Published in final edited form as:

J Affect Disord. 2020 October 01; 275: 329–338. doi:10.1016/j.jad.2020.03.091.

Heterogeneity in Fear Processing across and within Anxiety, Eating, and Compulsive Disorders

Abby J. Fyer, MD^{1,2,*}, Franklin R. Schneier, MD^{1,2,*}, Helen Blair Simpson, MDPH^{1,2,*}, Tse Hwei Choo, MS^{2,3}, Stephanie Tacopina, PhD², Marcia B. Kimeldorf, PhD², Joanna E. Steinglass, MD^{1,2}, Melanie Wall, PhD^{2,3}, B. Timothy Walsh, MD^{1,2}

¹Columbia University Department of Psychiatry

²New York State Psychiatric Institute

³Columbia University Department of Biostatistics

Abstract

BACKGROUND: To assess within and across diagnosis variability we examined fear processing in healthy controls (HC) and three diagnostic groups that share symptoms of pathological anxiety: obsessive compulsive disorder (OCD); social anxiety disorder (SAD), and anorexia nervosa (AN).

METHODS: Unmedicated adults (N=166) participated in a paradigm assessing associative fear acquisition, extinction, extinction recall, and fear renewal. Data were analyzed from two perspectives: comparison of each disorder to HC and exploratory latent class analysis (LCA) of the combined data.

RESULTS: The diagnosis-based analyses indicated significantly increased fear renewal in OCD and trends toward decreased extinction recall in OCD and increased renewal in SAD. The LCA indicated four Response Types, none of which were congruent with the diagnostic categories. Most participants had a normative response (50%) or a moderate extinction recall deficit (30%). The two remaining groups (8% each) had more extreme responses: one showed complete failure of extinction recall; the other persistent arousal in expectation of, but prior to, actual conditioning (threat sensitivity).

LIMITATIONS: Due to small sample size (N=20) results for AN are regarded as preliminary.

CONCLUSIONS: Our diagnosis-based findings are consistent with previous data suggesting an association between pathological anxiety and difficulties maintaining fear extinction. The LCA reveal substantial within-diagnosis heterogeneity in fear processing and support inclusion of empirically driven approaches as a complement to standard analyses. This heterogeneity may also

Address correspondence to: Dr. Abby J. Fyer (abby.fyer@nyspi.columbia.edu)(646-774-6712) New York State Psychiatric Institute, 1051 Riverside Drive (Box 82), New York, NY 10032.

*These authors contributed equally to this work.

Disclosures

Drs. Fyer, Wall and Kimeldorf, Tacopina and Mr. Choo report no financial relationships with commercial interests. During this study, Dr. Simpson received royalties from Cambridge University Press and UpToDate Inc and research support from Biohaven, Transcept Pharmaceuticals, and Janssen. Dr. Simpson receives a stipend from JAMA Psychiatry for serving as Associate Editor. Dr. Schneier received research funds from Allergan Laboratories, and receives royalties from Cambridge University Press and UpToDate Inc., and a stipend from Elsevier for serving as Associate Editor of Comprehensive Psychiatry. Dr. Steinglass receives royalties from UpToDate. Dr. Walsh reports receiving royalties from UpToDate, McGraw-Hill, Guilford Press, and Oxford University Press.

have implications for treatment, particularly cognitive behavioral therapy, which relies on strengthening extinction recall and requires patients to tolerate anxious expectation in order to engage with feared situations.

INTRODUCTION

Translationally-based laboratory paradigms, derived from rodent models, are widely used to investigate the physiology of normal and pathological fear and anxiety (Grillon, 2008) (Phelps and LeDoux, 2005). While this strategy has greatly clarified normal function, results for psychiatric disorders have not been robust (Dunsmoor and Murphy, 2015) (LeDoux and Pine, 2016). The NIMH Research Domain Criteria (RDoC) initiative has suggested that, as clinical diagnostic categories are unlikely to “align with underlying neurobiology,” (Hyman, 2010), a more productive strategy will be the study of observable, clinically relevant behaviors with a known relationship to specific neural circuits expected to be engaged by the paradigm (Kozak and Cuthbert, 2016).

We examined this question by applying both approaches to data from an established psychophysiological paradigm designed to assess associative fear learning, extinction, extinction recall, and fear renewal (Milad et. al., 2005). First, we compared healthy controls (HC) to three diagnostically defined groups which while clinically different, also share significant symptoms of fear and anxiety: obsessive compulsive disorder (OCD), social anxiety disorder (SAD), and anorexia nervosa (AN). Second, we conducted a latent class analysis (LCA) of the combined data from all four groups to identify data-driven patterns of response and explore intra-diagnostic heterogeneity.

The data reported in this paper are part of a larger study in which healthy controls (HC) and patients from the three diagnostic groups (OCD, AN, SAD) were assessed with three neurobehavioral paradigms: fear/extinction learning (described in this report), pre-pulse inhibition (PPI); and delayed discounting (DD). Our goals were to assess the overlap/distinctness of the diagnostic groups with respect to response to these paradigms and also explore whether response patterns might identify transdiagnostic groups that did not conform to the DSM diagnostic criteria. The latent class analysis reported here was conducted to address this latter exploratory aspect. As each paradigm has been linked to a different neural system (PPI: frontal striatal circuitry; fear/extinction learning-amygdalar-cortical circuitry, DD-cortical mesolimbic circuitry) we hoped this approach would provide new hypotheses about diagnostic interrelationships at a level closer to the underlying neurobiology. The three disorders were chosen because in addition to partial overlap in clinical symptoms, each has been reported to differ significantly from HC on at least one of the three different neurobehavioral paradigms (AN: DD, SAD: Fear/extinction, OCD: PPI and Extinction Recall) (Ahmari et. al., 2012; Hoenig et. al., 2005; Decker et. al., 2015; King et. al., 2016; Duits et. al., 2013; Milad et al, 2013) and recruitment and implementation were feasible at our center. Given the lack of precise knowledge about the neural bases of most psychiatric disorders and the consequent possibility of having completely negative outcomes (e.g. no difference from HC in any groups on any paradigm), we decided to choose disorders for which there is data suggesting that individuals with the disorder had an abnormal response (i.e. difference from HC) to at least one of the paradigms. Results from the other

two paradigms have been previously published (Steinglass et. al., 2017; Steinman et. al., 2016).

