Acquisition of Active Avoidance Behavior as a Precursor to Changes in General Arousal in an Animal Model of PTSD

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1. Introduction

1.1 Increased defensive reactions as a sign of PTSD

Post-traumatic stress disorder (PTSD) is a multi-symptom condition that includes three primary psychological features: reexperiencing, avoidance and emotional numbing, and hyperarousal (American Psychiatric Association, 2000). Historically, reexperiencing and hyperarousal have been the most studied features, from a neurobiological perspective, using various animal models. In these animal models, changes in defensive reflexive behaviors serve as the assessment measures for these symptoms; thus, both startle reactivity and freezing are now commonly used measures. Freezing behavior is advantageous because of its easy implementation; either the naked eye or an automated motor-tracking system can determine the duration and/or frequency of freezing behavior. In addition, freezing can occur in response to a specific fear-eliciting stimulus or to a fear-experienced context (Doyle & Yule, 1959; Bouton & Bolles, 1980; Fanselow, 1980). Because of these stimulus-response properties, freezing is the response commonly used to assess the experiencing of memories of conditioned stimuli that previously caused a heightened state of fear. At times, the acoustic startle response is used as an assessment of stimulus-elicited fear reactions (Davis, 1986; Hitchcock & Davis, 1987). Under this guise, similar stimuli used in conditioned freezing are experienced by the animal prior to a quick onset, relatively loud, acoustic stimulus. The result is a startle response that is enhanced over baseline levels, which is termed fear-potentiated startle.

However, in the case of PTSD, arousal is not necessarily tied to a memory or triggered by an explicit learned association. There are several examples of patients with PTSD exhibiting exaggerated startle responses in the absence of a known trigger (Butler et al., 1990; Orr et al., 1995; Yehuda et al., 1998; Orr et al., 2002). In fact, human longitudinal studies have found changes in startle reactivity occur over a period of time following the associated trauma (Shalev et al., 1998). Although there are possible confounding variables with any repeated test, such as developing an aversion to the startle testing context, there is a difference with PTSD patients as they fail to habituate to the startle test over months (Shalev et al., 1998). Increases in startle magnitudes can be elicited in rats in order to model this feature of PTSD by exposing them to inescapable shock. Interestingly, like some of the symptoms of PTSD,

this procedure increases startle magnitude in male rats several days following stressor exposure (Servatius et al., 1994; Servatius et al. 1995; Beck et al., 2002; Manion et al., 2007; Manion et al., 2010); in other words, there is a delayed sensitization of the startle response (Beck et al., 2002). As shown in Figure 1, enhanced startle reactivity may then be observed up to several days later (Servatius et al., 1995; Beck et al., 2002; Manion et al., 2007; Manion et al., 2010). The delayed expression of this enhanced defensive response could be due to competing processes that are similarly elicited by inescapable shock. For instance, some female rats exhibit a suppression of the startle response following stressor exposure that is clearly linked to the immune response elicited by shock exposure (Beck & Servatius, 2005; Beck & Servatius, 2006), but this suppression of startle reactivity is only evident under certain ovarian hormone conditions (Beck et al., 2008). Although males have not been shown to exhibit a reduction in startle reactivity, there may be similar acute physiological reactions that negate an immediate increase in startle reactivity. Hence, these inescapable stress models of enhanced startle reactivity are largely based on the concept that PTSD-like hyperarousal is a product of a single, uncontrollable, traumatic event (or period of repeated trauma over consecutive days).
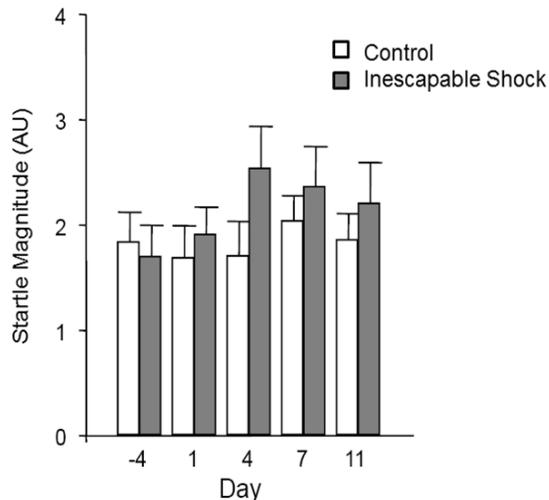

Fig. 1. Following 3 days of repeated tailshock exposure (40, 3 s, 2 mA shocks over 2 h), startle magnitudes are elevated in male Sprague Dawley rats 4 days thereafter [Stress x Day $F (4, 776) = 7.6, p < .001$]. The delayed expression of this increase has been used as a model of the emergent aspects of PTSD symptom expression. Startle magnitude is represented in arbitrary units (AU), as the amplitude is corrected for by body weight.

These models of hyperarousal in PTSD fail to account for potential innate differences in reactivity. The diathesis model of anxiety disorders indicates that anxiety symptomology are a combination of innate characteristics that are influenced by life events. Recent prospective research on PTSD symptomology has indicated elevated arousal may be predictive of anxiety symptoms (Guthrie & Bryant, 2005; Pole et al., 2009). Startle reactivity, as one measure, is elevated in children that upon follow-up were diagnosed with clinical anxiety (Merikangas et al., 1999). Thus, pathologic arousal exhibited in PTSD may reflect an innate

elevation in arousal, an increase in arousal due to experience, or a combination of innate characteristics that are exacerbated by experience.

In developing our model of anxiety vulnerability, we sought a rodent that reliably exhibited a set of behaviors that are analogous to an identified human vulnerability condition. Behavioral inhibition (or inhibited temperament) is extreme withdrawal in face of novel social and nonsocial situations (Kagan et al., 1987; Kagan et al., 1989; Hirshfeld et al., 1992) and is identified as a risk factor for future symptoms of anxiety disorders (Hirshfeld-Becker et al., 2008; Jovanovic et al., 2010). The Wistar-Kyoto (WKY) rat demonstrates aspects of behavioral inhibition in terms of withdrawal in tests of social interaction (Pardon et al., 2002) and lack of exploration in the open field test (Pare, 1994; Servatius et al., 2008). Hence, we tested WKY rats in a multi-intensity startle procedure that allows for assessment of startle sensitivity (percentage of startles elicited at various acoustic intensities) and startle responsivity (magnitude of responses to the highest intensity). Given startle is a defensive-reflex, increased responsivity can be viewed as an increase in general arousal (i.e. more energy used to respond to threat), whereas increased sensitivity can be viewed as an enhancement of vigilance (i.e. greater signal-detection of threats). With no prior manipulations, WKY rats exhibited similar startle sensitivity measures as Sprague Dawley (SD) rats, but exhibited higher startle responsivity (see Figure 2). These temperament and reactivity characteristics are reasonable analogs of the predisposing factors for developing symptoms of anxiety disorders; therefore, we adopted the WKY rat as our anxiety vulnerability model (Servatius et al., 2008; Beck et al., 2010; Ricart et al., 2011a; Ricart et al., 2011b; Jiao et al., 2011; Beck et al., 2011).
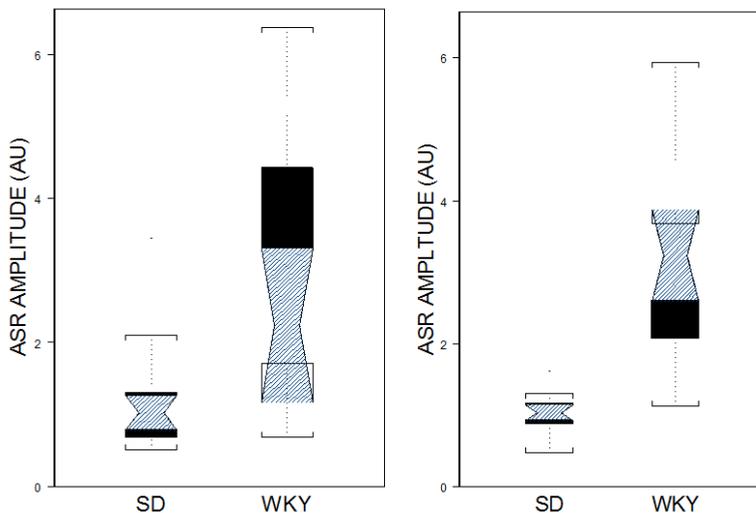

