Tackling Hard Problems

Neuroscience, Treatment, & Anxiety



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Disclosures: Conflicts

Sources of Research Support National Institute of Mental Health

Roles in DSM-5, RDoC

Role in cognitive training research

My perspective

Paid Editorial Relationship Am J Psychiatry– Deputy Editor

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Stock Equity (>\$10,000) None

Speaker's Bureau None

Outline

• Overview

Two Systems Theory

Reflections



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Two Systems Theory

Reflections

Research Goals

• Use neuroscience for clinical means

- Anxiety as a good starting point
- Areas generating key questions:

 Developmental change in symptoms
 Differences between risk & disorder
 Understanding and improving treatment





Environmental influences

Sweet spot: behaviors bridging basic and clinical work



1. "Disorders" composed of distinct components

2.Level of Analysis: brain-mind-symptom

3.Nature of perturbation differs across components

Addressing Measurement Problems



Outline

• Overview

• Two Systems Theory *An example of successful reduction?*

Reflections

Using Neuroscience to Help Understand Fear and Anxiety: A Two-System Framework

Joseph E. LeDoux, Ph.D., Daniel S. Pine, M.D.

REVIEWS AND OVERVIEWS



Defensive-Survival Circuit

Defensive-Survival Circuit

Overarching Conceptualization: 1. High Cross-Species Similarity 2. High Similarity Across Development 3. Perturbation: context-inappropriate deployment of an adaptive brain-mind reaction



Cross-Species Conservation



CONGRUENT

INCONGRUENT

NEUTRAL

Context Inappropriate:

- 1. In real danger, all show effect
- 2. Anxiety show in safe contexts



CONGRUENT

INCONGRUENT

n=54 Anxious (ANX) n=51 Healthy (HV)

	ANX	HV			
% Female	61	57			
Age (years)	12.12 (3)	12.74 (2)			
IQ	110 (16)	112 (12)			
SCARED-C	29 (14)	6 (6)			
SCARED-P	31 (12)	4 (6)			
STAI-trait	39 (7)	27 (5)			

NEUTRAL

Linking Three Levels:

Brain-Mind-Disorder

Amygdala-Insula Connectivity Across Event Types



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Inappropriate Deployment of Amygdala-PFC Connectivity

Attention Bias Modification Therapy (ABMT)



Successful reduction: •New treatment •Targets mind •Link to brain function

Linking Three Levels:

Brain-Mind-Disorder

Training of Attention

Attention Bias Modification Therapy (ABMT)



Study name	Hedges'	Statistics Standard error	for each s Lower limit	tudy Upper limit	Z-Value	P-Value			Hed	ges' g and 95%	a	
Amir et al (2008) ²⁹	0.168	0.203	-0.230	0.566	0.829	0.407						
Amir et al (2009) ³⁰	0.662	0.396	-0.113	1.438	1.674	0.094				- +		
Amir et al (2010)31	-0.076	0.261	-0.589	0.436	-0.292	0.771				— — —		
Amir et al (2011) ³²	0.606	0.192	0.230	0.983	3.157	0.002					-	
Baert et al (2010) ³³ S1	-0.218	0.285	-0.777	0.341	-0.764	0.445			_			
Baert <i>et al</i> (2010) ³³ S2	0.246	0.336	-0.411	0.904	0.734	0.463					-	
Beard & Amir (2008) ³⁴	0.656	0.385	-0.098	1.411	1.705	0.088						
Boettcher et al (2013)35	0.008	0.219	-0.421	0.436	0.035	0.972						
Bowler et al (2012) ³⁶	0.553	0.309	-0.053	1.159	1.787	0.074					_	
Carlbring et al (2012)37	-0.060	0.223	-0.497	0.377	-0.271	0.786						
Harris & Menzies (1998)38	- 0.096	0.296	-0.677	0.484	-0.326	0.745						
Hazen et al (2009)39	0.607	0.412	-0.201	1.415	1.472	0.141						
Heeren et al (2012) ⁴⁰	0.060	0.318	-0.563	0.684	0.190	0.850						
Hirsch et al (2007)41	0.535	0.402	-0.253	1.322	1.331	0.183					-	
Holmes & Mathews (2005) ¹² S2, C1	0.338	0.405	-0.457	1.133	0.834	0.404						
Holmes & Mathews (2005) ⁴² S2, C2	-0.197	0.432	-1.043	0.649	-0.456	0.649						
Hoppitt et al (2010)43 C1	0.236	0.288	-0.329	0.801	0.818	0.413						
Hoppitt et al (2010)43 C2	0.091	0.282	-0.461	0.643	0.323	0.746					- _	.
Lang et al (2012)**	0.280	0.382	-0.469	1.028	0.733	0.464						
Lester et al (2011) ¹⁰ S1	2.213	0.325	1.576	2.850	6.805	0.000						
Lester et al (2011)45 S2	2.404	0.312	1.793	3.015	7.712	0.000						
Li et al (2008) ⁴⁰	0.530	0.422	-0.296	1.356	1.258	0.209						
Mackintosh et al (2006)"' S2	0.755	0.338	0.093	1.418	2.236	0.025						
Mathews et al (2007) ⁴⁶	0.430	0.318	-0.192	1.053	1.356	0.175						
Murphy et al (2007)" C1	0.644	0.304	0.049	1.240	2.120	0.034						
Murphy et al (2007)** C2	0.331	0.298	-0.253	0.916	1.112	0.266						
Najmi & Amir (2010) ³⁰	0.137	0.273	-0.399	0.673	0.499	0.617						
Neubauer et al (2013)	-0.009	0.257	-0.513	0.495	-0.034	0.973						
Rapee et al (2013)	-0.134	0.202	-0.530	0.262	-0.663	0.508					-	
Salemink et al (2007)	0.351	0.184	-0.011	0./12	1.901	0.057				-+ -		
Salemink et al (2009) ²⁴	0.333	0.338	-0.328	0.995	0.987	0.324						
Salemink et al (2007)	0.237	0.221	-0.197	0.671	1.072	0.284						
Schmidt et al (2009)~	2.365	0.455	1.4/4	3,256	5.202	0.000						
Schoon et al (2013)	0.142	0.197	-0.244	0.529	0.722	0.470						
Sharpe et al (2012) S2	-0.363	0.404	-1.154	0.428	-0.900	0.368				╶─┼╋──_		
Steel et al (2010)-	-0.262	0.214	-0.681	0.15/	-122/	0.220					—	
Stellinan & reachinan (2010)	0.164	0.280	-0.385	0.713	0.585	0.558						
Watchis et al (2012)"	0.747	0.245	0.267	1.228	3.049	0.002						
Tienu et al (2005) 51	0.722	0.443	-0.140	1.591	1.030	0.103					-	
Viend at al (2005) ²⁵ S2	0.061	0.394	-0./12	1.095	0.155	0.877						
nenu et al (2000)= 53	0.222	0.440	-0.041	1.085	4.205	0.614				I	I	
	0.374	0.067	0.203	0.545	4.265	0.000	-3.00	- 1.5	0	0.00	1.50	3.00
								Eavours (control		Eavours CBM	

