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Prolonged physiological reactivity and loss: Association of pupillary reactivity with negative thinking and feelings

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Abstract

Prolonged psychophysiological reactions to negative information have long been associated with negative thinking and feeling. This association is operationalized in the RDoC negative affect construct of loss, which is nominally indexed by prolonged physiological reactivity, cognitive loss-related constructs such as rumination and guilt, and more feeling-related constructs such as sadness, crying, and anhedonia. These associations have not been tested explicitly. If thinking and feeling aspects of loss reflect different physiological mechanisms, as might be suggested by their putative neurobiology, different intervention pathways might be suggested. Here we examined the extent to which self-reported negative thinking and feeling constructs were associated with prolonged pupillary reactivity following negative words and a subsequent cognitive distractor in a diverse heterogeneously diagnosed sample of $N = 84$ participants. We also considered indices of abuse and variables associated with borderline personality disorder as possible moderators. Consistently, feeling-related negative affect constructs were related to prolonged pupillary reactivity during the distractor after a negative stimulus whereas thinking-related constructs were not. These data suggest that people who have sustained physiological reactions to emotional stimuli may be more strongly characterized by non-linguistic negative feelings than explicit cognitions related to loss. Sustained physiological reactions could reflect efforts to regulate feeling states. In contrast to cognitive and affective variables, abuse was associated with decreased physiological reactivity, consistent with decreased neural engagement. Interventions that target mechanisms underlying feelings and their regulation may be more mechanistically specific to sustained reactivity than those which directly address cognitions.

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1. Introduction

A variety of psychiatric conditions including depression, anxiety, and borderline personality disorder have been associated with years-long trait-like reactions to loss of something valued including a loved one (Turvey et al., 1999), pregnancy (Gong et al., 2013), an attachment relationship including marriage (Distel et al., 2011; Stalker and Davies, 1995), a job (Mandal et al., 2011), a capability such as vision (Zhang et al., 2013) or hearing (McDonnall, 2009), resources (Luyster et al., 2006), hair (Schmitt et al., 2012), or an expected reward (Huston et al., 2013). Repetitive thinking about what was lost, and about associated negative feelings has been identified with the transformation of loss into profound and often very negative outcomes (Nolen-Hoeksema et al., 1994). These prolonged psychological reactions on the time-course of months or years have been observed to be mirrored in prolonged psychophysiological reactions to stress (Brosschot et al., 2006), with higher trait rumination specifically associated with prolonged physiological reactivity (Gerin et al., 2006; Glynn et al., 2002; Siegle et al., 2003a,b). Thus, there are plausible associations of sustained loss reactions with repetitive negative thinking and prolonged psychophysiological reactivity. These associations are operationalized in the National Institute of Mental Health's Research Diagnostic Criteria (RDoC) initiative's (Insel et al., 2010) negative affect construct of loss, which is nominally indexed by prolonged physiological reactivity, as well as loss-reaction related constructs that are more cognitive such as rumination and guilt, and more feeling-centered such as sadness, crying, and anhedonia. That said, associations of prolonged psychophysiological reactivity with repetitive thinking, considered broadly, are more well-established than associations with other aspects of loss such as RDoC-named more purely cognitive features. Here, we used associations of behavioral and self-report measures with physiological reactions to emotional cues to provide an empirical basis for relationships between different theoretically implicated aspects of the RDoC loss construct.

These considerations are important for the long-term mission of using the RDoC model to personalize medicine by directing individuals to treatments that target their disease mechanisms. The promise of this work is to highlight currently available measures that could be used to evaluate whether treatments target mechanisms underlying loss-related pathologies. Currently available treatments do appear to target increased and sustained physiological reactivity. For example, antidepressants appear to decrease gaze towards negative stimuli (Wells et al., 2014). Both anti-depressants and Cognitive Therapy appear to decrease neural features of reactivity to emotional stimuli (DeRubeis et al., 2008; Harmer et al., 2006; McCabe et al., 2010). Thus, such interventions may be particularly appropriate for individuals with this profile. But if loss is, as is sometimes clinically observed, associated with features such as blunted reactivity to emotional stimuli, different interventions may be warranted.

In particular, there may be differential associations of prolonged physiological reactivity with more cognitive and more emotional aspects of loss, which can have differing biological substrates and thus could lead to different roles for physiology in planning for intervention. Indeed, our previous work has suggested that therapeutic response is associated with decreased physiological reactivity during a transition from more emotional to more

cognitive processing (Siegle et al., 2011), and that rumination is specifically associated with increased reactivity during initial emotional and subsequent cognitive processing but not that transition (Siegle et al., 2003a,b). Thus, using a similar paradigm to these previous investigations, we examined the extent to which self-reported negative thinking and feeling constructs were associated with prolonged pupillary reactivity following negative words and a subsequent cognitive distractor. This work was done in a diverse heterogeneously diagnosed sample of patients stratified on symptoms of borderline personality disorder, which inherently yielded a strong sampling of other features of psychopathology such as depression and anxiety.

We specifically considered reactions to negative information. Increased and sustained reactivity to negative information has been observed transdiagnostically in psychopathology throughout multiple domains. Implicated brain circuits include increased and sustained amygdala activity and decreased prefrontal regulatory control (Clark and Beck, 2010; Davidson, 2000). Increased neural reactions to errors (Holmes and Pizzagalli, 2008) and increased and sustained physiological reactions (Brosschot et al., 2006; Siegle et al., 2001, 2003a,b) have also been observed. Behavioral measures include increased attention to threat (MacLeod and Mathews, 1991), increased gaze towards negative information (Sanchez et al., 2013; Schofield et al., 2012), enhanced memory for negative information in depression (MacLeod and Mathews, 1991), and associations of these variables with self-reported traits such as rumination (Siegle et al., 2003a,b).

Prolonged physiological reactivity was operationalized here using a task designed to capture a variety of constructs which have been associated with emotion and its regulation. Features from initial attention to emotional information through sustained elaborative processing were captured by measuring physiological reactivity to emotional words. We assessed pupillary motility as a measure of sustained cognitive and emotional load (Beatty and Lucero-Wagoner, 2000), with studies of concurrent pupil and functional magnetic resonance imaging (fMRI) suggesting that the pupil provides a particularly strong index of activity in prefrontal brain structures involved in cognitive processing (Siegle et al., 2003a,b). Increased pupil dilation during the word period was presumed to reflect increased engagement with the stimulus including both initial reactions and potentially, attempted regulatory control. Gaze towards or away from the emotional stimuli was used to help interpret whether increases in pupil dilation represented attention to the emotional stimulus or efforts to disengage from it.

Ability to disengage from the emotional stimuli and subsequently sustained elaboration even following distraction were captured by trials requiring digit sorting following the emotion identification trial. We have used such “alternating task”—alternating between presentation of emotional stimuli and engagement in cognitive tasks—designs to show that depressed individuals, particularly those who ruminate, display increased and sustained amygdala activity (Mandell et al., 2014; Siegle et al., 2002), as well as increased and sustained peripheral physiological reactivity to emotional information (Siegle et al., 2003a,b).

