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Biological Psychiatry

A Human Open Field Test Reveals Thigmotaxis Related to Agoraphobic Fear

Nora Walz, Andreas Mühlberger, and Paul Pauli

ABSTRACT

BACKGROUND: Thigmotaxis refers to a specific behavior of animals (i.e., to stay close to walls when exploring an open space). Such behavior can be assessed with the open field test (OFT), which is a well-established indicator of animal fear. The detection of similar open field behavior in humans may verify the translational validity of this paradigm. Enhanced thigmotaxis related to anxiety may suggest the relevance of such behavior for anxiety disorders, especially agoraphobia.

METHODS: A global positioning system was used to analyze the behavior of 16 patients with agoraphobia and 18 healthy individuals with a risk for agoraphobia (i.e., high anxiety sensitivity) during a human OFT and compare it with appropriate control groups ($n = 16$ and $n = 19$). We also tracked 17 patients with agoraphobia and 17 control participants during a city walk that involved walking through an open market square.

RESULTS: Our human OFT triggered thigmotaxis in participants; patients with agoraphobia and participants with high anxiety sensitivity exhibited enhanced thigmotaxis. This behavior was evident in increased movement lengths along the wall of the natural open field and fewer entries into the center of the field despite normal movement speed and length. Furthermore, participants avoided passing through the market square during the city walk, indicating again that thigmotaxis is related to agoraphobia.

CONCLUSIONS: This study is the first to our knowledge to verify the translational validity of the OFT and to reveal that thigmotaxis, an evolutionarily adaptive behavior shown by most species, is related to agoraphobia, a pathologic fear of open spaces, and anxiety sensitivity, a risk factor for agoraphobia.

Keywords: Agoraphobia, Animal models, Anxiety sensitivity, Avoidance behavior, Open field test, Thigmotaxis

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Most animals exposed to an open space exhibit thigmotaxis—that is, they stay close to the walls of the open space and only later explore its center. Such behavior is adaptive, as the walls allow hiding and facilitate orientation, whereas entering the center of an open space is potentially dangerous because of potential exposure to predators. Thus, the open field situation may have been of evolutionary relevance for most animals, and entering an open space is very likely to elicit fear in most species (1). The open field test (OFT) is a well-established paradigm to examine fear in rodents and other animals (2). Such animal studies indicate that thigmotactic behavior is a valid behavioral indicator of fear, as it is suppressed by anxiolytic agents (2) and enhanced in rodents selectively bred for high anxiety (3). One of the first studies carried out with humans showed that thigmotaxis occurs when participants explore a room while blindfolded—using their haptic sense—or when they navigate through a virtual maze (4). However, this first study did not relate thigmotactic behavior to the participants' fear and lacked ecological validity, as it examined artificial situations (i.e., using a blindfold or a virtual maze).

The present study is the first to our knowledge to translate the well-established animal OFT to humans to examine the hypotheses that human thigmotactic behavior in an open space is related to the participants' fear. Specifically, we hypothesize that agoraphobic fear is associated with thigmotactic behavior and that patients with agoraphobia as well as healthy participants with a risk for agoraphobia exhibit exaggerated thigmotaxis. Such findings would greatly increase the validity of the OFT based on similarities between humans and animals in the effects of anxiety on OFT behavior.

In 1871, Westphal (5), in his influential first description of agoraphobia, stated "[…] the patient complains that it is impossible for him to cross an open space. If he attempts to do so he is immediately seized with a feeling of anxiety […]. In Berlin the Donhofplatz [an open place] is the most unpleasant for him…." Although the fear is not justified by an actual threat, and the patient is aware of the irrationality of the fear, the patient cannot resist avoiding the fear-triggering open space situation.

We propose that the pathologic avoidance of open places by patients with agoraphobia is a dysfunctional exaggeration of a biologically shaped, otherwise adaptive behavior (i.e., thigmotaxis). First, following the arguments of Bolles (6) and the compelling studies of Grossen and Kelley (7), it is reasonable to assume that thigmotaxis, at least in rats, is an innate species-specific defensive reaction, similar to fleeing,

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freezing, and fighting. Such behavior is very likely to occur when threatened and rapidly acquired as avoidance behavior. Second, open places may belong to the limited set of stimuli that were of survival significance during human evolution and therefore frequently may become triggers of phobic fear. For example, preparedness theory (8) assumes that such evolutionarily relevant threat stimuli become triggers of pathologic fear through association with an aversive experience (i.e., classic conditioning). The fact that these phobic stimuli also trigger fear in other species, especially primates (9,10), is evidence for the assumption of their evolutionary significance. Similarly, we know that open spaces trigger fear in most species, and therefore we may assume that this evolutionarily shaped fear, which triggers thigmotaxis, may be the biological basis of agoraphobic fear. The detection of an association between agoraphobic fear and thigmotaxis would support this claim.