Associative fear acquisition is a normal adaptive process whereby an organism develops fear or defensive responses to a previously neutral stimulus (CS+) that has been paired with an inherently aversive event (unconditioned stimulus, UCS). Extinction learning refers to decreasing conditioned responses to the CS+ after repeated presentations without the UCS. Extinction recall (or retention) is manifested by the persistence of decreased conditioned responses post-extinction, when the individual is re-exposed to the CS+. Fear renewal is the return of conditioned responses to the CS+ post-extinction, when an individual is re-exposed to the CS+ in a context different from the extinction context (often in the original fear-learning context). In discriminant conditioning, for purpose of comparison, a second neutral stimulus (CS-) that is never paired with the UCS is also presented (usually alternating with the CS+) throughout the experiment.

Most fear processing studies have compared responses of a single diagnostic category or an undifferentiated group of anxious individuals to HC (Lissek et. al., 2005) (Duits et. al., 2015). A meta-analysis of studies through 2013 found that patients differed from HC in having stronger response to the CS- during fear acquisition (suggesting fear generalization or deficient safety learning) and the CS+ during extinction (delayed or incomplete extinction) (Duits et. al., 2015). Acheson et. al. (2015) reported greater response to the CS+ at baseline as well as during acquisition and extinction in individuals with high anxiety symptom scores as compared to healthy controls and individuals with PTSD or depressive symptoms. In contrast, a recent transdiagnostic MRI study of four anxiety disorders (social anxiety, panic, generalized anxiety, and specific phobic disorders) found that patients did not differ from HC in skin conductance response (SCR), but had decreased activation in the ventromedial prefrontal cortex (vmPFC) during both early fear learning and extinction recall (Marin et. al., 2017).

Of the disorders in this report, OCD has the clearest fear processing findings. Two of the three studies found deficits in extinction recall compared to HC (Milad et. al., 2013) (McLaughlin et. al., 2015). The third found deficits in extinction but did not assess recall (Nanbu et. al, 2010). In contrast, results for SAD have been mixed, perhaps due to methodological differences between studies (Lonsdorf et. al., 2017), with some studies reporting increased strength of acquisition (Lissek et. al., 2008) (Pejic et al, 2013) (Schneider et. al., 1999), some extinction difficulties (Hermann et. al., 2002) (Rabinak et. al., 2017), and others no between- group differences (Tinoco-Gonzalez et. al., 2015). For AN, despite interest in the role of fear processing (Guarda et. al., 2015) (Strober, 2004) (Murray et. al. 2016), there are no published data.

Two studies have explored heterogeneity of fear processing, though not in anxiety disorder populations. The first, after observing inter-individual variability in extinction recall in a convenience volunteer sample, used computational modeling to demonstrate the likelihood of two different hypothesized mechanisms of extinction learning (Gershman and Hartley, 2015). The best fitting model indicated two classes with respect to extinction learning: one (17%) showing faster acquisition but higher probability of post-extinction fear recovery,

while the other (83%) learned more slowly but had more durable extinction. The second study (Galatzer-Levy et al, 2017) applied latent growth mixture modeling (LGMM) to fear potentiated startle (FPS) response to the CS+ during the extinction learning phase of a standard fear processing paradigm. Participants were drawn from a diverse primary care population reporting high levels of trauma. The best fitting model identified three classes: a Modal FPS group (79%), High FPS Extinguishers (15%) and High FPS Non-Extinguishers (6%). The first group followed the expected normative pattern, the second two both had significantly higher FPS throughout Acquisition but were distinguished by success vs. failure of extinction.

In this study, we used an established psychophysiological paradigm (Milad et al, 2005) in 166 unmedicated individuals (OCD, SAD, AN, and matched HC) to assess associative fear learning, extinction, extinction recall, and fear renewal. In our diagnosis-based analyses, which followed established analytic methods, we hypothesized that: 1) fear learning in each diagnostic group would not differ from that of HC and, 2) relative to HC: a) OCD would have decreased extinction recall; b) SAD would have decreased extinction and/or extinction recall; and, c) AN would show no differences (i.e., in the absence of data, the null hypothesis). In our transdiagnostic analyses, we used a latent class approach to identify patterns of fear processing and then compared these data-driven patterns to current diagnostic categories.

METHODS

These data come from a study conducted at the New York State Psychiatric Institute / Columbia University Medical Center. The NYSPI Institutional Review Board approved this study, and participants provided written informed consent before participating.

Participants

Adult volunteers aged 18–50 years, with a principal DSM-IV diagnosis of OCD, AN, or SAD, and matched HC, were recruited via media and referral. HC had no lifetime Axis I psychiatric disorders. OCD and SAD participants had no lifetime history of psychotic, bipolar, attention deficit hyperactivity, or primary hoarding disorder, and no other current Axis I disorder except specific phobias and tics. AN participants were inpatients, could have comorbid secondary OCD or SAD, and had a body mass index (BMI) of 16.0 kg/m²–18.5 kg/m². Diagnoses were made by a psychiatrist and confirmed by another clinician using a semi-structured interview (First et al, 2002). All participants were free from psychiatric medication for at least four weeks (six weeks for fluoxetine), except for one participant who took one dose of lorazepam two weeks prior to testing. Female participants were not pregnant, nursing, postmenopausal or using hormonal birth control. Menstruating females were tested during the first week of their menstrual cycle. Participants were compensated \$200.

Clinical Assessments

Participants were evaluated using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Storch et. al., 2010), Liebowitz Social Anxiety Scale (LSAS) (Heimberg et. al., 1999), and

the Quick Inventory of Depressive Symptoms (QIDS) (Rush et. al., 2003), and completed the Eating Disorder Examination-Questionnaire (EDE-Q) (Fairburn and Beglin, 1994), Anxiety Sensitivity Index (ASI) (Reiss, et. al., 1986), Personality Inventory for DSM-5 (PIDS-5) (Krueger, et. al., 2012), Spielberger State-Trait Anxiety Inventory (STAI) Trait Anxiety Scale (Spielberger et.al., 1983), the Neuroticism subscale of the NEO Personality Inventory (Costa and McCrae, 1992) and (Day 2 post study), self-report of association of risk of shock with each CS (i.e. contingency learning).