Given the increasing primacy of the RDoC model in national thinking about psychopathology, our primary goal was to empirically evaluate the validity of an RDOC-

consistent integrative model of the loss dimension, as described in that framework. Thus, using reliability analysis, we examined whether RDoC-named loss-associated constructs could be used to index a single latent construct across self-report, behavioral and physiological domains, particularly involving pupil dilation measured during successive phases of emotional information processing (initial exposure to the emotional stimulus, switching to more cognitive processing, cognitive information processing in the presence of the emotional stimulus, and sustained processing after the cognitive task is done). Our primary hypothesis was that indeed, loss could be thought of as a single dimension. A positive finding would be indicated by high internal consistency (Cronbach's $\alpha > .7$) across scales and measurement domains. A negative finding would be indicated by low internal consistency across the scales (Cronbach's $\alpha < .5$). Even if a single construct was supported, differential associations with one or multiple temporally defined features of sustained pupil dilation could suggest important nuances, and were thus investigated.

We also considered whether two trait variables often associated with feelings of loss moderated these associations including abuse and features of borderline personality disorder. Abuse has been broadly conceptualized as a loss of safety (Janoff-Bulman, 1992). Abuse may also be conceptualized as a loss of caregiving resources (Bowlby, 1969/1982). Altered reactivity to loss related stimuli may thus reflect associations with the abuse experience and subsequent coping attempts. Abuse has specifically been associated with increased amygdala reactivity (Dannlowski et al., 2013), decreased modulation of the amygdala by prefrontal regulatory circuitry (Birn et al., 2014) as well as disruptions of peripheral physiological reactivity (D'Andrea et al., 2013; Metzger et al., 1999; Orr et al., 1998).

Personality variables, particularly those associated with borderline personality (BPD) were also considered for moderation. Conceptualizations of BPD focus on the environmental etiology including outright abuse (Lieb et al., 2004; Schmahl et al., 2004) as well as repeated caregiver threats of abandonment (Lobbestael et al., 2005; Schmahl et al., 2003). Thus, the core symptoms of borderline pathology (identity fragmentation, affect dysregulation, and relational disturbance) have been theorized to function as attempts to prevent loss of attachment figures (Fonagy, 2000).

2. Method

2.1. Participants

In a study devoted to recruiting a sample stratified on features of BPD (MH056888) we completed physiological assessments on 104 participants from the outpatient assessment clinic and affiliated clinics at Western Psychiatric Institute and Clinic, other community mental health programs, and from the broader community. One individual was excluded due to a prior stroke affecting motor function and data for five individuals were lost due to equipment malfunction and data for 14 participants were acquired on other physiological assessment tasks but not the task that was analyzed for this manuscript due to time constraints. Thus, $N = 84$ were preserved for analysis. Preserved participants described no physical health problems that would interfere with testing, no eye problems or psychoactive drug dependence, and no history of psychosis, manic, or hypomanic episodes. Participants were not taking antipsychotic or anticholinergic medications. Participants scored in the

normal range on a cognitive screen, (Nelson and Willison, 1991); VIQ-equivalent > 85. Their demographics and clinical profile is described in Table 1.

2.2. Procedure

The design was cross sectional, involving multiple assessment days, the last of which involved psychophysiological assessment. After signing IRB-approved consent forms, participants completed a diagnostic interview (First et al., 1996), depression symptom interview (Hamilton, 1967), and word-list generation as part of an extensive assessment up to two weeks prior to testing. Participants completed the Beck Depression Inventory II (BDI-II (Beck et al., 1996)), an inventory frequently used to assess depressive severity, on the testing day. BDI items neatly correspond to RDoC named loss dimensions as noted below. At that time, participants also completed information processing tasks during pupillary assessment. A digit sorting task (repeatedly putting digits in numerical order) (Siegle et al., 2003a,b) to decrease novelty effects, was followed by other tasks not reported here (facial emotion identification, attention network task) and the primary task, an alternating emotion-identification/digit sorting task, administered in a counterbalanced order.

2.3. Alternating emotion-identification, digit-sorting task

The analyzed task involved 60 9.5-second compound emotion-identification/digit sorting trials as shown in Fig. 1. Emotion-identification consisted of a cue mask (0.5 s), word (presented alone for 3 s, but remained on the screen continuously through the remainder of the trial; 10 positive, 10 negative, and 10 neutral personally-relevant and 10 positive, 10 negative, and 10 neutral normed words (methods in Siegle et al., 2001; 2003 and Supplementary Data: Method: Word List Generation)) presented in a different pseudorandom order for each participant, during which participants were instructed to name the emotionality of the word using buttons for “Positive” (labeled “+”), “Negative” (“-”), or “Neutral” (“N”) as quickly and accurately as they could. The digit-sorting portion contained a cue mask (0.5 s), four digits (1.5 s), mask (1 s), and target digit from the set (3 s). Participants were told that when the digits appeared, they should read them from left to right, put them in numerical order in memory, and remember the middle digit in the sorted list; when the target appeared, they should push buttons for “yes” (“Y”) or “no” (“N”) to indicate whether the target was the middle digit from the previous set, as quickly and accurately as they could. Participants were told they should not use special strategies such as sorting the digits by moving their eyes on the screen or sorting only the first few digits, because we were examining the process of sorting items in memory.

2.3.1. Measures of RDoC self-report and behavioral loss-related constructs—

Multiple measures of symptom constructs described in the RDoC as loss-related included: Rumination (Rumination–Reflection Scale (Trapnell and Campbell, 1999); RRQ rumination subscale); Withdrawal/Amotivation (Beck Depression Inventory II (BDI-II) (Beck et al., 1996) loss of interest item); crying (BDI-II crying item); sadness (BDI-II Sadness item); shame (PANAS ashamed item); guilt (BDI-II guilt item); Morbid Thoughts/hopelessness (BDI-II suicide scale (hopelessness and suicidal thinking)); psychomotor retardation (median reaction time to digit sorting); anhedonia (BDI-II anhedonia scale); increased self-

focus (RRQ self-reflection scale, rated personal-relevance of normed words, e.g., as in (Dozois, 2007)); deficits in executive function (BDI-II executive function item; digit sorting percent correct); loss of drive (sleep, appetite, libido; BDI-II drive subscale including sleep, appetite, libido items).

2.3.2. Measures of abuse and personality potential moderators—Measures associated more traditionally with personality disorder and abuse were also considered potentially relevant moderators of reactions to loss. In particular we considered personality variables often observed in individuals with borderline personality disorder which is associated with cognitions around perceived loss such as feelings of abandonment. A number of subscales of the Personality-Assessment Inventory– Borderline Scale (PAI–BOR) (Morey, 1991) were thus employed including the identity fragmentation subscale, possibly associated with a loss of identity, the negative relationships scale, possibly associated with loss or threatened loss of functional relationships, and the affective instability subscale, possibly associated with a loss of stability.

