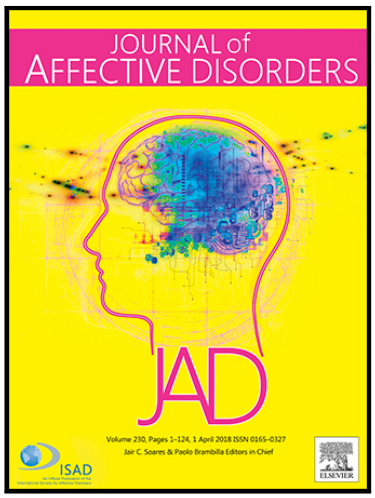

Threat-sensitivity in affective disorders: a case-control study

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Highlights

- It would be desirable to understand why anxiety disorders are highly comorbid with mood disorders yet distinguished by drug response and symptom structure.
- Current theoretical frameworks distinguish GAD from PD by in terms of sensitivity to complex versus simple threat.
- We tested this hypothesis using behavioural and self-report measures of threat-sensitivity in a case-control study with GAD, PD, MDD and healthy control groups.
- Our findings oppose the simple/complex threat dichotomy, instead suggesting elevated sensitivity to physical threat differentiates panic disorder from mood disorders, whereas elevated sensitivity to social threat is a risk factor for affective disorders in general.

Threat-sensitivity in affective disorders: a case-control study

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Research Paper

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Abstract

Background: Anxiety disorders are highly comorbid with major depression but differ in their symptom profiles and pharmacological responses. Threat-sensitivity may explain such differences, yet research on its relationship to specific disorders is lacking.

Methods: One-hundred patients (71 women) and 35 healthy controls (23 women) were recruited. Thirty-five had Panic Disorder (PD), 32 had Generalized Anxiety Disorder (GAD) and 33 Major Depressive Disorder (MDD). Threat-sensitivity was measured via behaviour (Joystick Operated Runway Task; JORT) and self-report (Fear Survey Schedule; FSS).

Results: Behavioural sensitivity to simple threat was higher in females compared to males (p=.03). Self-reported sensitivity to simple threat (FSS Tissue Damage Fear) was higher in PD patients compared to other groups (p≤.007) and in GAD patients compared to controls (p=.02). Behavioural sensitivity to complex threat was higher in females than males (p=.03) and a group by sex interaction (p=.01) indicated that this difference was largest in PD patients. Self-reported sensitivity to complex threat (FSS Social Fear) was higher in all patients compared to controls (p≤.001). Females scored higher than males on FSS Tissue Damage Fear and FSS Social Fear).

Conclusions: Our findings oppose the simple/complex threat dichotomy, instead suggesting elevated sensitivity to physical threat differentiates anxiety disorders from MDD, whereas elevated sensitivity to social threat is associated with both anxiety disorders and MDD.

Keywords:

Affective disorders; Panic Disorder; Generalized Anxiety Disorder; Personality; Joystick Operated Runway Task

1. Introduction

Approximately 14.0% of the EU population suffer from an anxiety disorder and 6.9% from major depression disorder (MDD; Wittchen et al. 2011), suggesting that these two categories of affective illness comprise a significant human disease burden. Understanding the causal basis of these disorders is therefore an important goal of

psychiatry but this research effort is complicated by sex-specificity and comorbidity, as affective disorders are approximately twice as common in women as men (McLean *et al.* 2011; Baxter *et al.* 2014), and also display high lifetime comorbidity (up to 80%; Gorwood, 2004; Wray *et al.* 2018).

A further complication arises from findings that such disorders are heterogeneous in their symptom profiles and pharmacological responses. For example, MDD typically responds best to antidepressant drugs (Cipriani *et al.* 2018) whereas benzodiazepines tend to be the most efficacious treatment for anxiety disorders (Starcevic, 2014). However, this is not the case for all anxiety disorders, as Panic Disorder (PD) is typically treated with antidepressants (Bandelow, Baldwin & Zwanzger; 2013) – this suggests a differentiation of anxiety and panic disorders, which also has been shown to have a neuropsychological basis (Gray & McNaughton, 2000). Conversely, some new treatment manuals for anxiety disorders (not exclusively for PD) suggest prescribing antidepressants before benzodiazepines (e.g., Andrews et al., 2016).

This phenotypic complexity could be interpreted as suggesting that the anxiety/depression distinction is arbitrary, but this seems unlikely as it echoes the long-standing clinical observation which relates anxiety disorders to threat and depression to loss (e.g., Freud, 1957). This notion is also supported by data showing that patients with anxiety disorders exhibit an attentional bias towards threat (Cisler & Koster, 2010), but to date there is a lack of direct, case-controlled, multi-method evidence to show that elevated threat-sensitivity distinguishes anxiety disorders from depression. Here we sought to address this gap in the literature by comparing the behavioural and self-reported threat-sensitivity of anxiety disorder patients to those of depressed patients and healthy controls. Given that female mammals tend to be more

sensitive to threat than males (e.g., Day et al. 2016) and anxiety disorders are more common in women than in men (Kessler et al., 2011; Tolin and Foa, 2006), we also sought to explore sex differences in threat sensitivity.

We tested whether male and female patients with different anxiety disorders display differential sensitivity to various threat categories and, in turn, are more sensitive to threat than MDD patients. Theoretical accounts based on rodent work posit that PD reflects altered functioning in relatively basic, fear-mediating systems in the mid-brain that govern responses to threats that can be simply avoided (McNaughton & Corr, 2004). Simple threats are hypothesised to elicit activity in the Fight/Flight/Freeze System that primarily encompasses mid-brain areas, especially the anterior cingulate, amygdala, medial hypothalamus and periaqueductal gray.

