SPECIFIC AIMS

Emotional disorders and suicide attempts result in significant social, personal, and medical costs (Kessler & Greenberg, 2003; SAMHSA, 2015; Smith & Smith, 2010). Unfortunately, there is limited understanding of the underlying core processes that predict the future course and aid treatment interventions for emotional disorders (Bühringer, 2006). One of the main reasons for this difficulty is the poor discriminative validity of diagnoses or self-report measures alone. The validity of current diagnostic tools is especially sensitive to certain Social Processes (e.g., Self-Knowledge) such as alexithymia—difficulty identifying and describing emotions (Luminet & Bagby, 2018)—as identified by the Research Domain Criteria (RDoC) of NIMH. This limitation is particularly concerning given that the prevalence of alexithymia is high among those with affective disorders: 45-50% in major depressive disorder (Honkalampi, Hintikka, Laukkanen, Lehtonen, & Viinamäki, 2001; Kim et al., 2008) and 28-34% in anxiety disorders (Cox, Swinson, Shulman, & Bourdeau, 1995) and that alexithymia is associated with increased suicide risk (De Berardis et al., 2017).

Instead of conceptualizing emotional disorders as diagnostic categories, evidence now indicates that such disorders should be considered at the level of normal-to-abnormal endophenotypic risk factors. This can be accomplished by assessing RDoC-related Positive Valance Systems (PVS) and Negative Valence Systems (NVS; Goldstein & Morris, 2016; Kozak & Cuthbert, 2016; Zalta & Shankman, 2016). However, given that alexithymics evidence poor Self-Knowledge, experimental implicit assessments (i.e., not requiring explicit self-report responses) of PVS and NVS disturbance are extremely strong candidates to provide a more precise prediction of future impairment, pathology, and suicidality.

Dr. Bartoszek, first as a doctoral student and now as an Assistant Professor and New Investigator, has led the development of the Implicit Measure of Distinct Emotional States (IMDES; Bartoszek & Cervone, 2017, 2020) over the past ten years. The IMDES is a revolutionary assessment tool that evaluates the internal emotions even if that information lies outside of explicit awareness. Using a rigorously-tested methodology that ensures both reliable and fast responding, the IMDES collects responses based on misattributions of internal emotional states onto a set of abstract images to yield information about key endophenotypic emotional states. It thus can help advance experimental therapeutic approaches by uncovering how people with alexithymia and emotional disorders internally experience PVS and NVS disturbance.

Evidence from a series of pilot studies outlined in this application indicates that (a) lower endorsement of happiness on the IMDES is associated with elevated symptoms of depression, (b) higher endorsement of fear on the IMDES is associated with elevated symptoms of anxiety, and (c) higher endorsement of anger on the IMDES is associated with elevated suicidality. These studies also robustly demonstrate that the IMDES uncovers internal emotional information more precisely than do even the most reliable and valid self-report measures, which cannot tap into specific internal emotional states of individuals with limited insight (e.g., alexithymia; Murphy, Catmur, & Bird, 2018).

Thus, the IMDES holds great promise as a unique predictor of emotional distress and suicidality, strongly consistent with current NIMH Strategic Research Priorities. However, as yet no studies involving the IMDES have examined these relationships in a representative preselected community sample or in individuals with alexithymia. Moreover, although the IMDES has evidenced strong reliability as well as incremental validity over self-report measures in predicting emotional states and distress, it has not been examined in relation to (a) specific PVS and NVS subconstructs or (b) functional impairment, which is a critical translational step.

Aims and Hypotheses

Specific Aim 1: Examine profiles of emotional states as assessed by the IMDES and self-report measures in relation to self-report measures of the PVS construct reward valuation and functional impairment.
Hypothesis: Emotional endophenotypic disturbance related to PVS on the IMDES (decreased happiness) will be associated with (a) functional impairment and (b) self-report measures examining loss among individuals with varying levels of disturbances in Social Processes (alexithymia).
Specific Aim 2: Examine profiles of emotional states as assessed by the IMDES and self-report measures in relation to self-report measures of the NVS subconstruct fear and functional impairment.
Hypothesis: Emotional endophenotypic disturbance related to NVS on the IMDES (increased fear) will be associated with (a) functional impairment and (b) self-report measures examining fear among individuals with varying levels of disturbances in Social Processes (alexithymia).
Specific Aim 3: Examine profiles of emotional states as assessed by the IMDES and self-report measures in relation to self-report measures of suicidality and functional impairment.
Hypothesis: Emotional endophenotypic disturbance related to NVS on the IMDES (increased anger) will be associated with (a) functional impairment and (b) self-report measures examining suicidality and frustrated non-reward among individuals with varying levels of disturbances in Social Processes (alexithymia).

SIGNIFICANCE

It is estimated that 6.6% of adults aged 18 or older will experience at least one major depressive episode over a 12 month period [1]. The likelihood of developing depression increases among those with anxiety disorders; for example, suffering from a specific phobia doubles this likelihood [2]. Unfortunately, there is limited understanding of the underlying core processes that predict the future course and aid treatment interventions for emotional disorders (Bühringer, 2006). Similarly, it is difficult to predict which subgroups of anxious individuals will develop depression over time (Winer et al., 2017). One reason for this difficulty is the poor discriminative validity of diagnoses or self-report measures alone. The validity of current diagnostic tools is sensitive to certain Social Processes (e.g., Self-Knowledge) such as alexithymia—difficulty identifying and describing one's own emotions (Luminet & Bagby, 2018)—as identified by the Research Domain Criteria (RDoC) of NIMH. This limitation is particularly concerning given that the prevalence of alexithymia is high among those with affective disorders: 45-50% in major depressive disorder (Honkalampi, Hintikka, Laukkanen, Lehtonen, & Viinamäki, 2001; Kim et al., 2008) and 28-34% in anxiety disorders (Cox, Swinson, Shulman, & Bourdeau, 1995). Alexithymia is also associated with increased suicide risk (De Berardis et al., 2017). Consequently, using alternative and innovative assessment strategies is essential for accurate and early detection of disturbances in RDoC-related Positive Valance Systems (PVS) and Negative Valence Systems (NVS; Goldstein & Morris, 2016; Kozak & Cuthbert, 2016; Zalta & Shankman, 2016).

Psychopathology and public health

Emotional disorders and suicide attempts result in significant social, personal, and medical costs (Kessler & Greenberg, 2003; SAMHSA, 2015; Smith & Smith, 2010). Depression is the leading cause of disability for people aged 15 to 44 [12, 13]. Additionally, people who suffer from depression have an 11 percent decrease in the probability of getting married and lose $10,400 per year in income by age 50 [14, 15]. The annual cost of depression is estimated at between $44 billion and $53 billion, and the total cost for those diagnosed with depression in comparison to controls is estimated at 2.1 trillion dollars [14, 15].