Fig. 2. Box plots of initial startle responsivity and latency of male SD and WKY rats (left) and female SD and WKY rats (right). Notched regions depict median ± 95% confidence interval. Boxed region depicts interquartile range (middle fifty). Whiskers depict range of data 1.5*interquartile range. Outliers depicted by '*'. WKY rats exhibit innate differences in ASRs, with greater amplitudes.

2. Avoidance as an alternative symptom to model

2.1 Behavioral avoidance

Avoidance, though not as well studied as hyperarousal or reexperiencing, is a common symptom to all anxiety disorders, including PTSD. Recent research indicates that the presentation of increased avoidant behavior has been found to track the general worsening of PTSD symptoms (Karamustafalioglu et al., 2006; O'Donnell et al., 2007) suggesting that acquisition of avoidance may have an etiological role in the development of PTSD. Many animal models of avoidance use tasks that are based on a tendency to exhibit passive avoidance. Tasks such as the elevated plus maze, measure how often rodents explore elevated open-arms (no walls) versus arms with high walled sides (closed arms). Rodents have a fundamental aversion to well-lit open spaces; therefore, prior exposure to stressors and anxiogenic drugs will reduce the limited tendency to explore the open arms (Pellow et al., 1985); conversely, anxiolytics increase exploration into the open arms. However, avoidance symptoms displayed in PTSD get progressively worse over time, and models such as the plus maze are not conducive to exhibit such a progression. In fact, avoidance and avoidant behaviors distinguish between those that develop PTSD and those who recover from trauma (Karamustafalioglu et al., 2006; Foa et al., 2006; O'Donnell et al., 2007). Thus the adoption of behavioral, cognitive, or emotional avoidance represents the detrimental process, which distinguishes those that successfully cope from those that develop pathological anxiety. Further, many avoidance behaviors in humans are active, that is, behaviors are not merely the absence of activity. Active avoidance is often more debilitating as the increased time and resources utilized for avoidance limit the capability of the individual to perform other tasks. Therefore, a task that allows for the observance of a methodical increase in active avoidant behaviors would be more akin to what is described in PTSD.

The process of learning active avoidance behaviors in rodents involves three steps. One, the rodent has to learn how to instrumentally dissociate itself from a noxious stimulus. This either may involve removing itself from the noxious stimulus (as in shuttle escape) or manipulating the environment such that the presentation of the noxious stimulus stops (as in lever-press escape or wheel-turn). Two, the rodent needs to recognize that the presence of certain stimuli in the environment precede the presentation of the noxious stimulus. These "warning signals" need to be distinct from the environment, with auditory stimuli serving as better signals than visual stimuli (Gilbert, 1971). This association may occur either during or following the acquisition of escape behavior. Three, the rodent needs to use the warning signal as a cue to emit an instrumental response prior to the actual onset of the noxious stimulus (i.e. avoidance behavior). The emitting of the response to the predictive warning signal removes the warning signal and the associated threat. In some regard, this process is more complicated for the rodent because it usually has to learn an escape response before it will reliably learn an avoidance response; although for some the transition from escape to avoidance behavior may involve less training sessions than for others. Humans can obviously learn to avoid people, animals, places, and situations without necessarily having to learn to escape from them first, but because this learning process is a bit more methodical in the rodents, we can understand how each stage of the process occurs and how it contributes to pathological avoidance.

Pathological avoidance is when the animal (human or non-human) responds to warning signals nearly 100% of the time. Although intuitively this may seem to be a responsible

strategy for the animal, it does not allow for the individual to be sensitive to contingency changes (i.e. when the warning signal no longer reliably predicts the noxious stimulus). At that point, the avoidance responses are being emitted to remove a possible (not probable) threat. Therefore, the animal may be expending energy, by moving to the lever and subsequently depressing it, trial after trial to avoid a threat that the warning signal no longer reliably predicts. For individuals with severe anxiety disorders, this strategy of avoiding possible threats can become very disruptive if 1) the individuals expend more energy to avoid situations than what would be required to actually deal with them and 2) the perceived warning signals become generalized, which narrows their ability to interact with the world. Therefore, identifying an animal model that will acquire an exceptionally high asymptotic level of avoidant behavior, and subsequently exhibits the predictable slow extinction of the response, can provide us with a valuable system for identifying the vulnerability factors that predict such avoidant behaviors as well as the neural mechanisms that bias their behavioral strategies to such an extreme.

There are various forms of active avoidance that can be modeled in rats, but the desire to track the development of increased avoidant behavior over time led us to adopt distinct lever-press avoidance as our active avoidance procedure. Lever-press avoidance has been utilized for decades to study learning, but it also has a history as a prominent model of anxiety (Pearl, 1963; D'Amato & Fazzaro, 1966; Hurwitz & Dillow, 1968; Gilbert, 1971; Dillow et al., 1972; Berger & Brush, 1975). Derived initially from the 2-factor theory of threat/fear motivation and learned avoidance (Mowrer, 1939a; Mowrer, 1939b; Mowrer & Lamoreaux, 1942; Mowrer & Lamoreaux, 1946), the general premise of this approach is that a learned fear of signals is sufficient to support avoidant behavior without requiring a continued re-exposure to the actual noxious stimulus or event. Others have provided alternative interpretations of the development of active avoidance learning. Herrnstein, Hineline, and Sidman all focused on the reduction in shock density over time and a second internal factor (e.g fear or anxiety) need not be required in order to explain the acquisition of avoidance behavior (Sidman, 1962; Herrnstein & Hineline, 1966; Hineline & Herrnstein, 1970). This is an important consideration, for without the theoretical need for an internal state, there is no reason to assume a general state of arousal should be evident in the absence of shock exposure. In short, once asymptotic performance is attained, because of the adaptation of the instrumental response to minimize shock frequency, general arousal should be reduced compared to early acquisition (when shocks are more frequent). Still, others have suggested that there may be another component to this acquired behavior – the attainment of perceived safety (Dinsmoor, 1977; Dinsmoor, 2001). This is an interesting proposition because it also does not require any rumination upon the animal's part to "know" the shock is coming. In this approach, the animal learns to exhibit the behavior because it leads to the attainment of perceived safety, which could be in the form of an explicit stimulus only present during periods of non-threat or simply as the absence of the warning signal. At the foundation of this theoretical discussion is a fundamental difference in the view of how animals perceive learning: a molecular (trial by trial, stimulus by stimulus) or molar (general state) analysis (Hineline, 2001; Bersh, 2001). One could argue that lingering changes in general arousal outside of the avoidance learning context may reflect overall changes in the animals that would be proposed by molar analysis theory.