In contrast, Generalized Anxiety Disorder (GAD) is thought to reflect altered functioning in the anxiety-mediating higher brain systems that govern responses to threats that require more complex responses than Fight/Flight/Freeze. These anxiety-mediated responses are grouped under the label of risk assessment and typically include forward and backwards oscillations, environmental scanning and olfactory sampling (Blanchard et al., 2003). They are elicited by potential threats such as the odour of a predator that require approach. This in turn generates goal conflict and thus activates the Behavioural Inhibition System (BIS), which comprises structures ranging from the hippocampus to the dorsolateral prefrontal cortex (McNaughton & Corr, 2004).

This analysis suggests that PD sufferers should display the greatest sensitivity to simple threats whereas GAD sufferers should display the greatest sensitivity to complex, goal conflict-related threats. However, preliminary attempts to test these hypotheses in healthy human subjects have produced mixed results. For example,

using a threat-scenario vignette methodology, it was found, as predicted, that individuals with high levels of self-reported fear (as measured by the Fear Survey Schedule, FSS; Wolpe & Lang, 1977) tended to select defensive responses entailing simple avoidance of threat (e.g., run away). However, contrary to the theory, high scorers on self-reported fear also tended to perceive threats in general as magnified, irrespective of threat type (Perkins *et al.* 2010). Using a behavioural measure of threat-sensitivity, known as the Joystick Operated Runway Task (JORT; Perkins et al., 2009; Figure 1A), it was found, again contrary to predictions, that the anti-anxiety drug lorazepam affects responses to simple threat (Perkins et al., 2013).

Figure 1 about here

The JORT measure of sensitivity to simple threat is known as Flight Intensity and is measured by subtracting average velocity in the one-way active avoidance trials that contained no threat of white noise (Figure 1C) from the average velocity in the one-way active avoidance trials with a threat of white noise (Figure 1D). JORT Flight Intensity therefore captures the degree to which threat (as indicated by the lightning flash icon) increased the velocity of the green dot cursor along the runway during one-way avoidance of the red dot cursor. In line with predictions, a candidate genetic risk factor for PD was associated with JORT Flight Intensity in healthy humans (Perkins *et al.* 2011).

The JORT measure of sensitivity to complex threat is known as Risk Assessment Intensity. This label stems from the original translated rodent task (the Mouse Defense Test Battery; MDTB, Griebel et al. 1997; Figure 1B). In the MDTB,

approach-withdrawal oscillation in the closed runway configuration is a component of rodent risk-assessment behaviour (Blanchard et al., 2003). Approach-withdrawal oscillation has been linked to anxiety in rodents by the finding that this behaviour is sensitive to anxiolytic drugs (Blanchard et al., 1990). When the task was translated for human use, Risk Assessment Intensity was the label chosen to describe the degree to which threat (as indicated by the lightning flash icon) increased the magnitude of approach-withdrawal oscillation of the green dot when trapped between the two red dot cursors. JORT Risk Assessment Intensity has proved sensitive to lorazepam in three studies (Perkins et al., 2009; 2013, Lippold et al., in review).

The face validity of the label of Risk Assessment Intensity may be considered limited, as in the human version of the task the approach-withdrawal oscillation serves no information-gathering function. Nevertheless, to remain consistent with the previously published research, the label has been retained in the present experiment with the proviso that the approach-withdrawal oscillation, labelled as Risk Assessment Intensity, should be viewed as echoing the hesitant oscillation behaviour that is a behavioural marker of goal conflict in rodents.

Risk Assessment Intensity in the JORT was accordingly calculated as the standard deviation of the average velocity in the two-way active avoidance trials that contained no threat of white noise (Figure 1E) subtracted from the standard deviation of the average velocity in the two-way active avoidance trials with threat of white noise (Figure 1F). This method of measurement can be utilised even if average velocity is identical in the threat trials and in the non-threat trials because velocity is not the variable of interest in these trials, since it is not related to goal conflict. The key requirement for goal-conflict related behavioural measurement is that the

magnitude of oscillation (i.e., the S.D. of the velocity) differs between the two trial types as this signifies greater or lesser goal conflict.

In order to provide a direct test of this theory in relevant clinical populations, we hypothesised that sensitivity to simple threat, as operationalised by scores on the constructs of JORT Flight Intensity and FSS Tissue Damage Fear, would be greatest in PD patients compared to other groups. Conversely, sensitivity to complex threat (as operationalised by scores on the constructs of JORT Risk Assessment Intensity and FSS Social Fear) should be greatest in GAD patients compared to other groups.

2. Methods

2.1. Participants

Patients were recruited from inpatient and outpatient services in and around Bonn, Germany, and were screened by an experienced clinical psychologist using the MINI International Neuropsychiatric Interview (Sheehan et al. 1998; German translation by Ackenheil et al. 1999). If both PD and GAD were present, the diagnosis that was more prominent based on our in-depth clinical assessment was used. Healthy controls were recruited from the community of the same geographical area and were screened for the exclusion criterion of any current or lifetime psychiatric diagnosis using the MINI. An additional exclusion criterion for all groups was a history of post-traumatic stress disorder (PTSD) as well as current substance abuse.