We also considered abuse as it is frequently conceived of as a loss of attachment relationships. Towards this end we used consensus clinical team ratings based on SCID interviews for abuse domains of physical (physical neglect, physical abuse, sexual abuse), psychological (psychological neglect, witnessing abuse, antipathy, or psychological abuse), and neglect (physical or psychological neglect), with each component above scored as 0–3 (no, minimal, moderate, and severe abuse). Components were totaled to yield scale scores for each type of abuse and a total abuse subscale given that loss pathology appears to scale linearly with adverse childhood experiences regardless of type (Murphy et al., 2014). Sensitivity analyses examined an alternate scoring system in which no-abuse and minimal-abuse were both not counted as abuse. These analyses did not differ qualitatively from the non-thresholded scales.

3. Data selection and analysis

3.1. Grouping self-report, behavioral, and clinical measures

Our primary goal was to relate self-report, clinical, and behavioral measures to psychophysiology. Given that there were a large number of considered variables, many of which overlapped in character, we used principal components analyses (PCA) to create parsimonious sets of interpretable variables for later analysis. One PCA was performed on the theoretically loss-related variables and another was performed on the candidate moderator variables. PCA was performed on the correlation matrix because variables were on different scales. Missing scores were imputed based on all non-missing measures and outliers rescaled, with varimax rotation. PCA of primary loss-related variables identified three factors via Scree plot, accounting for 65% of the variance in the measures. Interpreting loadings over 0.30 (threshold at which all but one variables were accounted for; loadings highlighted by magnitude in Table 2), the first factor contained most of the BDI items, representing depressive severity (43.6% of the variance). The second factor contained the rumination scales, personal relevance rating, BDI guilt, and PANAS ashamed items (12.04%), consistent with negative self-referent thinking — or, as it is conventionally conceived of, rumination. The third factor contained the digit sorting %-correct and reaction

time items consistent with cognition; the PANAS ashamed item also loaded on this scale as well as the second factor, which could reflect evaluation of performance on the cognitive task by people who found it difficult (9.2%). Though these factors largely represented the methods by which they were acquired (1 was a single homogeneous self-report measure, 2 was other self-report measures, 3 was behavior), they appeared valid as the assessed constructs were confounded with the methods of acquisition, and were thus used in subsequent analyses. To be sure of the extent to which results were consistent within factors, scale-level analyses were also considered as sensitivity analyses. Similarly for the potential moderators, a Scree plot suggested a two-factor solution that explained 73% of the variance in which the first factor consisted of all of the PAI-BOR scales (47.5% of the variance), consistent with borderline personality traits, and the second factor consisted of all of the abuse scales (26%).

3.1.1. Pupillary and eye-tracking data preparation—Pupil data and eye-tracking were cleaned using previously described procedures (Siegler et al., 2008; Silk et al., 2012). Blinks were automatically identified and samples during blinks were replaced with linear interpolation between the previous and subsequent non-blink data. Trials comprised of over 75% blinks were removed, $M(SD)$ drops = 3.63(5.08) equating to 6(8)% of trials. Pupillary responses were baseline-corrected within-trial by subtracting mean pupil diameter from the first 10 samples (167 ms) from the remainder of the trial. Trials with incorrect responses were excluded prior to analysis. Reaction time outliers outside the Tukey Hinges (75th percentile + 1.5 * Interquartile Range, 25th percentile – 1.5 * Interquartile range) were rescaled (Windsorized) to the nearest good value within that range. Reaction times were aggregated within participants via harmonic means and pupil data were aggregated via means. Eye-tracking data was removed for five participants whose gaze was not reliably tracked. Pupillary and eye-tracking outliers outside the Tukey Hinges subject-wise were interpolated based on adjacent samples within participants to yield smooth curves. For eye-tracking data, the Y-coordinate was preserved for interpretation with higher gaze representing looking up towards digit-stimuli and lower gaze representing looking down towards word stimuli.

3.1.2. Physiological data analysis—Because we were interested primarily in sustained pupillary responses, conventional statistics such as peak-response, which are not specific to the latter portion of the waveform, are not appropriate. Rather, we computed contrasts at each sample along pupillary and gaze-Y-coordinate waveforms; statistically significant tests thus represented temporal windows associated with effects of interest. To control type 1 error at $p < .05$ across the waveform, 35 consecutive samples (.56 s) of tests in a row, each significant at $p < .1$, considered replications, were deemed significant based on Monte Carlo simulations of data with similar autocorrelation to the observed waveforms (described in (Guthrie and Buchwald, 1991), (Siegler et al., 2008) and Supplementary Data: Method: Type I Error Control). Results report tests of the mean pupillary response in significant windows.

4. Results

4.1. Sociodemographic and behavioral data

Sociodemographic and behavioral data are presented in Table 1. Participants rated negative words as more negative than neutral words, $t(70) = 5.78$, $p < .005$, $D(\text{rating}) = 0.40(0.58)$, $d = 0.69$, or positive words, $t(70) = -9.32$, $p < .005$, $D(s) = -1.18(1.06)$, $d = -1.11$, and neutral words as less positive than positive words $t(70) = -13.92$, $p < .005$, $D(s) = -1.57(0.95)$, $d = -1.65$. Performance was excellent on digit-sorting (means > 90% correct following all types of words).

4.2. Psychophysiological manipulation check

Before examining individual differences, we considered the extent to which participants reliably displayed cognitive load on the task. Pupil dilation reliably increased across participants in response to the word and digit sorting tasks (Fig. 1A), potentially reflecting a change in cognitive load. Thus, factor analysis of the pupillary waveform yielded factors that reliably differentiated the components of the compound trials (Fig 1B).

4.3. Internal consistency of the loss construct

To examine the extent to which the loss construct, as operationalized in this study, was reliable enough for further investigation, we examined its internal consistency with respect to z-scored administered self-report and physiological scales. For this analysis, digit sorting percent correct and reaction time were reverse scored to yield an index of increased problematic cognition. Together, the administered self-report variables associated with loss in the RDoC had internal consistency (Cronbach's alpha) of 0.83 consistent with measurement of a single construct. The pupil variables had item-total correlations ranging from 0.2 to 0.48, which was in the same range as many of the self-report variables. Adding the pupil to the loss items did not change alpha appreciably ($\alpha = 0.81$) despite the difference in method-of-acquisition. To understand which measures most strongly contributed to a unified construct, Fig. 2a shows the item total (not including the item) correlation for each scale and Fig. 2b shows the change in alpha when each item is removed. Items except for the RRQ reflection and digit sorting %-correct scale were generally positively correlated with the underlying construct, and alpha increased only when removing the performance and reflection items, potentially suggesting the utility of separating items more associated with emotion from more purely cognitive processing. Removal of pupillary motility items decreased alpha. Thus, the pupil dilation data appears to be analyzable within the loss construct as a potential constituent measure.

