment, conclusions about advantages of additive strategies could be drawn. Furthermore, neither socio-demographic nor clinical (anxious, atypical, and melancholic) features were shown to moderate the effect of various switching options after the first non-successful attempt at treatment. A reasonable conclusion would be

to that future research should focus on finding treatment predictors, moderators, and biomarkers to maximize chances at implementing an effective treatment strategy right away. Efforts are underway to empirically address a question of what type of medication and what type of psychotherapy (and in what order, or simultaneously) to apply to treat a specific patient (Miller & O'Callaghan, 2013; Simon & Perlis, 2010). Research examining clinical, cognitive and biological factors characteristic of patients responding favorably to specific interventions will help clinicians in making choices for and with their patients.

MDD Research Advances and Relevance to Clinical Progress Experts agree that many fundamental questions about etiology and biology of depression still remain unanswered and are crucial to pursue to improve clinical outcomes (Drevets, Price, & Furey, 2008; Krishnan & Nestler, 2008; Preskorn & Drevets, 2009). In this section, the tangible ways in which research can help in identifying risk factors for depression, discovering biological abnormalities associated with depression and guide interventions based on empirical finding will be discussed.

To treat early or to prevent a disorder it is important to understand who is at risk for its development. At this time, the etiology of depression remains largely unknown. Twin studies indicate that there is 37% heritability which is lower than bipolar disorder or schizophrenia (Sullivan, Neale, & Kendler, 2000). Neither candidate genes nor genome wide association studies have yielded clear, replicated results, possibly because of the complexity of depressive illness (Major Depressive Disorder Working Group of the Psychiatric, 2013; Shyn & Hamilton, 2010). Initial

studies of gene by environment interaction generated exciting results suggestive that both biological and environmental (social, psychological) factors contribute to the onset of depression. A candidate gene - serotonin transporter gene s/l polymorphism in SLC6A4 (abbreviated 5HTTLPR) was found to interact with life stress to increase an individual's risk for the disorder (Caspi et al., 2003; Monroe & Simons, 1991). Subsequent studies yielded mixed results [for review, see (L. E. Duncan & Keller, 2011)], but sparked interest in other ways of looking for genetic vulnerability and environmental factors. A recent study found that a polygenic risk score rather than single candidate gene, coupled with another known environmental risk factor, presence of childhood trauma, contributed to an increase in depression vulnerability (Peyrot et al., 2014). Numerous genetic studies have also investigated the interaction between genetic factors and treatment response. For example, certain genes and antidepressant response or non-response appear to be related: GRIK4 and citalopram, BDNF polymorphism and SSRI drugs, COMT and response to multiple antidepressant drugs (Licinio, Dong, & Wong, 2009; Paddock et al., 2007; Perlis, Fijal, Dharia, & Houston, 2013). Better understanding of risk factors and causes would help in development of evidence based preventive measures (Muñoz, Beardslee, & Leykin, 2012; Saxena, Jane-Llopis, & Hosman, 2006) as well as assist in treatment choice based on genetic factors.

Recent decades have broadened our understanding of neurobiology of depression and its symptoms thanks to the rise of the non-invasive neuroimaging techniques. These tools have led to the identification of brain regions and neural processes impacted in the course of illness. There is substantial evidence that MDD is

associated with structural and functional brain changes, particularly in areas that are crucial for emotion regulation and reward responsivity (W. C. Drevets et al., 2008; Drevets et al., 1997b; Drevets et al., 2004).

Structural imaging studies found that depressed patients without any neurological symptoms differ from age-matched healthy subjects. The most prominent volumetric abnormalities of reduced gray matter are found in the prefrontal cortex, cingulate cortex and in the temporal lobes (Drevets et al., 2007) (Drevets et al., 2007). Studies are less consistent regarding the amygdala, striatum and hippocampus – structures important for emotional responses, reward, motivation, and memory. Decreases, no differences, or increases in volume were also reported in control versus depressed subjects and these results raise a possibility that yet undefined subtypes of patients show opposite patterns of changes in these regions of the brain (Drevets et al., 1997a; Drevets et al., 2004). Besides heterogeneity of illness, the differences between studies may reflect impact of medication and time of onset of depression (Bora, Harrison, Davey, Yücel, & Pantelis, 2012).

Additional evidence regarding biological alteration in MDD came from Positron Emission Tomography (PET) studies which allow in-vivo measures of regional cerebral blood flow and glucose metabolism (considered indicators of regional neural activity), as well as measurement of the distribution or activity of specific receptors types. Studies comparing depressed patients and healthy controls provide support for differences in resting metabolism linking limbic and cortical regions, with patients generally showing increased metabolic activity in the amygdala and orbital frontal cortices, leading to hypotheses of impaired regulation of emotional responses in

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depression (Drevets et al., 1999). Another region consistently implicated, and also involved in modulation of emotional behavior is the subgenual anterior cingulate cortex, (ACC), (Drevets, Savitz, & Trimble, 2008). PET studies also directly confirmed alterations in the serotonin, dopamine and opioid systems in depressed subjects (Kennedy Se, 2006; Reivich, Amsterdam, Brunswick, & Yann Shiue, 2004; Savitz & Drevets, 2012).

Functional MRI studies complement the findings of the volumetric studies and metabolic PET studies in identifying neural networks altered in MDD and their relation to behavioral symptoms of depression. Resting state studies, functional studies carried out in the absence of a task have provided evidence for altered function in depression (Gusnard, Akbudak, Shulman, & Raichle, 2001). The resting pattern of brain function differs in MDD in the inferior (ventral) part of the medial prefrontal cortex (vmPFC), and area important for emotional control of cognitive processing. Also, increased connectivity between vmPFC and anterior cingulate in individuals with depression versus healthy subjects was found resting-state connectivity and this particular characteristic correlated with the length of the depressive episode (Greicius et al., 2007).

How depressed individuals process emotion, react to reinforcement, and engage in cognitive processes has been studied using fMRI. Studies comparing healthy individuals and depressed patients during performance of cognitive tasks, often with manipulated emotional content, yield distinct patterns of differences between groups. Of those patterns, the most often replicated are altered limbic-frontal connectivity, increases in the amygdala in response to emotionally salient negative stimuli and

decreased activity in the anterior cingulate cortex (Hamilton et al., 2012).

Interestingly, activity in these brain areas changes over the course of both

pharmacological or cognitive-behavioral treatment, and those patients who respond

show post-treatment patterns resembling healthy controls at baseline (DeRubeis,

Siegle, & Hollon, 2008; Siegle, Carter, & Thase, 2006; Siegle, Thompson, Carter,

Steinhauer, & Thase, 2007).

The availability of non-invasive imaging techniques and their sensitivity to

mapping differences between depression and health in brain structures and brain

function is of great interest to clinicians. In addition to characterizing depression on

the biological level, these techniques can demonstrate changes over the course of

treatment, and characteristics of patients who respond versus do not respond to

particular interventions. The tools are available to investigate how a given intervention

works, and what biological processes accompany emotional and behavioral changes in

the course of a successful therapy.

Interestingly, the mechanism of action of even the most commonly prescribed

antidepressant medication is not well understood. Early in biologically based

depression research, the monoamine hypothesis was prominent (Duman, Heninger, &

Nestler, 1997; Heninger, Delgado, & Charney, 1996; Ressler & Nemeroff, 2000).

Drugs were developed in line with the hypothesis that a dysfunction in

monoaminergic transmission (i.e., serotonin, dopamine, norepinephrine and

epinephrine, and especially serotonin) is the biological basis of depression. Drugs

such as SSRI (selective serotonin reuptake inhibitors) alter monoamine levels after a

single dose, but antidepressant effects are delayed by weeks. Why the clinical

response to SSRI type medication is delayed remains an area of debate (Godlewska, Norbury, Selvaraj, Cowen, & Harmer, 2012). Even though monoamines have received most of the attention in the previous decades and are the mainstay of antidepressant therapy (Nelson, 1999), all major neurotransmitter systems have been implicated in depression suggesting widespread imbalance in neural transmission (W. C. Drevets et al., 2008). New approaches to treatment of depression increasingly target non-monoaminergic systems with hopes of achieving progress in clinical response of treatment resistant depression patients (C. Zarate et al., 2013), and there is evidence that drugs such as ketamine (glutamate antagonist) and scopolamine (cholinergic antagonist) produce rapid antidepressant response and may have a common biological pathway (Berman et al., 2000; Duman & Voleti, 2012; M. L. Furey & Drevets, 2006; C. A. Zarate, Jr, Singh, Carlson, & et al., 2006). Clinical research continues into possible applications of rapid antidepressants and also into discovering bio-behavioral characteristics of patients who may be good candidates for these, or other pharmacological or psychological interventions, leading the field into personalized medicine for depression. For example, there is evidence that treatment with scopolamine is more successful in women than in men (M. L. Furey, Khanna, Hoffman, & Drevets, 2010) and can be predicted based on symptoms reported by patients before treatment onset (M. Furey, Nugent, Speer, Drevets, & Zarate, 2011) or visual cortex activity during processing emotional stimuli (M. L. Furey et al., 2013). Greater alteration of delta sleep ratio may predict a response to glutamate agonist ketamine (W. C. Duncan, Selter, Brutsche, Sarasso, & Zarate, 2012). An fMRI study demonstrated that pre-treatment amygdala and subgenual cingulate cortex activity

during emotional information processing task may predict response to cognitive-behavior therapy (Siegle et al., 2006). Furthermore, evidence based on functional imaging studies published to date support that measures of activity in the anterior cingulate and medial prefrontal cortices and the amygdala may differ in patients who benefit from psychotherapy compared with antidepressants and that baseline experimental measures in these areas may provide guidance for future treatment choices (Phillips et al., 2015). The direct clinical application of these experimental findings in the community mental health system is not as of yet feasible, nevertheless, the recognition of unique bio-behavioral features of depression as potential biomarkers of treatment response is an important step toward improving the outcomes for MDD patients.

In summary, depression is recognized as both a behavioral and brain disorder associated with biological and psychological changes of not yet well understood etiology. The structural and functional changes in depression are widespread, major neurotransmitter systems are altered, and brain areas supporting emotion regulation and reward responsiveness differ functionally between healthy and depressed individuals. Successful treatments appear to correspond to functional changes in some of the affected brain areas and there is potential for use of baseline characteristics in predicting effectiveness of treatment interventions.

Core Symptoms of Depression

Experimental research into phenotype and treatment response of MDD patients points to the heterogeneity of both the behavioral and biological characteristics. However, the diagnostic process may fall short of appreciating that heterogeneity.

According to DSM-IV (American Psychiatric Association, 2001) as well as the recently published DSM-V (American Psychiatric Association, 2013), a diagnosis of a MDE is made if at least one out of the two core symptoms is present, accompanied by four other symptoms. The two core symptoms are (1) depressed mood and (2) loss of interest or pleasure, which implies presence of negative mood states as well as decreased positive affect. The remaining seven symptoms include (3) changes in appetite or weight, (4) increase or decrease of sleep, (5) psychomotor agitation or retardation (6) fatigue or loss of energy, (7) feelings of worthlessness and excessive guilt, (8) decrease in concentration and indecisiveness, and (9) thoughts of death, suicidal ideation or suicide planning. Any combination of the symptoms lasting for at least two weeks and leading to impairments in functioning (social, vocational, familial) qualify for the diagnosis of a MDD. Given these diagnostic criteria, there may be very little overlap between patients and the same diagnosis can be applied to two individuals who could have only one symptom in common. Opposite patterns corresponding to appetite, sleep and psychomotor activity can be present under the same formal diagnosis, raising questions of marked neurobiological heterogeneity when depression is diagnosed.

The two core symptoms of depression bring into focus two dimension of MDD, namely increase in negative affect and decrease in positive affect. Depressed mood is the first core symptom of depression, and becomes diagnostic if experienced frequently (most of the day, nearly every day), is reported as feelings of sadness, emptiness, or irritability, and is qualitatively different from occasional sadness or bereavement.

The second core MDD symptom of 'markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day' is often referred to as anhedonia. Higher levels of anhedonia in depressed patients are associated with more severe course and more resistance to treatment (McMakin et al., 2012; Uher et al., 2012; Vrieze et al., 2014). When defined as 'inability to experience pleasure' the construct of anhedonia refers to the internal experience of an individual and their recall of such experience upon questioning by a clinician or when responding to a questionnaire (Franken, Rassin, & Muris, 2007; Gorwood, 2008). Interestingly, for the clinical diagnosis of this symptom no differentiation between decreased motivation and reduction in experienced pleasure is necessary (Treadway & Zald, 2011). Given the standard diagnosis, it is difficult to conclude whether an individual endorsing 'lack of interest or pleasure' symptom is truly unable to enjoy activities or reluctant to approach and take part in activities. Thus, true experiential anhedonia, historically associated with melancholic depression, could very well be a different symptom from not engaging in previously enjoyed activities due to lack of motivation (Treadway & Zald, 2013). Since anhedonia is a core symptom, these two quite distinct components should be addressed and studied. Behaviors associated with anhedonia are the absence of engagement in activities that used to result in pleasure, as well as social withdrawal, lassitude and avoidance. As these behaviors are associated with lack of action, it is not clear whether an individual experiences loss of hedonic capacity or retains the ability to enjoy, but does not engage and inadvertently misses opportunities for enjoyment.

The motivation to engage, approach motivation, appears to be an important aspect of environmental reward related behavior that necessarily precedes actual

engagement and the experience of pleasure (or lack thereof) resulting from performing an activity. There is evidence that approach motivation is related to a hedonic deficit (Germans & Kring, 2000) and that severity of anhedonia influences task performance in different ways than severity of depression by slowing reward learning (Chase et al., 2010). Higher level of anhedonia is associated with a decrease in willingness to exert effort to obtain rewards (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). Also, reduced ability to sustain positive emotion rather than an inability to experience them at all may be characteristic of the hedonic deficits in depression (Heller et al., 2009). This emerging research into the nature of hedonic deficits in MDD suggests the involvement of related, but distinct processes that may underlie this core symptom of 'lack of interest or pleasure'. Understanding how these distinct processes result in anhedonic behavior could lead to better therapeutic interventions by targeting either motivation or hedonic expectation in psychotherapy, and – provided neurobiological correlates are identified – inform biology based treatments.