2.2. Demographic and clinical assessments

Demographic information (age, sex, level of education) was obtained from all participants using a self-report questionnaire. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield 1971). In patients, the global assessment

of functioning (GAF) scale of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was obtained as a measure of overall level of functioning. Illness duration was estimated retrospectively by the study clinician. All participants provided an estimate of verbal IQ (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B; Lehrl *et al.* 1995), where possible scores range between 0 and 37, with higher scores indicating better verbal abilities.

To measure the severity of GAD, PD and MDD symptoms in all groups, the Generalized Anxiety Disorder Questionnaire–IV (GAD-Q-IV) (Newman et al 2002), the Panic Disorder Severity Scale – Self-Report Version (PDSS-SR) (Shear et al 1997) and the Beck Depression Inventory (BDI-II) (Hautzinger et al 2006) were administered. On each inventory, higher scores indicate a greater expression of the relevant dimension.

Participants gave written, informed consent before participation, and the study was approved by the research ethics committee of the Faculty of Medicine at the University of Bonn (application number 139/14).

2.3. JORT and FSS stimuli

Threat-sensitivity was measured behaviourally using the Joystick Operated Runway Task (JORT; Perkins *et al.* 2009). The JORT (see Figure 1) is a computerized runway task that uses a force-sensing joystick to measure the intensity of avoidance of a simple pursuing threat (labelled Flight Intensity) and a more complex threat that requires approach (labelled Risk Assessment Intensity). The greater complexity of this trial type relates to the presence of two threat stimuli, one in front and one behind the cursor representing the participant. This creates a two-way active avoidance goal conflict; hence it is more complex than the trial types that only contain one threat

stimulus and thus entail one-way active avoidance, but not goal conflict. The threat stimulus comprises an onscreen lightning flash icon that signifies the participant will receive a 115-dB white noise burst if they fail to evade the threat. The JORT contains 48 trials each lasting seven seconds. In order to control for confounding factors, such as differences in participants' hand-eye coordination, responses were measured without threat in 50% of trials, as signalled by the absence of the lightning flash icon on screen.

Self-report threat sensitivity was measured using a German translation of the Fear Survey Schedule (FSS; Wolpe & Lang, 1977). The FSS comprises 108 items that take the form of mini-vignettes describing a range of aversive situations/stimuli, such as "Receiving injections", "Feeling rejected by others", "Failure", "Speaking in public, "Entering a room where other people are already seated", "Prospects of a surgical operation" or "Human blood". Participants use a scale of 0 (no fear) to 4 (very much fear) to indicate how much they would be distressed by each item. The FSS items form two major factors that are usually labelled as Tissue Damage Fear and Social Fear (Arrindell, 1980). The former contains the FSS items that describe simple threats such as "Receiving injections" whereas the latter contains the FSS items that describe socially relevant threats of a more complex, abstract nature, such as "Failure" or "Feeling rejected by others".

2.4. Statistical analysis

Data were analysed using IBM SPSS v25.0. The SPSS data and syntax files are available at https://osf.io/gzrp3.

First, descriptive statistics were computed, and distributions were inspected for all variables. Chi squared tests were employed to confirm matching of groups in terms of sex, education, handedness and, for patient groups, medication status.

Univariate analysis of variance (ANOVA) was used to compare groups in demographic and psychometric (age, verbal intelligence) measures as well as clinical variables (GAD-Q-IV, PDSS-SR, BDI-II, duration of treatment).

ANOVA was also used to compare groups on each dependent variable, i.e. scores on JORT Flight Intensity, JORT Risk Assessment Intensity, FSS Tissue Damage and FSS Social Fear. To reiterate, we were interested in investigating behaviourally and by self-report the sensitivity to simple and complex threats across anxiety disorders. Sensitivity to simple threats was operationalized using JORT Flight Intensity scores and FSS Tissue Damage Fear Scores. Sensitivity to complex threat was operationalized using JORT Risk Assessment Intensity scores and FSS Social Fear scores.

Group (GAD, PD, MDD, CON) and Sex (male, female) were used as independent variables in these models. In order to confirm that any observed group differences hold beyond the possible confounds of age and intelligence, analysis of covariance (ANCOVA) was used for each JORT and FSS dependent variable with Group (GAD, PD, MDD, CON) and Sex (male, female) as independent variables and age and MWT-B score as covariates.

In order to estimate overlap between behavioural and self-report dependent variables, Pearson correlations were carried out between JORT and FSS variables combined for the entire sample.

For all analyses, the alpha level was set at .05. For post-hoc t-tests following ANOVA, Bonferroni correction of the alpha level was carried out on the basis of the number of comparisons following each ANOVA.

3. Results

3.1. Descriptive statistics and intercorrelations

One-hundred patients as well as 35 age and sex-matched healthy controls completed the study. The patients comprised 32 patients with Generalized Anxiety Disorder (GAD), 35 with Panic Disorder (PD) and 33 with Major Depression Disorder (MDD). Comorbidity with MDD occurred, as expected, for 23 GAD patients and 20 PD patients.

Table 1 presents descriptive statistics of socio-demographic, clinical and dependent variables. For JORT variables, there was one missing value in each group due to technical problems. JORT Flight Intensity scores were positively skewed and, therefore, trimmed using a 90% winsorisation. Groups did not differ in age, sex distribution, handedness, education or verbal intelligence score (all $p>.20$). Patient groups did not differ in illness duration ($p=.12$) or medication status ($p=.93$).