Similarly, adults with specific phobias were likely to experience impairments in education, employment, and overall quality of life, even in the absence of any significant comorbidity (Mogotski, Kaminer, and Stein, 2000). They miss more workdays and have a poorer physical and mental quality of life compared to healthy members of the population (Alonso et al., 2004). Additionally, the lifetime prevalence of major depression in a sample of individuals with a specific phobia diagnosis was 40.7% compared with only 14% in those without a specific phobia diagnosis (Choy, Fyer, & Goodwin, 2007). Moreover, as the number of fears increases, so does the lifetime prevalence of major depression among adults.

Limitations of diagnostic categories and self-report measures of emotions

Despite the hope that diagnoses would provide direction forward, evidence strongly suggests that depression and anxiety should instead be conceptualized as normal-to-abnormal endophenotypic risk factors, as outlined by the RDoC of NIMH [3-5]. This can be accomplished by assessing PVS and NVS (e.g., mood, emotions). The most common method of assessing mood and emotions is self-report. Basic and applied investigators directly ask people to report the emotions they are feeling at a given time. Self-report measures have advantages (e.g., ease of administration). However, their limitations can impair progress in basic and applied psychology. Scientists obtain blurry views of distinct emotional processes, and clinicians acquire skewed diagnostic impressions of patients' emotional states.

In general, limitations of self-report emotion measures result from three assumptions. First, some individuals evidence limited insight into their own emotional experiences (e.g., Smith & Lane, 2016; Weinberger, Kelner, & McClelland, 1997). This is particularly the case among those with symptoms of psychopathology (Kring, Siegel, & Barrett, 2014) and such conditions as alexithymia (e.g., Murphy, Catmur, & Bird, 2018) or affective agnosia (Lane, Weihs, Herring, Hishaw, & Smith, 2015). Second, individuals are not always forthcoming in their reports and show biases in their responses by under- or over-reporting certain affective experiences (e.g., Barrett, 1996; Robinson & Clore, 2002). Third, the process of reporting one's emotional states changes the intensity of these states (Keltner, Locke, & Aurain, 1993) and decreases emotion-based psychophysiological activity (Kassam & Mendes, 2013). Therefore, even when individuals are perceptive about their emotions and unguarded in their reports, the use of self-report methods can be detrimental to the scientific study of affective states. Moreover, the fact that emotions may influence behavior but occur without conscious awareness further undermines the role of self-reports in the assessment of emotions (e.g., Winkielman & Berridge, 2004).

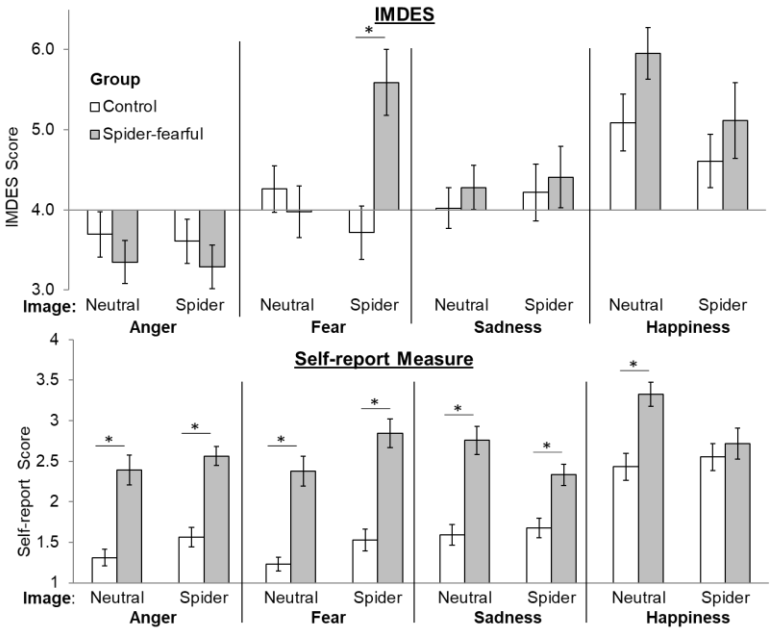
Implicit Measure of Distinct Emotional States (IMDES)

Given the limitations of self-report measures of mood and emotions, the field needs alternative implicit emotion assessments (i.e., not requiring explicit self-report responses) that are as convenient and efficient as the explicit self-report measures. Such implicit assessment methods are extremely strong candidates to provide a more precise prediction of future impairment, pathology, and suicidality.

Dr. Bartoszek, first as a doctoral student and now as an Assistant Professor and New Investigator, has led the development of the Implicit Measure of Distinct Emotional States (IMDES; cf. Bartoszek, 2017; Bartoszek & Cervone, 2017; Bartoszek & Cervone, 2020) over the past ten years. As discussed in detail in the Innovation section, the IMDES is a revolutionary assessment tool that evaluates the internal emotions of a research subject or patient, even if that information lies outside of explicit awareness. It is also the very first implicit measure that assesses and differentiates emotions of the same valence (i.e., anger, fear, sadness). Using a rigorously-tested methodology that ensures both reliable and fast responding, the IMDES collects responses based on misattributions of internal emotional states onto a set of ambiguous, abstract images to yield information about key endophenotypic emotional states. It thus can help advance experimental therapeutic approaches by uncovering how individuals with alexithymia and emotional disorders internally experience PVS and NVS disturbance.

IMDES and emotion profiles of individuals with specific phobia

Across several studies, the IMDES differentiated between control participants and spider-fearful individuals. In one study (Bartoszek & Cervone, 2017), controls and spider-fearful individuals were shown either spider or neutral images. We hypothesized that, when viewing spider images, spider-fearful individuals would evidence elevated fear compared to their non-fearful counterparts. However, because people with specific phobias do not generally evidence fear outside of the normal range unless exposed to the fear-inducing stimuli (e.g., Bartoszek & Winer, 2015; Brown et al., 1998), we did not expect the two groups to evidence different emotion profiles when viewing neutral images. As Figure (top panel) illustrates, the IMDES revealed the emotion profiles of these two groups exactly as suggested by these theoretical considerations: spider-fearful individuals differed from controls only in levels of fear and only when exposed to spider stimuli. In contrast, the emotion profiles revealed by the self-report measure (bottom panel) lacked any specificity.



Another study of spider-fearful individuals (Study 1 of Bartoszek & Cervone, 2020) replicated these findings while also showing that implicitly assessed fear correlated with psychophysiological (i.e., skin conductance levels) and behavioral responses (Table 1) even when controlling for self-reported fear.

