The (b)link between anorexia nervosa and dopamine

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INTRODUCTION

Anorexia nervosa (AN) has the highest mortality rate of any psychiatric disorder, yet its underlying neurobiology is not well understood. AN is characterized by food restriction, low body weight, fear of gaining weight and distorted body image[1,2] Dopamine (DA) is thought to be important in the pathophysiology of AN. Studies suggest that AN individuals have reduced DA levels and in response DA receptors increase in sensitivity or number; thus, they may be hypersensitive to salient stimuli[3,4] Given that research suggests low DA levels in AN, researchers sought to replicate these findings using spontaneous eyeblink rate (SBR)—a measure of DA activity[5,6]. Researchers have also used acoustic startle to behaviorally measure DA receptor sensitivity[7,8]. The results of these studies have been inconsistent, which may be due to some researchers not considering effects of medication and comorbid diagnoses on the DA system[9,10].

Objectives

1. To replicate previous SBR and startle studies and consider effects of comorbidity and medication.
2. To determine whether prediction error (PE) response—evoked when reward is unexpectedly received or omitted and is associated with brain DA level—is correlated with spontaneous eyeblink rate and acoustic startle response.

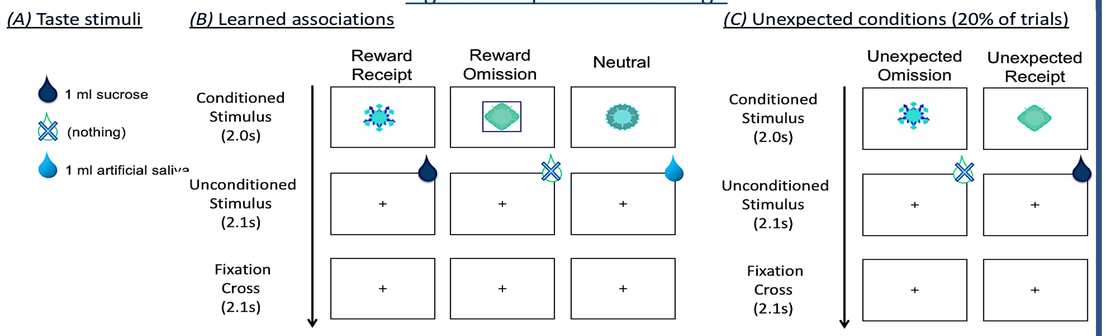
Hypotheses:

1. AN individuals will have lower SBR, but a higher change of blink amplitude from baseline during the acoustic startle task than healthy controls (HC)—reflecting low baseline DA levels, but heighted DA receptor sensitivity to salient stimuli
2. Individuals with AN and anxiety disorders will have a higher percent change of blink amplitude during the acoustic startle task then individuals with AN and mood disorders.
3. PE response will be positively correlated with SBR and startle response as they are indirect measures of DA.

MATERIALS AND METHODS

- Fifty female HC (age = 22.7 ± 5.4 years) and 21 females with AN (age= 23.52 ± 7.2 years) in a treatment program underwent functional magnetic resonance imaging (fMRI) and an eyeblink task (Table 1).
- During fMRI scan, participants learned to associate visual and taste stimuli (Fig. 1A-B). PE was evoked when this association was violated for 20% of the sucrose and no solution visual stimulus trials.
- For the eyeblink task (Fig. 1E), participants sat in a chair and faced a wall with a fixation cross that they focused on. An Eyeblink Conditioning System recorded the number of blinks and amplitude through an infrared sensor. Static noise was played through headphones to block out any distracting noises during SBR and four unexpected tones were presented during the startle task.
- All data was ranked transformed for normalization and analyzed with mood and anxiety disorders, antipsychotics and antidepressants as covariates. To determine group differences in the eyeblink task, a MANOVA was performed in SPSS 25 with avg. 60 sec SBR, avg. baseline amplitude, and percent amplitude change from baseline as dependent variables (Table 2). Images were processed using SPM12. A whole brain regression was run with a threshold of p< 0.001 and 100 voxels (Fig. 4).
- Partial correlations between behavioral and eyeblink measures in AN were run (Fig. 2). Spearman's correlations were run for HC with the same measures, but without covariates (Fig. 3). Bootstrapping was performed to control for multiple comparisions.