Fear and Extinction Learning Paradigm Procedures

Paradigm: Details for all paradigm procedures are in the Supplement Figure S3 and its Legend. We used a modified version of an established paradigm (Milad et. al., 2005) that included five phases over two consecutive days: Habituation, Acquisition, and Extinction on Day 1; Extinction Recall and Fear Renewal on Day 2. Extinction Recall was assessed in the same context as Extinction. Renewal was assessed in the same context as Acquisition. The contexts (CTX) were computer images of two different rooms and the CS's were a red or blue lightbulb in a lamp which appeared in each context. For each trial the context first appeared alone for 3 seconds, then the lightbulb (CS) was lit and remained on for 6 seconds. During Habituation participants were shown each CS–CTX combination twice. Acquisition included 12 trials (6 CS+, 6 CS–), with four (67%) of the CS+ reinforced with UCS during the last 0.5 seconds of the CS–CTX. The Extinction phase was divided into two equal parts, each of which included 10 trials (5 CS+, 5 CS–). Extinction Recall and Renewal each included 10 trials (5 CS+ and 5 CS–).

Psychophysiology and electrical stimulation: Stimulation and recording were controlled by a commercial system (Precision Instruments) which projected the visual CS+ and CS–, recorded skin conductance levels (SCL) and administered the electric shocks (UCS). Prior to testing, participants identified a level of shock that was “highly annoying but not painful”. This level was used throughout the experiment.

Instructions to Participants: Participants were told that during Habituation they would see all the study images but receive no shocks. Prior to Acquisition they were told that going forward: 1) they could receive shocks at any time; and 2) they might learn to predict the shocks if they paid attention.

Data Processing and Analysis: Data processing methods follow those previously reported (Supplement Figure S3) (Milad Orr, Pitman, Rauch 2005). The term CS+/CS– is used below to denote the difference between SCR to CS+ and SCR to CS– in each paired trial. Group differences in demographic and clinical measures were tested using one-way ANOVAs for continuous and Fisher's exact tests (FET) for categorical variables

Diagnosis-based analyses: To test for differences between each diagnostic group and the HC within each phase, general linear mixed effects models of the square-root-transformed SCR scores were used, including trial, CS Type (CS+,CS–), diagnostic group (HC, OCD, SAD, AN), and possible interactions of these variables, with a random intercept for repeated measures within individuals.

These models provided adjusted mean estimates of the difference in CS+ and CS– SCR scores (over each phase and trial) which were used to test contrasts of each diagnostic group with HC. Statistical significance was defined as $p < .05$ (two-sided). A separate mixed effects analysis (Supplement Section S8) was done to investigate whether differential habituation to CS– contributed to between group differences. We also assessed the Extinction Recall using the Index developed by Milad et. al. (2005, 2013), and compared the groups on this measure using ANOVA. A mixed effects linear regression analysis was used to assess the relationship between chosen shock level and SCR (See Supplemental 8b and c for details).

Analyses of Extinction, Extinction Recall and Renewal Excluding Non-Learners and Rapid Extinguishers:

The meaning of Extinction, Extinction Recall and Renewal outcomes can be difficult to interpret for two groups of individuals: those who do not show increased SCR to the CS+ (nor resultant CS+ vs CS– difference) during Acquisition; and those who did show a difference at some points but have apparently completed extinction before the start of the Extinction phase. To address this some investigators have adopted the convention of removing these individuals from analyses focused on Extinction and Extinction Recall (e.g., Dunsmoor et. al., 2015). Given this precedent, the diagnosis-based analyses of these phases were done in the whole sample and repeated in a subset (defined as participants with greater SCR to the CS+ than CS– during at least two of the last three trials of Acquisition) excluding these two groups. As there were minimal differences, results for the whole sample are presented below (Hypothesis 2, Figure 1). Results for the subset are in the Supplemental Figure S2.

Latent class analysis: Latent Class Analysis (LCA) was used to empirically cluster all 166 subjects into “Response Types” based on their trial-to-trial SCR scores across the paradigm. A range for the number of Response Types from 1 to 6 was tested, using full information maximum likelihood estimation, and the optimal number was determined using Bayesian Information Criterion (BIC), which favors more parsimonious models (Nylund et. al., 2007). Respondents were assigned a probability of belonging to each Response Type based on their SCR scores and were included in the Response Type to which they had the highest probability of belonging. General linear mixed effects models, like those described above, with Response Type as a predictor instead of diagnostic group, were used to test for between-type differences in SCR. As results of the LCA were similar with and without the AN group (Figure S4), the data including AN are reported here.

Gender and race: Race and gender were covariates in all general linear mixed effects models. Additional models were fit to test interactions of CS effects by race and gender within each phase. The only significant CS+/CS– by gender or race interaction occurred in Late Extinction, during which males had greater CS+/CS– difference than females ($p = .034$). Males actually had a slightly higher CS– response than females during late extinction (M Mean (SE) = 0.09 (0.02) vs. F Mean (SE) = 0.06 (0.02)), but males also had a substantially higher CS+ response than females (M Mean (SE) = 0.16 (0.02) vs. F Mean (SE) = 0.08 (0.02)), driving the significant difference between genders in CS+/CS– difference (M Mean (SE) = 0.06 (0.02) vs. F Mean (SE) = 0.02 (0.02)).

RESULTS

Participants

See Supplement (Figure S1 and Section S9) for a flow chart and details of participant inclusion/exclusion. The total analyzable sample ($N=166$, consisting of 64 HC, 41 OCD, 41 SAD and 20 AN) (Table 1) was used for both the diagnosis-based and LCA analyses. Diagnosis-based analyses of Extinction, Extinction Recall and Renewal were also conducted in the subset of participants who were not non-learners or rapid extinguishers (78%, $N=130$) (Figure S1). The four groups in the total sample ($N=166$) did not differ significantly in age, education or estimated IQ (Table 1). Significant differences were found for gender and ethnicity, reflecting the contrast between the white, female AN and the remaining three more diverse groups. Demographic characteristics of the subset ($N=130$, Table S1) were similar.