To test these hypotheses, we developed a human OFT as an ethoexperimental paradigm for studying the effects of agoraphobic fear on thigmotaxis. To ensure ecological validity and methodologic analogy with animal OFTs, we used a soccer field surrounded by wall-like vegetation as the experimental environment and instructed participants to explore the area for 15 minutes. In a further study, patients with agoraphobia and control subjects were asked to walk in the city to a meeting point that could be reached by walking directly through the local market square. For both tasks, spatiotemporal behavior was registered using a global positioning system (GPS) and analyzed for thigmotaxis. The study's main hypotheses are that both patients with agoraphobia and participants with high levels of anxiety sensitivity, an assumed diathesis factor for agoraphobia and panic disorder (11), exhibit thigmotaxis and avoidance of the open field's center as well as the city's market square compared with control subjects.

METHODS AND MATERIALS

Participants

Two experimental samples were examined and compared with control groups comparable in age and demographic characteristics. In the first sample, 16 patients with agoraphobia with or without panic disorder (AP group; 10 women and 6 men; mean age, 36.81 years [SD 12.12]; range, 21–60 years) were compared with 16 healthy control participants (HC group; 10 women and 6 men; mean age, 30.44 years [SD 10.50]; range, 22–60 years) ($t_{30} = 1.59$, $p = .122$). In the second sample, 18 participants with high anxiety sensitivity (HA group; 14 women and 4 men; mean age, 20.77 years [SD 2.80]; range, 18–30 years) were compared with 19 participants with low anxiety sensitivity (LA group; 12 women and 7 men; mean age, 20.74 years [SD 1.73]; range, 18–26 years) ($t_{35} = .05$, $p = .957$).

Patients were recruited when they presented for therapy in the outpatient clinic of the Department of Psychology, University of Würzburg. If telephone screening indicated agoraphobia or panic symptoms, the patients were invited for a diagnostic interview. A trained clinician confirmed the diagnosis using the Composite International Diagnostic Interview (12). If patients fulfilled the criteria for agoraphobia with or without panic disorder, they were asked if they would participate in a study on "orientation under anxiety." After a complete description of the study, written informed consent was obtained.

Patients with prior experience with exposure therapy ($n = 5$) were excluded because such therapy with its focus on behavior might have affected open field behavior; patients with incomplete GPS tracking ($n = 2$) also were excluded. Three patients were treated with selective serotonin reuptake inhibitors, but because they still reported typical agoraphobic avoidance in their daily life, they were included in the study. Current comorbid diagnoses, including unipolar depression and other anxiety disorders, were allowed unless they were of primary clinical concern. The HC group consisted of age-matched volunteers who were directly asked to participate; any clinical diagnosis was excluded by the Structured Clinical Interview for DSM-IV (13).

The HA and LA groups consisted of undergraduate students of psychology screened with the German version of the Anxiety Sensitivity Index (14). Individuals scoring in the upper (score of ≥26) and lower (score of ≤14) quartiles of the sample ($n = 105$) were recruited; any diagnosis was excluded by the Structured Clinical Interview for DSM-IV (13). The mean Anxiety Sensitivity Index scores were 31.33 (SD 4.54) and 10.58 (SD 2.59) in the HA and LA groups, respectively ($t_{35} = 17.21$, $p < .001$).

General exclusion criteria were psychotic disorders, borderline personality disorder, bipolar disorder, current alcohol dependence, and use of psychoactive illegal drugs. Somatic exclusion criteria were coronary or neurologic diseases, pregnancy, and impaired ability to walk for 15 minutes. Active soccer players were excluded because of familiarity with the open field area.

Human OFT

The open field consisted of a 146 m × 79 m soccer field without typical lines. The field was not in professional use but had denied access for the public during the daytime so that the OFT could be accomplished without interruption. The field was surrounded by bushes and trees, creating naturally grown walls. Each participant went to the soccer field by public transportation accompanied by the examiner. All participants were instructed when close to, but still outside, the open field; from there, GPS measurement was started. The written instruction was to complete a 15-minute solitary walk on the field. Liberty to choose the way to walk was emphasized, but the participants were told not to perform other activity and to avoid long stops. They could walk at their natural walking speed. After 15 minutes, they were to return to the starting point. The timing, but no additional information, was shown on the GPS watch. The examiner was outside the field but remained visible for the participant; the examiner looked down to avoid provoking feelings of being observed. After the OFT, the participants rated their level of anxiety, their bodily arousal, and their urge to avoid the center area on 11-point (0–10) scales. Each participant was tested in daylight and in mild, calm weather.

GPS Tracking

For GPS tracking, we used a Polar RS800CX (Polar Electro Inc., Kempele, Finland). The GPS sensor consisted of a

SiRFstarIII GPS chip (SiRF Technology Holdings Inc., San Diego, California), which ensures high accuracy of tracking. Predicted uncertainty of ~2–3 m according to the literature (15) was tolerable given the large scale of the soccer field. The GPS sensor was applied on the participant's right biceps above clothing. The recorder was a wristwatch. A first calibration of the GPS sensor was made outside the Department of Psychology, and a second was made after arrival on the soccer field, both on a fixed position to improve accuracy. The data were recorded with a sampling rate of 60 Hz.