2.2 Avoidance susceptibility as a model of anxiety vulnerability

As mentioned above, it is well documented that approximately 10% of those people who experience a significant trauma develop PTSD; therefore, there has been recent interest in

identifying vulnerability factors that cause some proportion of the public to be susceptible to developing PTSD symptoms. From a learning-diathesis approach, vulnerability for developing anxiety disorders comes from differences in acquiring associations. People self-ascribed as being behaviorally inhibited, as well as the rat model of behavioral inhibition (the WKY rat), exhibit quicker acquisition of classically conditioned responses (Ricart et al., 2011b; Myers et al., 2011; Beck et al., 2011). In addition, females also exhibit enhanced susceptibility to acquire associations. This is reflected in faster acquisition of predictive relationships (classical conditioning) (Spence & Spence, 1966; Wood & Shors, 1998; Shors et al., 1998; Holloway et al., 2011) and behavioral reactions to stimuli (instrumental learning) (Van Oyen et al., 1981; Heinsbroek et al., 1983; Heinsbroek et al., 1987; Saavedra et al., 1990; Dreher et al., 2007; Dalla et al., 2008; Lynch, 2008), the 2 primary components of avoidance learning (Mowrer & Lamoreaux, 1946). Based on these characteristics, it is not surprising that both female sex and behaviorally inhibited temperament are associated with a greater susceptibility to acquire active avoidance behaviors (Beck et al., 2010; Beck et al., 2011). As shown in Figure 3, male SD rats are slowest to acquire a lever-press avoidance response, compared to their same-strain female counterparts and WKY rats of both sexes. Interestingly, the relationships between the 4 groups change during extinction with male WKY rats extinguishing slower than both female groups and male SD rats. Females of both strains in this study both acquired and extinguished at the same rate.
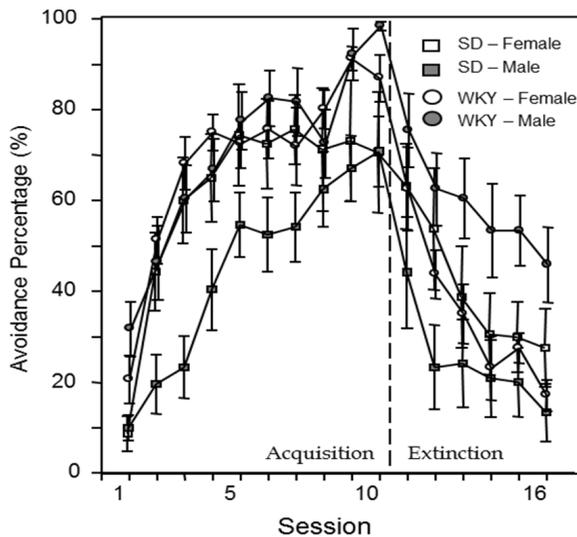

Fig. 3. Avoidance susceptibility can be observed by comparing rates active avoidance responses are acquired. In this example, WKY rats acquire a lever-press avoidance behavior quicker than male SD rats, main effect Strain $F_{(1, 36)} = 9.0$, $p < .005$. Female SD rats also acquired the behavior quicker than male SD rats, Sex x Session $F_{(9, 324)} = 2.6$, $p < .01$. Following session 10, the shock was removed in order to assess extinction of the avoidance response. In general, WKY rats extinguish the response slower than SD rats, but female SD rats were slower than male SD rats extinguishing the behavior, whereas male WKY rats were slower to extinguish the response compared to female WKY rats, Strain x Sex $F_{(1, 36)} = 6.0$, $p < .02$ and Sex x Session $F_{(5, 179)} = 2.2$, $p < .05$.

3. Behavioral avoidance as a precursor for increased arousal

For some time, the acquisition and performance of avoidance behavior was used as a tool to increase arousal in studies of physiological responsiveness in monkeys (e.g. stress-induced hypertension) because it was obvious to the investigators that control over the stimuli did not necessarily lead to a reduction in arousal (Forsyth, 1968; Forsyth, 1969; Natelson et al., 1976; Natelson et al., 1977). Since that time, avoidance learning fell out of favor as such a tool and was generally replaced by inescapable stressor paradigms. Therefore, with our rodent model of acquisition and extinction of active avoidance behavior, we questioned whether the process of acquiring avoidant behavior would influence general arousal outside of the avoidance-training context, which was not the case for some of the monkey studies (Forsyth, 1968; Forsyth, 1969).

Having established strain and sex differences in the acquisition and extinction of active avoidance, as well as differences in innate reactivity between strains, the question became whether the process of acquiring avoidant behavior would influence general arousal outside of the avoidance-training context. There are three possible periods of time startle reactivity may show changes as a function of acquiring lever-press avoidance and each would have associated with it a different theory of how the learning procedure was affecting general sensory reactivity. First, based on the above inescapable shock model, one could hypothesize that startle reactivity should be increased within days of the first few training trials, following the sessions the rats experience the most shock. Second, if the development of avoidant behavior follows the trajectory of developing anxiety, then one could hypothesize that startle reactivity should increase over acquisition. Yet, there is also a third option. That is, startle reactivity could increase if the association between the signals and the consequence becomes less certain. In this third possibility, startle reactivity could be increased if there is a change in the relationship between the signals that represent threat and the consequences following acquisition (such as conducting extinction trials). Another consideration is that only certain animals may be affected in a way that increases their general arousal. Strain differences in both acquiring the avoidant behavior and resistance to extinguish it may be a sign of anxiety vulnerability that could also be reflected in a change in general arousal (reflected as a persistent change in startle reactivity).

3.1 Acquisition of active avoidance and changes in startle reactivity

There are several examples of shock-induced changes in various behavioral indexes of anxiety-like reactions outside of the shock-exposure context (Servatius et al., 1994; Servatius et al., 1995; Beck et al., 2002; Cordero et al., 2003; Beck & Servatius, 2005; Manion et al., 2007; Daviu et al., 2010; Manion et al., 2010), which may lead one to assume that stressors which cause pain have a particularly significant role in causing context-independent changes in general arousal. However, in the case of acquiring behavior that is conducive to active avoidance of shock, the acute role of shock exposure in early acquisition can be contrasted with the expression of stimulus control during asymptotic performance levels. This is an important distinction in any avoidance-based model of PTSD, since the clinical condition does not necessarily involve an acute increase in arousal (as defined by startle reactivity), but the development of avoidance does parallel the general worsening of symptoms (O'Donnell et al., 2007). The implication of this correlation is that other symptoms, such as hyperarousal, may come as a result of increasing stimulus control, as active avoidance coping strategies strengthen.