Though the three patient groups had a greater SCR response to the first stimulus, all four diagnostic groups successfully habituated to the experimental environment, as demonstrated by non-significant CS+/CS− differences in the last trial of Habituation (Figure 1). The mean CS+/CS− difference during this phase did not differ significantly between HC and the three diagnostic groups ($p > 0.3$ for all contrasts). The mean shock level chosen by SAD participants was significantly higher than HC (2.11 vs 1.65, $p=0.030$), while those chosen by AN (1.74 mAmp) and OCD (1.70mAmp) groups did not differ from HC (>0.2). The four LCA Response Types did not differ significantly on chosen shock level. There was no significant relationship between chosen shock level and SCR ($F(1,9169)=0.06$, $p>0.8$). (See Supplemental 8c for details).

Diagnosis-based analyses

Hypothesis 1: Fear learning (Acquisition) in each diagnostic group (OCD, SAD, AN) will not differ from that in HC.—During Acquisition, the HC, OCD, and SAD groups each showed a significant separation between the CS+ and the CS−, with the response to the CS+ consistently higher, (Figure 1). Consistent with previous studies (Duits et al, 2015), OCD and SAD had a stronger response to the CS− than HC ($p<0.0001$). However, there were no significant HC vs OCD or SAD differences in rate or amount of habituation to the CS− in this or other phases or between HC and either of these groups in magnitude of Acquisition response (CS+ minus CS−) in the total sample (HC vs SAD, $p=0.194$, HC vs OCD, $p=0.39$) (Supplement 8a).

In contrast, AN had a moderate initial response to the CS+, which was lost by mid-phase. Compared to HC the mean CS+/CS− difference during Acquisition was significantly less in AN ($t=2.27$, $p=0.023$), but not in OCD ($t=0.87$, $p=0.39$) or SAD ($t=1.3$, $p=0.19$). The disorder specific rates of contingency learning did not differ significantly from rate in the healthy controls. (HC 83%, OCD 76%, SAD 85%, AN 74%) (all $p>0.3$)."

At the first point in Acquisition (pre-shock) all groups show a similar increase in response to both the CS+ and CS−. Participants were told that they will not receive shocks during Habituation, but that going forward from Acquisition on they receive shock at any time. As this increase precedes the shock and is the same for both stimuli, it appears to reflect an

anticipatory response to the possibility of shock at a point where participants do not yet know the contingency.

Hypothesis 2: As compared to HC: a) OCD will have decreased extinction recall, b) SAD will have decreased extinction and/or extinction recall; and, c) AN will show no extinction or recall differences.

Extinction: The HC, SAD and OCD groups demonstrated a decrease in response to the CS+ during the extinction phase (Figure 1). The response to CS- in these groups rose at the start of Extinction, but then decreased in parallel with the CS+. The AN response to CS+ and CS- had decreased during Acquisition and this lower level was maintained throughout. During Late Extinction the CS+ response of OCD and SAD groups increases somewhat leading to significant CS+ vs CS- differences ($p < .001$ and $p < .03$ respectively) (Figure 1). Despite this, the mean CS+/CS- differences for OCD, SAD and AN during this phase (Early and Late Extinction) did not differ significantly from HC. (Supplement 10)

Extinction Recall: Mean CS+/CS- response differences indicated a trend ($t = 1.71$, $p = 0.089$) toward decreased extinction recall (greater fear) in the OCD, but not in AN ($t = .15$, $p = 0.88$) or SAD ($t = 0.79$, $p = 0.43$) as compared to HC (Figure 1). Both OCD and SAD had lower (more fearful) Extinction Recall Indices (ERI) than HC and AN which were quite similar. (ERI = HC 82%, OCD 72%, SAD 55%, AN 87%). However only SAD differed significantly from HC ($p = 0.01$). (See Supplemental 8b for details and discussion).

Fear Renewal: OCD demonstrated a significantly higher mean CS+/CS- response as compared to HC (OCD vs HC, $t = -2.02$, $p = 0.044$) indicating greater fear renewal. SAD showed a trend toward greater fear renewal than HC (SAD vs HC, $t = -1.72$, $p = 0.086$). AN did not differ (AN vs HC, $t = -1.37$, $p = 0.17$) (Figure 1).

Analyses of Extinction, Recall and Renewal excluding Non-Learners and Rapid

Extinguishers: (Supplement Figure S2) Results were similar except that during Fear Renewal both SAD ($t = 2.16$, $p = .031$) and OCD ($t = 2.53$, $p = 0.012$) had significantly greater mean CS+/CS- responses (greater fear renewal) compared to HC.

Exploratory latent class analysis

The best fitting latent class (LCA) model indicated four Response Types (BIC: 5 class = 405, 4 class = 120, 3 class = 141). The mean trajectories, frequencies and salient trajectory features of each Type are shown in Figure 2 and Table 2. Figure 3 shows the relationship of the Response Types to the DSM diagnostic categories.

Description of Response Types—Response Type 1 (RT 1) (Nonfearful), which included over half of participants, showed a pattern previously described in healthy control populations (e.g., Lissek et al., 2005). Mean CS+/CS- differences in this Response Type were also lower than those in each of the other three Response Types (except for RT3 in Habituation). However, these differences only reached the 0.05 level of significance for Acquisition vs. RT2, Early Extinction vs. RT3, Late Extinction vs. RT3 or RT4, Retention vs. RT2 or RT3, and Renewal vs. RT3 or RT4. Type 2 differed only in having a more robust

Acquisition response and a moderate deficit in Extinction Recall. The remaining 16% of participants were evenly split between two more extreme patterns. Response Type 3 (Extinction Recall Failure) had incomplete extinction and a complete failure of Extinction Recall. The mean Type 3 CS+/CS– difference during Extinction Recall was significantly greater than that of all other groups ($p < .003$), and it was also greater than their own response during Acquisition (i.e., sensitization) ($p = .035$). Type 4 (Threat Sensitivity) demonstrated extreme arousal in expectation of, but prior to, the administration of the first shock in Acquisition. Both Types 3 and 4 also had significantly greater CS+/CS– differences during Fear Renewal (all p values $< .009$) than Types 1 and 2, which did not differ from each other.

Relationship to diagnostic categories and dimensional clinical measures—

None of the Response Types were congruent with the DSM diagnostic categories, and each included participants from all four diagnostic groups and vice versa. There were no significant Response Type x Diagnosis associations (Fisher's Exact test $p = 0.14$) (Figure 3B).