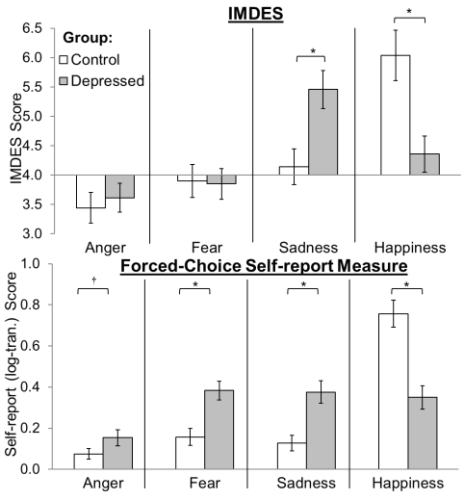
Table 1. *Correlations of Implicitly Assessed Emotions with Self-Reported, Behavioral, and Physiological Indices of Spider Phobia*

Implicit Emotion	FSQ Score	Avoidance Behavior$_{sqrt}$	S.SCRs		Peak Heart Rates
			Number$_{sqrt}$	Amplitude$_{sqrt}$	
Anger	.03	.01	**-.32***	.11	.10
Fear	**.35***	**.43****	**.59*****	.26	.28†
Sadness	-.13	-.03	-.14	-.08	-.24
Happiness	**-.36***	-.25	**-.35***	-.18	-.16

Note. FSQ = Fear of Spiders Questionnaire; S.SCR = Specific Skin Conductance Response. "sqrt" indicates a square-root transformed variable.
† $p < .10$. * $p < .05$. ** $p < .01$. *** $p < .001$.

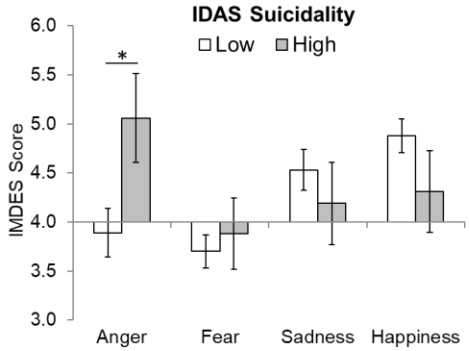
IMDES and emotion profiles of depressed individuals

One study examined the IMDES responses as a function of depression symptoms (Bartoszek, 2017). Depressed individuals exhibit decreased sensitivity to rewards and diminished approach-related behavior (e.g., Shankman, Klein, Tenke, & Bruder, 2007). Consequently, anhedonia and *low positive affect* represent the core feature and prove useful in the differential diagnosis of depression (e.g., Watson, 2009). Depression is also strongly linked to feelings of sadness (e.g., Winer, Salem, Bartoszek, & Snodgrass, 2015)—another central feature of depression (APA, 2013). Therefore, the PI hypothesized that, compared to controls, depressed individuals would evidence elevated sadness and decreased happiness but similar levels of fear and anger. As presented in Figure (top), the IMDES revealed precisely this pattern of results: Compared to controls, the depressed group attributed less happiness and more sadness to the IMDES images; but the groups did not differ in implicit anger or fear scores. The data again supported the incremental validity of the implicit measure, as implicitly assessed happiness and sadness were correlated with depression symptoms even when controlling for self-reported emotions. To ensure a fair comparison between implicit and self-report measures, a self-report emotion measure with a forced-choice scale similar to that of the IMDES was used. Notwithstanding, as Figure (bottom) shows, the self-reported measure still lacked specificity, indicating that the groups differed in happiness, sadness, fear, and (marginally so) anger.



IMDES and suicidality

According to the Centers for Disease Control and Prevention (CDC), suicide is the tenth leading cause of death overall and the second leading cause of death among individuals between the ages of 10 and 34 in the United States. One robust predictor of suicidality is anger (e.g., Swogger, Walsh, Homaifar, Caine, & Conner, 2011). Anger is associated with suicide attempts even when controlling for mood disorders (e.g., Esposito, Spirito, Boergers, & Donaldson, 2003) and can predict suicide attempts over 13 years (e.g., Daniel, Goldston, Erkanli, Franklin, & Mayfield, 2009). Consequently, a valid assessment of anger could help identify suicide-prone individuals. In one preliminary study (Bartoszek, unpublished data), suicidality was assessed with the Suicidality subscale of the Inventory of Depression and Anxiety Symptoms (IDAS). As shown in Figure, individuals with elevated suicidal tendencies also evidenced higher levels of implicitly assessed anger compared to those with no such tendencies. The two groups did not differ on any other emotions assessed by the IMDES. These initial findings highlight the potential of the IMDES in identifying individuals at risk for suicide.



IMDES and treatment implications

Effective treatment of emotional disorders depends on early and accurate detection of disturbances in mood and/or emotions (e.g., PVS, NVS) and prediction of the progression of these disturbances over time. Yet, considering the problems outlined above, clinicians cannot merely rely on the diagnostic categories or self-report assessment methods. The IMDES has the potential to greatly improve and facilitate the assessment of emotional disorders in several ways. **First**, the IMDES could play a critical role in the early detection of PVS and NVS disturbances and the prediction of these disturbances over time. This longitudinal research would test this possibility. In turn, early detection could lead to timely treatment and even the prevention of emotional disorders. **Second**, compared to self-report measures' poor specificity, the IMDES with its remarkable discriminant validity can aid in determining a differential diagnosis. This is crucial as the high comorbidity underscores problems with the current diagnostic systems and raises questions whether attempting to separate disorders at the syndrome level is ontologically or practically useful. Unlike self-reports, the IMDES can reveal emotion profiles that are unique to a particular emotional disorder. Such information will allow to better target the core emotional disturbances and will thus lead to more effective treatment strategies. **Lastly**, emotional disorders often lead to suicidal thoughts and tendencies. The IMDES already predicts avoidance behaviors in anxious individuals and shows the potential to predict suicidal tendencies in those afflicted by emotional disorders. It is difficult to overstate the benefits of predicting these tendencies.

Overall, the IMDES would facilitate a multimethod measurement and complement the existing self-report measures in clinical and research settings. The implicit measure could detect PVS and NVS disturbances early on, differentiate affective disorders by providing unique information about these highly comorbid conditions, and identify individuals who may be at risk for suicide.

IMDES and economic benefits

The use of the IMDES could thus have tremendous public health implications. For example, if identifying individuals with disturbances in PVS predicted successful outcomes for even 1% of the individuals who do not respond to therapy, it would mean a savings of approximately $800 million annually [14, 20]. [*ADD INFORMATION ABOUT THE ECONOMIC BENEFITS OF PREDICTING DISTURBANCES IN NVS, ANXIETY DISORDERS, OR SUICIDALITY.]*

INNOVATION

The Implicit Measure of Distinct Emotional States (IMDES) is a highly innovative method whose development is grounded in the scientific literature. The process and stages of the development of the measure are described in detail below.

The initial method for implicit assessment of emotional states: Three assessment strategies

The method for implicit assessment of emotional states exploits empirical findings that emotions affect cognition (e.g., evaluative judgments) through a heuristic process known as feelings-as-information (Schwarz & Clore, 1983; Schwarz, 2011). Specifically, people often use their current emotions as a source of information when evaluating ambiguous stimuli. Three assessment strategies, capitalizing on such findings and theoretical considerations, were initially implemented (Bartoszek & Cervone, 2017). First, the method requires participants to evaluate non-self targets (i.e., ambiguous stimuli) rather than describing their own feelings. The method is also devoid of any self-referential questions. Non-self ratings can reduce biases that may occur when people explicitly describe themselves (Paulhus & Reid, 1991). Second, both the instructions (i.e., to provide ratings "based on your first impression" and to "rely on your intuition") and the forced-choice response scale are designed to prompt heuristic processing, which is more common when people are not motivated to be accurate and can respond to with little effort (Forgas, 2001). Third, the measure uses (ambiguous) pictorial stimuli because pictures are more intrinsically related to emotional experience than words (Glaser & Glaser, 1989).