Cognition and Emotional Processing in Depression

Although MDD is a disabling and burdensome disorder, the exact nature of functional impairments is not fully understood (McClintock, Husain, Greer, & Cullum, 2010). Among diagnostic symptoms of depression, only one, 'diminished ability to think or concentrate, or indecisiveness' emphasizes cognitive difficulties. Pinpointing which cognitive difficulties present in MDD are specifically related to mood is complicated, given factors such as fatigue, low motivation and distractibility. Overall intelligence seems intact in depressed patients, however executive function and especially cognitive inhibition, problem- and task-planning consistently differ from

healthy controls, for review, see (Marazziti, Consoli, Picchetti, Carlini, & Faravelli, 2010). Performance on general neuropsychological batteries, such as Cambridge Neuropsychological Test Automated Battery (CANTAB) indicates moderate cognitive deficits in executive function, memory and attention in patients with depression relative to controls. Notably, most deficits (excluding memory) remain present in remitted patients (Rock, Roiser, Riedel, & Blackwell, 2013). Severity of depression, episode duration, recurrent episodes and psychotic features have all been associated with greater cognitive difficulties, yet a systematic review of findings points to inconsistencies and individual variability with some individuals experiencing significant impairments and others having no changes in cognitive function (McClintock et al., 2010). Those experiencing cognitive difficulties may improve following successful treatment, however, that improvement may lag behind mood changes (Trivedi & Greer, 2014).

A large body of research has been devoted to emotional processing in depression, and the influence of emotional salience on cognitive performance [for review, see (Roiser & Sahakian, 2013)]. When emotion is involved, depressed patients frequently perform differently from healthy controls, often demonstrating mood-congruent biases. For example, while performing the Affective Go/No-Go Task, depressed patients make more errors during happy versus sad word blocks and require more time to respond to happy than to sad words. In contrast, healthy subjects require more time to respond to sad than to happy words (Erickson et al., 2005). In studies utilizing facial stimuli displaying a variety of emotions, those diagnosed with MDD exhibit an attentional bias toward negative emotional cues (e.g. sad faces), an attentional bias away from

positive emotional cues (e.g. happy faces), and an enhanced memory for negative emotional material (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007; Surguladze et al., 2004). Interestingly, neutral faces are more often identified as emotional by depressed patients as compared to healthy controls (Jukka M. Leppänen, Milders, Bell, Terriere, & Hietanen, 2004) . Other types of tasks have also demonstrated negative processing biases in depression, for example, preferential recall of negative compared to positive material (Mathews & MacLeod, 2005), which is in contrast of healthy individuals' tendency to exhibit a positivity bias, [for review see (Peckham, McHugh, & Otto, 2010)].The existence of cognitive biases is predicted by cognitive theories of depression. Beck (1976) postulated that depressed individuals attend to those aspects of the environment that are congruent with their mood, schemas of loss, failure, worthlessness, and rejection, and neglect other types of information. Negative information is integrated into maladaptive thoughts, negative self-evaluation, worthlessness, thoughts of death, suicidal ideation and ruminative thinking over past failings. A vicious cycle of negative automatic thoughts, processing biases, and depressed mood is initiated and sustained.

Behavioral paradigms which elicit processing biases have been used in functional imaging to characterize neural correlates of mood congruent bias. These studies have consistently linked differential processing of emotion to medial prefrontal cortex (Elliott, Rubinsztein, Sahakian, & Dolan, 2002). Imaging data further indicate that MDD associated bias toward negative (sad) cues and away from positive cues and may be related to altered excitability of the brain emotion-related circuits as well as disruption of the cortico-limbic connections that are important in the regulation of

emotional responses [for a review, see (Jukka M Leppänen, 2006)]. There is evidence

for enhanced neural processing of negative information and for attenuation of such bias

after successful treatment for depression (DeRubeis et al., 2008; Siegle et al., 2006;

Szczepanik, Drevets, Nugent, Zarate, & Furey, 2011; Victor Ta, 2010).

Response to Rewarding Experiences in Depression

      Reward Related Behavior. Human behavior is shaped by environmental

interactions. Positive engagements drive activities not only directly related to the

species survival, such as obtaining food and procreating, but also those of social

collaboration and relevance to personal and professional goals (Bandura, 1974).

According to the theoretical 'hedonic principle', the experience of pleasure resulting

from positive reinforcement is integrally related to happiness (Kahneman, Diener, &

Schwarz, 1999). This experience of pleasure may not be accessible to individuals

suffering from depression. Multiple cognitive and behavioral stages occur between

becoming aware of a possible reward to experiencing pleasure from its attainment (K.

C. Berridge, Robinson, & Aldridge, 2009). A reward processing 'cycle' includes

recognizing and processing of reward cues, decision to take action to approach,

executing that approach, engaging in consummatory behavior, sustaining that

behavior, evaluating hedonic experience, and integrating the experience with one's

reinforcement history in the process of learning and memory. With so many aspects

requiring attentional, behavioral and emotional processing, the experimental results of

reward studies in both healthy and patient populations need to be carefully interpreted

(Diekhof, Falkai, & Gruber, 2008).

Reward Processing Tasks in Depression and Relevance to Anhedonia.

Reward processing studies in depression often utilize monetary incentives, a powerful secondary reinforcer that can be parametrically varied, to study responses during anticipation and feedback stages of reward processing. One issue with monetary incentives is the assumption that money and its increased amounts represent true, individually meaningful systematic rewards and that the subjects are motivated to respond in a way that maximizes monetary gain. Depressed individuals may be motivated more by avoiding losses (Smoski et al., 2008) and may not encode preferentially items associated with monetary gain (Dillon, Dobbins, & Pizzagalli, 2013). While healthy individuals seem to learn quickly, and even develop a bias to respond in a way that maximizes monetary reward, depressed patients fail to do so. Pizzagalli and colleagues studied depressed patients with a task requiring a cognitive decision (judging line length), in association with reward feedback to examine response bias (Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008). The difference between lengths of the two lines was very small, and one size was associated with reward, and the other with no reward. While healthy controls developed a bias to judge the length in accordance to which type was more often rewarded, depressed subjects failed to recognize or to implement such bias. The magnitude of the reward responsiveness bias specifically correlated with self-reported anhedonic symptoms (e.g., loss of pleasure, energy, interest, and libido) and predicted anhedonic symptoms 1 month later.

An incentive value is especially relevant given evidence of generalized hyposensitivity to reward, emotional blunting and an overarching negativity bias in

MDD [for a review, see (Eshel & Roiser, 2010)]. Evidence from animal studies pointed to another hypothesis of the basis of reward deficit in depression, namely a trade-off between effort and the reward magnitude. Effort based studies that involve choice of action to obtain small or larger monetary reward address a slightly different question, that of explicit motivation for larger possible gains. Again, an assumption is that the larger reward is more appealing (Treadway et al., 2009; Treadway, Bossaller, Shelton, & Zald, 2012). These studies find preference of depressed patients to exert smaller effort for smaller reward, consistent with animal studies (Salamone, Mingote, Farrar, & Correa, 2006). Nevertheless, the issue of how much *incentive* is there in a standard incentive for a depressed patient to maximize effort remains to be specifically addressed.

Fewer studies employed non – monetary rewards in human studies. Some studies utilized primary reward paradigms introducing pleasant and unpleasant smells and tastes. Again, the results have been mixed. Some studies of olfactory and gustatory anhedonia indicated little change in depressed patients in terms of preferences and pleasantness rating (Swiecicki et al., 2009) or sensitivity to sweet taste (Gabriel S. Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010), whereas others seem to point to the existence of olfactory anhedonia (Atanasova et al., 2010).

In a non-monetary reward effort based study, depressed and control participants rated cartoons and were presented with a choice of effort to view a preferred item. Depressed and healthy participants did not differ in their consummatory liking of the rewards, however, levels of reward liking predicted motivation to expend effort for

the rewards only in the control participants; in the depressed participants, liking and motivation were dissociated. In the depressed group, levels of anticipatory anhedonia predicted motivation to exert effort (Sherdell, Waugh, & Gotlib, 2012).   This line of evidence suggests a possibility that in individuals with MDD the ability to experience pleasure may be less or differently affected than motivation to approach and engage in pursuit of reward.

Dopamine and Reward. For decades, the main direction of study in understanding reward related behavior has focused on dopamine (DA) and the dysfunction of the mesolimbic system. Intracranial self-stimulation observed by Olds and Milner (Olds & Milner, 1954) in animal studies showed that stimulating certain brain areas is presumably pleasurable (based on observation of rats repeating behavior to obtain stimulation and preference of other activities), and that this effect was dopamine dependent. Through animal studies and imaging studies, the brain reward system (BRS) was identified, consisting of dopaminergic neurons originating in the ventral vegmental area (VTA) and projecting to the ventral and dorsal striatum, including nucleus sccumbens, and to cortical areas of anterior cingulate cortex (ACC) and orbito frontal cortex (OFC) (Roy A. Wise, 2002). The early PET studies in humans (Drevets et al., 2001) showed that feelings of euphoria accompanied pharmacologically enhanced DA transmission in the striatum, consistent with the BRS theory. Further findings in animal studies revealed that dopamine neurons discharge in response to conditioned stimuli predictive of food rewards, and initially fire when the food is consumed. However, once the association is learned, only the cues rather than the reward itself elicit DA firing, pointing to the

crucial role of DA function in reward learning (Schultz, 2001). DA neurons also respond to unexpected reward, but this activity ceases after previously unexpected reward becomes predictable, despite the fact that the hedonic value of the predicted reward is presumably unchanged (K. Berridge, 2007; Schultz, 1998).

The relation of DA system and reward processing has been validated; however, exactly which aspects of reward related behavior are highly dopamine dependent remains controversial (R. A. Wise, 2008; R. A. Wise, Spindler, deWit, & Gerberg, 1978; Roy A. Wise, 2002). The evidence appears strongest for the role of dopamine in reward learning and motivation for rewards than for hedonic capacity to experience enjoyment. Manipulation of DA system alters reward behavior in animals and humans. Dopamine depletion in rats decreases responses to large rewards requiring more effort and increases preference for easy, smaller rewards (Salamone et al., 2006). Yet, genetically DA depleted mice still show preferences for taste (Pecina, Berridge, & Parker, 1997; Pecina, Cagniard, Berridge, Aldridge, & Zhuang, 2003). However, the motivation to put forth effort to obtain preferred reward is decreased when DA levels are attenuated (Salamone, Correa, Farrar, & Mingote, 2007). In terms of the hypothesized 'subtypes' of anhedonia, this would support DA role in motivational rather than consummatory anhedonia.

Dopamine and Depression. If an intact dopamine BRS system is necessary for reward and enjoyment, and MDD is associated with hedonic deficits, there should be evidence of DA system dysfunction in MDD. Indeed, evidence for deficiencies in dopamine function in depression and its specific link to anhedonia has been established. The Parkinson's patients who develop depressive symptoms as their

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disease progresses have reduced DA binding in several brain regions crucial for

reward function, including the limbic system and the ventral striatum (Remy, Doder,

Lees, Turjanski, & Brooks, 2005). Manipulation of DA transmission by

administration of DA agonist pramipexole in healthy individuals affects negatively

reward learning (Barr, Pizzagalli, Culhane, Goff, & Evins, 2008) and depleting

catecholamines induces depressive and anhedonic symptoms in remitted depressed

patients (Hasler et al., 2008). Direct evidence for altered DA function in depressed

versus healthy individuals was observed after administration of stimulant, where

transient rewarding effects of medication were greater in depressed than healthy

(Tremblay, Naranjo, Cardenas, Herrmann, & Busto, 2002), and several brain areas

(VLPFC, OC, caudate and putamen) showed BOLD signal differences on an

emotional pictures task between healthy and depressed groups after stimulant

administration (Tremblay et al., 2005). Dopaminergic transmission enhancing drugs

are sometimes used as an adjunct in treatment of depression, but no clear advantage

for their use had been confirmed in randomized trials (Argyropoulos & Nutt, 2013).

Liking and Wanting, Given strong evidence for involvement of DA and BRS

in reward processing and yet evidence that dopamine alone was neither necessary nor

sufficient for all aspects of hedonic behavior, a theory of separate 'liking' and

'wanting' systems attempted to reconcile the empirical evidence. This theory posits

that the neural systems associated with the experience of anticipatory and

consummatory pleasure may be in close proximity, but separable from the incentive

processing and approach system (K. C. Berridge et al., 2009), and involve different

neural substrates. Liking and wanting systems involve several common brain areas

and may be precisely delineated using microinjections of μ-opioids into rodent nucleus accumbens. The role of μ-opioid receptors in human studies implicated importance of these neuropeptides in striatum and medial prefrontal cortex in hedonic and affective responses (Pecina, 2008). Also implicated in hedonic perception are GABA and endocannabinoid systems (Der-Avakian & Markou, 2012) pointing to the importance of neuromodulation other than dopaminergic in the experience of pleasure. Interestingly, GABA may also modulate the 'wanting': choice of how much effort including punishment (unpleasant sensation) is worthwhile for preferred reward. A recent study in primates demonstrated that motivation for greater effort toward obtaining greater reward is linked to pregenual cingulate cortex and can be differentially modulated by stimulating different populations of neurons (Amemori & Graybiel, 2012). The effects of simulation to neurons preferentially sensitive to low reward preference were reversed by administration of benzodiazepines, implying the possible role of GABA in balancing the approach/avoid decision and shift toward more difficult, but more rewarding choice. Also, serotonin, a neurotransmitter consistently implicated in depression and a direct target of a majority of antidepressant medication, has been shown to have a distinct role in intact and altered reward processing, sensitivity to feedback and reward responsivity in animal studies (Bari et al., 2010).

In summary, there is evidence that the mesolimbic dopaminergic transmission is implicated in intact processing of rewards and may be disrupted in depression, however, this system may be more closely associated with motivation and approach (i.e., 'wanting' of rewards than the experience of pleasure itself). The experience of

pleasure upon engagement and consumption of a reward is possibly dependent on other systems including endogenous opioids and other neurotransmitters, and may engage distinct brain regions. Depressed individuals who endorse symptoms of anhedonia based on current assessment may differ in the underlying biology if their primary deficit is in lack of motivation and approach rather than in hedonic capacity. This distinction may be both clinically and biologically important, and needs yet to be characterized with rigorous laboratory measures. Regardless of the type of reward used in a task, a question of meaningfulness of an incentive for a depressed individual remains an important issue.