Figure 1: Experimental design

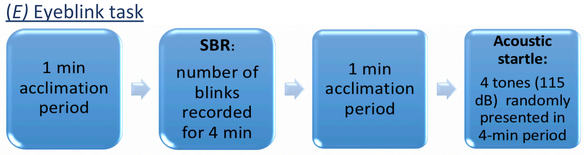


(D) Temporal difference model

$$\delta(t) = r(t) + \gamma\hat{V}(t+1) - \hat{V}(t)$$

Each participant's prediction error (PE) signal was modeled based on trial sequence and regressed with brain activation across all trials within subject using a learning rate of 0.2.

(E) Eyeblink task



RESULTS

Table 1: Demographics and behavioral measures

	HC (N=50)		AN (N=21)			
	Mean	SD	Mean	SD	t	p-value
Age (Years)	22.70	5.40	23.52	7.23	-0.529	0.598
BMI (kg/m^2)*	21.36	1.93	16.74	1.27	10.086	<0.001
Punishment Sensitivity*	5.10	3.75	11.43	4.68	-6.026	<0.001
Reward Sensitivity	6.06	3.48	6.71	4.671	-0.652	0.517
Harm Avoidance*	10.24	5.03	21.29	7.56	-7.23	<0.001
State Anxiety*	25.10	7.720	52.00	18.20	-8.796	<0.001
Trait Anxiety*	26.96	7.61	56.57	17.12	-10.143	0.002
Behavioral Inhibition System*	19.70	3.24	23.85	3.54	-4.713	<0.001
Behavioral Approach System	41.26	4.49	38.55	7.08	1.918	0.059
Breakfast Calories	615.90	148.04	551.10	156.18	1.66	0.102
	N	%	N	%		
Anti-depressant Use	0	0	11	52.4	---	---
Atypical Anti-Psychotic Use	0	0	1	4.8	---	---
Mood Disorder	0	0	13	61.9	---	---
Anxiety Disorder	0	0	18	85.7	---	---
Eyeblink by Group Data						
	Mean	SD	Mean	SD	F	p-value
Avg. 60 Sec SBR	34.84	21.06	38.76	19.81	0.339	0.598
Avg. Baseline Amplitude	36.58	21.08	34.62	19.99	0.249	0.059
Mean Amplitude Change from Baseline	36.16	20.14	35.62	22.30	0.059	0.809

Figure 2: SBR and startle response correlated to behavioral measures in AN, but not in HC.

	HC (N=50)			AN (N=21)		
	Avg. 60 Sec. SBR	Avg. Baseline Amplitude	Mean Amplitude Change from Baseline	Avg. 60 Sec. SBR	Avg. Baseline Amplitude	Mean Amplitude Change from Baseline
Harm Avoidance	-0.260	0.033	-0.143	0.495	-0.233	**0.586***
State Anxiety	0.070	**0.316***	-0.038	-0.191	-0.207	0.311
Trait Anxiety	0.018	0.166	-0.084	0.103	-0.162	0.474
Behavioral Inhibition	-0.067	0.193	-0.088	0.489	0.267	-0.450
Behavioral Approach	0.700	0.069	0.057	.0314	0.056	0.025
SP	-0.087	0.067	-0.153	**0.568***	-0.450	**0.536***
SR	0.047	0.902	0.069	0.051	-0.152	0.069

*p<0.05

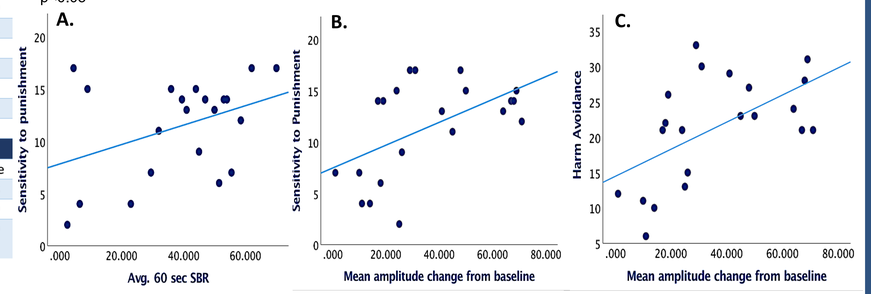


Figure 3: Avg. baseline amplitude is positively correlated with AN PE response

A partial correlation revealed significant positive correlations with PE response in AN and avg. baseline amplitude (Fig. 3A). There were no significant correlations between PE and SBR or startle response.