Procedure

The study started in the laboratory of the Department of Psychology where the participants signed the informed consent form. All participants then completed the State-Trait Anxiety Inventory (16) and the Positive and Negative Affect Scale (17). The GPS sensor was attached and calibrated outside the building on a fixed position for each participant. After that, the examiner and participant used public transportation (10 minutes) to reach the soccer field; the public transportation stops were located near the Department of Psychology and the soccer field. On arrival at the soccer field, the GPS was calibrated again, the instructions were given in written form (see Human OFT), and the OFT was started. After the OFT, the participants completed several predefined tasks (not reported here). After the examination, they completed the Mobility Inventory, the Agoraphobic Cognition Questionnaire, and the Body Sensation Questionnaire (18).

City Walk

After the OFT, we assessed naturalistic behavior of patients with agoraphobia and control participants with GPS during an unaccompanied walk through the city to a designated goal with the shortest route leading them through the marketplace of the city. These were 14 patients with agoraphobia (two patients resigned from this task because of anxiety) and 15 control participants (one was excluded because of technical problems) from the main study plus the two patients with agoraphobia who completed the OFT before but were excluded from OFT analyses because of incomplete GPS signals and one patient with agoraphobia and two control participants who were assessed after a pilot version of the OFT.

Data Analysis

GPS tracks first were visualized in Google Earth (Version 6.1.0) (19) and checked for missing data. The raw data output was in gpx format, and data for latitude and longitude measures were extracted and imported in IBM SPSS Statistics version 20 (IBM Corp., Armonk, New York). The coordinates were transformed into Universal Trans Mercator System and rotated by Helmert transformation (20). Next, the coordinates of a 3 × 5 raster covering the soccer field were defined. Of these 15 rectangles, the outer 12 composed the wall areas, and the inner 3 composed the center areas. For estimation of time spent within the wall or center areas, data points within the center and the wall areas were accumulated for each participant and averaged for groups. Thigmotaxis was defined by the number of line crossings within wall areas, center entries were defined by the number of entries into center areas, and ambulation was defined by the number of line crossings within center areas. These dependent variables were calculated for each participant and then averaged for groups. Mean distance and walking speed were calculated by the Polar RS800CX and extracted from text output.

The city walk paths were first visually inspected and categorized as "walk through the marketplace center" or "walk avoiding the marketplace center." In addition, the overall walking distance (meters) was extracted. The analyses compared groups regarding frequency of walks through the marketplace center (χ^2 test) and overall walking distance (t test).

Statistical Analysis

The significance level was set to .05 (two-tailed) for all analyses. Uncorrected degrees of freedom, corrected p and t values, and effect sizes are reported. Data on time and latency were not normally distributed and were examined with nonparametric Mann-Whitney tests. For ambulation parameters, t tests for independent samples were used. Comparisons were done separately for the AP group versus the HC group and for the HA group versus the LA group.

RESULTS

Open Field Thigmotactic Behavior

The GPS data indicate that the human OFT triggered characteristic exploration behavior in the experimental groups (Figure 1, top row). Visual analyses using heat maps of cumulated times spent in wall or center areas of the open field (Figure 1, lower row) indicate that patients in both the AP and HA groups tended to avoid the center area, whereas participants in the HC and LA groups explored the center.

For statistical analyses, we first quantified ambulation behavior compared with animal studies. We measured thigmotaxis (number of line crossings along the walls), center entries (number of entries into the open field's center), and ambulation within center (number of line crossings within the center). Confirming our hypotheses, we found that the AP group compared with the HC group (Figure 2A) showed significantly stronger thigmotaxis ($t_{30} = 2.21$, $p < .05$, $d = .80$), fewer center entries ($t_{30} = -3.06$, $p = .005$, $d = 1.08$), and less ambulation within the center ($t_{30} = -3.09$, $p < .01$, $d = 1.09$). Similarly, the HA group compared with the LA group (Figure 2B) exhibited stronger thigmotaxis ($t_{35} = 2.11$, $p < .05$, $d = .70$) and avoided entering the open field's center ($t_{35} = -3.20$, $p < .005$, $d = 1.06$). However, these groups did not differ in center ambulation ($t_{35} = -1.08$, $p = .286$, $d = .40$), meaning that when within the center, their behavior was comparable.

Statistical analyses of the timing of behavior further confirmed that agoraphobic fear was associated with avoidance of the open field's center as reflected in longer latencies for initial center entries (Figure 3A) by the AP group versus the HC group (Mann-Whitney $U = 187.5$, $p < .05$, $r = .4$), and the HA group versus the LA group (Mann-Whitney $U = 244.00$, $p < .05$, $r = .4$).