Approach and Avoidance in Major Depression

Theories and Neural Correlates. Few studies so far have investigated approach and avoidance in depression in direct relation to anhedonia, and conversely, reward processing studies tend to focus more on anticipation and consumption phases rather than approach and avoidance decisions. Approach and avoidance are thought to be fundamental concepts in how humans interact with the environment. Gray (1994a) proposed a theory of behavioral activation system and behavioral inhibition system (BIS/BAS) which govern approach and avoidance in interaction with the environment in addition to the most basic fight/flight system which serves immediate response to threat. Thus, approach and avoidance are viewed as major divisions of human behavior, and motivational research considers approach of positive and avoidance of negative outcomes to be a fundamental property of human behavior, also referred to as tendencies to promote positive outcomes and prevent negative outcomes (A. Elliot & Covington, 2001; Gray, 1990; Higgins, 1999).

The approach system is thought to involve a number of cortical and sub-cortical structures, including basal ganglia and prefrontal cortex (Rolls, 2000). Electrophysiological studies correlating self-reported behavioral tendencies correlated for approach with activity in left frontal areas (Coan & Allen, 2003). Glutamate, dopamine and GABA have been linked by Gray to approach motivation on the basis of medication challenges in animals and humans (Gray, 1990). The avoidance system partially overlaps with the approach system, but is lateralized to the right in the PFC. GABA, norepinephrine and serotonin are implicated in the BIS (Gray 1990) Projections from the subiculo-accumbens to the caudate-putamen, PFC, and cingulate cortex also serve the BIS by interrupting motor programs and influencing perception (Gray & McNaughton, 2000). Recent neuroimaging studies further characterized the approach/avoidance systems as dependent on the areas closely associated with reward and goal pursuit: dorsolateral pre-frontal cortex (DLPFC), with left laterality for approach and right for avoidance, confirming earlier studies (Spielberg et al., 2012), OFC, involved in goal evaluation (Hare, Camerer, & Rangel, 2009), ACC, modulating goal, reward and conflict processing (Rushworth, Behrens, Rudebeck, & Walton, 2007), amygdala, which not only supports rapid evaluation of potential threat and emotional salience (Adolphs, Tranel, Damasio, & Damasio, 1995) but motivational salience (Pessoa & Adolphs, 2010) and crucial for reward and action initiation basal ganglia (Haber & Knutson, 2010). The approach and avoidance systems may be activated simultaneously, and activate left DLPFC (Spielberg et al., 2012). This could reflect a general 'preparing to act' readiness, and the resulting conflict resolution depends on which system prevails. Positive or negative affect at

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the time of conflict between approach and avoidance decision influences behavior, possibly by modulating effort (Carver & White, 1994).

Approach/avoidance Dysregulation in Depression. Within this general framework of recognizing tendencies to approach and avoid as regulators of successful interaction with the environment, mood and anxiety disorders have been hypothesized to be imbalanced (Johnson, Turner, & Iwata, 2003). There is evidence that depression is associated with both decreased approach (Eastman, 1976; Wang, Brennen, & Holte, 2006) and increased avoidance (Kasch, Rottenberg, Arnow, & Gotlib, 2002; Ottenbreit, Dobson, & Quigley, 2014) in the interaction with the environment. Depressed individuals set fewer approach goals (Chambers, 2007), more avoidance goals and plans and engage in fewer social and exercise behaviors (Hopko & Mullane, 2008). Also, depressed individuals tend to choose less rewarding activities to avoid anxiety or disappointment (Hopko, Armento, Cantu, Chambers, & Lejuez, 2003), thus further restricting access to the environmental reinforcers. Decreased appetitive motivation and reward sensitivity negatively predict depressive symptom (Jones & Day, 2008), episode duration and general functioning (Kasch et al., 2002), further supporting the notion of decreased approach motivation in depression.

Many imaging studies found that depression is associated with relatively reduced activity over left prefrontal regions (Gotlib, 1998; Grimm et al., 2008). Because these areas are assumed to play an important role in approach-related motivation, at least some of the decreased reward responsiveness could be linked to this neurobiological alteration (Davidson, 2003; Henriques & Davidson, 1991). Other

nodes in approach/avoidance network – ACC, amygdala, basal ganglia and striatum are among the consistently implicated regions in pathophysiology of MDD. Thus, it may be difficult to isolate the specific neural alterations in approach and avoidance processing from other deficits in depression.

Addressing both approach and avoidance is important in the course of therapy for depression (Kanter et al., 2010; Trew, 2011). Psychotherapeutic interventions, such as Behavior Activation Treatment for Depression (Hopko, Armento, et al., 2011; Hopko, Magidson, & Lejuez, 2011; Lejuez, Hopko, & Hopko, 2001), see also (Jacobson et al., 1996) aim directly at increase of approach behavior that may result in positive reinforcement, and reduction of avoidance behaviors that may provide negative reinforcement, but interfere with individual's functioning (Hopko, Lejuez, Ruggiero, & Eifert, 2003). The relation of anhedonia and approach is crucially important to study, because it could be hypothesized that individuals who would enjoy if engaged versus those who would only be further disenchanted if engagement in favorite activity resulted in no joy at all need different types of intervention for their symptom, now assumed to be the same under the term 'anhedonia'. Current experimental measures of anhedonia or related constructs for use in depression research do not make such a distinction, which is surprising given both importance and interest in this symptom in clinical and experimental fields, as well as the evidence for different biological correlates. Also lacking are studies directly assessing motivation in MDD (Treadway & Zald, 2011).

Approach and Avoidance Tasks. Experiments investigating approach and avoidance use either button press reaction time measures or measures of movement

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toward or away from self, or a representation of self. An often employed method to study the constructs of approach and avoidance is to elicit motor response of the dominant hand (flexion and extension) in relation to the stimulus. The interest in this method followed the publication of *Latency of instrumental responses as a function of compatibility with the meaning of eliciting verbal signs* (Solarz, 1960) and the design has been employed frequently in experimental psychology. Movement toward self is considered to be indicative of approach, or an expression of directing behavior toward an outcome, while movement away from self implies avoidance, distancing self from an outcome. These manipulations are based on the idea that approach motivation is associated with bringing a rewarding object closer to the body (e.g., arm flexion) and avoidance motivation is associated with pushing an undesirable object away from the body (e.g., arm extension). To record the movement, experimental studies use two-dimensional joystick, an electronic input device, originally patented for the use in the military aircraft. Joysticks are widely used for video games and to operate electronic equipment, and were adapted for use in experimental research.

Research has supported the idea that approach-avoidance motor behaviors reflect cognitive processes consistent with the activated motivational state and that these movements are primed by affect and stimulus valence. Hence, joystick tasks were used to measure motivation for desired versus non-desired stimuli under various circumstances. Even though the hedonic principle and promotion/prevention theory state that approach is likely for desirable, and avoidance for undesirable outcomes, in reality approach and avoidance are often driven by both immediate and long term goals, which may introduce conflict that needs to be resolved by cognitive evaluation,

for example, in a dieter who needs to avoid their favorite food given long term weight loss goal, and thus will have a reduced approach of an item he likes but decides to avoid (Fishbach & Shah, 2006). Nevertheless, the dual, opposite action is consistent with the general theory of human behavior as driven by approach and avoidance motives (Carver & White, 1994; A. J. Elliot, 1999; A. Elliot & Covington, 2001; Gray, 1990), and there is considerable support for the idea that two separate systems regulate behavior (Elliot, 2008) and have overlapping, but distinct neural correlates (Amodio, Devine, & Harmon-Jones, 2008). For experimental purposes, these systems can be activated by tasks requiring motor behaviors associated with approach or avoidance and manipulated by conditions requiring movement congruent or incongruent with the stimulus valence. Motivational state, goals, and mood all influence cognitive processes necessary to perform approach and avoidance tasks (Chen & Bargh, 1999) Priming positive affect enhances approach behavior in healthy individuals (Custers & Aarts, 2005).

Because approach motivation is typically linked to positive outcomes [but see (Harmon-Jones & Peterson, 2008)] and avoidance motivation is typically linked to negative outcomes, many theorists argue that the activation of these motivational states should lead to valence consistent enhancement of cognitive processes: positive for approach states and negative for avoidance states (Cacioppo, Priester, & Berntson, 1993; Solarz, 1960). For example, when study participants were asked to evaluate words as good or bad by either pulling a lever (approach – movement toward the body) or pushing a lever (avoidance -movement away from the body) (Chen & Bargh, 1999), the results showed that participants were faster to make evaluations of

positive words when they pulled the lever, and faster to make evaluations of negative

words when they pushed the lever. Approach and avoidance can also be defined as

distance reduction or increase, and the movement does not need to be toward and

away as relating to the subjects body. For example, if subject's name is placed on the

computer screen, it can serve as a reference point for motor responses (Regina

Krieglmeyer & Deutsch, 2009). The 'toward self-away from self' directionality and

its consistency with approach and avoidance can be also manipulated as demonstrated

by a study where movements were dissociated from approach and avoidance (Eder &

Rothermund, 2008).   These studies point to importance of proper design and clear

instructions that emphasize the directionality and subject as a reference point if the

automatic approach and avoidance are of interest (R. Krieglmeyer, Deutsch, De

Houwer, & De Raedt, 2010). Furthermore, despite finding a reliable effect of

affective stimuli on approach and avoidance tendencies, recent meta-analysis of 29

studies cautions that interpreting joystick task results requires careful interpretation of

the movement measures as they were suggested to the participants either by the

instructions or the experimental context, rather than assuming automatic

representation of approach and avoidance by toward and away movements (Phaf,

Mohr, Rotteveel, & Wicherts, 2014).

    Joystick Tasks in Clinical Populations. A popular task used in social

psychology research and also employed in clinical populations is computerized

Approach Avoidance Task (AAT) where approach and avoidance movements are

performed in response to faces with different emotional expressions (Heuer, Rinck,

& Becker, 2007). Approach and avoidance of alcohol related picture cues was studies

in relation to treatment outcome and re-training of tendency to approach as an intervention (R. W. Wiers, Rinck, Kordts, Houben, & Strack, 2010; Reinout W. Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011).   Approach of feared stimulus in phobia was studied using pictures containing images of spiders (Rinck & Becker, 2007), and the approach movement was associated with enlargement of the picture of the stimulus, possibly enhancing its salience.

Seidel and colleagues investigated approach and avoidance during fMRI scans in healthy controls in one study, and depressed patients and healthy controls in the second study (Derntl et al., 2011; Seidel et al., 2010) using emotional faces (angry, happy, neutral) as stimuli in both explicit and implicit tasks. The explicit condition involved pressing a button indicating approach or avoidance according to subject's judgment (would you go toward or away from this person) and in implicit condition the subjects responded by designated pull or push response depending on the color of the frame pictures of faces were presented in on the screen. Hence, motor responses were quite different in explicit versus implicit conditions. Only the explicit condition showed differences between groups, and only on overall approach (fewer approach steps, regardless of emotion in the face) in the depressed group. Nevertheless, there were neural response differences between groups in the implicit condition, where patients versus controls on approach versus avoidance of happy faces showed more BOLD activity in right orbitofrontal and supramarginal gyrus, and more activation in left caudate nucleus on approach versus avoidance of angry faces. This study did not evaluate anhedonia symptoms in patients and used peak reaction time response as an outcome measure for approach and avoidance.

In summary, use of joystick based tasks is an established measure of automatic approach and avoidance responses in behavioral studies, and the stimulus valence (positive, negative) has been shown to facilitate approach and avoidance in the healthy subjects. Joystick based tasks of approach and avoidance are increasingly applied in clinical populations.

Development of Behavioral Approach Motivation Paradigm (BAMP)

The Goals of BAMP. The overarching goal of the behavioral approach motivation paradigm (BAMP) introduced here is to develop and test a behavioral measure of approach motivation to expand the existing knowledge of motivational deficits in depression. The measure is meant to capture motivational aspects of behavior using stimuli that are relevant to each individual's real life activity preferences and dislikes. Thus, we aim to experimentally evaluate approach and avoidance in a standardized, yet highly personalized manner.

In line with the previous research, approach would be elicited by engaging subjects in physical responses of arm flexion when a response requires pulling a joystick toward self, and avoidance by engaging in arm extension when a response requires pushing the joystick away. Thus, we aim to approximate approach and avoidance of real life activities for which each subject has familiarity due to knowledge and/or experience. By using idiographic, activity related word stimuli of known (previously rated) valence, in a task where a pull/ push response is *not* related to valence, we can examine the influence of mood and motivation on automatic tendencies to approach and avoid.

For the purpose of this work, an operational definition of 'approach motivation', which could be conceptualized in the context of depression as approximating 'motivational anhedonia', is the reaction time speed and duration of joystick movement toward self when the stimulus presented on the screen is a word representing a favorite activity. This condition is of particular importance, as it most directly assesses the behavior of interest. Other conditions to be included in the task are pushing away to favorite activities, pulling and pushing to disliked activities, and pushing and pulling to activities rated as 'neither like nor dislike'.

Several design considerations shaped our development of the task. First, we considered the use of idiographic pictures of activities, general scenes of activities or video clips of activities. However, idiographic words have been used effectively in eliciting differential approach and avoidance tendencies (Eddington, Dolcos, Cabeza, R. Krishnan, & Strauman, 2007). Subjects can form their own, unique associations with the word cues and evaluate activities based on what each word represents for them. A second consideration involved the decision on whether to include an explicit task condition, where the subjects are pulling in response to activities they like and push in response to the activities they dislike. However, our design allowed examination of other aspects of approach and avoidance behavior, including approach of disliked activities or avoidance or liked activities, and to control the number of responses to each response category.