Significant differences were found between the Response Types on several dimensional clinical measures: the LSAS ($p = .031$), STAI Trait Anxiety ($p = .035$), NEO Neuroticism ($p = .021$), PIDS Anxiousness ($p = .02$) and Attention Seeking ($p = .037$) scales (Supplement, Tables S2, S3). Pairwise contrasts indicated that Type 3 (Extinction Recall Failure) reported greater social anxiety (LSAS) than Types 1, 2 and 4 (3 vs 1, $p = .004$; 3 vs 2, $p = .009$; 3 vs 4 $p = .081$; 1 vs 2 vs 4 $p > 0.5$). Type 4 reported higher PIDS Attention Seeking (1 vs 2, $p = 0.94$; 1 vs 3, $p = .81$; 1 vs 4, $p = .005$; 2 vs 3, $p = 0.79$; 2 vs 4, $p = .006$; 3 vs 4, $p = .053$). Both Types 3 and 4 had higher scores than 1 and 2 on the Neuroticism, PIDS Anxiousness and STAI-Trait scales. However, these differences did not consistently reach significance.

DISCUSSION

Diagnosis-based analyses

Acquisition: Results during Acquisition were consistent with our hypotheses for OCD and SAD, but not AN. As hypothesized OCD and SAD did not differ from HC during this phase. However, despite an overall active range of SCR (meaning, there was no evidence of inability to measure SCR) throughout the paradigm, a significantly lower proportion of AN than HC participants had persistent CS+/CS– differences at the end of Acquisition. This may reflect a fear learning deficit or rapid extinction. Previous reports suggest decreased reward learning (Foerde and Steinglass, 2017), as well as neurocognitive deficits in AN (Steinglass and Walsh, 2016). Alternatively, the difference may be the result of gender imbalance. All AN were female while the HC were gender balanced. Some previous reports in HC suggest less robust SCR differences in women as compared to men during Acquisition (Milad et. al., 2006; Rosenbaum et. al., 2015). The present study cannot distinguish between these possibilities. However, our data do not support previous suggestions of global enhanced fear acquisition in this population (Strober, 2004; Murray et. al., 2016).

Extinction, Extinction Recall and Renewal: Our diagnosis-based analyses indicate that OCD and SAD, as compared to HC, have difficulties maintaining extinction of learned fear. OCD had significantly increased fear renewal and a trend toward decreased extinction recall. SAD showed a trend toward increased fear renewal. Both groups showed increasing loss of extinction (rise of SCR response to CS+ but not CS-) at the end of Late Extinction (Figure 1).

Two prior studies also found an extinction recall deficit in OCD (Milad et. al., 2013) (McLaughlin et. al., 2015), though the difference in our sample was smaller. One study, McLaughlin and colleagues also assessed renewal but found no difference as compared to HC. Many participants in the previous reports (as compared to none in our OCD sample) were on medication and/or reported current DSM-IV affective disorders. Either of these factors, or other undetected variations in sample may have contributed to the difference in outcomes.

We did not find published data on fear renewal in SAD, though one study in a non-patient sample reported an inverse relationship between the extent of fear renewal and NEO Extraversion scores (a measure of social outgoingness) (Martínez et. al., 2012). Another study found incomplete extinction in SAD and so could not evaluate recall or renewal (Rabinak et. al., 2017).

The response to the CS+ at the start of Extinction is the same as it was at the end of Acquisition. However, the response to the CS- has increased from Acquisition level leading to their being roughly equal at the start of the phase. This increase may reflect the paradigm design in which Extinction takes place in a different context than Acquisition and participants must re-orient to the paradigm as there is a break between Acquisition and Extinction in which the technician asks the participant what they have seen during Acquisition. Participants are not told about the new context in advance and the possibility of shocks is still present.

Exploratory Latent Class Analyses

The LCA indicates significant psychophysiological heterogeneity in fear processing both within and across the four diagnostic groups. None of the Response Types was congruent with DSM-IV diagnosis, and each pattern occurred in all diagnostic groups and vice versa (Figure 3).

Our findings are consistent with the two previous studies investigating heterogeneity in human fear processing, (Gershman and Hartley, 2015, Galatzer-Levy et. al., 2017) though neither was conducted in a diagnosed patient population. In both studies, while most participants (83%, 79% respectively) demonstrated the expected normative response, the remaining smaller group(s) showed distinctly different patterns. The smaller group (17%) in the Gershman and Hartley study demonstrated faster acquisition but higher probability of post-extinction fear recovery (i.e. recall failure). In Galatzer-Levy's study both smaller groups had significantly higher fear potentiated startle (FPS) responses to the CS+ during Acquisition. One group (High FPS Extinguishers, 15%) eventually extinguished, the other (High FPS Non-Extinguishers 6%) did not.

Taken in combination with our results, these data suggest considerable heterogeneity in fear processing both in healthy controls and clinical populations with pathological anxiety. Thus, using data driven methods to examine this heterogeneity may be an important complement to the standard analytic procedures of comparing mean values of outcome measures in categorically defined groups. For example, in our data set 45% of OCD and SAD participants and 31% of HC were in Response Types characterized by extinction recall difficulties; suggesting that this type of deficit is not a necessary or sufficient predictor of disorder. More speculatively, all three studies suggest that while the largest subset of individuals within each disorder follow a normative pattern of associative fear and extinction learning, there are small subsets whose marked variation would be missed by approaches using only mean values. These smaller, more behaviorally homogeneous groups might provide a useful starting point for pathophysiological studies, particularly if, as in our data, they are associated with specific patterns of increased anxiety (e.g. Extinction Recall Failure and social anxiety). Future studies are warranted to test the reproducibility of these patterns and how they map to underlying neural circuitry.

Finally, it would be of great interest to examine how different Response Types relate to clinical evaluation and treatment outcome, particularly with respect to cognitive behavioral approaches. Posttreatment relapse after successful exposure exercises (i.e., extinction recall failure) and refusal to engage in exposure due to excessive anticipatory anxiety and fear (i.e., heightened threat sensitivity) are common clinical problems that appear to parallel our Type 3 and 4 patterns respectively (Dunsmoor and Murphy, 2015) (Vervliet et. al., 2013). If such associations are demonstrated in future studies, then these patterns could help to identify those more likely to fail standard approaches and provide new targets for treatment development. For example, developing clinical assessments that could successfully screen for individuals likely to have extinction recall failure (Response Type 3) would enable preemptive implementation of focused treatment strategies (e.g. slower exposure pace, use of multiple exposure contexts) to maximize benefit and management of expectations, minimize demoralization and facilitate patient engagement and treatment completion. Similarly, prior to beginning their regular treatment individuals who are threat sensitive might be enrolled in a module focused on desensitization to interoceptive cues and reduction of catastrophic thinking.