For GAD-Q-IV, there was a main effect of Group ($F[3,131]=93.42$, $p<.001$, $\eta_p^2=.68$). Post-hoc tests showed that this effect was due to controls having lower scores than all patient groups (all $p<.001$), whereas the other comparisons were not significant after Bonferroni correction.

For PDSS-SR, there was a main effect of Group ($F[3,131]=38.96$, $p<.001$, $\eta_p^2=.47$). Post-hoc tests showed that this effect was due to controls having lower scores than all patient groups (all $p<.001$) and PD patients having higher scores than all other groups (all $p<.001$), whereas GAD and MDD groups did not differ significantly ($p=.35$).

Finally, for BDI-II, there was a main effect of Group ($F[3,131]=15.87$, $p<.001$, $\eta_p^2=.27$). Post-hoc tests showed that this effect was due to controls having lower scores than all patient groups (all $p<.001$), who did not differ significantly from each other.

Table 2 presents Pearson correlations between the threat sensitivity measures (JORT and FSS) and the clinical scales. There were no significant correlations between JORT scores and the clinical scales. There were significant correlations between both FSS subscales (Tissue Damage Fear and Social Fear) and all four clinical scales. There were no significant correlations between JORT and FSS variables.

Tables 1 and 2 about here

4.2. Group Differences in JORT Variables

For JORT Flight Intensity, there was a main effect of Sex ($F[1,123]=4.75$, $p=.03$, $\eta_p^2=.04$), indicating higher fear scores in females than males (Figure 2A). There was no main effect of Group ($p>.99$) and no Group by Sex interaction ($p=.43$).

For JORT Risk Assessment Intensity, there was a main effect of Sex ($F[1,123]=4.92$, $p=.03$, $\eta_p^2=.04$), indicating higher anxiety scores in females than males (Figure 2B). There was no main effect of Group ($p=.58$), but a Group by Sex interaction ($F[3,123]=3.87$, $p=.01$, $\eta_p^2=.09$). The pattern underlying this interaction indicated that the difference in scores between males and females was stronger in PD patients ($p=.004$) than in other groups (all $p>.07$) (Figure 2B). Conversely, there were no pairwise Group differences for either level of Sex (all n.s. after Bonferroni correction).

Including age and MWT-B verbal intelligence score as covariates yielded a qualitatively very similar pattern of results for both JORT variables.

4.3. Group Differences in Fear Survey Schedule Variables

For FSS Tissue Damage Fear, there was a main effect of Group ($F[3,127]=12.06$, $p<.001$, $\eta_p^2=.22$) and a main effect of Sex ($F[1,127]=4.20$, $p=.04$, $\eta_p^2=.03$), but no significant Group by Sex interaction ($p=.25$) (Figure 3A). The main effect of Sex indicated higher scores in females than males. The main effect of group derived from PD patients having higher scores than all other groups (all $p<.001$), but no further comparisons were significant at Bonferroni corrected alpha level (all $p>.01$).

For FSS Social Fear, there was a main effect of Group ($F[3,127]=14.42$, $p<.001$, $\eta_p^2=.25$) and a significant main effect of Sex ($F[1,127]=6.29$, $p=.01$, $\eta_p^2=.05$), but no significant Group by Sex interaction ($p=.23$) (Figure 3B). The main effect of Sex indicated higher scores in females than males. The main effect of group derived from controls having lower scores than all patient groups (all $p<.001$), which did not differ from each other (all $p>.03$; n.s. at Bonferroni corrected alpha level).

Including age and MWT-B verbal intelligence score as covariates yielded a qualitatively very similar pattern of results for both FSS variables.

Figures 2 and 3 about here

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4. Discussion

In this study, we sought to investigate whether anxiety disorders can be distinguished from each other and from MDD by means of experimental behavioural and psychometric self-report measures of sensitivity to simple and complex threat.

Sensitivity to simple threat is theoretically linked to panic disorder (PD) and sensitivity to complex threat to generalised anxiety disorder (GAD). Our data do not support this hypothesis, as only one out of four a priori results were in favour of our expectations, namely that PD sufferers scored higher on FSS Tissue Damage Fear than all other groups, irrespective of sex. Since FSS Tissue Damage Fear is a theoretically pure measure of sensitivity to simple threat, this finding is consistent with the hypothesis that PD, more so than other anxiety or mood disorders, reflects altered functioning in basic, mid-brain systems that govern responses to such threats (McNaughton & Corr, 2004). However, contrary to our hypothesis, this result was not replicated in our behavioural measure of sensitivity to simple threat (JORT Flight Intensity), which instead showed that females scored significantly higher than males, irrespective of group. Again, contrary to our hypothesis, our behavioural measure of sensitivity to complex threat (JORT Risk Assessment Intensity) showed an unexpected result, as female PD patients scored higher than male PD patients, with this sex difference being more pronounced in the PD group than in the other groups. Finally, and once more contrary to our hypothesis, we found that FSS Social Fear was elevated in all patient groups compared to healthy controls, whereas patient groups did not differ from each other. In addition, across diagnostic groups, females had higher FSS Tissue Damage and Social Fear scores than males.

Based on our results we suggest high sensitivity to social threat is associated with both anxiety disorders and depression, whereas high sensitivity to physical threat is associated with PD, in females at least. On a practical note, our data suggest that researchers requiring a quick, low-cost, general measure of threat-sensitivity that can screen for vulnerability to anxiety disorders and depression may wish to utilise the

FSS Social Fear scale, as this was the only measure that successfully distinguished all three groups of affective disorders patients from controls.