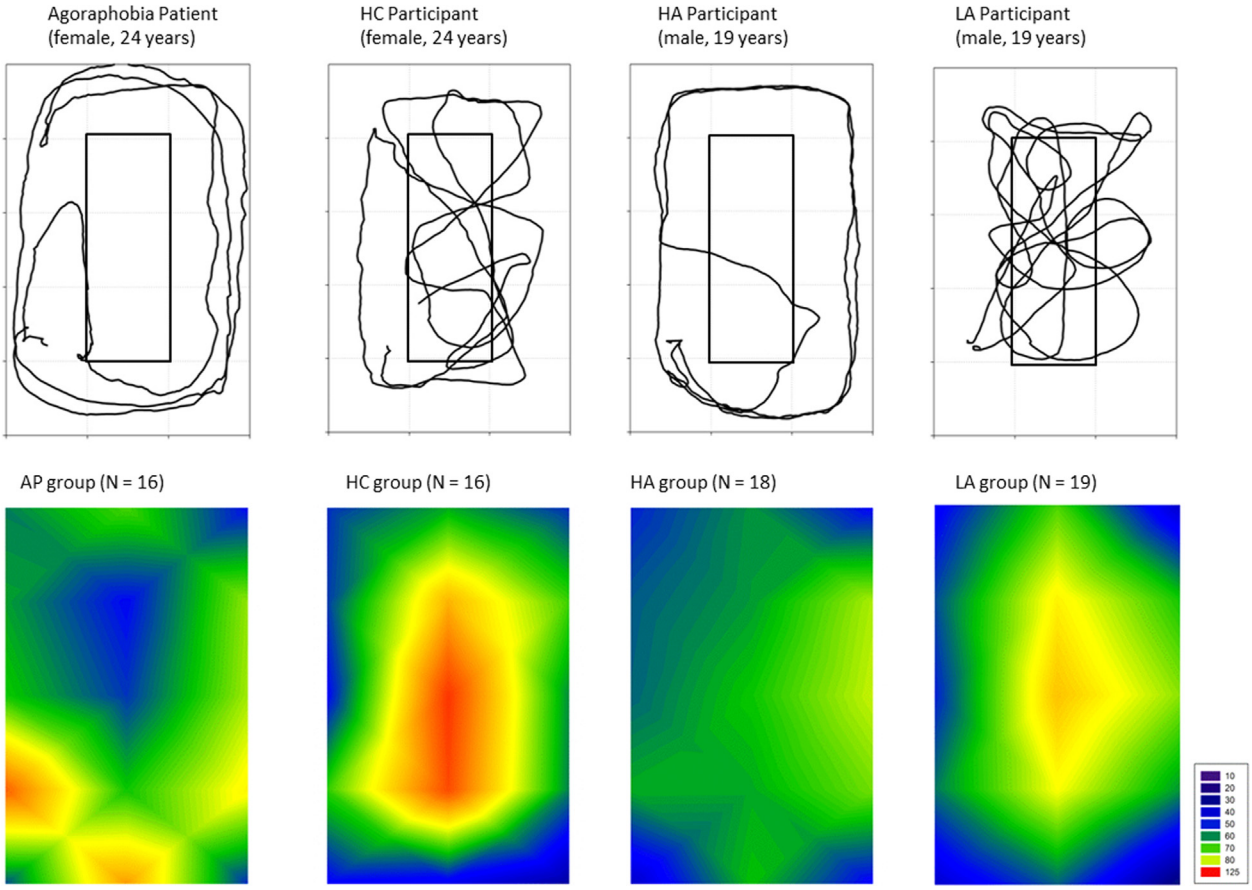

Figure 1. Exemplary motion patterns assessed with global positioning system and cumulative spatiotemporal behavior of agoraphobic patients (AP) vs. healthy control (HC) participants and participants with high anxiety (HA) vs. low anxiety (LA) sensitivity during a 15-minute open field test. The top row shows typical motion patterns of a patient with agoraphobia, an age-matched healthy control participant, and two participants with high vs. low anxiety sensitivity. The bottom row shows the group averaged mean cumulative time in seconds spent at a given location in the open field (the warmer the color, the more time was spent at that location).

In addition, the AP group spent less time in the open field's center (Figure 3B) than the HC group (Mann-Whitney $U = 36.50$, $p < .001$, $r = .6$); this difference was only marginally significant for the nonclinical HA group versus LA group (Mann-Whitney $U = 110.00$, $p < .10$, $r = .4$).

Finally, we looked at the averaged absolute distance to the nearest wall. The AP group on average stayed closer to the nearest wall (mean, 10.55 m [SD 5.97]) than the HC group (mean, 16.73 m [SD = 5.88]) ($t_{30} = -2.95$, $p < .01$, $d = 1.04$), and the HA group on average stayed closer to the nearest wall (mean, 12.93 m [SD 5.44]) than the LA group (mean, 16.62 m [SD 3.56]) ($t_{35} = -2.45$, $p < .05$, $d = .80$).

Other Behavioral Characteristics

We found no indication of group differences for AP group versus HC group or HA group versus LA group comparisons regarding more general behavioral characteristics as number of total line crossings, walking speed, overall path length, and average distance to the examiner's position (Table 1).

Postexperimental Assessment

Postexperimental assessments (Table 2) revealed that the AP group experienced higher anxiety, higher arousal, and a greater urge to avoid the open field's center compared with the HC group. In contrast, the HA and LA groups did not differ in ratings of anxiety or arousal, but the urge to avoid the center was higher in the HA group compared with the LA group.

City Walk

An exploratory analysis of the natural walk through the city revealed further evidence of thigmotaxis in the patients with agoraphobia (Figure 4). Only 2 of 17 patients in the AP group (11.8%) compared with 9 of 17 participants in the HC group (52.9%) crossed through the marketplace center ($\chi^2_{(2)} = 7.65$, $p < .05$, $\phi = 1.08$); the two groups did not differ in overall walking distance (1103 m vs. 1105 m).