Male SD and WKY rats were trained to acquire a lever-press, active avoidance behavior (or served as non-trained homecage controls), and were tested weekly to assess changes in startle sensitivity and responsivity. In concert with prior studies, male WKY rats demonstrated greater baseline startle magnitudes and equivalent startle sensitivity. Subsequently, acquisition of avoidance appeared to be equivalent between the strains. In addition, WKY rats reached greater asymptotic avoidance performance, as seen in previous studies (see Figure 4).
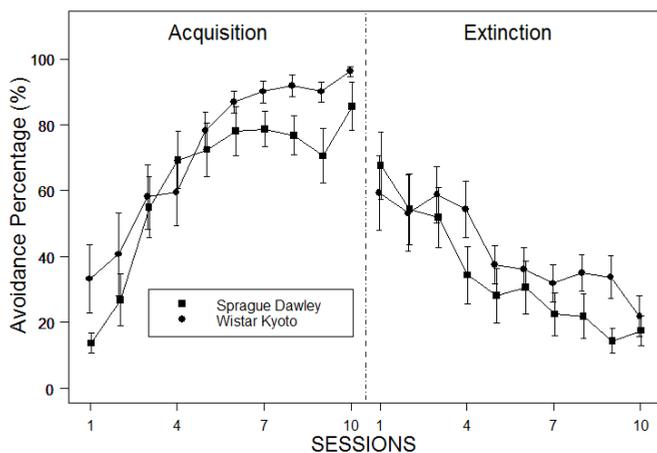
Fig. 4. Lever-press behavior to avoid intermittent footshock was reliably acquired in both strains of male rats (main effect Session, $F_{(9, 135)} = 25.0$, $p < .001$ and Session x Trial interaction, $F_{(171, 2394)} = 1.4$, $p < .001$), but WKY rats exhibited more avoidance responses per session in the later sessions of the acquisition phase. During extinction, differences between strains were not apparent across sessions, but they were significant within sessions (Strain x Trial interaction, $F_{(19, 266)} = 3.3$, $p < .001$.

Increases in startle sensitivity and responsivity are expected early in acquisition if shock exposure causes changes in vigilance and arousal, but, if learning and performing an avoidance behavior causes anxiety, startle measures should be elevated during the later weeks of acquisition. Thus, as shown in Figure 5, there was a strain-independent elevation in startle sensitivity displayed by those being trained in avoidance behavior. This difference is evident from the beginning of acquisition, when animals are receiving the most of shocks, and dissipates by the end of acquisition. Conversely, startle responsivity, as demonstrated by relative increases in startle magnitudes above baseline, is largely unchanged early in acquisition, when enhanced startle sensitivity is greatest. Startle responsivity in avoidance-trained animals increased toward the end of acquisition, during the refinement of avoidance behavior when few (if any) shocks are being received. Therefore, as startle sensitivity differences dissipate (possibly a sign of normalizing vigilance), enhancements in responsivity appear (a possible sign of increased arousal).

Historically, female rats are known to generally acquire discrete lever-press avoidance, as well as other active avoidance behaviors, better than their male counterparts (Beatty & Beatty, 1970; Scouten et al., 1975; Van Oyen et al., 1981; Heinsbroek et al., 1983; Beck et al.,
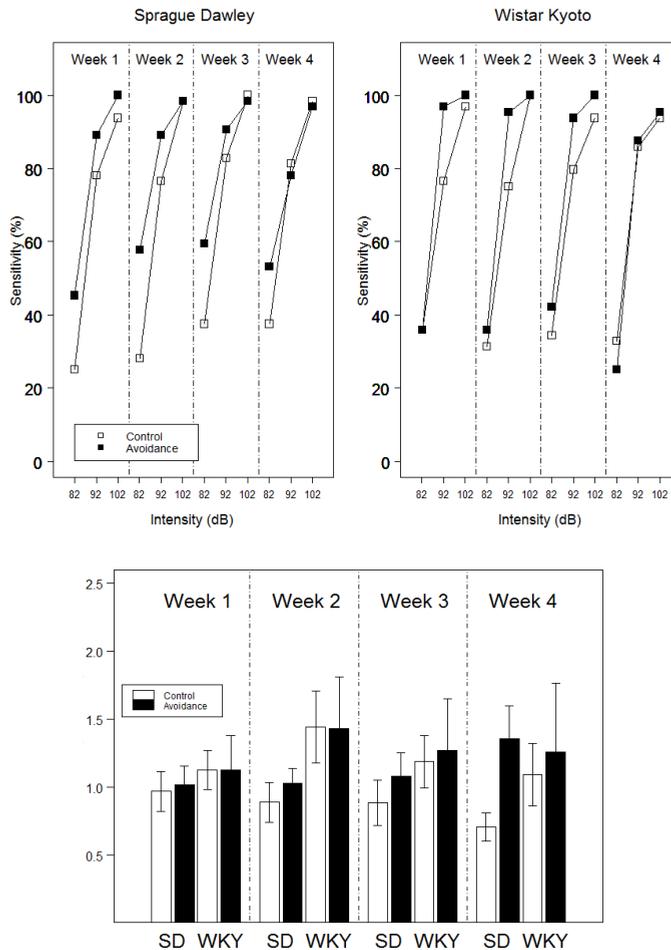
Fig. 5. Exposure to avoidance learning was associated with an increase in startle sensitivity in both strains of male rats (main effect Avoidance, $F(1, 28) = 4.2$, $p < .05$. Otherwise, significant differences across the three stimulus intensities used (main effect Intensity $F(2, 56) = 595.5$, $p < .001$) were coupled with a marginally significant difference in the percentage of startles elicited across the 4 weeks of acquisition (Avoidance x Week interaction $F(3, 84) = 2.4$, $p < .07$. By the fourth week of avoidance acquisition, differences in startle sensitivity between the avoidance-trained group and the homecage control group were greatly reduced. Although not statistically significant, signs of increased startle magnitude began to become apparent in SD rats by the last week of acquisition.

2010; Beck et al., 2011), suggesting that they may exhibit greater changes in general arousal, as indexed by startle reactivity measures, with the experience of shock and/or the acquisition of the avoidant behavior. Using the same procedures as described for the male rats, female rats demonstrated similar patterns of initial startle reactivity: greater startle magnitudes in WKY rats but equivalent startle sensitivity across strain. During avoidance

training, female rats exhibited rapid acquisition of the lever-press avoidance response (see Figure 6). However, the effect avoidance had on arousal was different than the effects observed in male rats of these strains. As shown in Figure 7, startle sensitivity was transiently elevated in SD rats training in avoidance learning, but WKY rats exhibited much less elevations in sensitivity early in acquisition. In stark contrast, at the end of acquisition, WKY rats trained in avoidance were showing a reduction in startle sensitivity. Thus, while female SD rats demonstrate an enhancement in sensitivity similar to male rats, WKY rats demonstrate a unique decrease in reactivity compared to their untrained controls in the later phase of acquisition. Also, unlike the male rats, no consistent changes in startle responsivity were observed in SD or WKY females as was seen in male rats.
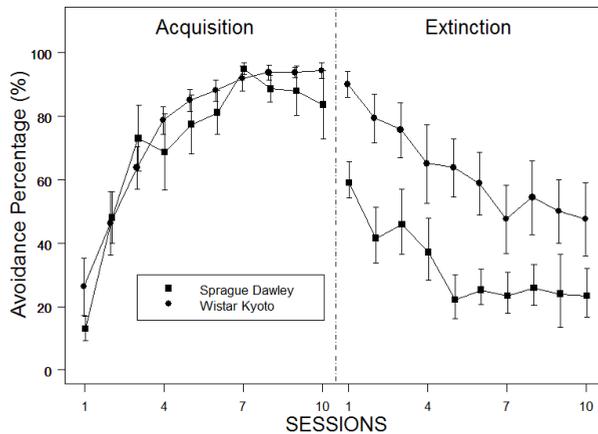

Fig. 6. Lever-press behavior to avoid intermittent footshock was reliably acquired in both strains of female rats (main effect Session, F (9, 135) = 33.4, p < .001 and Session x Trial interaction, F (171, 2394) = 1.5, p < .001). During extinction, differences between strains became evident within the first session and continued throughout the extinction phase of the experiment (main effects, Strain, F (1, 14) = 7.4, p < .05, Session, F (9, 135) = 13.7, p < .001, and Trial, F (19, 266) = 10.9, p < .001).