At first glance, a similar argument could be made for scores on the personality dimension of neuroticism and numerous other general neuroticism-type questionnaires (Claridge & Davis 2001). However, the special feature of the FSS Social Fear scale is that it contains specific item content that measures difficulties with social situations. This is interesting as it hints that the over-arching core of the affective disorders that are studied in the paper is not hyper-reactivity in brain systems that process threat of physical harm but hyper-reactivity in brain systems that process threat of social harm.

The possibility that sensitivity to threat of social harm is linked to vulnerability to anxiety and depression aligns with the recent finding that the observed overlap between anxiety and depression reflects a deficit in common executive function (Gustavson *et al.* 2018). This outcome appears to fit with the finding that social situations require abstract, socially-specific, complex cognitive processes that are linked to executive function (e.g., Carlson et al. 2015). This latter inference dovetails with data showing that susceptibility to depression is particularly influenced by proneness to loneliness (Cacioppo *et al.* 2010) and the finding that low conscientiousness (a plausible marker of impaired executive function) is associated with depression (Hakulinen *et al.* 2015).

More generally, the present finding of an over-arching role for social fear in affective illness dovetails with the social risk hypothesis of depression (Allen & Badcock, 2006) which portrays depression as an adaptive response to perceived threat of social exclusion. According to this theory, depression increases sensitivity to indicators of social threat, boosts behaviours that signal reduced social threat and

increased need for social support and reduces the tendency to engage in risky, appetitive behaviours.

The notion that sensitivity to physical threat may relate to vulnerability to anxiety disorders, particularly PD, can be reconciled with the finding in healthy humans that the anti-anxiety drug lorazepam reduces sensitivity to the threat of physical harm to oneself or inflicting it on others (Perkins *et al.* 2013a; 2013b). It also fits with epidemiological evidence that the personality trait of neuroticism is particularly elevated in both PD and GAD, compared to other anxiety disorders and depression (Weinstock & Whisman 2006).

Given that we also observed that experimental behavioural and psychometric self-reported measures of threat-sensitivity were not significantly correlated in this sample, our data also suggest that threat-sensitivity is a complex, heterogeneous phenotype that requires fine-grained measurement at different levels of analysis, akin to other neuropsychiatric endophenotypes such as impulsivity and inhibitory dysfunction (Aichert et al 2012; Cyders & Coskunpinar 2011). The divergence in results across levels of analysis supports the importance of a multi-method approach such as the one that deployed in the present research. Future research may wish to add further levels of analysis, including the neural level (Perkins et al., 2019), in order to paint a more comprehensive picture of threat-sensitivity across the affective disorder spectrum.

As a caveat it should be noted that this first patient study presented here is only one step towards further validating the JORT as a useful paradigm in this field, as experimental medicine research on human defensive behaviour is still at an early stage. Instead the present use of the JORT demonstrates in a preliminary and tentative way that it may be possible to deploy an objective behavioural measure of threat-

sensitivity in clinical contexts that, when replicated and refined, have mainstream psychiatric relevance.

JORT results showed a mixed pattern of significant sex differences, as females in general tended to score higher than males in both Flight Intensity but in Risk Assessment Intensity the sex differences were found only in PD patients, not controls. This pattern is at least partly in agreement with our self-report data which showed higher FSS Tissue Damage and FSS Social Fear scores in females than males. Therefore, and since JORT output comprises a difference score that is calculated by subtracting the intensity of avoidance behaviour under no threat from the intensity of avoidance behaviour under threat, the sex effect on JORT cannot be dismissed as an artefact of sex differences e.g. in physical strength or familiarity with computer gaming contexts. Instead, these data converge with the finding that female mammals tend to be more sensitive to threat than males (e.g., Day et al. 2016), and women are generally more susceptible to affective disorders than men (McLean et al 2011; Baxter *et al.* 2014). Whilst the JORT data are, therefore, difficult to interpret with certainty, they might indicate that the JORT can detect a clinically-relevant sex effect, similar perhaps to the sex differences we observed via self-report in the FSS Tissue Damage and Social Fear scales. Post hoc, the pattern of findings from the JORT fits a rodent study that was published after our study was completed which showed that, after learning, females were more sensitive than males to probabilistic punishment but less sensitive when punishment could be avoided with certainty (Chowdhury *et al.* 2019). An indication of the likely neural seat of sex differences in threat-sensitivity is provided by a recent study showing that there are sex differences in the trajectories of development of two major brain systems that are involved in processing threat, namely the amygdala and hippocampus (Fish et al., 2019).

4. 1. Limitations

Some limitations of this study should be considered. First, the generalizability of the study findings is limited by the relatively small sample sizes. Post-hoc power analysis revealed for self-report anxiety measures a probability to detect a true between-group effect of about 1–β(Power)=0.40, using an effect size of d=0.19, α<.05, N=130 and 4 groups. In order to demonstrate this effect conclusively, a total sample size of N=308 and a critical F>2.63 would be required. The generalisability of the results is also limited by the relatively narrow focus of the anxiety disorders studied here, as the clinical category of anxiety disorders not only includes PD and GAD but also agoraphobia, social phobia and specific phobias. However, the theory that we tested in this paper (McNaughton & Corr, 2004) is based on rodent work and is focussed on PD and GAD. Hence, whilst other anxiety disorders are clinically important, they are beyond the scope of this paper.