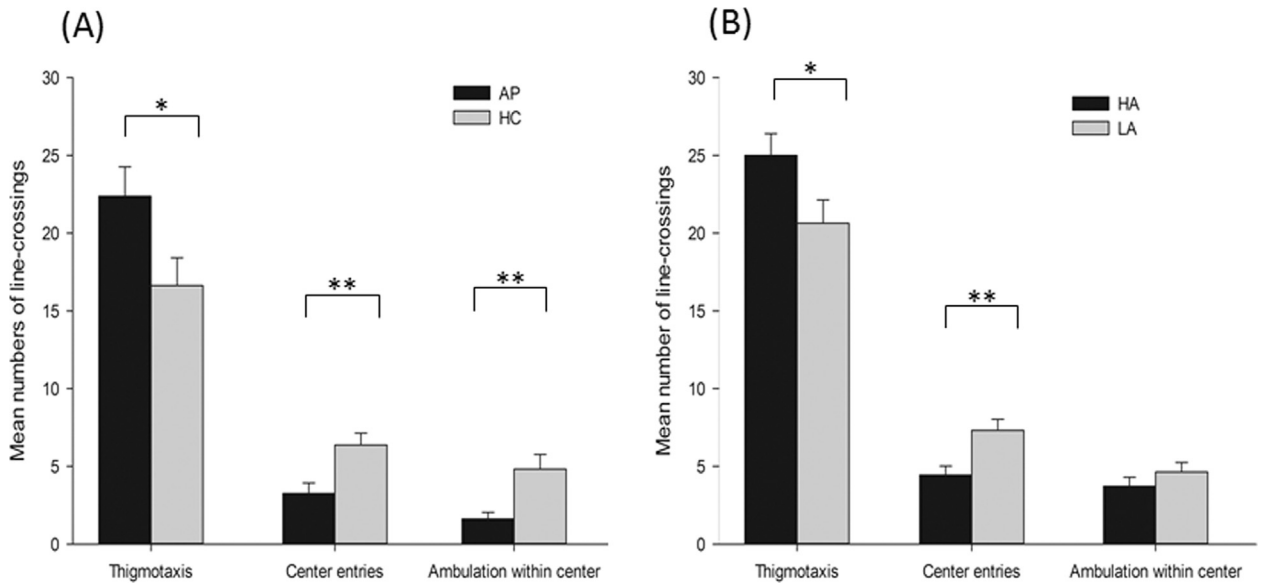

Figure 2. Thigmotaxis (frequency of line crossings within wall areas), center entries (frequency of line crossings into center areas), and ambulation within center (frequency of line crossings within center areas) of **(A)** agoraphobic patients (AP) vs. healthy control (HC) participants and **(B)** participants with high anxiety (HA) vs. low anxiety (LA) sensitivity. See Methods and Materials for the definition of wall and center areas. Means and SDs are shown. $^{*}p \leq .05$; $^{**}p \leq .01$.

DISCUSSION

The OFT is a well-established paradigm to examine fear in rodents and other animals (2). Results are frequently translated to humans, but this study is the first to our knowledge to examine the association between open field behavior and anxiety in humans. We used GPS to examine behavior of patients with agoraphobia and participants with high levels of anxiety sensitivity, an assumed diathesis factor for agoraphobia and panic disorder, compared with matched control groups during a naturalistic OFT. Analyses of human behavior, comparable with the conventional animal OFT parameters (21), revealed a successful translation. First, humans—similar to most animals—showed thigmotaxis (i.e., a general tendency to walk along the walls of an open field). Second, patients with agoraphobia and healthy participants with high anxiety sensitivity demonstrated enhanced thigmotaxis and reduced open field exploration, as reflected in longer and closer wall following behavior and later and briefer center entries. Third, these differences cannot be explained by general characteristics of ambulation behavior, as groups did not differ in total number of line crossings, walking speed, and overall path length. Finally, we were able to demonstrate the relevance of thigmotaxis for real-life behavior by showing that patients with agoraphobia more frequently than healthy control participants stayed close to the walls of a market square and avoided passing through the center of the market square even though this would have been the most direct path. Thus, patients with