4.4. Association of individual RDoC nominally loss-related variables with pupillary reactivity

Multiple pupillary motility factors were associated with self-report factors with $|r| > .15$ (Fig 3A; scatterplots showing each participant in Supplement Fig S3). Features of depressive severity were most strongly associated with sustained pupillary reactivity during the task-switching period in which participants were expected to disengage from the word and long after the digit probe was matched, during which there was no explicit task. Personally

relevant negative thinking was not strongly associated with pupil dilation. Trait cognition (interpreted as the reverse of the factor score, so better performance, shorter reaction times, and low shame are higher cognition) was associated with increased pupillary motility during the task components with the highest pupil dilation — judging the word's valence and probe's match potential. These associations were also present in an analysis in which the top and bottom half of component scorers were contrasted based on a median-split on the factor scores (Fig 3B) at every sample along the waveform as well as when the component scales were considered separately in a similar fashion (Fig 3C; significant regions, $p < .1$, for >0.58 s in Table 3). These analyses confirmed that the time-window factors performed as would be expected from the samples from which they were derived.

To aid interpretation of observed pupil dilation effects as reflecting either increased processing or efforts to disengage from emotional stimuli, eye-tracking throughout trials, analyzed analogous to pupil dilation was checked. As shown in Fig. 3D, the Y coordinate (up/down) for gaze largely followed the task design, with participants looking down towards the word during the word period and up towards the digits during the digit period. Participants higher in depressive severity tended to look down more at the word during the word period and after sorting digits (significant regions in Table 3).

4.5. Moderation of effects by personality and abuse variables

Borderline personality variables were associated with increased dilation in the task-switching period after the word is responded to and before the digit sorting period, likely associated with disengaging from the word, and abuse was associated with decreased dilation during the word period (Fig 4A) which could be seen in sample-wise waveforms for the top and bottom half based on a median split (Fig 4B; $p < .1$ for $> .58$ s in Table 3), and at the scale level (Fig 4C). These features did not interact with loss variables; only a cognition $\times$ abuse interaction was noted which did not survive type I error control (Fig 4D). These variables also did not strongly qualify primary effects — i.e., the same effects were largely observed in semi-partial correlations for the loss factors when personality effects were co-varied out (Fig 4E). Thus, effects of abuse and personality had observable effects on neural processing but did not strongly moderate those of the loss variables. Eye-tracking findings for personality paralleled those for depressive severity (Fig 4F, Table 3).

4.6. Differential association of time periods with loss constructs

To understand whether similar aspects of sustained pupillary reactivity were associated with each facet of the loss construct, we conducted regressions for each loss self-report factor in which all time factors were entered simultaneously as explanatory variables. As shown in Table 4A, the full models were significant for depressive severity, and cognition, but not personally relevant negative thinking. Table 4A, C highlights the time periods that were independently predictive for each self-report factor ($p < .05$). For all predictive variables, multiple periods long after the word was presented were predictive of pupil dilation.

4.7. Differential association of loss variables with pupillary reactivity

To understand whether similar aspects of loss were associated with each period of pupillary reactivity, we conducted regressions for each time factor in which all loss PCA factors were

entered simultaneously as explanatory variables. As shown in Table 4B, C the full models were not significant for the first periods (preparation, word, late-word, task-switch) but were significant for the last two periods, including probe comparison and post-comparison. Fig. 4B highlights the self-report factors that were independently significant for each time interval.

4.8. Effects of valence

The loss construct centers on reactivity to negative information. To understand the extent to which loss variables were associated only with negative information we also considered their association with physiological reactivity to positive and neutral information. Indeed physiological reactivity differed across the valences (Supplement V) and associations of the self-report, behavioral, and clinical variables differed as a function of the examined valence (Supplement VI–VIII). For example, many of the BDI variables that were positively associated with pupillary reactivity to negative words were negatively associated with reactivity to positive words.

5. Discussion

The construct of loss has been theoretically associated with many self-report domains and aspects of sustained physiological reactivity. Here we investigated whether these constructs strongly reflected a single or multiple constructs. The included self-report, behavioral, and physiological measures yielded an internally consistent construct (Cronbach's $\alpha > .8$). This basic finding supports the soundness of the RDoC loss construct across the domains of self-report, behavior, and physiology.

5.1. Differential associations of temporal windows of reactivity with self-report variables

Yet, self-report loss-related variables were differentially associated with pupillary reactivity across the time course of response to negative stimuli suggesting possible nuances worthy of clinical attention. Cognitive features were associated with increased pupillary reactivity in association with the normative time-course of cognitive and emotional information processing, consistent with inefficient processing. Depressive severity was associated with increased and sustained pupillary reactivity long after the emotional stimulus, which was accompanied by increased gaze towards the emotional stimuli, consistent with increased processing of emotional information. Personally relevant negative thinking and rumination was not strongly associated with pupillary reactivity. Together, these data suggest that there may be physiologically separable aspects of the RDoC loss construct.

Results specifically suggested that people who have sustained pupillary reactions to negative emotional stimuli that last into a time where they are trying to do something besides have an emotion may be more strongly characterized by negative affect (depressive severity) rather than explicit ruminative negative cognitions or cognitive inefficiency. Such sustained reactions are unlikely to reflect regulation of feeling states given the increased gaze towards the emotional words.

5.2. Moderation of reactivity by abuse and personality variables

Candidate moderators of loss-reactivity were also related to pupillary reactivity. Abuse was associated with decreased early reactivity, possibly suggesting decreased neural engagement. This decreased reactivity was present for both positive and negative stimuli, consistent with overall blunted reactivity. Variables associated with borderline personality, like those associated with depressive severity, were associated with increased reactivity during task switching, potentially reflecting increased effort at disengagement from emotional stimuli, consistent with inefficient regulatory control. That said, these variables did not moderate loss-related variables' relationship to physiological reactivity (Fig. 4D). They also did not account for the same variance as the loss variables to the extent where the loss-related variables were nonsignificant (Fig. 4E). Thus, we suggest, they may represent separable enough constructs that they do not need to be rolled into most investigations of loss. For example, in contrast to cognitive features of loss reactivity such as uncertainty, abuse may reflect both temporally distal events and a more certain rupture in attachment. Perhaps, the associated decreased pupillary reactivity is reflective of withdrawal in situations that evoke helplessness. Thus, cognitive features may reflect a state of active distress whereas abuse could reflect constructs more like helplessness, and disengagement with affective material. Whereas low prolonged physiological reactivity has, at times, been interpreted as a sign of resilience, well-being, and psychological stability (Mancini and Bonanno, 2009), such an interpretation, as representing active withdrawal, could suggest that both increased and decreased reactivity represent potential vulnerabilities.

5.3. Clinical implications

These results have implications for basic and clinical research. A consideration relevant to basic research regards the utility of including loss in the RDoC negative affect spectrum. The identified components of loss hung together psychometrically and were individually related to one-another. That said, the current data suggest that this intuitively simple term may represent the result of multiple of neural and phenomenological features, and separation of more purely executive functions from more purely affect-related functions may be useful. Intuitive moderators such as abuse may serve to decrease reactivity that could otherwise be intuitively attributed to loss, but does not account for variance explained by loss-related variables.