Limitations

This study had several limitations. Our sample was powered for comparisons between the three disorder groups and HC, not between the three groups themselves. Thus, we cannot address their overlap/distinctness to each other. The AN sample was also small and demographically different, so observations must be considered as preliminary. Finally, LCA's are subject to limitations inherent in their categorical outcomes and dependence on the nature of variation within a specific sample. Thus, we regard the patterns identified here as preliminary data reflecting the specific characteristics of our sample (e.g. inclusion of only HC and disorder groups) and focus our conclusions on their significance as evidence for psychophysiological heterogeneity within and across these diagnostic categories.

Conclusions

Both our diagnosis-based and transdiagnostic analyses are consistent with the literature in suggesting an association between pathological anxiety and difficulties maintaining extinction of learned fear. The finding of several transdiagnostic response patterns supports the hypothesis of neurobiological heterogeneity within diagnostic categories. It also suggests that, in studying pathological anxiety, the use of empirically driven approaches which engage complexity and enable the study of heterogeneity is an important complement to standard analyses. These patterns may also have implications for treatment outcome, particularly in the application of cognitive behavioral therapy which relies on extinction learning, strengthening extinction recall, and a willingness to tolerate anxiety to engage with feared situations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by a grant from the National Institute of Mental Health (NIMH) R01MH091694 (PI's F Schneier, HB Simpson, AJ Fyer) and by the New York State Office of Mental Health

References

1. Ahmari SE, Risbrough VB, Geyer MA, Simpson HB (2012). Impaired sensorimotor gating in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology*. 37:1216–23. [PubMed: 22218093]
2. American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.).
3. Costa PT & McCrae R (1992). *Revised NEO Personality Inventory (NEO-PI-R) and NEO Five Factor Model (NEO-FFI) Professional manual*. Odesa, FL; Psychological Assessment Center.
4. Decker JH, Figner B, Steinglass JE (2015). On Weight and Waiting: Delay Discounting in Anorexia Nervosa Pretreatment and Posttreatment. *Biol Psychiatry*. 78:606–14. [PubMed: 25641636]
5. Duits P, Cath DC, Lissek S, Hox JJ, Hamm AO, Engelhard IM, van den Hout MA, Baas JM (2015). Updated meta-analysis of classical fear conditioning in the anxiety disorders. *Depress Anxiety*. 32:239–53. [PubMed: 25703487]
6. Dunsmoor JE, Campese VD, Ceceli AO, LeDoux JE, Phelps EA (2015). Novelty-facilitated extinction: providing a novel outcome in place of an expected threat diminishes recovery of defensive responses. *Biol Psychiatry*. 1:203–9.
7. Dunsmoor JE, Murphy G (2015). Categories, concepts, and conditioning: how humans generalize fear. *Trends Cogn Sci*. 19:73–7. [PubMed: 25577706]
8. Fairburn CG, Beglin SJ (1994). Assessment of eating disorders: interview or self-report questionnaire? *Int J Eat Disord*. 16:363–70. [PubMed: 7866415]
9. First MB, Spitzer RL, Gibbon M, Williams J (2002). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P)* New York: Biometrics Research, New York State Psychiatric Institute.
10. Foerde K, Steinglass JE (2017). Decreased feedback learning in anorexia nervosa persists after weight restoration. *Int J Eat Disord*. 50: 415–423. [PubMed: 28393399]
11. Galatzer-Levy IR, Andero R, Sawamura T, Jovanovic T, Papini S, Ressler KJ, Norrholm SD (2017). A cross species study of heterogeneity in fear extinction learning in relation to FKBP5 variation and expression: Implications for the acute treatment of posttraumatic stress disorder. *Neuropharmacology*. 116:188–195. [PubMed: 28025095]

12. Gershman SJ, Hartley CA (2015). Individual differences in learning predict the return of fear *Learn Behav.* 43:243CS–250. [PubMed: 26100524]
13. Grillon C (2008). Models and mechanisms of anxiety: evidence from startle studies. *Psychopharmacology.* 199:421–3 [PubMed: 18058089]
14. Guarda AS, Schreyer CC, Boersma GJ, Tamashiro KL, Moran TH (2015).: Anorexia nervosa as a motivated behavior: Relevance of anxiety, stress, fear and learning. *Physiol Behav.* 152:466–72. [PubMed: 25846837]
15. Heimberg RG, Horner KJ, Juster HR, Safren SA, Brown EJ, Schneier FR, Liebowitz MR (1999). Psychometric properties of the Liebowitz Social Anxiety Scale. *Psychol Med.* 29:199–212. [PubMed: 10077308]
16. Hermann C, Ziegler S, Birbaumer N, Flor H (2002). Psychophysiological and subjective indicators of aversive pavlovian conditioning in generalized social phobia. *Biol Psychiatry.* 52:328–37. [PubMed: 12208640]
17. Hoenig K, Hochrein A, Quednow BB, Maier W, Wagner M (2005). Impaired prepulse inhibition of acoustic startle in obsessive-compulsive disorder. *Biol Psychiatry.* 15:1153–8.
18. Hudson JI, Hiripi E, Pope HG Jr., Kessler RC (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry.* 61:348–58. [PubMed: 16815322]
19. Hyman SE (2010). The diagnosis of mental disorders: the problem of reification. *Annu Rev Clin Psychol.* 6:155–79. [PubMed: 17716032]
20. Insel T, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 167(7):748–51. [PubMed: 20595427]
21. King JA, Geisler D, Bernardoni F, Ritschel F, Böhm I, Seidel M, Mennigen E, Ripke S, Smolka MN, Roessner V, Ehrlich S (2016). Altered Neural Efficiency of Decision Making During Temporal Reward Discounting in Anorexia Nervosa. *J Am Acad Child Adolesc Psychiatry.* 55:972–979. [PubMed: 27806865]
22. Kozak MJ, Cuthbert BN (2016). The NIMH Research Domain Criteria Initiative: Background, Issues, and Pragmatics. *Psychophysiology.* 53:286–97. [PubMed: 26877115]
23. Krueger RF, Derringer J, Markon KE, Watson D, & Skodol AE (2012). Initial construction of a maladaptive personality trait model and inventory for DSM-5. *Psychological Medicine.* 42: 1879–1890. [PubMed: 22153017]
24. LeDoux JE, Pine DS (2016). Using Neuroscience to Help Understand Fear and Anxiety: A Two-System Framework. *Am J Psychiatry.* 173:1083–1093. [PubMed: 27609244]
25. Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, Pine DS (2005). Classical fear conditioning in the anxiety disorders: a meta-analysis. *Behav Res Ther.* 43:1391–424. [PubMed: 15885654]
26. Lissek S, Levenson J, Biggs AL, Johnson LL, Ameli R, Pine DS, Grillon C (2008). Elevated fear conditioning to socially relevant unconditioned stimuli in social anxiety disorder. *Am J Psychiatry.* 165:124–32. [PubMed: 18006874]
27. Lonsdorf TB, Menz MM, Andreatta M, Fullana MA, Golkar A, Haaker J, Heitland I, Hermann A, Kuhn M, Kruse O, Meir Drexler S, Meulders A, Nees F, Pittig A, Richter J, Römer S, Shiban Y, Schmitz A, Straube B, Vervliet B, Wendt J, Baas JMP, Merz CJ (2017). Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear. *Neurosci Biobehav.* 247–285
28. Marin MF, Zsido RG, Song H, Lasko NB, Killgore WDS, Rauch SL, Simon NM, Milad MR (2017). Skin Conductance Responses and Neural Activations During Fear Conditioning and Extinction Recall Across Anxiety Disorders. *JAMA Psychiatry.* 1:622–631.
29. Martínez KG, Castro-Couch M, Franco-Chaves JA, Ojeda-Arce B, Segura G, Milad MR, Quirk GJ (2012). Correlations between psychological tests and physiological responses during fear conditioning and renewal. *Biol Mood Anxiety Disord.* 17:2–16.
30. McLaughlin NC, Strong D, Abrantes A, Garnaat S, Cerny A, O'Connell C, Fadok R, Spofford C, Rasmussen SA, Milad MR, Greenberg BD (2015). Extinction retention and fear renewal in a lifetime obsessive-compulsive disorder sample. *Behav Brain Res.* 280:72–7. [PubMed: 25446749]