The implicit assessment method: Initial findings

Across three initial experiments (Bartoszek & Cervone, 2017), ratings of ambiguous images revealed the expected changes in distinct emotional states. In Study 1, participants exposed to a sadness-inducing story inferred more sadness and less happiness in ambiguous images. In Study 2, an anger-provoking interaction increased anger ratings. In Study 3 (described in the "Significance" section), spider (versus neutral) images increased fear ratings in spider-fearful participants but not in controls. Taken together, in each experiment, the implicit task indicated elevated levels of the target emotion but no changes in non-target negative emotions; the task thus differentiated among emotional states of the same valence. The assessment method captured emotional states even when participants were unaware of the covert emotion-manipulation procedures. Correlations also supported the convergent, discriminant, criterion, and incremental validity of the implicit method. In stark contrast, the self-report measure of emotions indicated elevations in all negative emotions. Many other studies also revealed this weak discriminant validity of self-reports (McLaughlin et al., 2016; Polivy, 1981).

Notably, several other researchers have already used this implicit assessment method to successfully capture changes in participants' emotional states (Bryant, Winer, Salem, & Nadorff, 2017; Holt, Furbert, & Sweetingham, in press; Mantantzis, Maylor, & Schlaghecken, 2018; Wisneski & Skitka, 2017), and others advocated its use as an assessment tool (Cervone & Little, 2019; Mackie & Smith, 2017; Wróbel, 2018).

Although promising, this initial assessment method was not sufficient to measure emotional states among all persons. Rather, the method's validity was robust primarily among participants who responded quickly to test items. That is, the effects of emotion manipulations on ratings of ambiguous images were much stronger among participants who rated the ambiguous images quickly rather than slowly. Indeed, the participants who responded slowly displayed virtually no effect of the emotion inductions. Overall, results supported the validity of the implicit measure only among fast-responding participants. These findings are consistent with the theoretical considerations described next and led to further improvement of the structure of the implicit assessment method.

The role of response speed in implicit assessment of emotional states

The feelings-as-information mechanism mentioned above is a heuristic, intuitive, and emotion-based process that requires relatively little time. In fact, slow, deliberative thinking may eliminate the influence of emotions on evaluative judgment (Evans & Stanovich, 2013; Palkovics & Takáč, 2016; Schwarz, 2011). These theoretical considerations and empirical results have an important implication for the design of implicit measures of emotional states. They suggested that *the speed of participants' responses is key to the validity of an implicit emotion measure.*

As described in the preceding section, our initial studies were consistent with these predictions by showing that naturally occurring variations in participants' response speed are related to the validity of the implicit assessment method. However, given that the response times were not experimentally manipulated, the results remained open to interpretations. It was hypothesized that fast responding directly increased reliance on the intuitive feelings-as-information heuristic while precluding the use of deliberative, unemotional processes. An alternative was that a third variable—a stable individual difference (e.g., salience or clarity of emotional experience)—influenced both response speed and ratings of the ambiguous images.

To test these competing hypotheses and to obtain stronger evidence of the role of response speed in increasing the robustness of the implicit assessment method, response times were manipulated experimentally (e.g., by imposing time pressure). Prior studies showed that time pressure increases reliance on emotions in judgments (e.g., Finucane, Alhakami, Slovic, & Johnson, 2000). For example, participants responding under time pressure (versus no time pressure) more readily use their affect in interpretations of ambiguous situations (Kosnes, Pothos, & Tapper, 2010), judgments of life satisfaction (Siemer & Reisenzein, 1998), evaluations of an outgroup member (Dijker & Koomen, 1996), or risky decision-making (Hu, Wang, Pang, Xu, & Guo, 2014). Risky decision-making, when made under time pressure, is also more strongly related to participants' skin conductance levels, an index of emotional arousal (Persson, Asutay, Hagman, Västfjäll, & Tinghög, 2018). Therefore, imposing time pressure in responding should increase reliance on the fast, heuristic, emotion-based processes; however, such a time restriction would not be expected to affect stable individual differences.

The fourth assessment strategy: Time pressure in responding

Two published studies examined whether experimental manipulation of response time would affect the validity of the implicit assessment method. One study used the prior paradigm: exposure of spider-fearful and control individuals to spider images (Study 2 of Bartoszek & Cervone, 2020). However, this time, participants had to rate each abstract image within five seconds, as shown in Figure. The implicit measure showed that the expected differences between control and spider-fearful groups in implicitly assessed fear were of large effect size (d = 1.35) as compared to the medium effect size (d = 0.46) obtained previously. Moreover, the correlations between implicit fear and self-reported and behavioral indices of spider phobia were all significant (rs = .46 to .53, all ps < .001) and significantly larger than the corresponding correlations in the previous study (comparisons based on Fisher r-to-z transformations). Moreover, implicit fear predicted participants' avoidance behaviors even after controlling for self-reported fear (r = -.27, p = .013). Altogether, imposing time pressure in rating ambiguous images enhanced the sensitivity as well as construct, criterion, and incremental validity of the Implicit Measure of Distinct Emotional States (IMDES).

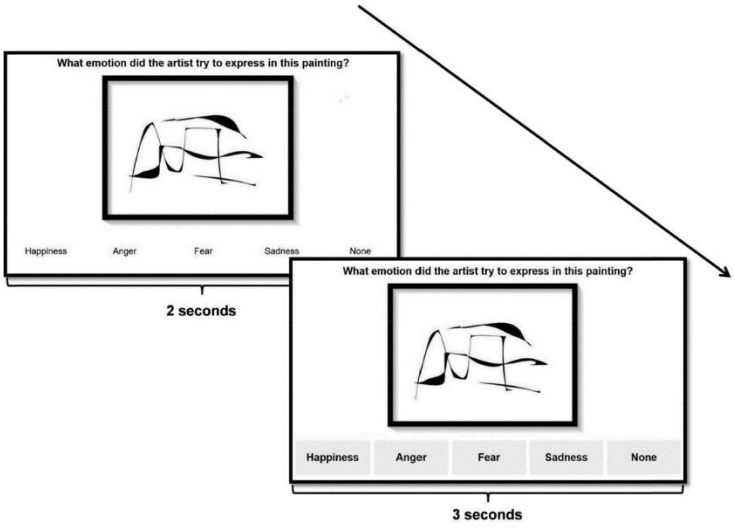
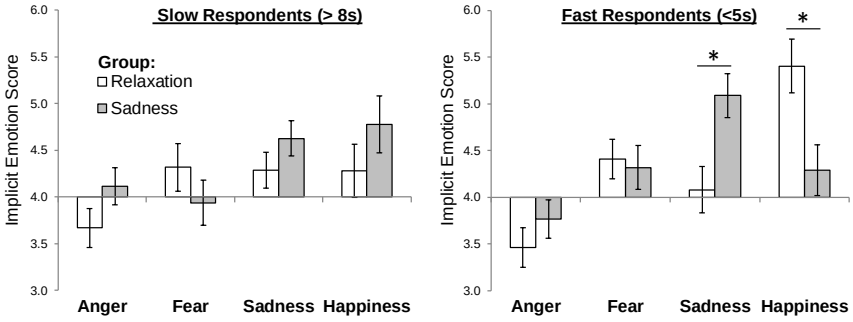