A further limitation is, that despite our efforts to obtain clearly diagnosed PD and GAD patients, the majority of patients in each group showed comorbidity with MDD. It should be noted, however, that in clinical reality, psychiatric diagnostic criteria do not carve nature by its joints, hence the observed comorbidity may indeed reflect the reality that clinicians tend to encounter in their consultations with patients. This is also shown in the results of the clinical scales we used for GAD, PD and MDD symptom severity, which failed to differentiate clearly between patient groups, apart from the PDSS which showed that PD patients scored significantly higher than other patient groups. This tendency to homogeneity in our three patient sample seems likely to have diminished any differences in threat-sensitivity that may exist between patient groups that show less overlap and comorbidity.

An additional limitation concerns the fact that a sizable portion of patients were treated with different drugs, although the percentage of medicated patients did not differ significantly between patient groups. Given that we have previously observed effects of acute drug challenges on JORT performance (Perkins et al 2009, 2013), this issue allows for the possibility that clinical treatment may also have affected the JORT measurements obtained in this study. Future studies should therefore prioritise drug-naïve patients.

5. Conclusions

Our results suggest that self-reported elevated sensitivity to physical threat differentiates patients with panic disorder from those with depression and that elevated sensitivity to social threat is associated with vulnerability to both anxiety disorders and MDD. Our findings also point to the importance of characterising patient groups at different levels of analysis, with data obtained from questionnaires adding to the picture obtained from the behavioural JORT paradigm in this study.

Author Statement

All authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

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Contributors: The study was designed by AP, JGB, and UE. Data were collected by JGB. Results were analysed by AP and UE. The draft manuscript was written by AP and UE. Later versions of the manuscript were seen and commented upon by all authors.

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Conflict of Interest Disclosures

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Table 1: Descriptive Statistics of Demographic, Clinical and Dependent Variables

	GAD (N=32)	PD (N=35)	MDD (N=33)	CON (N=35)
Age	35.66 (11.46)	34.49 (12.38)	33.12 (13.20)	34.77 (10.63)
Sex (m/f)	11/21	8/27	10/23	12/23
Handedness (r/l/m)	31/1/0	33/1/1	29/3/1	33/2/0
MWT-B	29.31 (3.86)	27.37 (3.96)	28.55 (4.45)	29.23 (4.65)
GAF	55.88 (6.85)	57.63 (7.97)	56.59 (6.38)	98.71 (2.53)
GAD-Q-IV	9.11 (2.18)	8.42 (2.06)	7.61 (2.41)	1.56(1.73)
PDSS-SR	5.91 (4.53)	10.29 (4.85)	7.61 (2.41)	0.06 (0.34)
BDI-II	12.34 (11.92)	12.49 (10.24)	14.85 (7.28)	1.54 (3.53)
Illness duration	9.48 (9.20)	6.05 (5.65)	6.42 (6.74)	-
Medicated (N)	18	20	20	-

JORT FI	.20 (.39)	.41 (.91)	.21 (.39)	.18 (.37)
JORT RAI	-.03 (.08)	.01 (.11)	-.01 (.09)	-.004 (.08)
FSS TDF	33.22 (19.86)	51.77 (21.21)	28.15 (16.33)	22.46 (13.51)
FSS SF	52.54 (24.53)	60.43 (23.25)	49.21 (20.44)	25.03(16.91)

Legend: Data represent means (standard deviations) for all variables except for sex, handedness and medication. Sex is given as number of males (m) and females (f). Handedness is given as number of right-handed (r), left-handed (l) or mixed-handed (m) participants. Illness duration is given in years. MWT-B is the Mehrfachwahl-Wortschatz-Intelligenztest verbal intelligence test score. GAF, Global Assessment of Functioning Scale. GAD-Q-IV, Generalized Anxiety Disorder Questionnaire–IV. PDSS-SR, Panic Disorder Severity Scale – Self-Report Version. BDI-II, Beck Depression Inventory. JORT, Joystick Operated Runway Task; FI, Flight Intensity; RAI, Risk Assessment Intensity; GAD, generalised anxiety disorder; PD, panic disorder; MDD, major depressive disorder; CON, controls; FSS, Fear Survey Schedule; TDF, Tissue Damage Fear; SF, Social Fear.

Table 2. Correlations

Variable	1	2	3	4	5	6	7	8	9
1. JORT FI	-								
2. JORT RAI	.183*	-							
3. FSS TDF	.078	.043	-						
4. FSS SF	-.061	-.082	.703**	-					
5. MWT-B	-.092	-.039	-.071	.016	-				
6. GAF	-.037	.073	-.347**	-.541**	.041	-			
7. GAD-Q-IV	.043	.042	.415**	.652**	-.054	-.795**	-		
8. PDSS-SR	-.138	.017	.411**	.478**	-.143	-.588**	.557**	-	
9. BDI-II	.027	-.057	.199**	.513**	-.028	-.536**	.630**	.457**	-