The clinical parallel involves the extent to which translational research should work to target loss as a construct. Rather, the current work suggests that there may be room for multiple mechanistic interventions targeting different aspects of the loss construct. Indeed there are currently available cognitive training interventions that target executive function and different interventions (e.g., Cognitive Therapy) that target aspects of depressive symptomatology, and still others that target repetitive negative thinking more uniquely (Watkins et al., 2011). Initial data suggests that intervening on one of these domains such as executive functioning can affect the others including both depressive symptomatology and rumination (Calkins et al., 2014; Siegle et al., in press). That said, combining or separating such targeted interventions has largely not been tried, because the component domains have been considered so similar. Targeting abuse separately from these other constructs may be particularly useful. Whereas decreasing reactivity for individuals with high levels of loss

related symptoms may generally be key, increasing engagement with emotional information for some individuals, particularly those with abuse histories, may be similarly important.

In addition, initial analyses suggested that clinical variables related to loss may have as much to do with reactivity to positive information as they do to negative, possibly suggesting a blurring of the RDoC lines. Continuing to elucidate such relationships across RDoC categories may be as important as understanding the nature of the categories themselves.

5.4. Limitations

This study has a number of limitations. Foremost is that the examined self-report variables, while theoretically associated with loss by the RDoC negative affect committee, do not directly reference loss. There is no measure of an event of loss or what was lost in this study. Whether anything we have discussed is truly related to specific losses has not been tested. The sampling, of participants varying in BPD features, diagnoses, and treatment status, yielded a highly heterogeneous group, which could be considered an advantage from the standpoint of a generalizable psychometric study, but a limitation in terms of the potential for inference regarding traditional diagnostic groups. Pupil dilation inherently measures brain activity associated with both cognitive and emotional information processing. As such, without additional information, inferences regarding what aspects of information pupil dilation represents a specific response to are difficult. Because the task had separable cognitive and affective components, and because eye-tracking was measured, the current design mitigates this problem to some extent, but if emotional information processing occurred during the nominally cognitive task and participants were not looking at the emotional stimulus, we would not be able to know. Specifically, load associated with emotional reactivity and regulation are confounded and inseparable, so increased pupil dilation could reflect increased unregulated reactivity or increased regulatory effort that was not successful in helping participants move their gaze. We have thus stayed, carefully, away from interpretations that rely on separating these constructs. Finally, there was no explicit manipulation of constructs central to this manuscript such as repetitive negative thinking. Thus, inferences regarding variability in such constructs are correlational and causality cannot be established.

5.5. Summary

These limitations notwithstanding, this study adds significantly to the literature on the “loss” construct, which has been catapulted to salience with the emergence of the RDoC. There has been a great deal of research on specific types of loss, such as grief, and in specifically homogeneously diagnosed populations. The current data suggests that in a more general context, there may indeed be a central loss construct, but that it has separable features more clearly associated with depressive symptoms, repetitive thinking, and cognition, and that these are differently associated with one measure of sustained physiological reactivity, pupil dilation. Potentially different mechanistically targeted interventions would target neurobiology underlying these separable components.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Beatty, J.; Lucero-Wagoner, B. The pupillary system. In: Cacioppo, JT.; Tassinary, LG.; Berntson, GG., editors. *Handbook of Psychophysiology*. Cambridge University Press; New York, NY: 2000. p. 142-162.
- Beck, AT.; Steer, RA.; Brown, G. *Beck Depression Inventory Second Edition Manual*. San Antonio: The Psychological Corporation; 1996.
- Birn RM, Patriat R, Phillips ML, Germain A, Heringa RJ. Childhood Maltreatment and Combat Posttraumatic Stress Differentially Predict Fear-related Fronto-subcortical Connectivity. *Depress Anxiety*. 2014; 31(10):880–892. [PubMed: 25132653]
- Bowlby, J. *Attachment and loss Attachment Vol I*. Basic Books; New York: 1969/1982.
- Brosschot JF, Gerin W, Thayer JF. The perseverative cognition hypothesis: a review of worry, prolonged stress-related physiological activation, and health. *J Psychosom Res*. 2006; 60(2):113–124. [PubMed: 16439263]
- Calkins AW, McMorran KE, Siegler GJ, Otto MW. The effects of computerized cognitive control training on community adults with depressed mood. *Behav Cogn Psychother*. 2014:1–12. [PubMed: 23552390]
- Clark DA, Beck AT. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. *Trends Cogn Sci*. 2010; 14(9):418–424. [PubMed: 20655801]
- D'Andrea W, Pole N, DePierro J, Freed S, Wallace DB. Heterogeneity of defensive responses after exposure to trauma: blunted autonomic reactivity in response to startling sounds. *Int J Psychophysiol*. 2013; 90(1):80–89. [PubMed: 23896169]
- Dannowski U, Kugel H, Huber F, Stuhrmann A, Redlich R, Grotegerd D, et al. Childhood maltreatment is associated with an automatic negative emotion processing bias in the amygdala. *Hum Brain Mapp*. 2013; 34(11):2899–2909. [PubMed: 22696400]
- Davidson RJ. Affective style psychopathology and resilience: brain mechanisms and plasticity. *Am Psychol*. 2000; 55:1196–1214. [PubMed: 11280935]
- DeRubeis RJ, Siegler GJ, Hollon SD. Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nat Rev Neurosci*. 2008; 9(10):788–796. [PubMed: 18784657]
- Distel MA, Middeldorp CM, Trull TJ, Derom CA, Willemsen G, Boomsma DI. Life events and borderline personality features: the influence of gene-environment interaction and gene-environment correlation. *Psychol Med*. 2011; 41(4):849–860. [PubMed: 20594379]
- Dozois DJ. Stability of negative self-structures: a longitudinal comparison of depressed, remitted, and nonpsychiatric controls. *J Clin Psychol*. 2007; 63(4):319–338. [PubMed: 17279521]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JB. *Structured Clinical Interview for DSM IV Axis I Disorders Patient Edition vol 20*. Biometrics Research Department New York State Psychiatric Institute; New York: 1996.
- Fonagy P. Attachment and borderline personality disorder. *J Am Psychoanal Assoc*. 2000; 48(4): 1129–1146. discussion 1175–1187. [PubMed: 11212185]
- Gerin W, Davidson KW, Christenfeld NJ, Goyal T, Schwartz JE. The role of angry rumination and distraction in blood pressure recovery from emotional arousal. *Psychosom Med*. 2006; 68(1):64–72. [PubMed: 16449413]