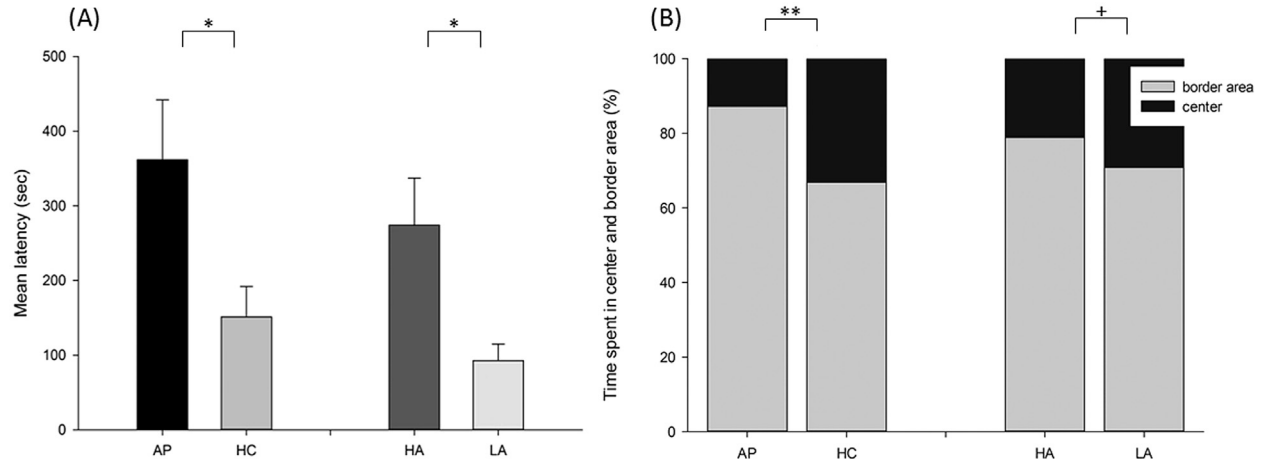

Figure 3. Mean latency until center entry **(A)** and time spent at the open field's border and in center areas **(B)** of agoraphobic patients (AP) vs. healthy control (HC) participants and participants with high anxiety (HA) vs. low anxiety (LA) sensitivity. Means and SDs are shown. $^{*}p \leq .05$; $^{**}p \leq .01$; $^{+}p \leq .10$.

Table 1. Overall Behavioral Characteristics of Agoraphobia Patients Versus Healthy Control Participants and High Anxiety Sensitivity Participants Versus Low Anxiety Sensitivity Participants

	AP Group (n = 16)		HC Group (n = 16)		Analysis			
Parameter	Mean	SD	Mean	SD	t	df	p	d
Number of Total Line Crossings	27.25	7.60	27.81	8.2	−.20	30	.842	.07
Walking Speed (km/h)	3.89	.76	4.12	.80	−.84	30	.409	.29
Overall Path Length (m)	889.19	282.79	963.38	227.59	−.82	30	.420	.29
Distance to Examiner (m)	59.91	10.76	61.53	6.96	.50	30	.618	.18
	HA Group (n = 18)		LA Group (n = 19)					
	Mean	SD	Mean	SD	t	df	p	d
Number of Total Line Crossings	33.16	4.83	32.58	4.93	.37	35	.716	.12
Walking Speed (km/h)	4.31	.96	4.37	.55	−.27	35	.792	.08
Overall Path Length (m)	1095.0	131.94	1063.0	130.01	.73	35	.468	.24
Distance to Examiner (m)	67.38	6.48	66.48	6.29	.43	35	.672	.14

AP, agoraphobic patients; HA, high anxiety sensitivity; HC, healthy control; LA, low anxiety sensitivity.

agoraphobia showed enhanced thigmotaxis not only in an experimental OFT but also in real life.

This study adds to a growing literature on reverse translation—that is, attempts to create human tests homologous with animal tests to identify species conserved mechanisms likely implicated in disease. For example, the human virtual Morris water maze task was very helpful in extending to humans animal research demonstrating the pivotal role of hippocampal theta in spatial navigation (22), and a human radial arm maze task was recently used to confirm hippocampal–dorsolateral prefrontal cortex coupling as a species-conserved cognitive mechanism (23). Similarly, translation of animal studies on fear conditioning to human research and using fear-potentiated startle as a translational outcome measure greatly advanced understanding of anxiety disorders (24,25). In the same vein, the present study is an important first step in demonstrating the face validity of the animal OFT by revealing similar behavior in humans and suggesting construct validity, as results point to a common etiology of such anxiety behavior in animals and humans. Following the arguments of Bolles (6), anxiety-related avoidance behavior is mainly developed on the basis of species-specific defense reactions, and thigmotaxis seems to be such a defense reaction in rats (7) and presumably also in humans as revealed here. Further research may build on animal and human OFTs to assess the tests' predictive validity—that is, whether both tests are sensitive to the same (e.g., pharmacologic) manipulations—and to elaborate whether thigmotaxis is a species conserved mechanism contributing to development of agoraphobia.

Table 2. Ratings of Agoraphobia Patients Versus Healthy Control Participants and High Anxiety Sensitivity Participants Versus Low Anxiety Sensitivity Participants

	AP Group (n = 16)		HC Group (n = 16)		Analysis		
Questionnaire	Mean	SD	Mean	SD	t	df	p
Anxiety	2.44	2.56	.19	.54	3.44	30	<.01
Arousal	2.63	2.87	.31	.60	3.15	30	<.01
Urge to Avoid Center	3.13	1.63	1.06	.25	5.01	30	<.001
	HA Group (n = 18)		LA Group (n = 19)				
	Mean	SD	Mean	SD	t	df	p
Anxiety	.39	.61	.31	.75	.33	35	.747
Arousal	.94	1.11	.74	.99	.60	35	.552
Urge to Avoid Center	2.11	1.23	1.37	.68	2.28	35	<.05

Anxiety, arousal, and urge to avoid center were rated on 11-point (0–10) subjective units of distress scales.

AP, agoraphobic patients; HA, high anxiety sensitivity; HC, healthy control; LA, low anxiety sensitivity.