In summary, BAMP was designed to elicit differences in motor responses (flexion and extension of the dominant arm) to favorite, neutral and disliked stimuli as they are approached and avoided in a joystick task. We expected to observe
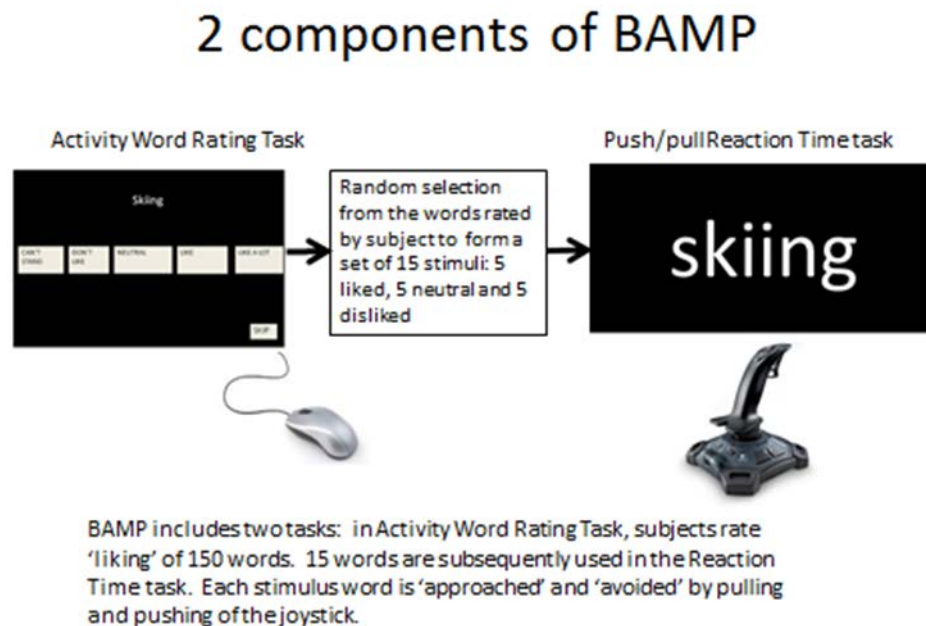
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differences between depressed and non-depressed individuals reflecting altered interaction with the environmental reinforcers in these two groups. We hypothesized that the reaction time measures would show decreased approach motivation in depression and allow us to characterize motivation to approach activities which were found to be enjoyable in the past, and are currently rated as 'liked' or 'liked a lot'.

BAMP Task Components. There were two experimental components in the BAMP task: rating of activity words (Word Rating Task, WRT) and reaction time joystick task (Lexical Decision Reaction Time Task, LDRTT). The first component, the WRT, required each subject to rate 150 verbs on a 5 point Likert scale ranging from 'like a lot' to 'can't stand'. Thus, each word acquired a number representing individually assessed appetitive value where 0 and 1 represented disliked items, 2 neutral, and 3 and 4 liked items. The second component, the LDRTT, involves subjects performing a reaction time joystick task which required pulling the joystick toward self or pushing it away from self in response to the previously rated activity words. The stimulus set was unique to each subject. Specifically, the stimuli in the RT task were generated by randomly selecting 5 words from each rating category: 5 from words rated as liked, 5 from rated neutral and 5 from rated disliked, resulting in a total of 15 unique stimuli for each subject. In the final version of the task, the words for category 'liked' were randomly selected from items rated 4 ('like a lot') however, if a subject rated fewer than 5 items with 4, items rated 3 'like' were randomly selected and included to complete the category. Similarly, for disliked items, the random selection was made from items rated 0 ('can't stand') and supplemented if necessary by words rated 1 ('don't like') also by random selection to complete the 'disliked' category. The RT

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task could not be performed if a subject did not rate at least 5 items as 'neutral', as it was a distinct category with only one rating, 2, 'neutral'.   The push or pull response to the stimuli was not dependent on the word meaning, nor its appetitive value, but the sensory characteristic (upper versus lower case, early version of the task) or lexical decision (word versus non word, final version of the task). Speed of response and response accuracy were measured. The final design of the experiment is described in detail in the following sections.

Figure iii

Task summary. See Figures i and ii for more detailed information on task components.

2 components of BAMP

BAMP includes two tasks: in Activity Word Rating Task, subjects rate 'liking' of 150 words. 15 words are subsequently used in the Reaction Time task. Each stimulus word is 'approached' and 'avoided' by pulling and pushing of the joystick.

Task Development: Stimuli. The final design resulted from several phases of pilot studies conducted at the University of Maryland, (UMD), College Park, at the Center for Addiction, Personality and Emotion Research. The goal of the first phase of the task development was to establish a comprehensive activity list which would cover

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a variety of experiences, hobbies and social activities. Because the objective of the experimental task was to examine subjects' responses to stimuli representing different activities that have been individually evaluated in terms of their appetitive value, the first step in developing the task was identifying the right set of stimuli. Ideally, the subjects would generate the stimuli themselves, by listing their favorite activities as well the activities they dislike and do not care about (neutral). This approach, however, would not guarantee obtaining neither a sufficient number nor the standard properties of the stimuli. For linguistic consistency, we decided to only use verbs and to limit stimuli to activities that can be presented as a single word, (e.g. exclude phrases such as 'going to the movies'). Another reason to limit the stimuli to single verbs was a concern that nouns or phrases introduce additional semantic processing variables which possibly engage different neural substrates (Shapiro et al., 2005) and as such would preclude applying the paradigm to neuroimaging studies.

The unique challenge was in creating the list of verbs that were likely to be rated as disliked, neutral or liked in sufficient numbers to ensure all three valence categories contained enough stimuli for the reaction time task. There were certainly assumptions made as far as which words were likely to generate negative or positive ratings, even though individual appeal of the activities was emphasized and an activity could be – and was expected to be –rated differently by different individuals. The initial list of 140 words was loosely based on Pleasant Events Schedule (Lewinsohn, 1975). The pilot studies with the word list were conducted as an extra credit assignment in a Social Psychology class. The students who wished to participate were asked to rate the initial list of 140 activity words as a paper and pencil questionnaire and to give each verb a

rating from -2 to +2 (don't like at all to like a lot) and had an opportunity to write in additional activities that they liked and disliked. The ratings for each word on a scale from -2 to + 2 were analyzed and found to have desired clusters around extreme values and around 0, suggesting sufficient variety of choices to categorize activities into liked, neutral and disliked.   The final list of 150 items used in BAMP study (Appendix, p. x) incorporated students' feedback and includes words depicting activities only recently introduced to popular culture such as 'blogging', 'texting' and 'tweeting'.

The next phase in the paradigm development was to implement a computerized version of the Word Rating Task to obtain individual ratings and to serve as a reaction task stimuli generating module. In this version of the task, each subject is presented with all of the 150, 2-4 syllable verbs such as 'bowling', 'hiking', 'cooking', one at a time on the computer screen, along with the rating choices of 'can't stand', 'don't like', 'neither like nor dislike', 'like', and 'like a lot', as well as a choice to 'skip'. To make a response, subjects were instructed to move the cursor to the appropriate rectangular button and to click the mouse. The subjects are allowed to skip up to 10 words if they had no experience with an activity or did not wish to rate one. This part of the experiment is not timed, the participants are encouraged to think about their own experiences with the activities represented by each word, and if a word is vague, for example, 'playing', to rate whatever activity this word brings up for them. 'Playing' may have multiple meanings, such as playing an instrument, playing a sport, playing cards or just having fun, and each subject was free to rate an activity that word uniquely represented for him. If a subjects had never engaged in an activity, the choice was to rate the potential experience based on knowledge, or to skip the word altogether. Full

instructions and the word list are included in the appendix. The illustration of the stimulus presentation for the Word Rating Task is in Figure i.

Task Development: Reaction Time Task. The next step in the development of BAMP was designing a reaction time task. The goal in this phase was to establish the task's sensitivity to independent variables of interest, depression and anhedonia, while measuring automatic tendencies to approach and avoid when responding to stimuli of varied valence. Two versions of the task were tested with the University of Maryland undergraduate students, recruited for participation in exchange for research credit and monetary compensation (first version) and research credit only (second version). The study was approved by the University of Maryland IRB (10-0429), PAS #3201.

The first version of the reaction time task was a Letter Case Decision Reaction Time Task (LCDRTT). Because the intrinsic approach motivation of liked versus neutral or not liked activities was of primary interest, the task was designed to elicit responses that were not explicitly related to stimulus valence, as this has already been established in the WRT. Hence, the design of the task was to elicit both approach and avoidance movement to the same activity word stimuli independently of word's meaning or valence. In this version, the subjects were asked to respond to the stimuli on the screen, the previously rated activity words presented one by one in either upper or lower case, depending on sensory features (upper or lower case). Whether the required response was to push to upper and pull to lower case font or vice versa was randomized between participants. The 15 stimulus words were presented twice each in both upper and lower case, thus regardless of randomization, each participant performed approach (pull) and avoidance (push) movements in response to words

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across three valence categories.   The total number of responses required of each

subject was 60 (30 pull and 30 push responses).

     After analyzing the data of 60 participants in the LCDRTT, we did not observe

the expected modulation of approach or avoidance responses by stimulus valence and

only significant finding was a main effect of direction (faster approach than avoidance,

t-test, *p<.03*). As a result, several modifications to the reaction time task design were

implemented. The task was changed from sensory based decision (upper case versus

lower case font) to lexical decision (word versus non-word) to enhance the depth of the

stimulus processing (McNamara & Altarriba, 1988). For this added non-word

condition, stimuli were generated by scrambling words used in each subject's reaction

time task, and constituted 30% of the total number of items.   We increased the number

of push and pull responses to words to 90. Hence, the total number of responses for

each subject was now 120, each activity word received 3 push and 3 pull responses and

each unique non-word received one push and one pull response. LDRTT is described

in further detail in the current study method section.

     Preliminary Study with the Revised BAMP task. A total of 105 UMD

undergraduate students participated in the study with the second version of the task,

Lexical Decision Reaction Time (LDRTT). In this non-clinical sample, we

hypothesized that the task conditions would differentially influence performance of

groups split at the clinical cutoff for mild depressive symptoms of 14 on the Beck

Depression Inventory II (BDI-II, Beck, Steer and Brown, 1996) (Low: N = 78,

M25/F53; Elevated: N=27, M6/F21). The initial RT (start of the movement) showed

main effect of stimulus valence (liked versus disliked), ANOVA, *p = 0.04* as well as

valenceXgroup interaction, $p = 0.02$. These results were driven by faster reaction time to disliked versus liked activities in the elevated BDI group (within subjects t-test, $p = 0.02$). We observed a non-significant trend for low BDI group to respond faster than high BDI group to liked stimuli (between subjects t-test, $p = 0.07$). Another outcome measure, response duration (RD, termination of response-initial RT), revealed an interaction of stimulus valence and movement direction (ANOVA, $p = 0.04$), and a non-significant trend for an effect of direction ($p = 0.08$) and toward a three way interaction of direction, valence and group ($p = 0.09$).

Results were driven by a significant difference between duration of responses to disliked words: longer in avoidance condition (pushing away) and shorter in approach condition (pulling toward) in the elevated BDI group (within subject t-test, $p = 0.02$). In the dislike away (avoidance) condition the difference between groups approached significance at $p = 0.06$ as the elevated BDI group tended to take more time than the low BDI group when pushing away in response to disliked activity words. Extended response duration may also indicate decrease in strength, and as such imply weaker avoidance of disliked activity stimulus in the high BDI group.

Furthermore, we explored the impact of anhedonia on the task performance. The participants were divided into high (N=51, 20M/31F) and low (N = 54, 11M/43F) level of anhedonia symptoms based on median split (score of 19) on combined Chapman Physical and Social Anhedonia Scale. The group with elevated anhedonia symptoms had also significantly lower appetitive motivation, reward reactivity, and overall depressive symptoms level. The results showed that the initial responses in push and pull conditions differed between subjects with low and high level of symptoms of

anhedonia. Low anhedonia subjects initiated approach faster than avoidance *(p = 0.05)* and subjects with elevated anhedonia symptoms were slower to initiate approach than subjects with low anhedonia symptoms *(p = 0.01)*. We found that both presence of depressive symptoms and presence of symptoms of anhedonia influenced performance on the Lexical Decision Reaction Time Task. With regards to depressive symptoms, our results of the initial RT pointed to a bias in the high BDI group to have a faster RT to words representing disliked versus liked activities and a tendency to respond slower than subjects with low BDI to liked activity words. Additionally, the analysis of RD showed a bias in high BDI group to process disliked word stimuli longer in the away condition than in the approach condition. This result could also imply weaker response to disliked activity words in the avoidance condition.

Despite the use of a nonclinical sample, a pattern of responses consistent with our prediction as well as the literature on negative processing bias in depression was evidenced in those above the clinical cutoff. The fact that this bias was elicited by stimuli which by themselves did not necessarily have inherent appetitive or aversive properties, but for which the valence is individually evaluated and assigned, suggests a broadening of the negativity bias. The response duration in avoidance of disliked activities condition hints at an interesting hypothesis that extensive engagement in avoidance of disliked may be consuming cognitive resources and diverting them from other activities.

The presence of anhedonia in our sample modulated a different aspect of the initial stimulus processing, namely initiation of movement direction. The slower approach and the faster avoidance in the high versus low anhedonia group suggested

that the initial, automated response to activity stimuli is to avoid them when anhedonia is high and approach them when anhedonia is low. Interestingly, this pattern is different from the pattern of responses related to overall symptoms of depression, where reaction times were modulated by the valence of the stimuli.

The conclusion of these preliminary studies was that performance on the behavioral approach/avoidance paradigm (BAMP) was differentially influenced by symptoms of depression and anhedonia in a non-clinical, unscreened sample of college students. Thus, we have achieved an objective of developing a task appropriate to conduct further study with the clinical population of depressed patients. Following these initial findings, the current study endeavored to utilize BAMP as a tool to experimentally assess approach of potentially rewarding activities as well as other aspects of approach and avoidance behavior in depressed patients with various levels of anhedonia symptoms.