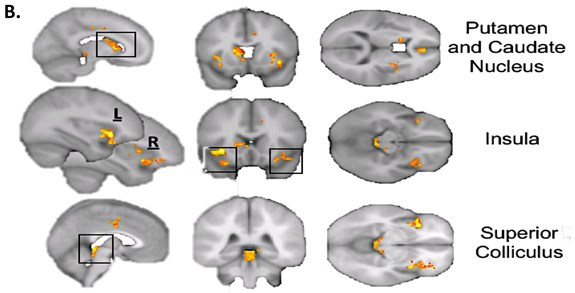
A whole brain regression revealed significant positive correlations between avg. baseline amplitude and AN PE response in the putamen, caudate nucleus, insula, and superior colliculus, but not in HC (Fig. 3B). There were no significant correlations between PE and SBR or startle response.

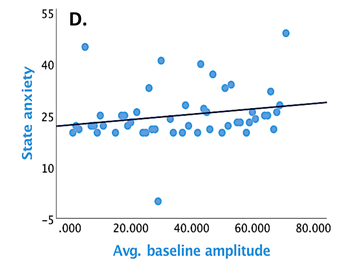
A.

AN (N=21)												
Avg. Baseline Amplitude with:	Left Caudate Head	Right Caudate Head	Left Nucleus Accumbens	Right Nucleus Accumbens	Left Putamen	Right Putamen	Left Inferior Orbitofrontal Cortex	Right Inferior Orbitofrontal Cortex	Left Dorsal Anterior Insula	Right Dorsal Anterior Insula	Left Ventral Anterior Insula	Right Ventral Anterior Insula
Correlation (r)	**0.650****	**0.655****	**0.601***	**0.712****	**0.507***	0.447	0.478	**0.496***	0.413	0.456	**0.563***	0.457

*p<0.05, **p<0.005

B.





A partial correlation revealed a significant positive correlation between SBR and sensitivity to punishment (SP; Fig. 2A). Mean amplitude change from baseline was positively correlated with harm avoidance and SP (Fig 2B-C).

Spearman's correlation revealed a significant positive correlation between state anxiety and avg. baseline amplitude, in HC (Fig. 2D). No other correlations in HC were significant.

DISCUSSION

- Contrary to previous studies, there were no differences in SBR and startle response between AN individuals and HC. Researchers have suggested altered serotonin (5-HT) activity in AN, which can have opposing effects on DA activity[11] Thus, startle response may be more complex in AN because the pathway of startle response involves both DA neurons and 5-HT neurons. There is no established neurocircuitry of SBR, so it is possible that alterations of 5-HT activity in AN may have similar effects on SBR. Future research should seek to identify the neurocircuitry of SBR to help better understand inconsistences in SBR research.
- Consistent with previous studies, AN individuals with high harm avoidance (HA) have greater startle responses[12] Because HA and SP are related, it makes sense that higher SP results in a greater startle response[13]. It is important to note that HA may be related to DA and 5-HT function; thus, 5-HT alterations in AN may be mediating inconsistent findings in startle research.
- In the present study, higher avg. baseline amplitude was associated with greater PE response in AN, but avg. baseline amplitude was not correlated to any behavioral measures. Previous research has not reported on avg. baseline amplitude; thus, it is important to replicate this study using a higher power sample.
- Lack of a correlation between SBR and startle response with PE may be a result of the potential role of 5-HT in SBR and startle response.

Limitations: fMRI does not directly measure dopaminergic signaling, but the PE model used has been validated in previous studies. This study was limited by sample size.

Future directions: Replication of this study with a larger sample and assessing the potential role of 5-HT in SBR and startle response.

References: 1. American Psychiatric Association, 2013; 2. Nielsen, 2011; 3. Kaye et al., 1984; 4. Frank et al., 2005; 5. Barbato et al., 2006; 6. Phillipou et al., 2018; 7. Bellodi et al., 2013; 8. O'Hara et al., 2016; 9. Blumenthal et al., 1995; 10. O'Brien-Simpson et al., 2009; 11. Kaye et al., 2013; 12. Corr et al., 1995; 13. Danner et al., 2012.