These data suggest there are different aspects to an avoidance-induced change in vigilance and/or general arousal (as reflected by an increase in startle sensitivity and responsivity, respectively). Increases in startle sensitivity generally occurred proximal to experiences with periodic foot-shock during the early phase of acquisition (when rats are slowly transitioning from a majority of escape responses to an increasing number of avoidance responses). This pattern appears consistent, albeit to varying degrees, across both sexes of each strain, and suggests experience with a painful stimulus is increasing vigilance in those animals. However, strain and sex differences become evident as avoidance responses occur in a greater majority. Of note are the changes in startle responsivity in male SD rats and startle sensitivity in female WKY rats. These groups exhibited divergent changes, with male SD rats exhibiting enhanced startle responsivity and female WKY rats exhibiting decreased startle sensitivity. The enhancement in startle responsivity, as a possible index of general arousal, observed in male SD rats is akin to the described usage of avoidance decades ago, where daily sessions of non-cued avoidance (i.e. Sidman avoidance) over several months
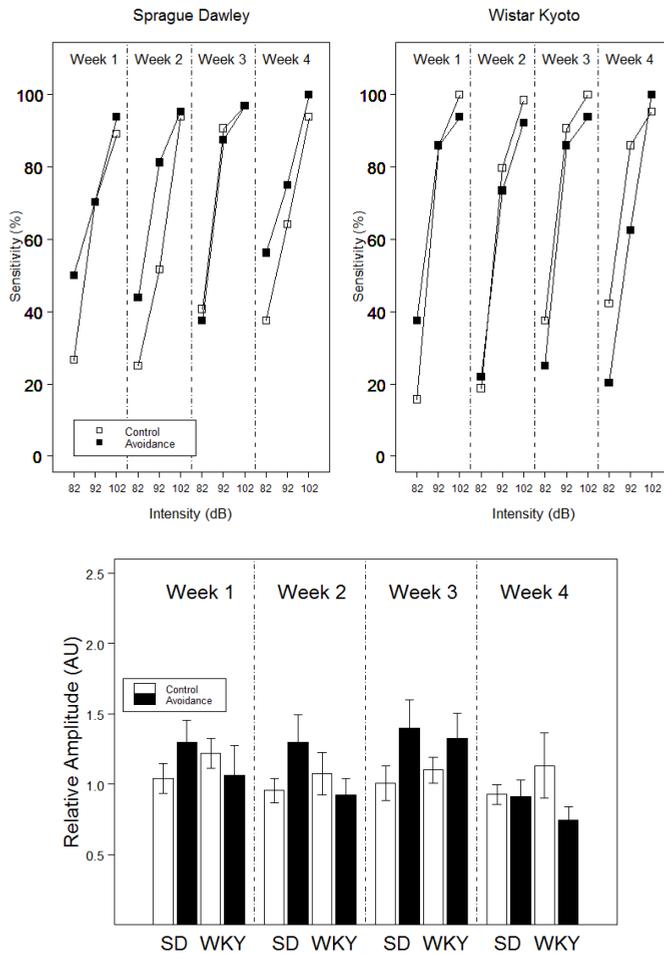
Fig. 7. Exposure to avoidance learning was associated with strain and intensity-dependent changes in startle sensitivity. Early acquisition showed elevations in the startles elicited at the lowest intensity. For SD females this continued into the second week and expanded to the middle intensity. Differences within the SD strain declined over the later two weeks, but, at the same time, a decrease in startle sensitivity became apparent in the female WKY rats. These impressions were confirmed by significant Strain x Avoidance, $F (1, 28) = 5.2$, $p < .03$, Strain x Intensity, $F (2, 56) = 11.3$, $p < .001$, and Avoidance x Week x Intensity, $F (6, 168) = 3.0$, $p < .007$, interactions. Startle magnitudes did not significantly differ between groups across the four weeks of acquisition.

caused reported increases in agitation towards the researchers and chronic increases in mean systolic and diastolic blood pressure in well-avoiding monkeys (Forsyth, 1969). In contrast, the reduction in startle sensitivity, in female WKY rats, is suggestive of an avoidance-induced reduction in general vigilance. Might this suggest female WKY rats

adapt better to a stressful environment? If so, would these changes in vigilance and arousal be maintained in the absence of the actual threat? On the other hand, is the reduction in startle responsivity evidence for a difference in the underlying associations made during the acquisition of the avoidance behavior? Continued assessment of startle sensitivity and responsivity during the extinction phase should provide further evidence for or against these interpretations.

3.2 Extinction of active avoidance, removal of avoidance context and persistent changes in startle reactivity

As shown in Figure 4, unlike previous studies, there was minimal difference in the extinction rates of male SD and WKY rats; still the WKY rats extinguished slightly slower. Nonetheless, the resultant effects on the indexes of startle were rather clear. As with the end of the acquisition phase, startle sensitivity did not appreciably change during the extinction phase; however, differences in startle responsivity grew in appearance (see Figure 8). Differences first observed at the end of acquisition in the male SD rats continued to be present during the first two weeks of extinction. Interestingly, by the end of the extinction phase, avoidance-trained WKY rats were also exhibiting greater startle responsivity than their non-trained counterparts. This suggests the arousal displayed by male SD rats is contingent upon emitting a certain level of avoidance behavior, even in the absence of shock. In contrast, the male WKY rats show differences as they extinguish the avoidant behavior. This may reflect an increase in arousal due to the slow abandonment of the avoidant behavior. Following this logic, the male WKY rats could have perceived that their behavior does not control the presence or absence of the shock anymore; the result is an increase in general arousal during extinction.

The female rats exhibited a substantial difference in their rates of extinction (see Figure 6), with female WKY rats extinguishing much slower than female SD rats. This may be attributable to differences in how the females of these strains extinguish the response, since both groups exhibited very similar acquisition rates and attained a similar asymptotic level of responding. However, under similar avoidance learning conditions we have not observed such a difference (see Figure 3). The one difference in procedure from our previous experiments is the addition of the weekly startle tests. This may be an example of the vigilance/arousal test influencing performance on subsequent avoidance acquisition/extinction session days. The results of the startle test showed that intra-strain differences in the startle sensitivity continued from the end of avoidance acquisition. As shown in Figure 9, female WKY rats showed reduced responding, which eventually normalized through the extinction period. Female SD rats still showed signs of increased startle sensitivity early in the extinction phase. These data suggest that elevated vigilance continues to be expressed in female SD rats for a period of time even in the absence of shock. Conversely, the decreased vigilance in female WKY rats, attributed to the reduction in shock exposure, continues, as the shocks remain absent in extinction, then eventually normalize.