- Glynn LM, Christenfeld N, Gerin W. The role of rumination in recovery from reactivity: cardiovascular consequences of emotional states. *Psychosom Med.* 2002; 64(5):714–726. [PubMed: 12271102]
- Gong X, Hao J, Tao F, Zhang J, Wang H, Xu R. Pregnancy loss and anxiety and depression during subsequent pregnancies: data from the C-ABC study. *Eur J Obstet Gynecol Reprod Biol.* 2013; 166(1):30–36. [PubMed: 23146315]
- Guthrie D, Buchwald JS. Significance testing of difference potentials. *Psychophysiology.* 1991; 28(2): 240–244. [PubMed: 1946890]
- Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol.* 1967; 6(4):278–296. [PubMed: 6080235]
- Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry.* 2006; 59(9):816–820. [PubMed: 16460693]
- Holmes AJ, Pizzagalli DA. Spatiotemporal dynamics of error processing dysfunctions in major depressive disorder. *Arch Gen Psychiatry.* 2008; 65(2):179–188. [PubMed: 18250256]
- Huston JP, Silva MA, Komorowski M, Schulz D, Topic B. Animal models of extinction-induced depression: loss of reward and its consequences. *Neurosci Biobehav Rev.* 2013; 37(9 Pt A):2059–2070. [PubMed: 23466533]
- Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010; 167(7):748–751. [PubMed: 20595427]
- Janoff-Bulman, R. *Shattered Assumptions: Towards a New Psychology of Trauma.* Free Press; New York, NY: 1992.
- Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. *Lancet.* 2004; 364(9432):453–461. [PubMed: 15288745]
- Lobbestael J, Arntz A, Sieswerda S. Schema modes and childhood abuse in borderline and antisocial personality disorders. *J Behav Ther Exp Psychiatry.* 2005; 36(3):240–253. [PubMed: 15953584]
- Luyster FS, Hughes JW, Waechter D, Josephson R. Resource loss predicts depression and anxiety among patients treated with an implantable cardioverter defibrillator. *Psychosom Med.* 2006; 68(5):794–800. [PubMed: 17012535]
- MacLeod, C.; Mathews, AM. Cognitive experimental approaches to the emotional disorders. In: Martin, PR., editor. *Handbook of Behavior Therapy and Psychological Science An Integrative Approach.* Vol. 16. Allyn & Bacon; MA: 1991. p. 116-150.
- Mancini AD, Bonanno GA. Predictors and parameters of resilience to loss: toward an individual differences model. *J Pers.* 2009; 77(6):1805–1832. [PubMed: 19807863]
- Mandal B, Ayyagari P, Gallo WT. Job loss and depression: the role of subjective expectations. *Soc Sci Med.* 2011; 72(4):576–583. [PubMed: 21183267]
- Mandell D, Siegle GJ, Shutt L, Feldmiller J, Thase ME. Neural substrates of trait ruminations in depression. *J Abnorm Psychol.* 2014; 123(1):35–48. [PubMed: 24661157]
- McCabe C, Mishor Z, Cowen PJ, Harmer CJ. Diminished neural processing of aversive and rewarding stimuli during selective serotonin reuptake inhibitor treatment. *Biol Psychiatry.* 2010; 67(5):439–445. [PubMed: 20034615]
- McDonnell MC. Risk factors for depression among older adults with dual sensory loss. *Aging Ment Health.* 2009; 13(4):569–576. [PubMed: 19629782]
- Metzger LJ, Orr SP, Berry NJ, Ahern CE, Lasko NB, Pitman RK. Physiologic reactivity to startling tones in women with posttraumatic stress disorder. *J Abnorm Psychol.* 1999; 108(2):347–352. [PubMed: 10369045]
- Morey, LC. *Personality Assessment Inventory, Professional Manual.* Psychological Assessment Resources, Inc.; Lutz, FL: 1991.
- Murphy A, Steele M, Dube SR, Bate J, Bonuck K, Meissner P, et al. Adverse Childhood Experiences (ACEs) questionnaire and Adult Attachment Interview (AAI): implications for parent child relationships. *Child Abuse Negl.* 2014; 38(2):224–233. [PubMed: 24670331]
- Nelson, HE.; Willison, J. *The National Adult Reading Test.* Nfer-Nelson Publishing Co.; Berkshire, England: 1991.

- Nolen-Hoeksema S, Parker LE, Larson J. Ruminative coping with depressed mood following loss. *J Pers Soc Psychol.* 1994; 67(1):92–104. [PubMed: 8046585]
- Orr SP, Lasko NB, Metzger LJ, Berry NJ, Ahern CE, Pitman RK. Psychophysiological assessment of women with posttraumatic stress disorder resulting from childhood sexual abuse. *J Consult Clin Psychol.* 1998; 66(6):906–913. [PubMed: 9874903]
- Sanchez A, Vazquez C, Marker C, LeMoult J, Joormann J. Attentional disengagement predicts stress recovery in depression: an eye-tracking study. *J Abnorm Psychol.* 2013; 122(2):303–313. [PubMed: 23421524]
- Schmahl CG, Elzinga BM, Vermetten E, Sanislow C, McGlashan TH, Bremner JD. Neural correlates of memories of abandonment in women with and without borderline personality disorder. *Biol Psychiatry.* 2003; 54(2):142–151. [PubMed: 12873804]
- Schmahl CG, Elzinga BM, Ebner UW, Simms T, Sanislow C, Vermetten E, et al. Psychophysiological reactivity to traumatic and abandonment scripts in borderline personality and posttraumatic stress disorders: a preliminary report. *Psychiatry Res.* 2004; 126(1):33–42. [PubMed: 15081625]
- Schmitt JV, Ribeiro CF, Souza FH, Siqueira EB, Bebbler FR. Hair loss perception and symptoms of depression in female outpatients attending a general dermatology clinic. *An Bras Dermatol.* 2012; 87(3):412–417. [PubMed: 22714757]
- Schofield CA, Johnson AL, Inhoff AW, Coles ME. Social anxiety and difficulty disengaging threat: evidence from eye-tracking. *Cogn Emot.* 2012; 26(2):300–311. [PubMed: 21970428]
- Siegle GJ, Granholm E, Ingram RE, Matt GE. Pupillary response and reaction time measures of sustained processing of negative information in depression. *Biol Psychiatry.* 2001; 49:624–636. [PubMed: 11297720]
- Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS. Can't shake that feeling: fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry.* 2002; 51:693–707. [PubMed: 11983183]
- Siegle GJ, Steinhauer SR, Carter CS, Ramel W, Thase ME. Do the seconds turn into hours? Relationships between sustained pupil dilation in response to emotional information and self-reported rumination. *Cogn Ther Res.* 2003a; 27(3):365–382.
- Siegle GJ, Steinhauer SR, Stenger V, Konecky R, Carter CS. Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. *NeuroImage.* 2003b; 20(1):114–124. [PubMed: 14527574]
- Siegle GJ, Ichikawa N, Steinhauer S. Blink before and after you think: Blinks occur prior to and following cognitive load indexed by pupillary responses. *Psycho-physiology.* 2008; 45(5):679–687.
- Siegle GJ, Steinhauer SR, Friedman ES, Thompson WS, Thase ME. Remission prognosis for cognitive therapy for recurrent depression using the pupil: utility and neural correlates. *Biol Psychiatry.* 2011; 69(8):726–733. [PubMed: 21447417]
- Siegle GJ, Price RB, Jones NP, Ghinassi F, Thase ME. You gotta work at it: pupillary indices of task focus are prognostic for response to a neurocognitive intervention for depression. *Clin Psychol Sci.* 2015 in press.
- Silk JS, Stroud LR, Siegle GJ, Dahl RE, Lee KH, Nelson EE. Peer acceptance and rejection through the eyes of youth: pupillary, eyetracking and ecological data from the Chatroom Interact task. *Soc Cogn Affect Neurosci.* 2012; 7(1):93–105. [PubMed: 21775386]
- Stalker CA, Davies F. Attachment organization and adaptation in sexually-abused women. *Can J Psychiatry.* 1995; 40(5):234–240. [PubMed: 7553541]
- Trapnell PD, Campbell JD. Private self-consciousness and the five-factor model of personality: distinguishing rumination from reflection. *J Personal Soc Psychol.* 1999; 76(2):284–304.
- Turvey CL, Carney C, Arndt S, Wallace RB, Herzog R. Conjugal loss and syndromal depression in a sample of elders aged 70 years or older. *Am J Psychiatry.* 1999; 156(10):1596–1601. [PubMed: 10518172]
- Watkins ER, Mullan E, Wingrove J, Rimes K, Steiner H, Bathurst N, et al. Rumination-focused cognitive-behavioural therapy for residual depression: phase II randomised controlled trial. *Br J Psychiatry.* 2011; 199(4):317–322. [PubMed: 21778171]