Figure 1. Illustration of a single IMDES trial

In another study, participants experienced either sadness or relaxation induction via an audio-recorded story (Study 3 of Bartoszek & Cervone, 2020). To better understand the mechanisms underlying responses on the IMDES, participants were also compelled to respond to each item of the IMDES either fast (< 5s) or slowly (> 8s). Again, the emotion manipulation affected fast-, but not slow-, responses to the IMDES. When responding quickly, participants who listened to the sadness-inducing story rated more images as expressing sadness and fewer images as expressing happiness than did those who listened to the relaxation-inducing story (Figure). In contrast, neither significant effects nor interactions were evident among those responding slowly.



Taken together, imposing time pressure on the IMDES increases the sensitivity and validity of the measure. Incorporating the four theory-based and data-supported assessment strategies, the IMDES emerges as an innovative, sensitive, and accurate implicit measure of emotions that does not require the respondents to possess conscious access to their emotional states.

Implicitness of the IMDES

In order to show that a measure is implicit, research should provide evidence that the measure indexes the construct automatically (De Houwer et al., 2009). The data across several of our studies indicate that the process through which the IMDES indexes the emotional states appears to possess several features of automaticity, as this process appears to be fast, unintentional, and uncontrollable (Moors & De Houwer, 2006).

Because only quick (rather than slow) ratings reflect raters' emotional states, the process is relatively *fast*. The misattributions of emotions to the ambiguous images also seem to be *unintentional* for two reasons. First, participants are not directed to use their feelings when rating the images but instead are asked a non-self-referential question (i.e., "what emotion did the artist try to express in this painting?"). Second, when asked about their strategy in rating the abstract images, only 8 (2.9%) of 275 participants evidenced an awareness of the effects of the emotion-manipulation procedure on their responses to the implicit measure items (Study 3 of Bartoszek & Cervone, 2020). Lastly, in the fear-inducing studies, participants were instructed to disregard the emotion-eliciting stimuli (i.e., the spider images) when rating the abstract images. Despite this instruction, participants' ratings were still influenced by these stimuli, and thus the process appears to be *uncontrollable*.

These automatic responses on the IMDES are in contrast to the reflective nature of responses on self-report measures. One implication is that, as revealed by the studies described above, implicitly assessed emotions predict unique variance of emotion-related constructs (e.g., avoidance behavior, psychophysiological reactivity) unexplained by self-reported emotions. Furthermore, because the IMDES does not seem to require conscious consideration of one's emotions, it may be better in capturing emotional states in people with impaired access to such states (e.g., alexithymia, affective agnosia, defensive repression; e.g., Kring, Siegel, & Barrett, 2014; Lane, Weihs, Herring, Hishaw, & Smith, 2015).

APPROACH

Summary of Preliminary Studies

Psychology, akin to other sciences, is responsible for an accurate assessment of not only cognitive qualities (e.g., intelligence) but also psychological states (e.g., emotions). As outlined in the Significance and Innovation sections, this R15 award will employ the Implicit Measure of Distinct Emotional States (IMDES) as a prospective endophenotypic predictor of PVS and NVS disturbances in a longitudinal study. Considering the numerous disadvantages of explicit self-report measures, the IMDES would allow researchers and clinicians to gain a better insight into their participants'/patients' emotional states and to predict disturbances in PVS and NVS early on. Furthermore, the IMDES would help determine differential diagnoses with the aim of selecting better-targeted treatment approaches. In addition to detecting early onsets of depression and/or anxiety disorders, the IMDES could also help predict a subsample of depressed individuals who are likely to become suicidal. Ultimately, this novel implicit measure of emotions would serve as a diagnostic tool in clinical settings. In addition to testing the predictive power of the IMDES, the project will provide valuable training opportunities for undergraduate and graduate students to gain research skills.

Scientific Team (please see budget justification and research environment for expanded descriptions)

Principal Investigator. Dr. Bartoszek is a new and early stage investigator with expertise in cognitive and emotional processes underlying affective psychopathology, particularly anxiety and depression, and an established history mentoring over 60 undergraduate and graduate students. Dr. Bartoszek also pioneered the main measure outlined in this proposal (IMDES; Bartotszek & Cervone, 2017; Bartotszek & Cervone, 2020); the IMDES is currently the only measure that capable of implicitly assessing and differentiating emotional states of anger, fear, sadness, and happiness. He is about to begin his fourth year as an Assistant Professor at William Paterson University. Since 2015, Dr. Bartoszek has published 8 papers or chapters, including 7 peer-reviewed articles. Highlighting this work are two major first-author papers on implicit assessment of emotional states. Thus, Dr. Bartoszek is an early investigator with a strong background whose accomplishments and promise are consistent with the R-15's mission.

Dr. Bartoszek will have overall responsibility for the project; this includes training and mentoring graduate and undergraduate students, chairing project meetings, overseeing coverage and assessments of suicidality if a subject presents in crisis, conducting statistical analyses, writing manuscripts, and presenting findings. He will also oversee the training initiatives of the grant.

Consultant. Dr. Winer has expertise in the experimental and self-report study of positive system disturbance related to reward devaluation, depression, anhedonia, anxiety, and suicide risk. He has 45 total publications either published or in press, including work in high-end peer-reviewed journals on each of these topics. He also has grants management expertise as a current PI on an R15 AREA Award that has been renewed twice with perfect scores on competitive review (R15 MH101573), as well as expertise on a wide range of experimental tasks associated with positive valence, negative valence, and cognitive systems RDoC domains. He has also led the development of university- and department-level infrastructure for the successful recruitment and retention of clinical subjects (including hitting their retention estimates for our 6-week and 6-month longitudinal studies for the initial and renewal projects or R15 MH101573), which ensures the feasibility of high-level longitudinal experimental psychopathology research at our institution that incorporates undergraduate and graduate student researchers at each level of the project. Furthermore, he has served as a Co-Investigator/Mentor on two other R-15 applications, and provided materials to five other faculty members for preparation of their awards (five of these applications were scored, and three have been funded, including one on which he is currently a Co-Investigator). Thus, he has established expertise in the R-15 mechanism and in helping to mentor New Investigators with the science and execution of their grants.

Graduate Assistants. Two graduate student researchers in William Paterson University's new doctoral program in clinical psychology will receive tuition remission and 12-month stipends for two years as part of the training initiatives of this R-15 proposal. One graduate student will receive tuition remission and 12-month stipend for the third year, and one will receive a 3-month summer stipend, consistent with the recruitment and retention needs of the grant as well as providing students with ample training opportunities over the course of the grant.