Current Study, Aims and Hypotheses

As described in the previous section, we developed a novel experimental measure to assess approach and avoidance of stimuli representing individually relevant activities. In the course of preliminary investigations, we found that both depressive symptoms and anhedonia influence approach and avoidance of liked and disliked activity stimuli in college students. These findings led to the hypotheses that general depressive symptoms decrease reactivity to stimuli representing liked activities, and that anhedonia level primarily affects the drive to approach and engage irrespective of stimulus valence in MDD patients. At this stage, the current study will be limited to the behavioral investigation; however, the task is intended to be applicable to neuroimaging

study of approach versus avoidance response with the particular interest in circuits in basal ganglia, limbic system and prefrontal cortex. Given our preliminary results, we expected to demonstrate behavioral differences on the task between healthy subjects and depressed patients and to interpret the experimental results in relation to validated measures of constructs such as appetitive motivation and anticipatory anhedonia. The BAMP paradigm was set up to measure hedonic capacity (WRT), and four behaviors related to activity stimuli on LDRTT task: movement toward liked (approach of reinforcement), movement away from liked (avoidance of reinforcement), movement away from disliked (rejecting punishment), and movement toward disliked (approach of punishment). We expected patients to demonstrate reductions in both 'wanting' and 'liking' measures in relation to previously enjoyed activities. Furthermore, the BAMP paradigm was evaluated as a tool for evaluation of change in approach motivation following behavioral or pharmacological interventions in patients. Specifically, given a conceptual relation to behavioral activation intervention, BAMP could be especially useful in predicting response to BAT-D because of the conceptual link between the therapy aims and the task design.

Chapter 2: Method

Recruitment

The subjects for the current study were a subset of participants recruited for research studies at the National Institute of Mental Health by means of community advertising and internet advertising including the ClinicalTrials.gov website. Subjects contacted the mood disorder studies hotline or emailed moodresearch@mail.nih.gov and expressed their interest in participating in the studies as either healthy controls or as currently depressed individuals with a primary diagnosis of MDD. Individuals meeting eligibility criteria based on the phone interview were screened in person at the NIH Clinical Center. Those eligible for research under protocol 01-M-0254 were invited to take part in the BAMP study, upon signing of an additional NIMH protocol consent, 07-M-0021, entitled *Development of Functional and Structural Magnetic Resonance Imaging Techniques for the Study of Mood and Anxiety Disorders*. This protocol was specifically designed to enable testing of new neuroimaging and cognitive tools for application in research on depression. At the time of screening, which took place either at an NIH outpatient clinic or at an inpatient unit, all subjects underwent a thorough evaluation including a medical and psychiatric history, laboratory testing, drug screening and physical examination. The psychiatric diagnosis was established using the Structured Clinical Interview for DSM-IV (SCID-IV; First & Gibbon, 2004) and a semi-structured interview with a psychiatrist. Participants were excluded if they had serious suicidal ideation or behavior, major medical or neurological disorders, a history of drug or alcohol abuse within the past year, a lifetime history of drug or alcohol dependence, or current pregnancy or breastfeeding. Additional exclusions

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applied to the HC subjects included a history of any psychiatric disorder including alcohol or drug addiction, and having a first-degree relative with an Axis 1 diagnosis. The age eligibility was between 18 and 50. After signing the informed consent form, participants completed a 2 hour testing session which included self-ratings, questionnaires, two computerized tasks, and debriefing. Participants were compensated $40 for their time.

Participants

The total of 44 participants met all inclusion criteria and completed the study. There were 23 healthy controls, 14 males and 9 females, and 21 depressed patients, 13 males and 8 females. Of the MDD patients included in the study, 8 participated in other NIH outpatient protocols, and 13 were inpatients enrolled in experimental treatment protocols.

All depressed patients were medication-free at the time of testing for at least 14 days. Demographic information characterizing the sample is provided in Table i.

Assessment Measures

Selected approach/avoidance, mood and anhedonia measures were administered as a part of the study. For assessment of mood, we used Beck Depression Inventory-II (Beck, Steer, Ball, & Ranieri, 1996) which is composed of 21 questions related to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack enjoyment. This scale is one of the most widely used self-report inventories of

depressive symptoms for both clinical and research purposes. This scale has been used in research in both non-depressed and depressed populations.

In addition to the level of depressive symptoms, measures of anhedonia were of particular importance for this study. Initially developed for assessment of anhedonia in schizophrenia, the Chapman scales - Physical Anhedonia Scale / Social Anhedonia Scale (CPAS/CSAS) (Chapman, Chapman, & Raulin, 1976) were chosen for their broad exploration of hedonic process and distinction between social and physical anhedonia. They are thought to indicate a trait level hedonic capacity. These scales consist of 160 short statement sentences which subjects rate as true or false. To assess current (state level) hedonic capacity, Snaith Hamilton Pleasure Scale (SHAPS) was administered. The SHAPS consists of 14 items that are similar to those in CPAS and CSAS but rather than simple true/false items the scale offers four choices: strongly disagree, disagree, agree, and strongly agree. Each item is a simple sentence expressing enjoyment in an activity; for example 'I would enjoy my favorite TV program'. We used modified scoring of SHAPS (Snaith et al., 1995) on a 4 point scale rather than the two point scale, with 1 denoting the least and 4 the most anhedonic response.

The psychological processes underlying tendencies to approach and avoid activities and social situations are assessed by the BIS/BAS scales (Carver & White, 1994; Smillie & Jackson, 2005) and are thought to reflect motivational components of behavior. These scales are widely used to measure behavioral inhibition, behavioral activation and affective responses to rewarding activities as well as reward sensitivity. The Jackson Appetitive Motivation Scale was included as an established trait level measure of reward motivation (Jackson & Smillie, 2004; Smillie & Jackson, 2005).

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Experimental Task: BAMP (Word Rating Task, Lexical Decision Reaction Time Task). The final version of the BAMP task was administered to all participants in the study. The sessions were held in a quiet room either in an outpatient clinic area or on the inpatient unit. Each session started with participants performing the Word Rating Task (WRT). The development of the task was described in the prior sections of this manuscript. The computerized version was programmed in Visual Basic, with the output directed to Microsoft Access. The rating of each word by each participant was documented on a scale from 0 to 4 (most disliked to most liked). For stimulus presentation, we used lower case letters with a font size of 32 pt., white on black background. The screen had a resolution of 1024x760. After the WRT, and completion of self-measures and questionnaires, the lexical decision reaction time task (LDRTT) was administered. Before beginning the experiment, the subjects were asked to adjust their position in front of the standard 20 inch desktop computer screen such that they could comfortably move the Logitech ATK3 Joystick back and forth; the joystick was positioned between the subject and the computer screen. The joystick stand remained parallel to the edge of the table. The instructions emphasized moving the joystick away from or toward oneself as quickly and as accurately as possible in response to words versus non-words presented one at a time on the computer screen in push and pull conditions. Emphasis was placed on directionality in relation to self rather than simply instruction to perform push and pull, since it was found that manipulating task instructions can lead to re-categorization of approach and avoidance responses (Seibt, Neumann, Nussinson, & Strack, 2008). The instructions describing the task were presented on the computer screen and read out loud by the researcher or a research

assistant to ensure full understanding of the procedures. The subjects then had an

opportunity to practice push and pull conditions and ask question if anything was

unclear. Two blocks of the LDRTT task were administered in a randomized manner.

One of the blocks required pushing to words and pulling to non-words, the other one had

opposite instructions. The word stimuli were 15 words from 3 valence categories (liked,

neutral, disliked), and each one was shown 3 times per block. The 15 non-word stimuli

were created by scrambling the target words, and appeared once per block in each push

and pull condition. Hence, the non-words constituted 33% of the stimuli, and were

matched by sensory properties, number, size and shape of letters to the word stimuli.

The word or non-word stimuli stayed on the screen until a response was initiated, or 3s

elapsed. The fixation cross appeared on the screen between the trials for 5s. Each block

of the task took approximately 8 minutes to complete.

Data Analysis

Descriptive statistics (mean, SD) were calculated to characterize the sample and

between group differences in demographic variables were assessed by independent

samples t-tests, or Mann-Whitney U-tests where appropriate The experimental outcome

measures collected in WRT were ratings of activity words, and subsequent

classification of words into three categories, liked, neutral and disliked. Despite the

fact that the primary aim of WRT was for stimulus selection for LDRTT, the valence

ratings of activity words were of interest, as they represented the 'liking' component of

the task, and served as the measure of the subject's conscious (explicit) hedonic

capacity. Also, classifying items according to perceived emotional valence is an

important information processing step potentially influenced by mood and processing

bias. The numbers of words in liked and disliked categories were compared in patients versus healthy control groups using one-way ANOVA, followed by the post-hoc independent samples t-test to describe specific differences in the ratings. The numbers of words in liked and disliked categories were correlated with mood and anhedonia measures across all subjects using Pearson correlations.

For the LDRTT, both accuracy and reaction time (RT) data were collected. The accuracy was expected to be very high given preliminary results and ease of the task. The primary outcome measure of interest was reaction time, and specifically the time spent moving the joystick toward and away from self in response to liked and disliked stimuli. Consistent with previous research on approach and avoidance, only correct responses were included in the analyses (Bargh, Chaiken, Govender, & Pratto, 1992), also (Fazio, 1986).

We considered several approaches to the analysis of the RT and response duration data. A common problem with RT data is presence of outliers and skewed distribution of the response times. Ratcliff (Ratcliff, 1993) suggested that reasonable approaches to correcting for these problems include a general cut-off of a pre-defined duration, calculating data-specific cut offs (for example, based standard deviation), log transformation, and inverse transformation. Other considered approaches included analyzing median responses for each subject, as well as exclusion of extreme outliers based on visual inspection of results (R. Krieglmeyer et al., 2010). In this study reaction time analysis was conducted on log10 transformed values for each task condition, similar to the analyses conducted in the preliminary studies. Response duration, which reflects the entire process of active approach and avoidance of liked

and disliked stimuli, was used as the primary outcome measure. Even though the initial RT is the most established measure of cognitive processing efficiency, it only reflects the onset of movement of the joystick after the presentation of the stimulus. Given that our hypotheses focused on the approach and avoidance actions in response to the stimulus, the measurement of the complete movement toward or away from the stimulus was of central interest. The RD was computed by subtracting the time to initiate a response (classic reaction time) from the time at which the movement of the joystick was complete, which corresponds to releasing the joystick when it reached the maximum extension allowed by the device or when the subject terminated movement and released pressure. This reaction time related variable can be also conceptualized as response force (RF) and is thought to reflect important psychological processes and provides a more complete picture of approach and avoidance motor behavior (Puca, Rinkenauer, & Breidenstein, 2006). Some studies refer to this variable as 'movement time' (MT) (Roelofs, Elzinga, & Rotteveel, 2005)   The response duration was computed from log10 transformed values.

A total of 5280 responses to stimuli in LRDT task were obtained from 44 participants: 120 responses per person, 60 away and 60 toward, 45 to words and 15 to non-words in each direction. Data was inspected for outliers by examining initial reaction time and removing responses faster than 200 ms and slower than 3000 ms. Only 4 responses were <200 ms and 2>than 3000 ms. Response times in that broad acceptable range were then log10 transformed to minimize the impact of outliers. In the next step, the incorrect responses were removed because movement direction which determined correct response was considered a separate variable. The final steps in

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calculating the RD for each subject and each stimulus was converting the time of termination of the response to log 10 value, and subtracting from the log 10 response termination time the converted RT value. All analyses were conducted on RT and RD values using SPSS 20 software. The principal analysis was a repeated measures analysis of variance (ANOVA) to investigate the effects of group (depressed versus healthy), movement direction (toward and away) and valence (liked, neutral and disliked) on performance. Post-hoc t-tests were planned to investigate specific effects. The analyses were performed with and without inclusion of the neutral condition and are presented here for liked and disliked conditions only. Previous research has shown that the neutral condition may assume either appetitive or aversive stimulus properties and the perception of a neutral stimulus may be subject to bias (Jukka M. Leppänen et al., 2004).

To further assess approach motivation for potentially rewarding activities, we planned a correlation between the experimental results of LDRTT and a self-report measure of appetitive motivation. For that purpose we chose the JAMS, as a scale most closely reflecting the construct of interest, and used Pearson's r test to correlate JAMS score and response duration for four task conditions, approach of liked and disliked, and avoidance of liked and disliked.

Chapter 3: Results

Experimental Findings: Word Rating Task

The results of the WRT revealed differences in the number of activities considered liked and disliked between healthy controls and depressed patients (one-way ANOVA, $p < 0.01$): healthy controls rated more activities as liked than MDD patients, while MDD patients rated more activities as disliked. Nevertheless, both groups rated more activities as liked than disliked, ($p < 0.001$), see Figure iv.

Exploratory post-hoc correlational analysis revealed a relation between the number of activities rated as liked to greater appetitive motivation (JAMS), higher level of activation (BAS), lower level of anhedonia (SHAPS and Chapman scales), and less behavioral inhibition (BIS) and lower level of depressive symptoms (BDI), $p < 0.03$. The opposite pattern was true for the number of activities rated as disliked ($p < 0.005$).

The correlations are depicted in tables ii and iii, p.75-76.

Experimental Finding: Lexical Decision Reaction Time Task

BAMP LDRTT Task Accuracy. As expected, the accuracy of the task performance was high across both groups and all conditions including non-words; 124 of the total of 5280 (2.3%) responses were incorrect. The proportion of errors in approach and avoidance conditions did not differ between healthy controls and patients, $p > .07$, nor did the performance on non-word trials ($p > .05$).

BAMP Task Reaction Time. The analysis of the initial reaction time for 4 experimental conditions (away liked, toward liked, away disliked, and toward disliked) showed a 3 way interaction (valence by direction by group), $[F(1,42) = 4.608, p = 0.04]$.

However, no significant difference was found in direct comparisons between groups or within groups, $p > 0.07$, hence this interaction cannot be interpreted. The analysis of the primary experimental outcome of response duration, approached but did not meet the threshold for significance for the main effect of valence [$F(1/42) = 2.904$, $p = 0.10$] and a significant three way interaction (valence by direction by group), [$F(1,42) = 8.714$, $p < 0.01$]. Follow-up t-tests showed no differences between groups (healthy controls, depressed patients) in performance on any of the 4 conditions ($p > 0.10$). Within group paired comparisons showed a significant difference on response duration in approaching versus avoiding disliked activity stimuli in depressed patients ($t = 2.410$, $p = 0.03$). The response was shorter (movement was stronger) *toward* disliked stimuli than *away* from disliked stimuli. Also in depressed patients, faster approach of the disliked versus liked stimuli did not meet the threshold for significance ($t = -1.83$, $p = 0.08$), see Figure iv.