Cristea et al. 2015

Training of Attention

Treating Two Components

320

.340





.310 .340 .340 .350 .340

.340

300

.310

.340 .380 .380 .400 .390 .390 .320

CBT-Defensive Actions

300

.340

.340

.340

.320

.320

33.0

.350

.360 .390 .390 .400 .390 .390 .390

300 .300 .300 .400 .360 .360 .380

20 .340 .340 .330 .276 .270 .280

.280 .300 .300 .300 .260 .250 .250

270 .290 .300 .300 .250 .240 .240

.250 .270 .270 .280 .240 .240 .230

ABMT-Defensive Reactions

72 patients randomized to active or placebo ABMT

All patients receive CBT

Attention Bias Modification Training (ABMT): Adapt Dot Probe to Implicitly Alter Threat Reactions

Less Post-Treatment Anxiety in Active than Placebo Condition

Effect Size=0.45 *t* =1.9; *p*=0.06





ABMT-Specific Treatment Outcome

PPI Analysis: fMRI Connectivity at Baseline Group [active vs. placebo]-by-\DARS-by-Event Type

> Figure Displayed at *p*<0.005 Threshold n=40 (22 placebo, 18 active)





CBT + PLACEBO ABMT

CBT + ACTIVE ABMT

Defensive-Survival Circuit

Overarching Conceptualization: 1. High Cross-Species Similarity 2. High Similarity Across Development 3. Perturbation: context-inappropriate deployment of an adaptive brain-mind reaction

Cognitive (appraisal?) Circuit

Overarching Conceptualization: *1. Low Cross-Species Similarity 2. Low Similarity Across Development 3. Perturbation: poorly understood*

Diagnosis of Anxiety

- Self-Report of Distress
- Model of Consciousness

Self-Report & Development

- 1. Reliability increases with age
- 2. Concept of "self" also changes
- 3. Accuracy increases with age

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Self-Report & Development

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- 4. May relate to dIPFC maturation
- 5. Brain-Mind-Symptom & development?



Extinction recall fMRI



Visit 1: Conditioning; Extinction Visit 2 (20 days later): Recall





Extinction recall fMRI

None



Visit 1: Conditioning; Extinction Visit 2 (20 days later): Recall n=200, ~50 in each group 0.0003 0.0002 0.0001 Healthy adult Anxious adult 0 Healthy child Afraid Stream Anxious child -0.0001-0.0002 -0.0003 Level of dlPFC Engagement



How afraid are you

6

A lot





Two Systems Theory

Reflections

Progress in Brain Imaging?

Old Problems

- Disorder definitions do not match brain components
- Work insufficiently critical, overly broad

Solutions

- Tightly link brain to narrow, component behaviors
- Expect no larger than medium effects
- Leverage treatment to test falsifiable ideas
- New Problems
 - Clinical problems involve subjective distress
 - How deeply to pursue consciousness?

Outline

• Overview

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