Each student will be trained on delivering assessments, experimental programming, data collection, data analysis, conference dissemination, and manuscript preparation. Both students will also join the Association for Psychological Science and the Society for the Science of Clinical Psychology, and receive travel and expenses to attend at least one conference each year. The department of psychology will also commit in-kind funding of at least $XXX annually to supplement travel expenses for graduate and undergraduate student researchers to attend conferences or didactic trainings.

Undergraduate Assistants. Two undergraduate student will be provided funding for all 27 academic months. In addition, two undergraduate students will be funded in the summer, with one undergraduate student funded for 20 hours/week and one funded for 10 hours/week. These researchers will contribute by running experimental subjects and will be provided with ample opportunity to gain experience with experimental programming, data analysis, national conference attendance and presentation, and manuscript preparation.

General Study Criteria and Overall Design

A longitudinal study will examine the IMDES responses and self-reported endorsement of psychological distress and dysfunction in relation to disturbances in positive valence, negative valence, and cognitive systems constructs and functioning along normal-to-abnormal dimensions to determine task parameters and temporal unfolding of these disturbances.

Those who meet screening criteria will be asked to complete behavioral and self-report measures of PVS, NVS, and CS domain constructs outlined by the RDoC and occupational and social functioning (LIFE-RIFT). This will include an initial assessment, a second assessment 3 months in the future, and a follow-up assessment at 12 months total. Participants will be paid $20 for the initial assessment, $40 at 3 months, and $100 at the one-year follow-up.

Design Considerations

Severe psychopathology and healthy controls. Participants with suicidal ideation will be included in the study in order to examine participants with severe psychopathology. Participants' suicidal intent will be monitored throughout the study, and participants will be provided referral information. Participants endorsing suicidal intent will be given a Columbia-Suicide Severity Rating Scale [35], the gold standard in comprehensive suicide risk assessment, by Dr. Bartoszek, licensed as clinical psychologist in the state of New Jersey, or an advanced graduate clinician who will then consult with Dr. Bartoszek. Participants who evidence active suicidal intent will be withdrawn from the study and immediately referred for mental health treatment, as outlined in the protection of human subjects section. In addition, a small percentage of asymptomatic individuals will be included to compare RDoC constructs in normal-to-abnormal dimensional analyses.

Behavioral task selection. The various behavioral measures we intend to incorporate provide a range of tasks that allow for delineation of important processes associated with symptoms of anxiety and/or depression. Specifically, the tasks outlined below assess how basic cognitive/affective elements such as [to be completed] contribute to anxiety, depression, and dysfunction over time.

The Implicit Measure of Distinct Emotional States (IMDES) was chosen because of its prospective unique ability to assess and differentiate emotions without relying on respondents' ability to consciously access these affective processes (Bartoszek & Cervone, 2017; Bartoszek & Cervone, 2020). Thus the IMDES can index disturbances in PVS and NVS.

Recruitment and Screening

Recruitment strategies include a multimedia campaign in clinical and nonclinical sites throughout the community that will advertise in CMHCs, surrounding hospitals, and via postings at local Universities in the surrounding areas. Advertisements will be tailored toward individuals with and without psychopathology, to ensure recruitment of both distressed individuals and healthy controls. Potential participants will be directed to an online screener at which point they will complete the Patient Health Questionnaire 9 (PHQ-9) [55-57]. A total of 60 individuals aged 18-65 will be recruited, at least 20 of whom will meet cutoff for severe symptoms of depression (PHQ-9>19). Up to 33% (n = 20) of the clinical sample may have significant but moderate levels of depression and anxiety (PHQ-9 between 10 and 19), as indicated by the NIMH Research Domain Criteria guidelines, which state that studies should include participants experiencing significant symptoms of a disorder but who do not quite meet diagnostic criteria. In addition, 33% (n = 20) of subjects will be individuals ranging in age from 18-65 who have mild or minimal symptoms of depression (PHQ-9<10). The inclusion of these individuals is in line with RDoC Guidelines and recommendations to allow normal-to-abnormal dimensional investigation that is heterogenous across multiple RDoC dimensions of interest and has no inclusion/exclusion criteria based on diagnoses.

In addition to preselecting participants as a function of depression, additional individuals (n = 30) reporting high levels of spider phobia on the Fear of Spiders Questionnaire (FSQ>70) will be recruited for the study. Each spider-fearful participant will be yoked with with non-fearful participant based on age and depression score. This group will allow us to examine which subgroup of individuals with simple phobia is prone to develop depression over time. We will also examine to what extend the IMDES predicts psychophysiological reactivity and avoidance behaviors in these individuals when exposed to fear-provoking stimuli.

Upon meeting preselection criteria, participants will be contacted by phone for an initial session. The initial session will include an examination of current suicidal intent as part of an initial diagnostic interview, mental status screening, and assessment of the behavioral, self-report, and interview measures noted below.

Exclusion criteria. Potential participants with any of the following characteristics will be excluded from the study: (1) the presence of cognitive impairment, as indicated by the Montreal Cognitive Assessment (MoCA; [58]; total score < 26); (2) current suicidal intent or need for immediate treatment as determined by PI or Co-Is; (3) the presence of psychosis indicated by the the Psychotic Symptom Rating Scales (PSYRATS; Haddock et

al., 1999; Drake et al., 2007; Woodward et al., 2014); and/or (4) unwillingness/inability to give initial verbal assent or to sign informed consent at the first full assessment.

Participant retention. With regard to retention, a comprehensive tracking strategy will be used to maximize retention of all study participants: (1) A computerized log will be kept with a record of all contact attempts including date, time of day, and the outcome of the contact attempt; (2) At the initial assessment session, participants will complete a Locator Form requesting detailed location and contact information for themselves and important others (whom we will seek written permission to contact); (3) Participants will be provided with multiple numbers and means of contacting research personnel (including stamped, pre-addressed postcards for updating contact information if needed). (4) Participants will be informed about the prospective nature of this study and specific tracking procedures as part of the consent procedure. Using these methods, Dr. Winer, the consultant on this project, was able to keep retention rates for the main aims of his initial R15 very high, with subject retention at 87% (13% attrition) in a longitudinal study.

Assessment of potential clinical moderators. At each assessment, we also will assess potential clinical moderators including recent stressful life events using the Schedule of Recent Experiences [59, 60], a widely used checklist of debilitating environmental events that commonly precede psychological distress. Furthermore, participants will be asked if they are currently undergoing psychotherapeutic or psychopharmacological treatment, with past clinical treatment history in the previous 6 months assessed at each assessment. This allows for the assessment of relevant clinical factors in advance of translating assessment of disturbances in PVS and NVS as a target for experimental therapeutics.

Self-Report Measures

Each self-report measure will be administered at each assessment session and the follow-up session.

Toronto Alexithymia Scale (TAS-20). TAS-20 is a 20-item questionnaire used to measure alexithymia, a construct conceptualized as the inability to identify and describe feelings. Factor analysis of the twenty-items yield three inter-correlated factors: difficulty identifying feelings; difficulty describing feelings; externally-oriented thinking. Participants rate the degree to which they agree with each statement on a 5-point Likert scale (1 = *never true*; 5 = *very often true*). The TAS-20 has shown excellent internal consistency and good test-retest reliability (Bagby et al., 1994).