Thigmotaxis and avoidance of an open field are supposedly biologically rooted, evolutionarily adaptive behaviors helping to prevent possible threats (e.g., exposure to predators) (26). As a consequence, most animals and—as this study revealed—humans show thigmotaxis when exposed to an open space. Such behavior is most likely to be motivated by fear triggered by the open space, which may also be linked to extraterritorial fear (1). Thus, fear of open spaces may have increased survival, and we conclude that thigmotaxis and avoidance of open fields in humans are not per se pathologic, but rather are evolutionarily based adaptive responses. Pathologic agoraphobic fear can be considered as an exaggerated maladaptive response of an evolutionarily shaped biological function. In patients with agoraphobia, this mechanism may be hyperactive or hypersensitive, perhaps secondary to specific learning experiences (27) or intraindividual (11) or genetic vulnerabilities; agoraphobia is the anxiety disorder with the strongest heritability (28). Consequently, open spaces or associated situations in these patients trigger overwhelming fear, a strong urge to avoid these situations, and thigmotaxis. Similarly, pathologic fear of snakes or spiders, both specific phobias, are very likely to be an exaggerated response of a biologically rooted fear module that coordinates evolutionarily adaptive fear responses to these potentially life-threatening animals (8). Such models are discussed for most phobias, such as specific phobia types height and water phobia (8) and social phobia (29), and the present study suggests that this model also may help to understand agoraphobia.

Thigmotaxis may have an additional function besides avoiding exposure to possible threat. Thigmotaxis could help in encoding an unknown or novel space by first following its global structure (30,31). However, why should encoding of space be modulated by anxiety? First, we may speculate that anxious individuals have fewer resources to encode the spatial

Figure 4. Global positioning system tracks during natural city walks, which included a passing of the market square (Marktplatz) of agoraphobic patients (left) vs. healthy control (right) participants. Most agoraphobic patients avoided the open field of the market square, whereas most healthy control participants passed through it, as this was the shortest way. [Images from (19) with superimposed walking paths.]

information. Therefore, they have to follow the global structure longer and need more time to capture the entity of a space. Alternatively, we might assume that anxiety increases the motivation to encode the potentially threatening context and therefore deepens its encoding (30), which is related to hippocampal place learning. Our group (32) observed facilitated contextual fear conditioning in high trait anxious individuals and with the same paradigm revealed that such contextual learning is associated with hippocampal activity (33). The present findings may also indicate an increased motivation in fearful individuals to reliably encode the context.

Finally, it is essential to discuss other interpretations of our findings. First, we cannot definitively exclude the possibility that the observed group differences in open field behavior are related to state rather than trait anxiety. However, state anxiety cannot explain why participants with high and low anxiety sensitivity differed in open field behavior but not in state anxiety. In addition, differences in state anxiety are very likely to be the consequences of the individuals' trait anxiety. Second, demand characteristics of the experiment and experimenter bias may have affected the results. However, we have no objective indication of such effects because the groups did not differ in basic behavioral parameters (i.e., walking speed or path length and distance to the experimenter). In addition, although the AP group may have deducted the experimenter's hypotheses, as is the case with any behavioral test with patients with anxiety disorders, this was very unlikely to be the case for the HA group. Also, for the city walk, the experimenter asked participants to choose the direct way; thus, demand effects worked against the hypotheses.

In conclusion, this study successfully translated the animal OFT to humans and revealed human thigmotaxis during free exploration of an open field which—as in animal studies—was modulated by the participants' fear. Patients with agoraphobia exhibited the greatest extent of wall following behavior and avoidance of the open field's center, followed by nonclinical participants with high anxiety sensitivity, a diathesis factor for anxiety disorders (11). These findings indicate that agoraphobic fear is associated with thigmotaxis, which is very likely to have an evolutionary significance related to avoidance of threat and spatial orientation. We suggest that agoraphobic fear reflects the exaggerated response of an evolutionarily shaped fear module, as is assumed for other phobic disorders as well.

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ARTICLE INFORMATION

From the Department of Psychology (Biological Psychology, Clinical Psychology, and Psychotherapy) (NW, AM, PP), University of Würzburg, Würzburg; and Department of Psychology (Clinical Psychology and Psychotherapy) (AM), University of Regensburg, Regensburg, Germany.

Address correspondence to Paul Pauli, Ph.D., Department of Psychology, University of Würzburg, Marcusstrasse 9-11, 97070 Würzburg, Germany; E-mail: pauli@psychologie.uni-wuerzburg.de.

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REFERENCES

1. Marks IM (1987): Fears, Phobias and Rituals: Panic, Anxiety and Their Disorders. New York: Oxford University Press.
2. Prut L, Belzung C (2003): The open field as a paradigm to measure the effects of drugs on anxiety-like behaviors: A review. Eur J Pharmacol 463:3–33.
3. Belzung C, Griebel G (2001): Measuring normal and pathological anxiety-like behavior in mice: A review. Behav Brain Res 125:141–149.
4. Kállai J, Makany T, Karadi ACK, Nadel L, Jacobs WJ (2007): Cognitive and affective aspects of thigmotaxis strategy in humans. Behav Neurosci 121:21–30.
5. Westphal CFO (1871): Die Agoraphobie, eine neuropathische Erscheinung. Archiv für Psychiatrie und Nervenkrankheiten Berlin 3: 138–161.