Approach Motivation and Lexical Decision Reaction Time Task

The post-hoc analyses were conducted to examine the nature of the relationship of the experimental outcome measures on LDRTT with subjective ratings of the constructs of interest: anhedonia and appetitive motivation. The correlations of self-ratings and the response duration in the four examined conditions (approach/avoid liked, approach/avoid disliked) were conducted across all subjects. Response duration of pushing joystick away in response to the liked activity stimuli correlated positively with the scores on Jackson Appetitive Motivation Scale, $r = .41$, $p < 0.01$ (Figure iv). Weaker/slower movement away from stimuli rated as liked is hence correlated with higher appetitive motivation.

Chapter 4: Discussion

Study Findings and Conclusions

The current work was undertaken to develop a behavioral task to examine how depression and anhedonia influence behavioral approach and avoidance of individually relevant liked and disliked activities in currently depressed patients. Initial pilot studies were conducted to establish the psychometric soundness of the tasks. Specifically, results indicated the tasks sensitivity to depressive symptoms and anhedonia level in an unscreened sample of undergraduate college students.

Based on the results of these pilot studies and empirically-based task modifications, the primary study presented here was conducted in a clinical setting with screened healthy controls and un-medicated patients with MDD to elucidate differences in approach and avoidance of liked and disliked activities represented by previously rated activity words. We were also interested in performance on the BAMP tasks in terms of separating the 'liking' and 'wanting' components of the reward related behavior of depressed individuals.

The tasks were completed by all participants enrolled in the study with very high accuracy across all task conditions. The response duration analysis results showed significant impact of experimental conditions (direction of movement, valence) and diagnostic status (MDD versus healthy) on performance. However, no direct between group comparisons showed significant differences in approach and avoidance of liked and disliked activities. Given lack of statistical significance, we cannot interpret patterns of responses between the two groups. Nevertheless, we found a pattern within the depressed group of responding significantly faster/stronger when approaching rather

than avoiding unpleasant activities. This may indicate that in the initial stages of evaluating a potential reinforcer, attention and action is being drawn to the negative. Such behavior possibly jeopardizes chances of pursuing the liked, even if the approach of the liked experiences is not compromised. This result could also point to decreased ability of depressed patients to avoid what they themselves identify as unpleasant; this could be a deficit in negative reinforcement response, not stopping/withdrawing from unpleasant stimulus, or compromised punishment learning at the automated level of response.

Assessment of Liking and Wanting. Our study showed how 'liking' and 'wanting' may be impacted in MDD and relates to anhedonia. 'Liking' was tested explicitly in the WRT. Of the 150 arbitrarily selected activity words, depressed patients rated significantly more words as disliked, and significantly fewer of them as liked compared to the healthy controls. Hence, the environment as perceived by the depressed patient has fewer identified reinforcers. Nevertheless, MDD patients still rated significantly more activities as 'liked' than disliked. We relied on subjective ratings, thus we cannot make any conclusions if the 'liking' (or disliking) ratings had truly the same hedonic value for the patients and healthy controls. Most studies, however, do not address this potential issue, and use stimuli generally accepted as liked or disliked (for example, positive or negative facial expressions) or assume motivational salience as positive or negative (gaining versus losing money). We conclude that the hedonic range of MDD patients is narrower than that of healthy controls, as fewer activities are found as potentially reinforcing, and more as aversive and potentially punishing.

In addition to the limited perceived reinforcement opportunities, the patients' 'wanting' behavior may further undermine their access to potentially rewarding activities. On the LDRT task, MDD patients demonstrated automatic pursuit of *disliked* experiences, and thus depressed individuals' 'wanting' appeared misdirected toward what they themselves rated as undesirable. This counter- productive process may be depleting one's resources or require more conscious effort to recognize and re-direct automatic tendency away from what does not have the potential for pleasure. The tendency to be slow in avoiding the unpleasant coupled with the tendency to approach the disliked faster than the liked is an interesting finding implying the role of *negative* rather than just the limited positive environmental interaction in explaining the 'lack of interest or pleasure' core symptom of MDD.

Automaticity and Negativity Bias. As designed, our reaction time task examined the *implicit* impact of stimulus salience and an early phase of interacting with an activity stimulus. Whether an activity was liked or disliked was not relevant to the approach or avoidance movement, only the lexical decision was associated with the response type. Hence, our task examined automated tendencies to approach/avoid the liked and approach/avoid the disliked. Surprisingly, and contrary to our hypothesis, the approach of liked on our task was not altered in MDD patients, and equaled the approach of liked of the healthy sample. Instead, the primary difference was an automated preference towards disliked stimuli in the MDD patients. There are circumstances under which a preference toward 'disliked' or 'less liked' is a desired response. For example, a dieter may have a stronger response to non-preferred food because of the self-control consistent with a stated weight loss goal, and a student may choose to engage in a less liked

activity for the sake of achieving a long term goal which influences the current

motivational state (Fishbach & Shah, 2006). In case of the depressed patients seemingly

preferring approach of activities they dislike, such a goal state could be hypothesized to

be the maintenance of depressed mood by seeking out experiences not likely to bring

pleasure and to confirm the biased, negative view of the environment. There is evidence

of preferences of depressed individuals to engage in depression perpetuating ruminations

(Nolen-Hoeksema, 1991) and tendencies to selectively attend to, remember and interpret

events in a way that is congruent with the negative mood state (J. M. Williams, Mathews,

& MacLeod, 1996; Wray, Freund, & Dougher, 2009). It could be further hypothesized

that the cognitive resources, given the cognitive biases, are misdirected toward

experiences which are non-reinforcing or punishing to *not* give oneself a chance to

experience pleasure even if capable to do so. The hedonic principle – repeating

behaviors that can lead to pleasure, may have been replaced by the 'anti-hedonic'

principle – repeating behaviors likely to result in negative experience and maintain

negative view of self, the world and the environment.

Complexity of Avoidance Behavior. Another aspect potentially related to the

question of anhedonia is the ability to avoid what is negative and unpleasant in one's

environment and to seek out the positive. The findings in our study contrast with the

theories in the literature pointing to enhanced avoidance in MDD. For example, Ferster's

model of depression (Ferster, 1973) states that the depressed person engages in a high

frequency of avoidance and escape from aversive internal and external stimuli with such

behaviors as withdrawing or complaining, and that these efforts preempt positively

reinforced behavior. Hence, excessive engagement in avoidance of unpleasant may

compromise access to positive and pleasurable experiences. On our task, however, depressed patients showed a different behavior: weak avoidance of disliked activities. This finding will need to be replicated and clarified, as this may be characteristic of early automated behavior, or have to do with what we define as approach or avoidance behavior. Let's consider a situation where instead of going out with friends (which is a liked activity) one choses to stay home and complain, as in Ferster's (1973) example, 'Complaints and other negatively reinforced components of the depressed person's repertoire are sometimes accompanied by high frequencies of agitated activities such as hand wringing, pacing, or compulsive talking' (p.858). The chosen behavior might be viewed a replacement of approach of liked (going out with friends) by non-avoidance of, or engagement in, what one would most likely rated as not liked (staying home alone, pacing or complaining). Failure to avoid negativity has been previously demonstrated in depression (Joorman, 2005), and here we demonstrated that the negativity may be automatically approached rather than avoided. Thus, motivation for seeking out unpleasant, punishing experiences, or not resisting what's an easy albeit not liked option could be reflected in the response pattern we observed in MDD. Consequently, insufficient resources may be left to pursue positive activities. This finding can be also interpreted in terms of negative bias in depressed individuals: expanding negative bias beyond influence on perceptual, cognitive and memory functions and also driving a choice of activity engagement.

Appetitive Motivation Correlates. Yet another aspect of pursuing reward/reinforcement in the environment emerged from our study. We tested whether the level of appetitive motivation is related to approach and avoidance behavior, and found

the effects in a condition of avoidance of liked stimuli, and relation of greater *reluctance* to avoid what one likes to appetitive motivation across all subjects. An individual who is sensitive to opportunities to engage in one of their favorite activities will not want to reject them, consistent with the response elicited by our task: HC subjects had high appetitive motivation scores and slow avoidance response to words representing favorite activities, and MDD patient had lower scores on appetitive motivation scale, and faster avoidance response to their favorite activity words. We concluded that in terms of responsivity to positive reinforcement and motivation for positive experiences, depressed individuals may be prompt to reject environmental opportunities. Previously, research demonstrated that MDD patients may fear failure and thus avoid engagement even if an opportunity presents itself (Hopko, Armento, et al., 2003), however, our LDRTT task tested automated process unlikely to involve an extensive cognitive evaluation and could be interpreted as 'lack of positive' bias demonstrated in previous studies (Joormann, Talbot, & Gotlib, 2007; Pizzagalli et al., 2008).

As noted before, our study focused on examining the act of the initial approach/avoidance rather than actual participation and sustained or recurrent engagement. This mostly automated reaction to external stimuli under the task instructions emphasizing accuracy and speed is an early aspect of approaching and engaging. Furthermore, we did not study spontaneous actions but rather actions driven by task conditions. Nevertheless, the performance of these actions was modulated by the personally relevant valence of the activity word stimuli. As in previous experimental studies where emotional content of stimuli was manipulated, we found evidence of the negative attentional and cognitive biases in MDD. Our research was principally

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motivated by the question of why depressed individuals stop participating in activities that have previously been a source of pleasure and enjoyment. We also posed the question whether this lack of participation was a result of no longer 'liking' the activity, or not having the motivation to take action. In terms of the 'liking' and 'wanting' model, our findings point to a possible alteration of hedonic principle in the major depression, namely, wanting the disliked. A question emerging from this study is whether allocation of cognitive resources to seek out punishing experiences, consistent with the negative mood state takes away such resources away from pursuing reinforcement. If confirmed, that would indicate an additional dimension to the concept of anhedonia – inability to enjoy, because what is potentially enjoyable is not attended to while the resources are devoted to the disliked in the environment.

Approach Motivation and Reinforcement. Regarding motivational aspect of the reward relevant behavior, we did not find evidence of diminished reward approach motivation on the experimental task, as no difference of approach of liked items emerged between the groups. However, we found evidence of increase in punishment motivation, as evident by faster approach of disliked and slower avoidance of disliked in the MDD group. The overall conclusion of this study based on the findings in our sample is that in Major Depressive Disorder, narrower hedonic range of activities and a tendency to approach what's negative rather than reinforcing may undermine the role of the positive behavioral approach motivation and limit access to the potentially reinforcing activities. The approach motivation itself may not be compromised, but could be overshadowed or replaced by automated tendencies of approaching the negative. Such use of cognitive

resources may serve as a mechanism of maintaining lack of interest or pleasure, in a similar way to how ruminations and depressive cognitions maintain depressed mood.

Strengths and Limitations

Several strengths of this study can be noted: we operationalized an important concept of 'liking' and 'wanting' which has emerged from the reward processing literature and applied this concept to study anhedonia in MDD. The activity word rating part of the study enabled us to assess activity 'liking' directly and to validate the process of selecting 'liked' stimuli pool by delegating this task to the participants themselves. The 'wanting' aspect was studied as movement toward self in response to the activity stimulus. Additionally, our operational definition of behavioral approach motivation as a physical movement toward a stimulus representing individually relevant activities was to our knowledge the first laboratory experiment which attempted to precisely model action toward liked activity in depressed patients. Previous studies used more distant proxies of desirable stimuli (happy faces, emotional words, monetary incentive).

Furthermore, this study was conducted with medication-free MDD patient sample and rigorously screened healthy controls allowing us to clearly define population of interest and limit variability related to medication in MDD and familial depression risk in HC, essential for examining basic bio-behavioral process of approach of potential reinforcement and punishment.

The current study had several limitations. The first set of limitations is related to the apparatus used to record reaction time measures. In administering the task steps were taken to ensure the standard administration procedure and both the joystick and

screen position were the same for all participants, the testing took part in different rooms and the testing apparatus had to be set up every time. Given different testing conditions there may have been more variability in the spatial relations of the subject and the apparatus. Also, the standard ATK3 joystick was used with the same resistance setting for all participants, and the movement toward and away was distinct, however, the movement to the sides was not restricted and may have introduced additional error of measurement. A more sensitive joystick providing only movement directly toward and away might further improve sensitivity and decrease variance of the responses due to the apparatus properties.

The second set of limitations is related to the sample size and sample composition. Based on the preliminary studies, we aimed at recruiting 30 subjects per group of healthy controls and MDD patients in order to demonstrate an expected moderate, statistically significant effect size. We were unable to reach this recruitment goal. Hence, our study may have been underpowered. Increasing sample size would help to clarify the results which in our study approached but did not reach statistical significance. Furthermore, our groups were equivalent in the numbers of males and females, however, the number of males exceeded the number of females. The epidemiology of MDD indicates higher prevalence of MDD among women than men, hence increasing the number of females in the study would improve generalizability of the results.

Implications and Future Directions

Clinical Implications. Our findings have implications for cognitive - behavioral interventions such as BATD and suggest steps which would be easy to implement by

therapists. We demonstrated reluctance to avoid disliked activities by MDD patients, hence, besides selecting activity goals to engage in, appropriate *avoidance* goals could be reasonably set, to allow for better resource allocation. This could be achieved by identifying activities which do not foster well-being and positive experiences, nor are subjectively pleasurable, yet may be accessible and available. Typically, the patients identify relations between life areas, values and activities which foster wellbeing and health; participation in these activities becomes a goal to be pursued in the course of treatment (Lejuez, Hopko, Acierno, Daughters, & Pagoto, 2011). Daily monitoring includes keeping track of the goal activities performed and rating of enjoyment and importance. Conceptually, BAT-D does raise an issue of unproductive and detrimental activities and encourages reducing time spent in less valued activities to make room for high reinforcement value activities, and better time management to re-direct resources toward desired and identified goals. It is conceivable that for many participants choosing goals and streamlining efforts toward positive is sufficient, as evident by studies of effectiveness of BATD. For some patients, however, further examination of barriers to pleasure might be advisable, and automatic approach and possible engagement in the negative activities could be identified and addressed. For example, if a patient does not manage to engage in goal activities as planned, it is important to find out what was done instead, and to what degree these alternative activities can be eliminated if they do not contribute to patient's wellbeing and consume time and resources. Certain disliked activities may have to be performed as a part of a daily life, for example paying bills, cleaning an apartment or interacting with difficult co-workers. Keeping track of engagement in 'disliked', whether by choice or necessity could

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provide valuable information on resource allocation. Then, steps could be taken toward

elimination or efficient completion of such of activities, which might free time and

energy for the pursuit of what one likes.