Following extinction training, all rats were allowed to remain in their home cages for a number of weeks, with startle measures taken every week, as during acquisition and extinction. These sessions allowed for the measurement of long-term changes in arousal and vigilance following avoidance training. In male rats, the elevations in startle responsivity returned to baseline. Thus changes in arousal that were evident during avoidance training did not persist following cessation of training. The same was seen in female rats, where the
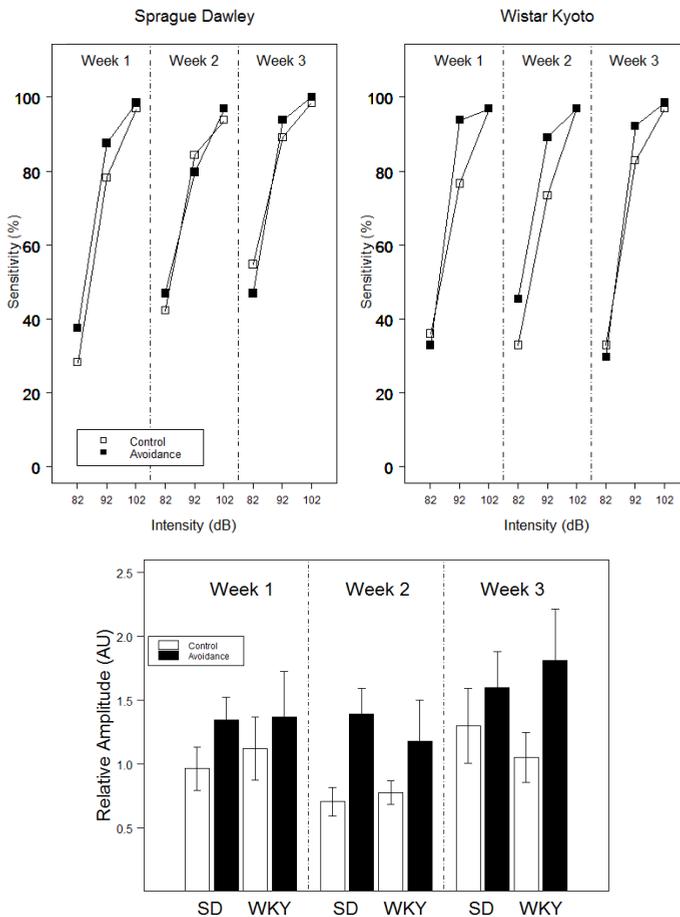
Fig. 8. During the extinction phase, avoidance-trained male SD and WKY rats did not show significantly different startle sensitivity measures compared to their same-strain controls. However, differences in startle magnitude continued into the extinction phase for those male SD rats that had been trained in avoidance behavior. In addition, in the midst of extinction sessions, startle magnitudes of male WKY rats were elevated compared to their homecage control counterparts (main effects of Avoidance, $F_{(1, 28)} = 4.1$, $p < .05$ and Week, $F_{(2, 56)} = 10.5$, $p < .001$).

decreases in startle sensitivity seen in WKY female rats did not persist. Innate differences in startle behavior, however, remained. WKY rats of both sexes demonstrated higher startle responsivity compared to SD rats.

Since these between-group differences in startle responsivity are not observed during the subsequent month where they remained in the home-cage, these results suggest there is a connection between displaying some level of active-avoidance behavior, on a regular basis, and persistent changes in vigilance or general arousal. For males, differences were observed
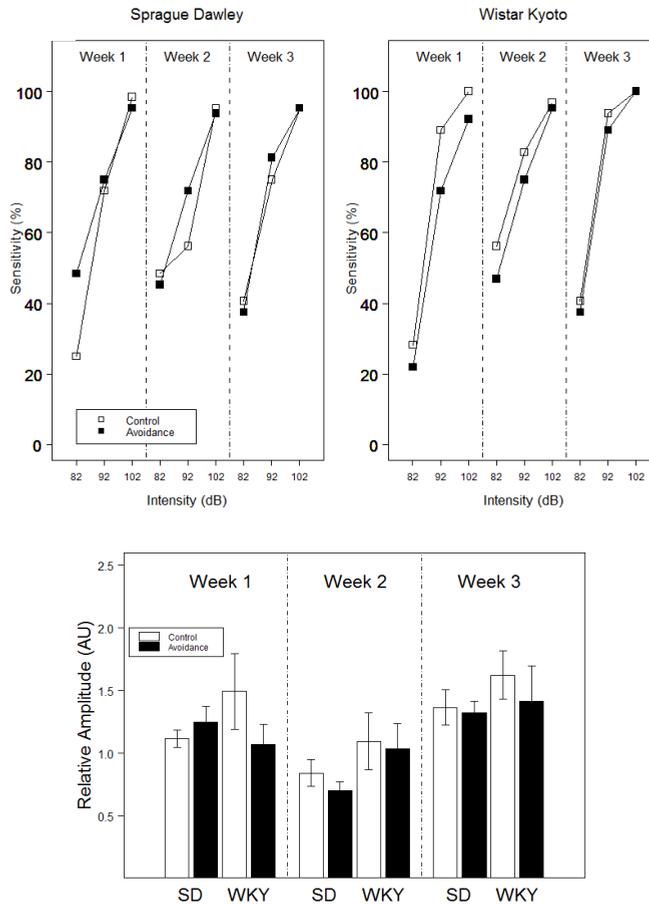
Fig. 9. Exposure to avoidance learning was associated with strain and intensity-dependent changes in startle sensitivity in female rats that persisted into the extinction phase. For SD rats startle sensitivity was still elevated during the first week of extinction. In a similar fashion, female WKY rats this continued to show a reduction in startle sensitivity into the initial week of extinction. These impressions were confirmed by significant Strain x Avoidance, $F (1, 28) = 4.6$, $p < .04$, Strain x Intensity, $F (2, 56) = 6.5$, $p < .002$, and Week x Intensity, $F (4, 112) = 12.6$, $p < .001$, interactions. There were no significant differences during the extinction phase measures of startle responsivity attributable to prior avoidance learning.

during extinction (in both strains) suggesting that the behavior itself (not actual response to shocks) may be sufficient to induce a state of general arousal. Herein lies the possible connection to the growth of general PTSD symptoms with the trajectory of avoidance symptoms (O'Donnell et al., 2007). Similarly, the persistent elevation in vigilance observed in female SD rats can also fit the description of PTSD. It may be that avoidance learning causes changes in the brain systems underlying fundamental defensive behaviors. For

example, since the males learned to manipulate the environment to avoid noxious stimuli, maybe defensive reactions are enhanced; the animal is more "at-the-ready". Increases in vigilance may cause the female SD rats to perceive their environment in a more apprehensive manner. Interestingly, inescapable shock causes a transient reduction in SD startle responsivity without affecting startle sensitivity (Beck et al., 2002; Beck & Servatius, 2005). With this in mind, it was surprising to see reductions in startle sensitivity in the female WKY rats, although we should acknowledge it was long after the type of shock experienced during inescapable shock that reduces female SD startle responsivity. We could speculate that this lack of sensitivity to the startle pulses in the WKY females is the counterpoint to "increased vigilance", being post-stress "numbness", but we do not have any other data to substantiate such a claim. Additional testing across other modalities may give us a better idea of the scope of this reduction in reactivity that appears to be correlated with high levels of active avoidance behavior.

These data provide an interesting example of how startle reactivity can be enhanced by prior exposure to an escapable and avoidable stressor. Moreover, as was observed following inescapable stress (Servatius et al., 1995; Beck et al., 2002; Manion et al., 2007; Manion et al., 2010), the presentation of enhanced startle reactivity in male rats did not occur proximal to any period of significant shock exposure. This finding is important for 2 reasons. First, it shows that inescapable and uncontrollable stress is not necessary to increase startle reactivity, and yet, the appearance of the startle enhancement is still delayed following predictable and controllable shocks. Second, these features are suggestive that a mechanism not specifically triggered by the shock is causing: 1) general arousal to increase over time in male rats; 2) vigilance to remain elevated in female SD rats; and 3) vigilance to be reduced in female WKY rats (possibly a transient numbing effect). It is important to also note the differences in these patterns across subject groups can be translated into different symptoms associated with PTSD: arousal, vigilance, and numbness. These group differences may help us understand why different individuals present with certain symptoms yet, in total, still constitute a PTSD diagnosis.