31. Milad MR, Orr SP, Pitman RK, Rauch SL (2005). Context modulation of memory for fear extinction in humans. *Psychophysiology* 42:6–64.
32. Milad MR, Furtak SC, Greenberg JL, Keshaviah A, Im JJ, Falkenstein MJ, Jenike M, Rauch SL, Wilhelm S (2013). Deficits in conditioned fear extinction in obsessive-compulsive disorder and neurobiological changes in the fear circuit. *JAMA Psychiatry* 70: 608–18. [PubMed: 23740049]
33. Milad MR, Goldstein JM, Orr SP, Wedig MM, Klibanski A, Pitman RK, & Rauch SL (2006). Fear conditioning and extinction: Influence of sex and menstrual cycle in healthy humans. *Behavioral Neuroscience*, 120:1196–1203. [PubMed: 17201462]
34. Morris J, Christakou A, van Reekum CM (2016). Nothing is safe: Intolerance of uncertainty is associated with compromised fear extinction learning. *Biol Psychol*. 121:187–193. [PubMed: 27178640]
35. Murray SB, Treanor M, Liao B, Loeb KL, Griffiths S, Le Grange D (2016). Extinction theory and anorexia: deepening the mechanisms. *Behav res Ther*. 87:1–10. [PubMed: 27580026]
36. Nanbu M, Kurayama T, Nakazawa K, Matsuzawa D, Komiya Z, Haraguchi T, Ogura H, Hashimoto T, Yoshida S, Iyo M, Shimizu E (2010). Impaired P50 suppression in fear extinction in obsessive-compulsive disorder. *Prog Neuropsychopharmacol*. 34:317–22.
37. Nylund K, Asparouhov T, Muthen B (2007). Deciding on the number of latent classes in latent class analysis and finite mixture modeling: A Monte Carlo simulation study, *Structural Equation Modeling*. 14: 535–569.
38. Pejic T, Hermann A, Vaitl D, Stark R (2013). Social anxiety modulates amygdala activation during social conditioning. *Soc Cogn Affect Neurosci*. 8:267–76. [PubMed: 22198970]
39. Phelps EA, LeDoux JE (2005). Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron*. 48:175–87. [PubMed: 16242399]
40. Rabinak CA, Mori S, Lyons M, Milad MR, Phan KL (2017). Acquisition of CS–US contingencies during Pavlovian fear conditioning and extinction in social anxiety disorder and posttraumatic stress disorder. *J Affect Disord*. 207:76–85. [PubMed: 27716541]
41. Reiss S, Peterson RA, Gursky DM, & McNally RJ (1986). Anxiety sensitivity, anxiety frequency, and the prediction of fearfulness. *Behavior Research and Therapy*. 24: 1–8.
42. Rosenbaum BL, Bui E, Marin MF, Holt DJ, Lasko NB, Pitman RK, Orr SP, Milad MR (2015). Demographic factors predict magnitude of conditioned fear. *Int J Psychophysiol*. 98:59–64. [PubMed: 26151498]
43. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self-Report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*. 54:573–583. [PubMed: 12946886]
44. Schneider F, Weiss U, Kessler C, Müller-Gärtner HW, Posse S, Salloum JB, Grodd W, Himmelmann F, Gaebel W, Birbaumer N (1999). Subcortical correlates of differential classical conditioning of aversive emotional reactions in social phobia. *Biological Psychiatry*. 45:863–71. [PubMed: 10202574]
45. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, & Jacobs GA (1983). *Manual for the State-Trait Anxiety Inventory*.
46. Steinglass JE, Walsh BT (2016). Neurobiological model of the persistence of anorexia nervosa. *J Eat Disord*. 4:19. [PubMed: 27195123]
47. Steinglass JE, Lempert KM, Choo TH, Kimeldorf MB, Wall M, Walsh BT, Fyer AJ, Schneier FR, Simpson HB. (2017). Temporal discounting across three psychiatric disorders: Anorexia nervosa, obsessive compulsive disorder, and social anxiety disorder. *Depress Anxiety*. 34:463–470 [PubMed: 28009473]
48. Steinman SA, Ahmari SE, Choo T, Kimeldorf MB, Feit R, Loh S, Risbrough V, Geyer MA, Steinglass JE, Wall M, Schneier FR, Fyer AJ, Simpson HB. (2016). Prepulse Inhibition Deficits Only in Females with Obsessive-Compulsive Disorder *Depress Anxiety*. 33:238–46. [PubMed: 26878422]