6. Bolles RC (1970): Species-specific defense reactions and avoidance learning. Psychol Rev 77:32–48.
7. Grossen NE, Kelley MJ (1972): Species-specific behavior and acquisition of avoidance in rats. J Comp Physiol Psychol 81:307–310.
8. Öhman A, Mineka S (2001): Fears, phobias, and preparedness: Toward an evolved module of fear and fear learning. Psychol Rev 108: 483–522.
9. Cook M, Mineka S (1990): Selective associations in the observational conditioning of fear in rhesus monkeys. J Exp Psychol Anim Behav Process 16:372–389.
10. Mineka S, Davidson M, Cook M, Keir R (1984): Observational conditioning of snake fear in rhesus monkeys. J Abnorm Psychol 93: 355–372.
11. Schmidt NB, Lerew DR, Jackson RJ (1999): Prospective evaluation of anxiety sensitivity in the pathogenesis of panic: Replication and extension. J Abnorm Psychol 108:532–537.
12. Kessler RC, Andrews G, Mroczek D, Üstün B, Wittchen HU (1998): The World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF). Int J Methods Psychiatr Res 7: 171–185.
13. Wittchen HU, Zaudig M, Fydrich T (1997): Strukturiertes Klinisches Interview für DSM-IV. Göttingen, Germany: Hogrefe.
14. Reiss S, Peterson RA, Gursky DM, McNally RJ (1986): Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther 24:1–8.
15. Elgethun K, Fenske RA, Yost MG, Palcisko GJ (2003): Time location analysis for exposure assessment studies of children using a novel global positioning system instrument. Environ Health Perspect 111: 115–122.
16. Laux L, Glanzmann P, Schaffner P, Spielberger CD (1981): Das State-Trait-Angstinventar (STAI) [State Trait Anxiety Inventory (STAI)]. Weinheim, Germany: Beltz Test GmbH.
17. Krohne HW, Egloff B, Kohlmann CW, Tausch A (1996): Untersuchungen mit einer deutschen Version der "Positive and Negative Affect Schedule" (PANAS) [Investigations with a German version of the Positive and Negative Affect Schedule (PANAS)]. Diagnostica 42: 139–156.
18. Ehlers A, Margraf J (2001): AKV—Fragebogen zu körperbezogenen Ängsten, Kognitionen und Vermeidung, *2nd ed.* Göttingen, Germany: Beltz Test GmbH.
19. Google Inc. (2012): Google Earth-Kartenservice. Version 6.0. Available at: http://www.google-earth.com. Accessed November 12, 2012.
20. Helmert FR (1924): Die Ausgleichsrechnung nach der Methode der kleinsten Quadrate: Mit Anwendungen auf die Geodäsie, Physik und die Theorie der Messinstrumente. Leipzig, Germany: Teubner.
21. Carola V, D'Olimpio F, Brunamonti E, Mangia F, Renzi P (2002): Evaluation of the elevated plus-maze and open field tests for the assessment of anxiety-related behavior in inbred mice. Behav Brain Res 134:49–57.
22. Cornwell BR, Johnson LL, Holroyd T, Carver FW, Grillon C (2008): Human hippocampal and parahippocampal theta during goal-directed spatial navigation predicts performance on a virtual Morris water maze. J Neurosci 28:5983–5990.
23. Bähner F, Demanuele C, Schweiger J, Gerchen MF, Zamoscik V, Ueltzhöffer K, *et al*. (2015): Hippocampal-dorsolateral prefrontal coupling as a species-conserved cognitive mechanism: A human translational imaging study. Neuropsychopharmacology 40: 1674–1681.
24. Davis M, Walker DL, Miles L, Grillon C (2010): Phasic vs sustained fear in rats and humans: Role of the extended amygdala in fear vs anxiety. Neuropsychopharmacology 35:105–135.
25. Grillon C (2002): Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. Biol Psychiatry 52:958–975.
26. Treit D, Fundytus M (1988): Thigmotaxis as a test for anxiolytic activity in rats. Pharmacol Biochem Behav 31:959–962.
27. Bouton ME, Mineka S, Barlow DH (2001): A modern learning theory perspective on the etiology of panic disorder. Psychol Rev 108:4–32.
28. Kendler KS, Karkowski LM, Prescott CA (1999): Fears and phobias: Reliability and heritability. Psychol Med 29:539–553.
29. Öhman A (1986): Face the beast and fear the face: Animal and social fears as prototypes for evolutionary analyses of emotion. Psychophysiology 23:123–145.
30. Fanselow MS (2002): Contextual fear, gestalt memories, and the hippocampus. Behav Brain Res 110:73–81.
31. Kállai J, Kazmer K, Feldmann A (2009): Anxiety-dependent spatial navigation strategies in virtual and real spaces. Cogn Process 10: 229–232.
32. Glotzbach-Schoon E, Tadda R, Andreatta M, Tröger C, Ewald H, Grillon C, *et al*. (2013): Enhanced discrimination between threatening and safe contexts in high-anxious individuals. Biol Psychol 93: 159–166.
33. Andreatta M, Glotzbach-Schoon E, Mühlberger A, Schulz S, Wiemer J, Pauli P (2014): Initial and sustained brain responses to contextual conditioned anxiety in humans. Cortex 63:352–363.