3.3 Active avoidance and general physiology

Reactivity to stressors may be further characterized by their effect on the general physiology of the rats. Growth, as measured by changes in bodyweight from the beginning of the experiment, provides a measure to investigate the effects of avoidance on general physiology, and to see if correlations exist between these changes and startle reactivity. In male SD rats, growth was suppressed during acquisition, but recovered by the termination of extinction training (see Figure 10). In WKY rats, the exact opposite effect was observed. Differences in bodyweight slowly emerged across training, with decreased growth in avoidance trained rats becoming evident in extinction and further developing following the end of training. Thus while male SD rats demonstrate a decrease in growth proximal to shock administration, WKY rats demonstrate a continual decrement in growth that developed after the removal of the shock. In females, SD rats demonstrated a similar pattern to male WKY rats, with differences in growth emerging over training. In female WKY rats, no differences in growth are seen at any point during training. Thus it appears that changes in bodyweight, often thought to reflect physiological reactions to stress, do not mimic all of the changes observed in startle sensitivity and responsivity across all groups; although, changes in startle responsivity in male rats do somewhat follow periods of lower body weight (especially in WKY rats).
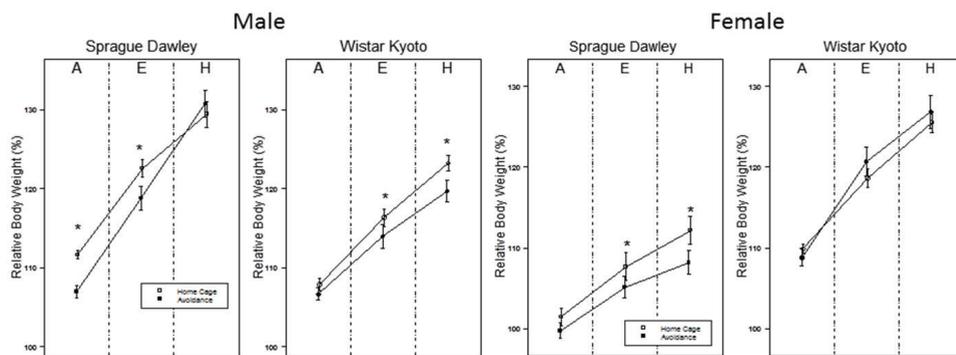
Fig. 10. Relative body weight of male and female SD and WKY rats. Data are averaged into phases: A-Acquisition, E-Extinction, and H-Home Cage. Relative body weights were determined by dividing average weight during a phase by the weight during the pre-training startle session. Male SD rats gain more relative weight than male WKY rats. Male SD rats that underwent avoidance demonstrated suppressed growth during acquisition and extinction. Male WKY rats demonstrated a diverging growth pattern; rats that underwent avoidance learning gained less weight than their home cage controls, an effect that did not emerge until extinction and persisted into the home cage phase. Female WKY rats gained more relative weight than female SD rats. Female SD rats that underwent avoidance demonstrated suppressed growth during extinction and the home cage phase relative to home cage controls. These differences in growth were not observed in female WKY rats. *p< .05

3.4 Active avoidance, shock exposure and changes in startle reactivity

The confounding variables of shock exposure controllability and exposure to shock limited our ability to make firm conclusions regarding what caused the enhanced startle responses to occur in avoidance-trained rats. Hence, we designed a follow-up study that substituted an additional control group for our baseline comparison of avoidance-trained rats. This control group was placed in the training boxes at the same time the others were being trained to avoid the shock. The rats in this new condition were each paired to a rat in the avoidance-training condition such that when an avoidance rat was shocked, so was the paired control (yoked condition). Thus, the yoked rats in this experiment heard, saw, and felt the same stimuli as their avoidance learning paired counterparts, but the lever in their chambers was disabled. For these yoked controls, they may learn the predictive relationship between the stimuli and the shocks, but they will not learn or experience any perceived control over the occurrence of shock.

As shown in Figure 11, the rats of both strains exhibited a clear acquisition of a lever-press avoidance response. WKY rats exhibited a much higher level of asymptotic performance than did SD rats. Furthermore, the subsequent extinction of the response was less apparent in WKY rats compared to SD rats. The analysis of startle sensitivity found that both strains of rats trained in avoidance learning increased their sensitivity to the acoustic startle pulses the day following the first training session, as did the yoked controls from baseline. This confirms that the short-term change in startle sensitivity is a product of shock exposure, not the acquisition process involved in learning to escape or avoid the shocks. Moreover, the
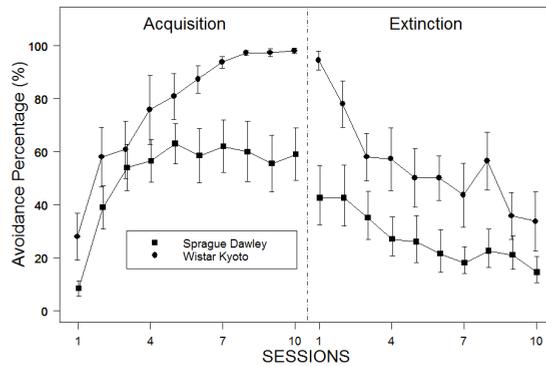
Fig. 11. Avoidance performance of SD and WKY rats. Strain designations are in the figure legend. WKY rats acquire the avoidance response faster and reach higher asymptotic performance than SD rats (main effect, Strain, $F_{(1, 15)} = 9.2$, $p < .01$ and Session x Trial interaction, $F_{(171, 2565)} = 1.3$, $p < .001$. WKY rats also extinguished the response less than SD rats (main effect, Strain, $F_{(1, 15)} = 7.0$, $p < .01$, Strain x Trial, $F_{(19, 285)} = 2.1$, $p < .01$ and Session x Trial, $F_{(171, 2565)} = 1.4$, $p < .01$ interactions).

effect is not strain dependent and dissipates as the rats are exposed to fewer shocks. With respect to startle magnitude, WKY rats exhibited higher startle magnitudes than SD rats (see Figure 12). In SD rats, no differences in relative startle magnitudes were observed between avoidance and yoked rats, but in WKY rats, elevations in startle responsivity developed late
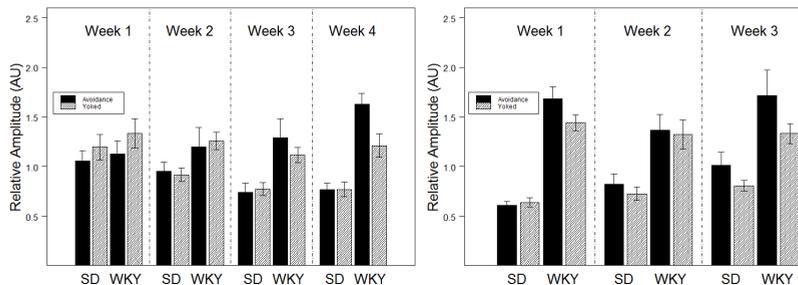