Our study found that appetitive motivation is related to non-avoidance of

favorite activities, and that the MDD patients show a strong automatic avoidance

response to their favorite activities. This tendency toward avoidance of reinforcement is

already a known therapeutic target in BA, however, knowledge of the automatic reaction

of reinforcement avoidance may inspire additional exploration of prompt rejection of

opportunities if the patient fails to follow through on their engagement goals.

Clinical Research Implications. As the treatment of MDD becomes more specific

in addressing symptoms in a personalized manner, BAMP paradigm could help address a

question of behavioral activation in the treatment of anhedonia. For example, increasing

activation – be either pharmacological means, with DA augmentation or behavioral

activation could be beneficial if the approach is reduced, but the capacity to enjoy is

retained. However, if there is indeed little deficit in the capacity to approach the liked

activities, but a tendency to approach the disliked is stronger (which we observed at our

study at a trend level), this could shed light on why dopaminergic drugs are not as

effective as they should be given DA role in increasing motivation for rewards. A study

with DA augmentation in conjunction with BAMP performance in healthy and depressed

groups might be valuable in further evaluation of the DA role in anhedonia: we would

not expect an increase in hedonic range (WRT), but we would expect effects on approach

behavior (LDRTT). The differences between groups would be expected with regards to the effect magnitude, as previous studies showed differential responses on rating of euphoria and reward responsivity.

Our findings could also help explain why BA does not work for some patients who can't sufficiently experience positive reinforcement effects despite adequate compliance with the treatment.   Increase in activation and approach without change in the negative bias and hedonic capacity could be hypothesized as reasons for negative outcomes in some patients; BAMP as well as anhedonia, approach and avoidance measures before and after interventions could be used to test this hypothesis, and possibly characterize the patient for whom activation therapy is a promising intervention.   Furthermore, the cognitive resource distribution in relation to approach and avoidance of environmental opportunities should be further examined. A study of cognitive resource allocation under conditions of high interference (Levens, Muhtadie, & Gotlib, 2009) demonstrated that higher levels of rumination correlated with poor performance on a cognitive task requiring high but not low level of engagement, suggesting that MDD patients were inefficient in performing an attentional task and that disengaging from negative interferes with goal-directed behavior (Kaiser et al., 2014).   While no difference was found in faster approach to negative over liked activity stimuli, the effect did approach significance and could be important to follow up in future studies.

From a perspective of advancing knowledge about the symptom of anhedonia for the clinical field, future studies should further explore the role of weak avoidance of negative, disliked activities, and relative strength of approaching self-defeating situations as contributing processes to 'lack of interest or pleasure' symptomatology. If the

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capacity to experience pleasure, 'liking' is there (even for fewer activities), and the approach of liked activities, 'wanting' is not altered, the question becomes of allocating resources toward mood maintaining environmental experiences. We have examined this process on implicit, mostly automated level. Adding an explicit approach/avoidance condition utilizing similar stimuli, possibly with feedback (such as enlarging stimulus as it is approached or decreasing in size when avoided) would help with clarifying whether the bias toward approaching the negative is altered at explicit processing level which could be potentially related to sustained engagement in negative versus positive activities.

Avoidance behavior in depression has not been sufficiently studied and is difficult to assess (Trew, 2011). Our study identified two types of avoidance behavior which may be detrimental to patients well-being and contribute to anhedonic symptoms: avoidance of liked activities and lack of avoidance of disliked activities. BAMP paradigm could help in examining the neural correlates of these avoidance processes in healthy and depressed individuals. Based on previous studies, we would expect the effects to involve the putative avoidance network, Clinically, it would be expected that in the course of BAT-D, avoidance would decrease and appetitive motivation and approach of positive activities would increase, hence the BAMP paradigm could be used before and after BAT-D therapy for examination of the effects this therapeutic intervention. Even though such studies have been conducted using monetary reward paradigm and emotion priming paradigm (G. S. Dichter, Felder, & Smoski, 2010; Gabriel S. Dichter et al., 2009), and response to music in a single subject (Gawrysiak et al., 2012), use of BAMP would be novel because of the close conceptual association of

the task and the intervention. The WRT effects could involve the amygdala especially during evaluation of disliked vs liked words, and LDRTT would be expected in the areas specifically associated with approach and avoidance and affective stimulus evaluation (Spielberg et al., 2012) : pre-frontal cortex, middle frontal gyrus, lateralized to the right for unpleasant activity and avoidance, and lateralized to the left for pleasant emotion and approach.   We would also expect the involvement of ACC in performance of both tasks as an area implicated integrating emotions and decisions.

   Tasks Applications. In addition to study of neural correlates of BATD, both components of BAMP paradigm have a potential for a wider application. We found significant effects of diagnosis on WRT, a finding consistent with theories emphasizing importance of evaluative categorization of stimuli and situations into the positive and negative dimensions. In our study, we utilized activity words to closer approximate action relevance of the experimental stimuli, and found that for this particular type of word stimuli the classification outcome is highly related to measures of anhedonia, approach motivation and reward sensitivity. WRT should be studied for its potential to measure hedonic capacity.

   This simple task could be utilized with various populations including severe disorders because it is easy to administer and not demanding. Use with the neuroimaging techniques such as fMRI or EEG/MEG would help discerning if the action word classification is different from typically used positive/negative words and constitutes a qualitatively different type of negativity bias. Other types of stimuli, for example sets of activity pictures, could be rated in addition to words. The word list

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could be adapted for repeated use (by developing additional versions containing unique subsets of verbs) and administered during and post treatment to enable to evaluate change in approach motivation, anhedonia and anti-depressant treatment response; for this purpose, the word list could be altered to contain a certain percentage of novel activity words each time it would be administered. Alternatively, the same list of words could be tested to determine if adding the novel items is necessary.

The reaction time task met our expectations of sensitivity to depression, approach and avoidance and individually rated valence as the results showed a three way interaction of diagnosis, direction of movement and activity valence. However, the post-hoc tests were only significant for one comparison within the depressed group. It would be of importance to replicate the results with a larger sample of subjects to further validate LDRTT as tools for investigating specific constructs: appetitive motivation (LDRTT, avoidance of liked), failure to reject punishment (LDRTT, avoidance of disliked), punishment seeking (LDRTT, approach of disliked).   An important future study should follow up the unexpected finding of lack of effect on actual approach of potentially rewarding activities (LDRTT, approach of liked). In this study we focused on implicit, automated level processing, and our findings may be specific to the phase of approach behavior. Adding an explicit approach/avoidance condition utilizing similar stimuli would help with clarifying whether the bias toward approaching rather than avoiding the negative is also evident at an explicit processing level. Results of a study comparing automated and decision based approach responses in MDD would inform intervention strategies regarding how negative and positive activities are identified, chosen and sustained.

MDD is a disorder which impacts one's view of self, the world and the future, and for many diminishes the very essence of existence – the ability to enjoy life. This diagnostically defined single symptom of 'loss of interest or pleasure' may entail unexpected complexity and contradictions. We conclude that both approach and avoidance behavioral changes in depressed individuals identified in our experiments may contribute to inadequate engagement in reinforcing activities in their everyday life, and that further research on these components could ultimately lead to better interventions for anhedonia in MDD.

Tables

Table i

Demographic information

	Overall (n =44)	HC (n =23)	MDD (n =21)	Statistic	p value
Demographics					
Age, mean (SD)	33.6(7.9)	31.8(8.0)	35.5(7.5)	t(42)	.12
Gender					
Male, %	61.4	56.5	61.9		.94*
Female, %	38.6	43.5	38.1		
Education, years	16.7(2.3)	17.1(1.8)	16.32.8)	t(42)	.31
Assesments					
BDI-II	16.5(17.0)	1.7(2.8)	32.7(9.5)	t(42)	.00
SNAITH-S	28.3(10.5)	19.6(5.0)	37.8(5.6)	t(42)	.00
JAMS	12.7(3.8)	15.3(2.5)	9.9(2.8)	t(42)	.00
BAS-drive	9.8(3.1)	11.3(2.6)	8.1(2.7)	t(42)	.00
BAS-reward	15.8(3.6)	18.0(1.9)	13.5(3.5)	t(42)	.00
BAS-fun	10.3(2.9)	11.8(2.1)	8.7(2.8)	t(42)	.00
BIS	21.4(5.0)	18.4(4.2)	24.6(3.7)	t(42)	.00
BAS total	36.0(8.2)	41.1(5.2)	30.3(7.1)	t(42)	.00
Chapman Social Anhedonia	13.3(10.1)	6.7(4.8)	20.6(9.3)	t(42)	.00
Chapman Physical Anhedonia	15.3(11.8)	9.1(6.4)	22.0(12.7)	t(42)	.00
Chapman Anhedonia Total	28.4(21.0)	15.5(9.8)	42.6(21.1)	t(42)	.00

*Mann-Whitney U

Table ii

Correlations of the number of activity words rated as 'Liked' and self-report measures for all participants (N=44).

	1	2	3	4	5	6	7	8	9	10	11	12
1.WORDS_LIKE	--	-.532***	.581***	.434**	.435**	.540***	.551***	-.260	-.635***	-.642***	-.667***	-.496**
2.SNAITH_S		--	-.648***	-.506***	-.436**	-.704***	-.650***	.507***	.676***	.605***	.664***	.854***
3.JAMS			--	.535***	.753***	.656***	.753***	-.492**	-.551***	-.540***	-.566***	-.711***
4.BAS_Drive				--	.601***	.570***	.835***	-.297	-.321*	-.269	-.310*	-.592***
5.BAS_Fun					--	.650***	.862***	-.374**	-.355*	-.329*	-.354*	-.535***
6.BAS_Reward						--	.878***	-.397**	-.582***	-.577***	-.605***	-.650***
7.BAS_total							--	-.416**	-.499**	-.468**	-.504***	-.693***
8.BIS								--	.392**	.269	.342*	.678***
9.CH_socA									--	.844***	.956***	.666***
10.CH_phyA										--	.963***	.494**
11.CH_totA											--	.602***
12.BDI-II												--

***p < .001; ** p < .01, * p < .05

Table iii

Correlations of the number of activity words rated as 'Disliked' and self-report measures for all participants (N=44).

	1	2	3	4	5	6	7	8	9	10	11	12
1.WORDS_LIKE	--	.487**	-.476**	-.378*	-.362*	-.467**	-.473**	.401**	.530***	.500**	.532***	.506***
2.SNAITH_S		--	-.648***	-.506***	-.436**	-.704***	-.650***	.507***	.676***	.605***	.664***	.854***
3.JAMS			--	.535***	.753***	.656***	.753***	-.492**	-.551***	-.540***	-.566***	-.711***
4.BAS_Drive				--	.601***	.570***	.835***	-.297	-.321*	-.269	-.310*	-.592***
5.BAS_Fun					--	.650***	.862***	-.374**	-.355*	-.329*	-.354*	-.535***
6.BAS_Reward						--	.878***	-.397**	-.582***	-.577***	-.605***	-.650***
7.BAS_total							--	-.416**	-.499**	-.468**	-.504***	-.693***
8.BIS								--	.392**	.269	.342*	.678***
9.CH_socA									--	.844***	.956***	.666***
10.CH_phyA										--	.963***	.494**
11.CH_totA											--	.602***
12.BDI-II												--

***p < .001; ** p < .01, * p < .05
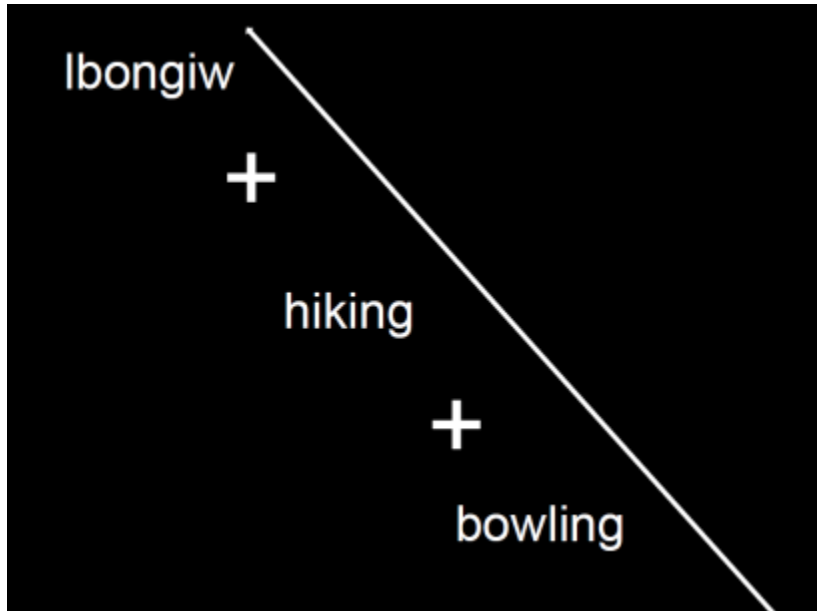
Figures

Figure i

An example of a trial in the Word Rating Task

After reading the instructions to rate each word and to evaluate how much they

'like' an activity each word represents, subjects were shown a Likert scale giving them an

option of 5 ratings. They were allowed to skip up to 10 words. This part of the

experiment was not timed, and the display stayed on until a subject responded with

clicking the mouse while the cursor was positioned on one of the rectangles. The cursor
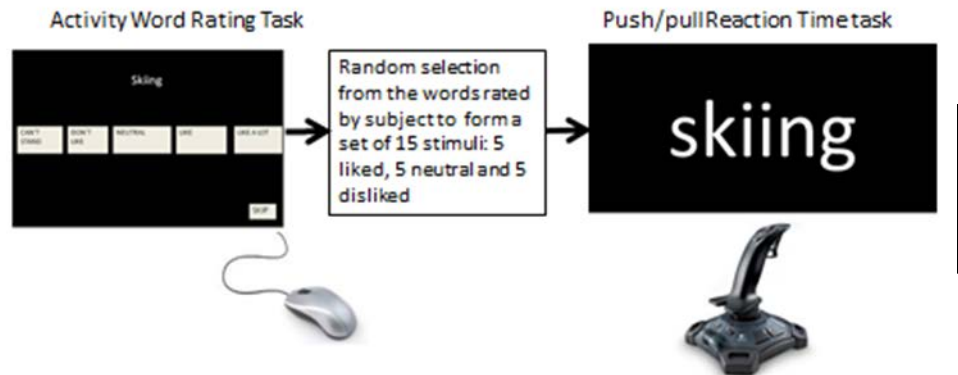
resets after each item.