The Patient Health Questionnaire (PHQ-9). PHQ-9 is a 9-item self-report measure used to screen for depressive symptoms. Participants rate on a 4-point scale (0 = *not at all*; 3 = *nearly every day*) how often they were bothered by symptoms of depression over the last two weeks. The PHQ-9 assesses the following symptoms: 1) anhedonia; 2) depressed mood; 3) sleep patterns; 4) energy levels; 5) changes in appetite; 6) guilt, shame, or worthlessness; 7) concentration; 8) feeling slowed down or restless; and 9) thoughts of self-harm or suicide. The PHQ-9 has been found to have high sensitivity and high specificity for the diagnosis of major depression in adult populations, as well as good criterion validity and construct validity (Kroenke et al., 2001).

Suicide Behaviors Questionnaire-Revised (SBQ-R). SBQ-R is made up of four items, each indexing a different dimension of suicidality. SBQ-R Item 1 assesses lifetime suicide ideation and suicide attempt; Item 2 assesses the frequency of suicidal ideation over the past twelve months; Item 3 assesses into the threat of suicidal behavior; Item 4 assesses self-reported likelihood of suicidal behavior. For each item, participants circle the number beside the statement or phrase that best applies to them. Acceptable internal consistency reliability (alpha) estimates have been reported (Osman et al., 2001), as well as adequate concurrent validity (Rueda-Jaimes et al., 2017).

Positive and Negative Affect Scale – Extended Form (PANAS-X). The selected subscales of the PANAS-X will assesse emotions explicitly. Participants report, on a five-point Likert scale (1 = *not at all* to 5 = *extremely*), the extent to which each of emotion adjectives describes their current emotions. Each emotion adjective will refer to one of four PANAS-X subscales: Hostility (*anger*), Fear, Sadness, or Joviality (*happiness*). The measure has good convergent and discriminant validity (PANAS-X; Watson & Clark, 1994).

Fear of Spiders Questionnaire (FSQ). FSQ is an 18-item self-report measure examining spider phobia. FSQ items refer to a restricted time period (e.g., "If I encounter a spider now, I would have images of it trying to get me") and participants rate their level of agreement with these statements on a 7-point Likert scale (0 = *strongly disagree*; 6 = *strongly agree*). The FSQ has adequate test-retest reliability (Muris & Merckelbach, 1996), excellent internal consistency (Cronbach's alpha .92), good convergent validity, and differentiates well between spider phobics and non-phobics (Szymanski & O'Donohue, 1995).

Specific Phobia Questionnaire (SPQ). SPQ is a 45-item self-report questionnaire developed to assess fear and interference of different objects or situations. Respondents are asked to indicate how fearful they are of each situation using a 5-point scale that ranges from 0 (no fear) to 4 (extreme fear) and how much their fear of each situation interferes with their life using a 5-point scale that ranges from 0 (no interference) to 4 (extreme interference). The SPQ also demonstrates good convergent and discriminant validity with measures of worry, depression, and other specific phobias, and good test-retest reliability. SPQ scores are useful for discriminating individuals with specific phobias from those without specific phobias, and for identifying specific phobia types (Ovanessian et al., 2018).

Generalized Anxiety Disorder-7 (GAD-7). GAD-7 is a seven-item self-report measure that assesses symptoms of generalized anxiety over the past 2 weeks. Items are rated on a 4-point Likert-type scale ranging from 0 (not at all) to 3 (nearly every day), with higher scores indicating greater generalized anxiety. The GAD-7 has demonstrated acceptable reliability and validity in previous studies (Löwe et al., 2008, Spitzer et al., 2006).

Beck Anixiety Inventory (BAI). Anxiety symptoms will be measured with the 21-item Beck Anxiety Inventory, a reliable and valid measure of anxiety (BAI; [67, 68]) will allow us to examine whether symptoms of anxiety alter the relationship between depression, impairment, and tasks examining reward devaluation over time. Previous research indicates that symptoms of depression and not anxiety are most predictive of avoidance of positivity [18], but this finding has not been extended to the other tasks described in this proposal or assessed over time.

Social and occupational functioning. Social and occupational functioning will be measured by the Range of Impaired Functioning Tool (LIFE–RIFT; [62]), a brief measure of functional impairment. It contains subscales assessing functioning in occupational, relationship, satisfaction, and recreational domains. The LIFE-RIFT has shown good reliability, with the internal consistency of the scale yielding alpha coefficients ranging from .81 to .83, and intraclass correlation of .94. The LIFE-RIFT is also predictively valid, with research having demonstrated that impairment measured by the LIFE-RIFT is positively associated with subsequent recurrence of depressive symptoms and negatively associated with recovery.

Measures of Cognitive Processes

Appraisal Questionnaire. [to be added]

Behavioral Tasks and Indirect Measures

Behavioral tasks will be administered in the order listed below and will be administered at each of the assessments and the follow-up assessment by independent assessors.

The Implicit Measure of Distinct Emotional States (IMDES). The IMDES assesses four emotions: anger, fear, happiness, and sadness, implicitly (i.e., without participants' awareness) On each trial of the IMDES, participants see and abstract image and have 5 seconds to indicate what emotion, if any, is expressed in the image. Once the participant chose one of the options or the 5 seconds elapse, the next trial is presented, and the cycle continues automatically until all 24 abstract images are presented. The composite scores of the measure were derived from the ratings of the last twenty abstract images (actual trials). If no response option was selected during the 3-second time window, that actual trial's datum was coded as missing. To adjust for missing data, the emotion scores for each participant were multiplied by the ratio of the maximum possible number of responses (i.e., 20) to the number of provided responses (this ratio equals 1 for those with no missing data on the implicit measure).

Dot-probe task. Each trial sequence will consist of a picture pair being presented for either 500ms, 1000ms, or 2000ms, followed by a dot, at which point participants will have up to 10000 ms. to make their choice by striking one of two keys. The inter-trial interval will be the standard 1000 ms [69-74]. Stimuli will consist of positive-neutral and negative-neutral picture pairs. Eight positive pictures, 8 negative pictures, and 16 neutral pictures that are balanced for arousal will be used. Stimuli will be randomized across tasks, and three blocks of 64 trials will be presented, consisting of 8 positive-neutral word pairs and 8 negative-neutral word pairs, each presented four times. Stimulus presentation will counterbalance for visual fields [75]. Our previous R15 examined words in this task, and thus examining pictures in this paradigm represents an important advance. Moreover, evidence suggests that longer presentation times may be more closely related to avoidance of positivity on the dot-probe task, so we have included longer durations in this renewal than were included on our initial R15.