- Wells TT, Clerkin EM, Ellis AJ, Beevers CG. Effect of antidepressant medication use on emotional information processing in major depression. *Am J Psychiatry*. 2014; 171(2):195–200. [PubMed: 24030200]
- Zhang X, Bullard KM, Cotch MF, Wilson MR, Rovner BW, McGwin G Jr, et al. Association between depression and functional vision loss in persons 20 years of age or older in the United States, NHANES 2005–2008. *JAMA Ophthalmol*. 2013; 131(5):573–581. [PubMed: 23471505]

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Fig. 1. A. Mean pupillary reaction to the task, demarcating task segments including word valence identification, digit sorting, and identifying whether the probe number is the middle digit in the sorted list. B. Factor loadings from a principal component analysis on time for the task showing that components naturally capture each relevant feature of the task.

Fig. 2.

A. Item total correlations for each administered scale and pupil dilation factor. B. Change in Cronbach's alpha when item is deleted. Negative changes represent a decrease in internal consistency when the item is removed; positive changes represent an increase when the item is removed.

Fig. 3.

A. Correlations of each PCA-derived temporal component of pupil dilation with PCA-derived components across nominal self-report and behavioral measures of loss. Significant correlations ($p < .05$) are marked with a “*”. Correlations with $|r| > .15$ are highlighted. B. Mean pupillary motility curves for top and bottom half, based on a median split on each self-report factor; yellow = $p < .1$, red = $p < .05$. C. Sample by sample correlations of pupillary motility with each self-report and behavioral measure of interest. D. Mean eye-tracking Y coordinate curves for top and bottom half, based on a median split on each self-report factor; yellow = $p < .1$, red = $p < .05$. Lower values represent looking down towards the word. Higher values represent looking up towards the digit-sorting stimuli.

Fig. 4.

A. Correlations of each PCA-derived temporal component of pupil dilation with PCA-derived components across candidate moderator measures. Significant correlations ($p < .05$) are marked with a “*”. Correlations with $|r| > .15$ are highlighted. B. Mean pupillary motility curves for top and bottom half based on a median split on each candidate moderator factor; yellow = $p < .1$, red = $p < .05$. C. Sample by sample correlations of pupillary motility with each candidate moderator measure. D. Semi-partial of each PCA-derived temporal component of pupil dilation with interactions of PCA-derived components for candidate moderator and loss measures; highlighting and significance as in A. E. Semi-partial correlations of each PCA-derived temporal component of pupil dilation with PCA-derived loss factors after covarying out candidate moderator measures. Highlighting as in A. F. Mean eye-tracking y-coordinate curves for top and bottom half based on a median split on each candidate moderator factor; yellow = $p < .1$, red = $p < .05$. Lower values represent looking down towards the word. Higher values represent looking up towards the digit-sorting stimuli.

Table 1**Demographics.**

Measure	Mean (standard deviation)	Range	N (%)
N			84
Male			31 (37)
Caucasian			48 (57)
Age	46.51 (10.44)	25–61	
Education	13.71 (1.98)	10–18	
BDI	16.08 (13.67)	0–57	
HAM-D	13.82 (9.19)	0–41	
PAI			
Total	29.46 (15.17)	2–65	
Affective instability	8.39 (4.66)	0–18	
Identity	7.77 (4.97)	0–18	
Negative relationships	8.32 (4.09)	1–17	
Self harm	4.98 (3.86)	0–16	
Abuse			
Abuse total	4.43 (3.92)	0–18	71 (85)
Physical	.98 (1.44)	0–6	40 (48)
Psychological	2.32 (2.04)	0–9	64 (76)
Neglect	1.13 (1.42)	0–6	46 (55)
Abuse total (minimal scored as no abuse)	3.23 (3.85)	0–18	50 (60)
Physical (minimal scored as no abuse)	0.71 (1.48)	0–6	20 (24)
Psychological (minimal scored as no abuse)	1.69 (2.05)	0–9	44 (52)
Neglect (minimal scored as no abuse)	0.82 (1.43)	0–6	26 (31)
Borderline Personality Disorder (consensus)			25 (30) > = 3 sx
> = 5 sx meet DSM diagnostic criteria			11 (13) > = 5 sx
Unipolar depression			24 (29)
Emotion ratings for negative normed words (1 = very negative–7 = very positive) M(SD)	1.71 (0.66)	1–4.3	
Personal relevance ratings for negative normed words (1 = not relevant, 5 = very relevant) M(SD)	1.84 (0.67)	1–4.40	
Emotion ratings for positive normed words M(SD)	5.84 (0.76)	3.4–7.00	
Personal relevance ratings for positive normed words (1 = not relevant, 5 = very relevant) M(SD)	3.02 (0.94)	1.0–5.0	
Emotion ratings for neutral normed words (1 = very negative–7 = very positive) M(SD)	3.65 (0.46)	1.40–4.90	
Personal relevance ratings for neutral normed words (1 = not relevant, 5 = very relevant) M(SD)	1.45 (0.42)	1.0–3.0	
Digit sorting %-correct	76 (24)	5–100	
Digit sorting rt (ms)	1138 (312)	124.5–1686.5	

Table 2

PCA on self-report and behavioral measures associated with loss. Loadings higher than 0.3 (threshold at which all examined component measures were included) are highlighted.