Figure ii

Illustration of Lexical Decision Reaction Time Task

The subjects were required to make a decision whether an item was a word or a non-word, and push or pull the joystick depending on the item category.

Figure iii

2 components of BAMP

Activity Word Rating Task

Skiing

Random selection from the words rated by subject to form a set of 15 stimuli: 5 liked, 5 neutral and 5 disliked
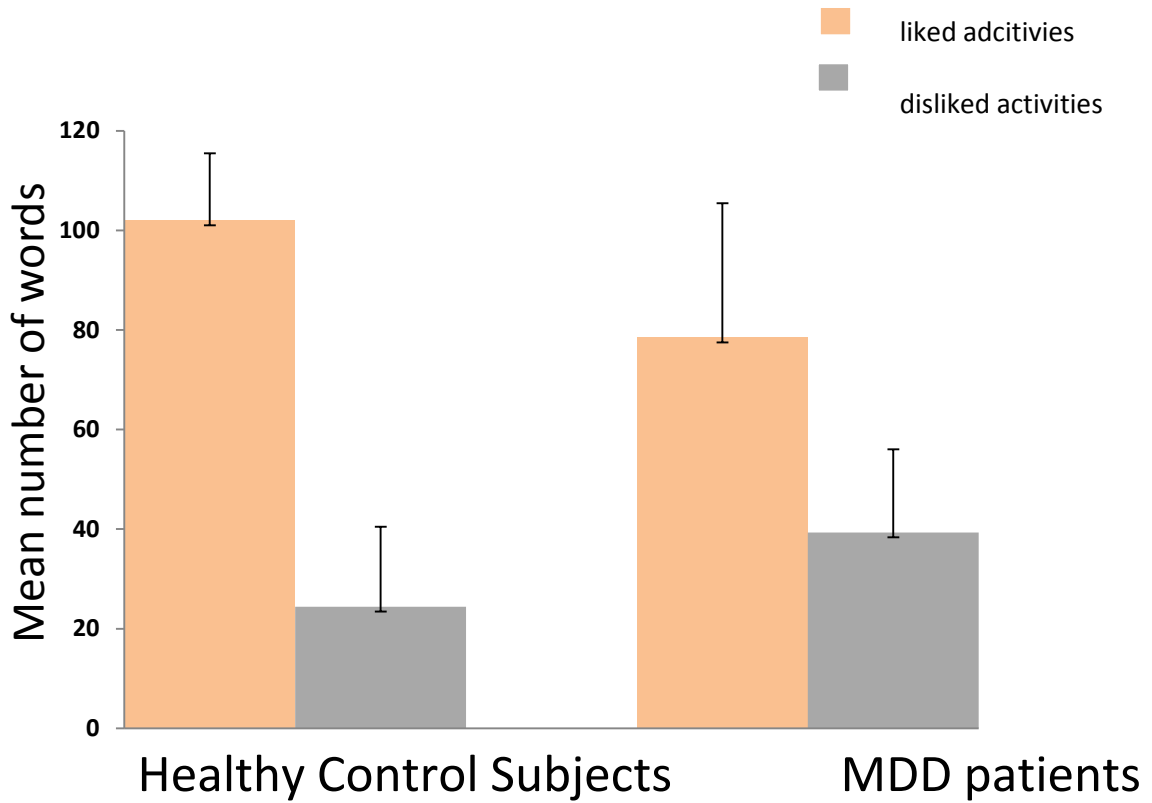
Push/pull Reaction Time task

skiing

BAMP includes two tasks: in Activity Word Rating Task, subjects rate 'liking' of 150 words. 15 words are subsequently used in the Reaction Time task. Each stimulus word is 'approached' and 'avoided' by pulling and pushing of the joystick.

and pushing of the joystick.

Figure iv
Results of activity word rating task. HC rated more words as liked and fewer than disliked than MDD patients.
Both groups rated more words as liked than disliked.

'liking' of 150 words. 15 words are subsequently used in the Reaction Time task. Each stimulus word is 'approached' and 'avoided' by pulling and pushing of the joystick.

Figure v *Approach and avoidance of liked and disliked stimuli. Response duration: group x direction x valence, p < 0.01*
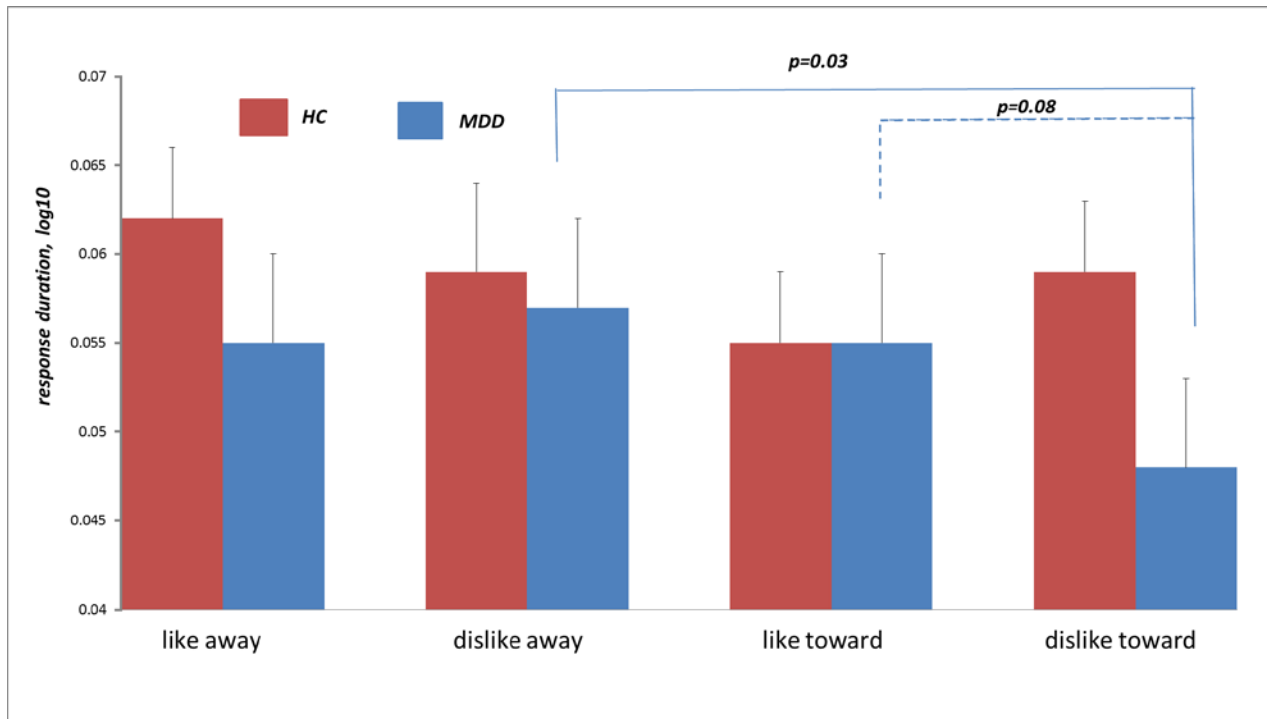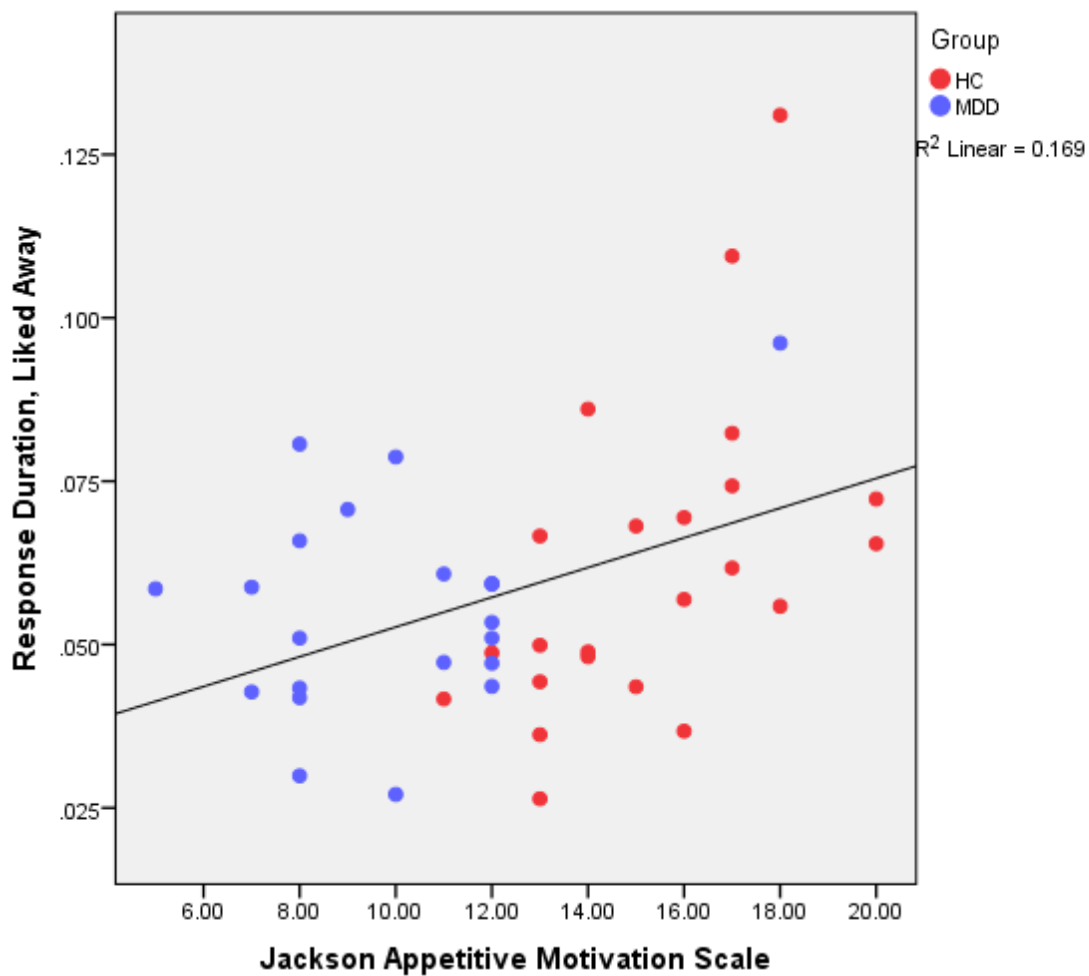
Figure vi *Appetitive motivation is related to reluctance to avoid reinforcing activity*

stimuli

Appendix

List of stimulus words

achieving	exercising	resting
acting	experimenting	restoring
admiring	fighting	reuniting
advising	fishing	rollerblading
baking	flirting	running
bathing	flying	sailing
beachcombing	gambling	saving
bicycling	gardening	scrapbooking
biking	gathering	scubadiving
blogging	golfing	sculpting
bowling	gossiping	selling
brainstorming	grilling	sewing
budgeting	helping	sharing
building	hiking	shaving
camping	hitchhiking	shooting
caving	hunting	shopping
chatting	introducing	sightseeing
cheering	investing	singing
cleaning	jogging	skateboarding
climbing	joking	skating
coaching	jumping	skydiving
collaborating	kayaking	sleeping
collecting	kidding	smiling
coloring	kissing	smoking
competing	knitting	snacking
complimenting	laughing	snorkeling
composing	learning	snowmobiling
contributing	lecturing	socializing
cooking	listening	solving
coordinating	lovemaking	spending
counseling	managing	spying
crafting	leading	studying
crocheting	meditating	sunbathing
cuddling	meeting	surfing
dancing	napping	teaching
dating	nurturing	teasing
daydreaming	observing	testing
decorating	organizing	thinking
designing	parachuting	traveling

dining	photographing	trekking
discussing	playing	twitting
diving	praising	visiting
donating	praying	volunteering
drawing	preaching	wading
dreaming	pretending	walking
drinking	protesting	winning
driving	racing	woodworking
drumming	relaxing	working
eating	reminiscing	wrestling
entertaining	repairing	writing

BAMP task instructions:

WRT:

The objective of this task is to find out about activities you enjoy.

You will see several words representing different activities people sometimes enjoy.

Please read each word and evaluate how you like the activity each word represents.

Think of your experiences and enjoyment that each activity brings you when you

engage in it. If you have not experienced an activity from the list, think of how much

you might enjoy it.

Notice that some words are vague, and could represent different activities for different

people, so when you encounter them, think of what they represent for you, and

evaluate that particular word in the context of your own experiences and preferences.

There are no right and wrong answers and there is no time limit on this task.

LDRTT:

In this task, you will see either words or non-words presented one at a time on the

computer screen. Your task is to push or pull the joystick in response to the items

presented on the screen as quickly and as accurately as you can. There will be two runs

of the task, and the instructions will tell you what to do in each of the runs.

1. First, you will perform a short practice. Please PUSH the joystick when you a word. Please PULL the joystick when you see a non-word. Relax when you see a cross in the middle of the screen.

2. Now, you will perform the first run of the task. Please PULL the joystick when you see a word. PUSH the joystick when you see a non-word. Try to be as fast and as accurate as you can. Relax when you see a cross in the middle of the screen.

3. Now, you will perform the second run of the task. Please PUSH the joystick when you see a word. PULL the joystick when you see a non-word. Try to be as fast and as accurate as you can. Relax when you see a cross in the middle of the screen.

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