Fig. 12. Differences in startle magnitude emerged between the avoidance and yoked-shock group during the later phase of acquisition in male WKY rats. This impression was confirmed by a significant Strain x Week interaction, $F_{(3, 90)} = 6.1$, $p < .001$ and a marginally significant Avoidance x Week interaction, $F_{(3, 90)} = 2.3$, $p < .07$. Unlike the previous experiment, male SD rats did not attain a level of avoidance performance proximal to that of the WKY rats, and failed to develop enhanced startle responsivity over training (left). The differences in startle magnitude between avoidance and yoke-control male WKY rats continued during the extinction phase of the experiment (right). This impression was confirmed by a significant Strain x Week interaction, $F_{(2, 60)} = 7.5$, $p < .001$ and a marginally significant Avoidance x Week interaction, $F_{(2,60)} = 2.5$, $p < .08$. Two of the three weekly startle tests found higher startle magnitudes between those trained in avoidance behavior and their yoked controls in the WKY strain.

in acquisition in both avoidance and yoked rats. These differences persisted into extinction and following the termination of training. Because each yoked rat experienced the same stimuli as an avoidance-trained rat, they should have learned the predictability of the stimuli. However, what is not learned is that they have any controllability. The poorer learning by the avoidance-trained SD rats in the yoked-avoidance experiment would conform to this idea. Because they did not acquire the response to the same level as those in the earlier experiment, this may have led them to also fail to show any difference in startle responsivity from their yoked controls as training progressed. Observed differences in avoidance-trained WKY rats suggest they too may have similar increased arousal with the adoption and use of active avoidance behavior.

4. Conclusions

Active avoidance requires attentiveness, memory, and, arguably, anxiety (Mowrer, 1940; Miller, 1948; Solomon & Wynne, 1954; Hoffman & Fleshler, 1962; Dinsmoor, 1977). Others have utilized active avoidance procedures as a tool to study chronic stress effects on physiology (Forsyth, 1968; Forsyth, 1969; Natelson et al., 1976; Natelson et al., 1977), but an explicit connection between the behavioral symptoms of PTSD needed to be tested. In both experiments, an initial increase in startle sensitivity occurred in response to the initial experiences with shock. This supports our contention that an acute increase in startle sensitivity occurs as a function of shock exposure – not startle responsivity. In other words, the level of vigilance is changed for a period of time following shock exposures. Conversely, startle responsivity, general arousal, increases as the avoidance response is refined and can even persist into extinction sessions. This supports our and others' past work that found inescapable shock only increases startle reactivity after some period of time has passed since the acute exposure to the shock (in the range of days)(Manion et al., 2007; Servatius et al., 1995; Beck et al., 2002), unless the subject under study is female (Beck & Servatius, 2005; Beck et al., 2008). Thus, we also replicated that sex difference by failing to find any increases in startle responsivity in female rats following shock exposure (Beck & Servatius, 2005; Beck et al., 2008).

One could surmise that the strain and sex differences in startle sensitivity and responsivity during later acquisition and through extinction occur as a function of differences in learning controllability over their general environment. Controllability over stressful situations cause different long-term effects, but these effects are commonly thought to be regarded as a means to buffer the deleterious effects of stress (Baratta et al., 2007). This work questions that general assumption, and, in fact, suggests for some individuals diagnosed with PTSD, hyperarousal could be the result of being overly controlling and not "testing the waters" to see if perceived warning signals still predict aversive events. This appears to be the male pattern, which may vary in expression across strain, but is most consistent in the WKY rats. For the females, some have proposed emotional numbing in PTSD patients is actually a result of hyperarousal to negative valenced stimuli being contrasted to a lack of arousal to positive stimuli (Litz et al., 1997; Litz & Gray, 2002). Our data do not support that relationship, but the reduction in startle sensitivity in female WKY rats appears to parallel documented lower startle reactions in female PTSD patients with comorbid depressive symptoms (Medina et al., 2001). WKY rats have been touted as a model for depression and maybe this sex-specific response reflects some aspect of those characteristics (Pare & Redei, 1993). Overall, these divergent changes in arousal and vigilance are likely a bi-product of

strain and sex differences in learning processes that are involved in forming predictive associations under conditions where some level of stress is involved (Wood & Shors, 1998; Ricart et al., 2011a; Ricart et al., 2011b; Beck et al., 2011). When the requirement to cope is brought to the fore, these inherent differences in learning processes can be seen both in their rate to acquire an avoidance coping response (i.e. gaining control) and any subsequent resistance to cease that response (maintaining control).

The problems associated with anxiety disorders, such as PTSD, are multifaceted and variable. In part, this is because different individuals perceive and cope with stressors differently. Active-avoidance behavior, using a lever-press, is rarely uniform within a group of animals, and, as evidenced from the data from our lab; the resulting effects on startle responses can be variable in when they emerge over time. Yet, the variability caused by having a subject-controlled manipulation of stressor exposure is important for understanding the disorder. Controllability may selectively influence certain individuals in a manner that causes increases in general arousal whereas others are not so affected. Moreover, when we consider vulnerability factors, such as demonstrated by the WKY rats (behavioral inhibition and higher baseline startle responses), individual differences in coping with stressor and different rates of acquisition of avoidant strategies should occur – as in the human condition. Gaining an understanding of the relationship between different symptoms, as demonstrated here between avoidance and arousal, will provide us with the knowledge to broaden our expectations for how different populations may develop the symptoms of PTSD. As shown here, our data suggest that the acute experience of pain is not sufficient to immediately increase startle responsivity, and it may not be a good marker for tracking the development of PTSD. Our data suggests that the avoidance process is already well-acquired when this other symptom becomes evident. As has been suggested from the clinical literature, increased expression of avoidance may be a very good marker for tracking the development of the disorder (Karamustafalioglu et al., 2006; O'Donnell et al., 2007). Further, breaking the adoption and utilization of avoidance strategies may lead to a reduction in general arousal (at least in males); therefore, some non-pharmacological therapeutic approaches (e.g. cognitive-behavioral therapy) may have beneficial effects on these two core features of PTSD. Additional research is required to better understand and track the developmental course of symptom expression in different subpopulations (e.g. women) such that our animal model systems can be better tailored to reflect the cascade of changes occurring in those people, especially for those at risk for developing the symptoms of PTSD.

5. Acknowledgements

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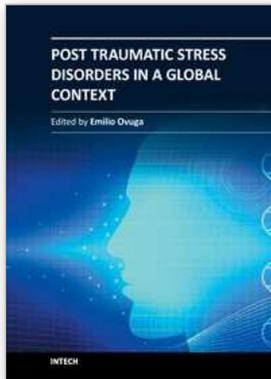
Post Traumatic Stress Disorders in a Global Context

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If, as a health care or social service provider, one was called upon to help someone who has experienced terror in the hands of a hostage taker, an irate and chronically abusive spouse or parent, or a has survived a motor vehicle accident, landslide, earthquake, hurricane or even a massive flood, what would be one's priority response? What would be considered as the most pressing need of the individual requiring care? Whatever the answer to each of these questions, people who have experienced terror, suffer considerable psychological injury. Post-Traumatic Stress Disorder in a Global Context offers some answers to meet the needs of health care and socials service providers in all settings, whether in a hospital emergency room, at the war front, or natural disaster site. The take home message is, after providing emergency care, there is always a pressing need to provide mental health care to all victims of traumatic stress.

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