49. Storch EA, Rasmussen SA, Price LH, Larson MJ, Murphy TK, Goodman WK (2010). Development and psychometric evaluation of the YaleCS–Brown Obsessive-Compulsive Scale–Second Edition. *Psychological Assessment*. 223–232. [PubMed: 20528050]
50. Strober M (2004). Pathologic fear conditioning and anorexia nervosa: on the search for novel paradigms. *Int J Eat Disord*. 35:504–8. [PubMed: 15101066]
51. Tinoco-González D, Fullana MA, Torrents-Rodas D, Bonillo A, Vervliet B, Pailhez G, Farré M, Andión O, Perez V, Torrubia R (2015). Conditioned Subjective Responses to Socially Relevant Stimuli in Social Anxiety Disorder and Subclinical Social Anxiety. *Clin Psychol Psychother*. 22:221–31. [PubMed: 24464952]
52. Vervliet B, Craske MG, Hermans D (2013). Fear extinction and relapse: state of the art. *Annu Rev Clin Psychol*. 9:215–48. [PubMed: 23537484]

Highlights

Fear processing was assessed in OCD, anorexia nervosa and social anxiety disorder
Difficulties maintaining extinction were seen in OCD and social anxiety disorder
Transdiagnostic analyses identified four patterns; none congruent with diagnosis The
findings support neurobiological heterogeneity within and across these disorders Two
patterns (threat sensitivity, extinction recall failure) may be relevant to treatment

Figure 1:
Paradigm Outcome for Participants in Total Sample by Diagnostic Group (N=166)

2A. Mean Skin Conductance Response (SCR) to CS+ and CS- by Trial and Latent Class Response Type

2B. Mean CS+/CS- Difference in Skin Conductance Response (SCR) by Paradigm Phase and Latent Class Response Type^b

Figure 2:
Paradigm Outcome by Latent Class Response Type (N= 166)^a

A. Distribution of Diagnoses within each Latent Class Response Type

B. Distribution of Latent Class Response Types within each Diagnostic Group

Figure 3: Relationship between Latent Class Response Types and Diagnoses^a

^aHC= Healthy Controls, AN= Anorexia Nervosa, OCD= Obsessive Compulsive Disorder, SAD= Social Anxiety Disorder

Table 1:

Demographic and Clinical Characteristics of Participants (N=166)

Characteristic ^d	Healthy Controls (N=64)		Anorexia Nervosa (N=20)		Obsessive Compulsive Disorder (N=41)		Social Anxiety Disorder (N=41)		One Way ANOVA p value ^b	Pairwise Significance ^c
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age, years	28.0	6	26.1	8	29.0	6	29.5	7	NS	-
Education, years	15.8	2	14.6	2	15.4	2	15.4	2	NS	-
Estimated IQ (NAART)	110.5	9	108.6	9	110.5	8	110.4	8	NS	-
Age at Onset (years)	N/A	N/A	15.7	2	13.4	6	11.6	7	.042	SAD<AN, AN=OCD, OCD=SAD
Body Mass Index (BMI)	24.4	4	17.3	1	24.4	5	24.0	6	.0001	AN < HC = OCD = SAD
EDE-Q-Global	0.52	0.6	3.54	2	0.93	0.9	0.88	0.9	.0001	HC < OCD < AN HC = SAD < AN, SAD=OCD
LSAS, Mean	11.7	8	47.3	16	23.5	17	75.7	20	.0001	HC < OCD < AN < SAD
QIDS, Mean	2.5	2	13.1	5	5.5	4	5.6	4	.0001	HC < OCD = SAD < AN
Spielberger Anxiety Scale										
Trait	31.7	5	55.4	10	42.6	11	48.3	9	.0001	HC < OCD < SAD < AN
State, at procedure	25.1	5	55.1	11	37.3	12	39.9	11	.0001	HC < OCD = SAD < AN
YBOCS-Total	0.3	1	12.2	11	25.2	4	3.2	6	.0001	HC < SAD < AN < OCD
NEO Neuroticism	15	4	23	5	18	6	25	5	.0001	HC < OCD < SAD = AN
	N	%	N	%	N	%	N	%		
Gender, Female	34	53	20	100	19	46	22	54	.001	HC=SAD=OCD < AN
Ethnicity										
White	36	56	19	95	21	51	16	39		
Black	13	20	0	0	9	22	7	17	.03	HC-SAD-OCD vs AN
Asian	4	6	0	0	2	5	4	10		
Hispanic	10	16	1	5	8	20	10	24		
Other	1	2	0	0	1	2	4	10		

^aNAART=North American Adult Reading Test, EDE-Q= Eating Disorder Examination-Questionnaire, LSAS= Liebowitz Social Anxiety Scale, QIDS= Quick Inventory of Depressive Symptoms, YBOCS=Yale Brown Obsessive Compulsive Scale

^bComparing the four groups HC, AN, OCD, SAD; SD=Standard deviation; NS = not significant p>0.05, two sided.

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HC= Healthy Controls, AN=Anorexia Nervosa, OCD=Obsessive Compulsive Disorder, SAD= Social Anxiety Disorder. The “ $<$ ” indicates $p<.05$ in pairwise contrasts.

Table 2:

Latent Class Response Types: Characteristics and Frequency

Response Type		Trajectory Characteristics	Frequency % (N)
1	Non-Fearful	Expected response in all phases	54% (89)
2	Extinction Recall Deficit	Moderate Extinction Recall deficit More robust Acquisition response Expected response in remaining phases	30% (50)
3	Extinction Recall Failure	Incomplete Extinction Extreme Extinction Recall deficit Fear during Extinction Recall > Acquisition	8% (13)
4	Threat Sensitivity	Extreme arousal at Acquisition baseline (prior to shock) Fear recurrence during Extinction Fear generalization in Extinction Recall & Renewal	8% (14)
TOTAL SAMPLE			100% (166)