Effort-Expenditure for Rewards Task (EEfRT). Participants will initially be presented with a 1000ms fixation and then given a 5000ms choice period in which they are told of the higher reward magnitude of the hard task (e.g., 200% of that of the easy task), and the probability of receiving any reward. They are then provided with a 1000ms “ready” screen and make rapid button presses to complete the chosen task for either 7s (easy task) or 21s (hard task). Participants then will be instructed whether they have completed the task and whether they received any money for that trial. Importantly, each trial presents a choice between a hard task and an easy task. Hard-task trials require participants to make 100 button presses using their non-dominant little finger within 21 seconds; easy-task trials require participants to make 30 button presses, using the dominant index finger, within 7 seconds [47]. One block of 50 trials will be used, as is standard [46-49, 76]. This task will remain unchanged from our initial R15.

Affective N-Back Task. Participants will be presented with 47 positive and 49 negative pictures, matched for arousal. Four blocks of 24 trials will be presented in which a single picture is presented for 500ms following a central fixation and then by a 2500 ms intertrial interval [44, 45, 77]. Participants are instructed to indicate whether the picture onscreen matches or does not match the valence of the picture presented two trials previously (i.e., 2-back). Responses to negative and positive stimuli can be evaluated with regard to which pictures preceded them, to evaluate inhibition of negative information and updating of positive information. Our previous R15 examined words in this task, and thus examining pictures in this paradigm represents an important advance.

The Probabilistic Reward task (PRT). The PRT measures ability to modify behavior as a function of reward [51, 52]. The PRT yields measures of reward responsiveness and reward learning, including separable measures of stimulus discrimination and response bias [78] The task is highly related to anhedonia, and thus along with the EEfRT provides a potential behavioral indicator of blunted reward to be compared to measures of reward devaluation. Standard parameters will be implemented (e.g., [51]) incorporating 300 trials, divided into 3 blocks of 100 trials. A mouthless cartoon face is initially presented in the center of the screen, and after a delay of 500 msec either a short mouth or a long mouth is presented for 100 msec. The face without the mouth then remains on the screen until which type of mouth is identified. Reward feedback is then varied in conditions to create differential reinforcement schedules to examine whether individuals with heightened melancholia or anhedonia are more or less likely to evidence bias due to reinforcement.

Statistical Analyses

To analyze these data, the proposed study will utilize a multilevel (hierarchical) linear model. Multilevel linear modeling is an ideal statistic to utilize for these data as it allows for missing data and unequal sample sizes between time points, which are common in longitudinal research. Further, it allows the flexibility to test individual differences using growth curves. All analyses outlined below will be examined over time to assess both cross-sectional and longitudinal relationships among variables. All tasks will be examined over time including emotional valence (positive, negative) as applicable as a within-subject variable and symptoms of depression and/or spider phobia as between-subject variables. [to be extended]

Accounting for Sex and Age as Biological Variables. Sex and age will be assessed via self-report in all subjects, and will be factored into research designs and analyses initially as a covariate and subsequently as a predictor depending on the level of predictive ability in the analyses described below. Age is a potential factor with regard to completion of cognitive tasks that rely on reaction time, perceptual accuracy, and motor

performance, and thus will be included as a covariate in analyses. We also anticipate recruiting at least twice as many women as men, consistent with representative epidemiological estimates of sex/gender breakdowns of depression. Moreover, some of the cognitive/behavioral tasks that we outline in this renewal have sometimes evidenced sex/gender differences (e.g., [47]), so we will have the opportunity to comparatively assess that via our multi-modal investigation.

Power analyses: [need to redo and confirm] Power analyses were conducted using a repeated measures ANOVA estimate for a between-within interaction. Power for finding an effect was set to 90% and alpha error probability set at .05, number of groups estimated at 2, number of measurements set at 3 and the effect size estimating the between-subjects difference between depressed and non-depressed individuals of the within-subjects comparison of attentional biases for positive and neutral stimuli (i.e., reward devaluation of positive stimuli; effect size estimate noted in Table 1 in the significance section, g = .399). Given this estimate, 56 individuals would be required to provide required power, for which we will recruit 80 individuals to allow for 30% attrition and preselect for various levels of depression to ensure adequate between-subject variability.

Expected Results: We expect that happiness and sadness assessed by the IMDES will predict symptoms of depression and impairment over time and that this will be primarily evident in tasks [to be added upon final task selection] consistent with previously established cross-sectional findings [18]. We also expect that fear assessed by the IMDES will predict symptoms of spider phobia and related psychophysiological reactivity to and behavioral avoidance of spider images. We will also examine the moderating effects of alexithymia on the predictive power of the two types of emotion measures; we expect that high levels of alexithymia will reduce the predictive capability of the self-report measure but will not impact the predictive validity of the IMDES. Exploratory analyses will also investigate the specificity and overlap of each task to determine whether particular task elements are more sensitive or specific predictors of psychological crisis and impairment.

Potential difficulties and limitations

Although highly unlikely given that our recruitment strategy is based on the one established in our consultant's R15, there is a possibility that subject recruitment will be slower than anticipated. In order to proactively manage this problem, we have set inclusion criteria that will enroll individuals with subthreshold but elevated symptoms and healthy controls. Still, some subjects may drop out before completing multiple assessments. To ensure completion, subjects will receive a bonus payment at the last session. Lastly, because of the long period of time between the first and the last session, subjects will only be required to attend the three month session to be included in the study.

Timeline (see budget justification for a figure representation of the following)

Year 1. In the first four months, apparatus and instruments will be prepared, graduate and undergraduate students will be trained on experimental protocols and interview instruments, and subject recruitment efforts will begin. In the next 3-months subject screening will begin and approximately 8 subjects/month will complete first assessments in the final 8 months. Three-month assessments will begin in the last five months of Year 1 and will provide an initial estimate of retention rates (i.e., of the 40 participants that will have begun assessments, we anticipate that at least 28 will have returned for three-month assessments). By the end of Year 1, approximately 64 subjects will have begun assessments.

Year 2. In Y2, approximately 8 subjects/month will be entered into the study until 80 initial subjects have been entered into the protocol. The initial sessions will be complete during the 2nd month. Three-month assessments will continue until the 5th month, at which point one-year follow-up assessments will begin. Data analyses, manuscript production, and conference dissemination will begin in month 6 of Year 2 and continue throughout the award.

Year 3. One-year follow-up data collection will continue through the second month of Year 3. Papers will be submitted for presentation at professional conferences by the investigators and graduate and undergraduate students affiliated with the project, publications to peer-reviewed journals will also be prepared and submitted, and data collected will also serve as pilot data for future grant proposals from the research team.

Future Plans

Our ultimate goal is to, via an experimental therapeutics approach, use the IMDES in the early detection, treatment, and prevention of PVS and NVS disturbances and suicidal tendencies. For example, treatments guided by this research could incorporate experimental indicators in advance of best practices treatments to identify individuals who are at risk of developing depression. Because of its remarkable discriminant validity, the IMDES can help clinicians in making differential diagnoses and thus result in selecting better targeted and more effective treatment approaches.

Funding from this R15 will allow the PI and his research team to continue this meritorious program of research that is consistent with the RDoC and experimental therapeutics approaches of the NIMH Strategic Plan for Research and will allow continued world-class scientific opportunities for students of a university and state traditionally underfunded by NIH.