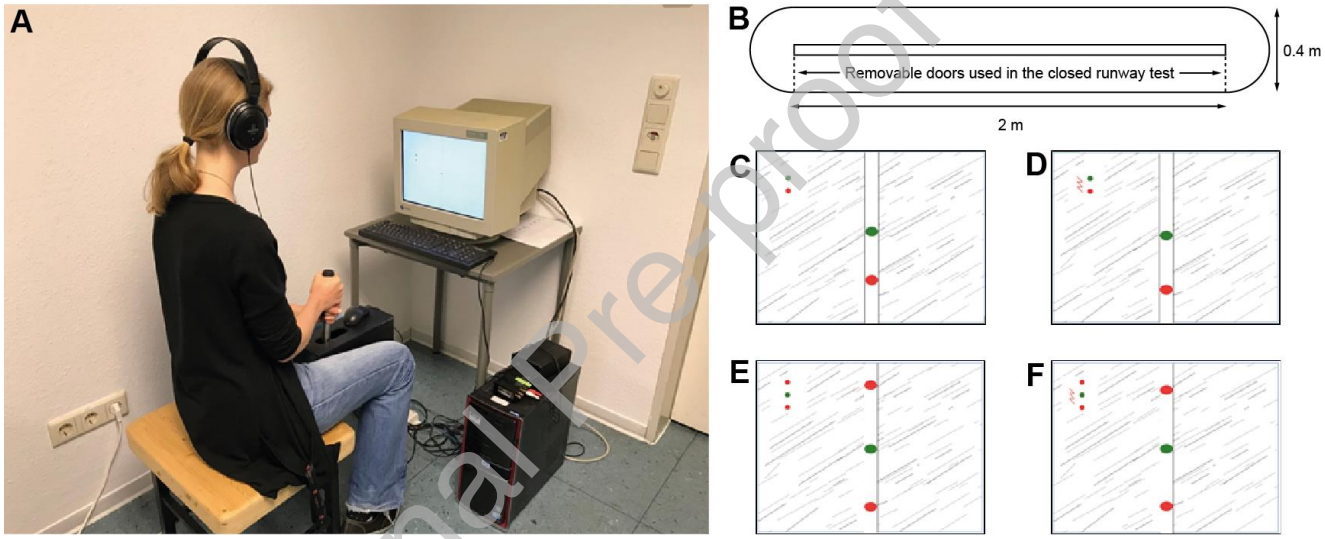
* $p<.05$.

** $p<.01$.

Legend: The table shows Pearson's r coefficients in the combined sample. JORT, Joystick Operated Runway Task; FI, Flight Intensity; RAI, Risk Assessment Intensity; FSS, Fear Survey Schedule; TDF, Tissue Damage Fear; SF, Social Fear; MWT-B, Mehrfachwahl-Wortschatz-Intelligenz test verbal intelligence test score; GAF, Global Assessment of Functioning Scale; GAD-Q-IV, Generalized Anxiety Disorder Questionnaire–IV; PDSS-SR, Panic Disorder Severity Scale – Self-Report Version; BDI-II, Beck Depression Inventory.

Running head: Threat-sensitivity in affective disorders

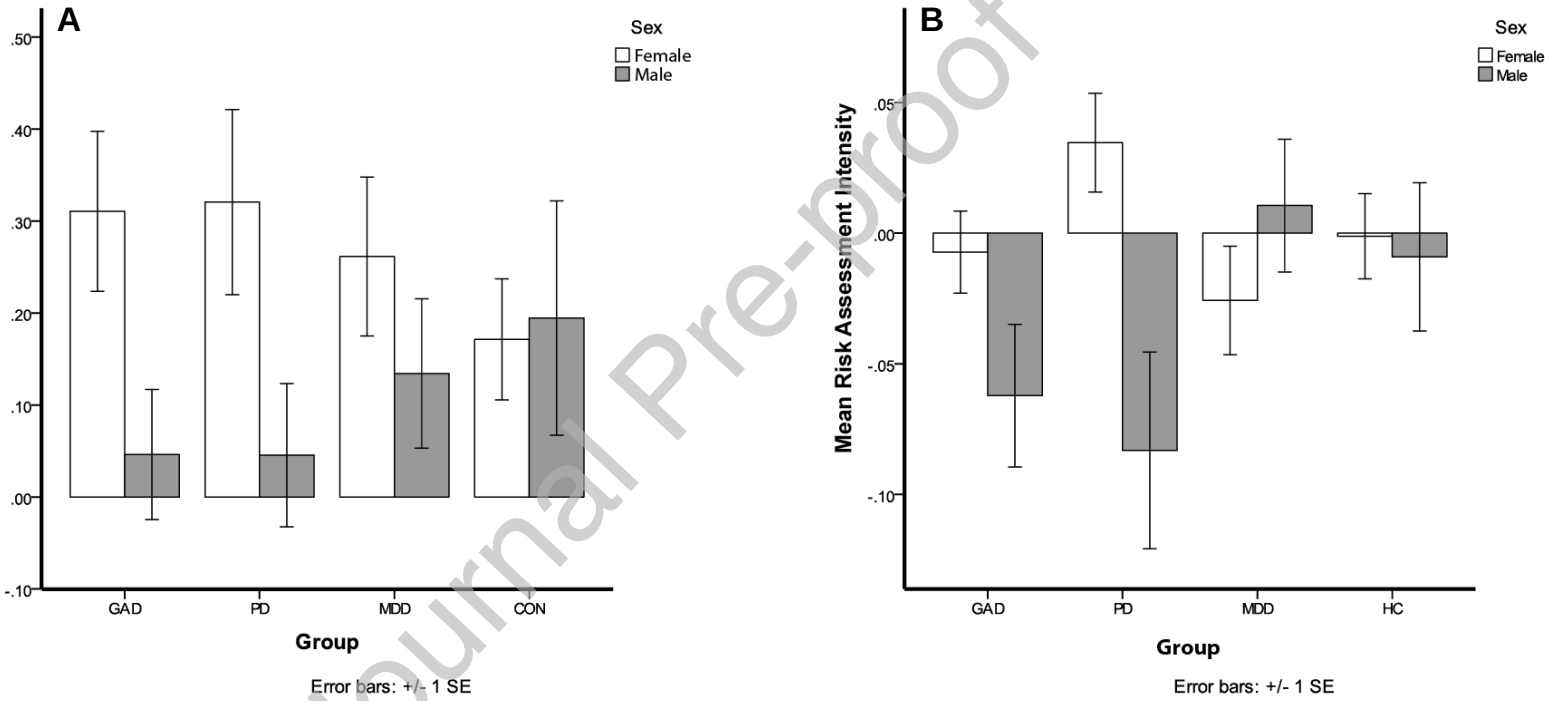
Figure 1: The Joystick Operated Runway Task (JORT)