Digit sorting percent correct	-0.10	0.38	-0.31	Abuse physical	0.05	0.54
Digit sorting RT	-0.16	-0.04	0.71	Abuse psychological	-0.00	0.68
RRQ reflection	-0.21	0.48	-0.14	Abuse neglect	-0.03	0.52
RRQ rumination	0.13	0.38	0.03	PAI affect instability	0.58	-0.08
Personal relevance rating	-0.07	0.50	0.18	PAI identity fragmentation	0.58	0.03
BDI guilt	0.22	0.31	-0.04	PAI negative relationships	0.57	0.02
PANAS ashamed	0.03	0.31	0.38			
BDI withdrawal	0.37	0.00	0.01			
BDI suicidal	0.38	-0.03	-0.14			
BDI executive function	0.30	0.14	0.16			
BDI crying	0.37	-0.07	-0.13			
BDI sadness	0.35	0.03	-0.07			
BDI anhedonia	0.36	0.01	0.17			
BDI drive	0.31	0.06	0.19			
	1	2	3		1	2

Table 3

Temporal regions of significant associations ($p < .1$, >35 samples (.58 s)) for comparisons of upper and lower half of participants ($N = 42$ per group). Times listed in seconds following stimulus onset.

RDoC loss variables	
Pupil dilation	
Factor level	
Depressive severity	6.60 to 7.20 s: $t(82) = 1.76$, $p = 0.08$, $D = 0.05$, $d = 0.38$ 8.22 to 9.60 s: $t(82) = 2.46$, $p = 0.02$, $D = 0.04$, $d = 0.54$
Rumination	
Cognition	1.52 to 3.20 s: $t(82) = -3.19$, $p < .005$, $D = -0.08$, $d = -0.70$ 5.22 to 8.07 s: $t(82) = -2.81$, $p = 0.01$, $D = -0.07$, $d = -0.61$
Scale level	
Digit sorting percent correct	1.48 to 3.25 s: $r = 0.36$, $t(78) = 3.36$, $p = 0.001$ 5.97 to 8.48 s: $r = 0.28$, $t(78) = 2.55$, $p = 0.013$
Digit sorting RT	0.47 to 2.73 s: $r = -0.31$, $t(78) = -2.91$, $p = 0.005$ 3.57 to 8.02 s: $r = -0.37$, $t(78) = -3.53$, $p < .001$
RRQ reflection	3.63 to 4.22 s: $r = -0.22$, $t(81) = -1.99$, $p = 0.050$
RRQ rumination, personal relevance rating, BDI guilt, PANAS Ashamed, BDI drive	None
BDI withdrawal	3.80 to 4.90 s: $r = 0.24$, $t(75) = 2.14$, $p = 0.036$
BDI suicidal	3.45 to 5.02 s: $r = 0.31$, $t(75) = 2.78$, $p = 0.007$
BDI executive function	3.18 to 4.82 s: $r = 0.26$, $t(75) = 2.29$, $p = 0.025$
BDI crying	3.33 to 4.15 s: $r = 0.24$, $t(75) = 2.14$, $p = 0.035$ 8.15 to 9.53 s: $r = 0.25$, $t(75) = 2.23$, $p = 0.029$
BDI sadness	3.57 to 4.77 s: $r = 0.23$, $t(75) = 2.08$, $p = 0.041$
BDI anhedonia	3.85 to 4.82 s: $r = 0.21$, $t(75) = 1.84$, $p = 0.069$
Eye tracking	
Factor level	
Depressive severity	0.10 to 0.93 s: $t(77) = -2.21$, $p = 0.03$, $D = -0.08$, $d = -0.50$ 1.13 to 3.88 s: $t(77) = -3.13$, $p < .005$, $D = -0.13$, $d = -0.71$ 7.22 to 9.33 s: $t(77) = -2.43$, $p = 0.02$, $D = -0.09$, $d = -0.55$
Rumination	
Cognition	
Possible moderators	
Pupil dilation	
Factor level	
Personality	3.25 to 4.88 s: $t(82) = 2.63$, $p = 0.01$, $D = 0.05$, $d = 0.57$
Abuse	0.30 to 2.27 s: $t(82) = -2.48$, $p = 0.02$, $D = -0.04$, $d = -0.54$
Scale level	
Abuse total	1.48 to 2.58 s: $r = -0.22$, $t(82) = -2.02$, $p = 0.046$
Abuse neglect	1.37 to 2.47 s: $r = -0.23$, $t(82) = -2.17$, $p = 0.033$

RDoC loss variables	
Abuse physical, abuse psychological, abuse super-threshold, abuse physical superthreshold, abuse psychological superthreshold, abuse neglect superthreshold	None
PAI affect instability	3.30 to 5.00 s: $r = 0.27$, $t(82) = 2.52$, $p = 0.014$
PAI negative relationships	3.42 to 4.95 s: $r = 0.29$, $t(82) = 2.76$, $p = 0.007$
PAI identity fragmentation	None
Eye tracking	
Factor level	
Personality	1.53 to 2.25 s: $t(77) = -2.03$, $p = 0.05$, $D = -0.12$, $d = -0.46$ 2.82 to 3.65 s: $t(77) = -2.01$, $p = 0.05$, $D = -0.08$, $d = -0.45$ 7.87 to 8.63 s: $t(77) = -2.07$, $p = 0.04$, $D = -0.08$, $d = -0.47$
Abuse	

Table 4

Multivariate associations of loss dimensions and pupillary motility dimensions. A., using all five temporal factors to explain variance in each self-report factor, B., using all three self-report factors to explain variance in each temporal factor, with C. reporting the significance of beta weights from each of the regressions in A and B.

A. Self-Report factors explained by all temporal factors				
Depressive Severity:	$R^2 = 0.19$	$F(83,77)=3.00$		$p=0.01$
Rumination:	$R^2 = 0.07$	$F(83,77)=0.96$		$p=0.46$
Cognition:	$R^2 = 0.25$	$F(83,77)=4.19$		$p<0.005$
B. Temporal factors predicted from all self-report factors				
Prep	$R^2 = 0.01$	$F(83,80)=0.17$		$p=0.91$
Word	$R^2 = 0.07$	$F(83,80)=2.08$		$p=0.11$
Late Word	$R^2 = 0.06$	$F(83,80)=1.61$		$p=0.19$
Task switch Digits	$R^2 = 0.12$	$F(83,80)=3.72$		$p=0.01$
Probe Comparison	$R^2 = 0.14$	$F(83,80)=4.38$		$p=0.01$
Post Comparison	$R^2 = 0.14$	$F(83,80)=4.46$		$p=0.01$
C. Significance of betas for each factor in models for A,B.				
Depressive Severity	0.5	0.8	0.06	0.01
Rumination	0.35	0.53	0.16	0.08
Cognition	0.58	0.91	0.18	0.26
	Preparation	Word	Late Word	Switch/Digits
	0.74	0.9	0.97	0.54
	0.51	0.63	0.07	0.02
	0.63	<0.005	0.05	0.13
	0.05	0.83	<0.005	0.09
	0.01	0.49	0.09	0.09
	Depressive Severity	Rumination	Cognition	Post Comparison