Legend for Figure 1: The picture shows the laboratory setup of the JORT as it was used in this study (A). It also shows the rodent task from which the JORT was developed (the Mouse Defense Test Battery; B). Also shown are the four trials types of the JORT: simple avoidance with no threat of white noise (C); simple avoidance with threat of white noise (D); two-way avoidance with no threat of white noise (E); two way avoidance with threat of white noise (F).

Running head: Threat-sensitivity in affective disorders

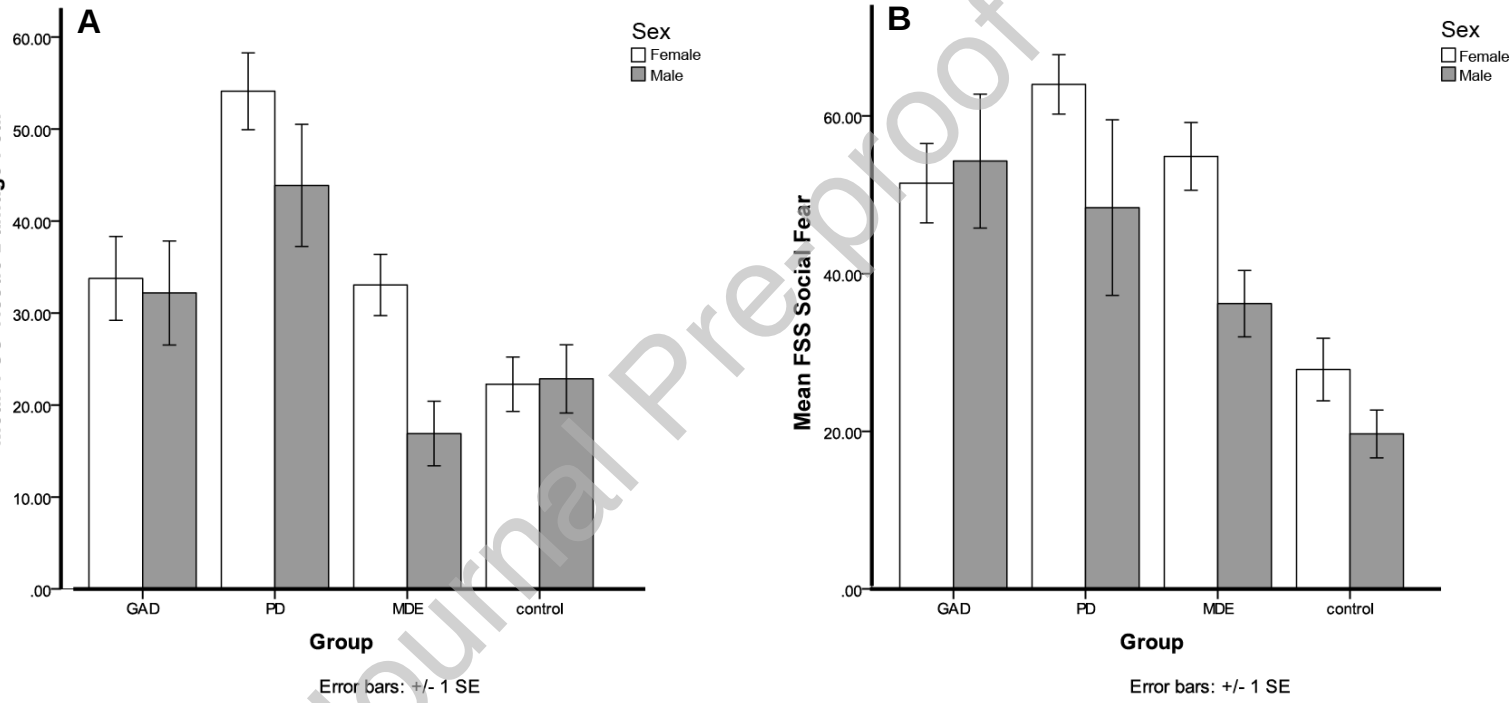
Figure 2: Effects of Group and Sex on JORT Performance



Legend for Figure 2: The figure shows the JORT performance as a function of group and sex. Error bars show 1 standard error of the mean. JORT, Joystick Operated Runway Task; GAD, generalised anxiety disorder; PD, panic disorder; MDD, major depressive disorder; CON, controls. (left) Flight Intensity; (right) Risk Assessment Intensity

Running head: Threat-sensitivity in affective disorders

Figure 3: Effects of Group and Sex on Fear Survey Schedule Scores



Legend for Figure 3: The figure shows Fear Survey Schedule (FSS) Scores as a function of group and sex. Error bars show 1 standard error of the mean. GAD, generalised anxiety disorder; PD, panic disorder; MDD, major depressive disorder; CON, controls. (left) Tissue Damage Fear; (right) Social Fear