The clinical application of fMRI data in a single-patient diagnostic conundrum: Classifying brain response to experimental pain to distinguish between gastrointestinal, depressive and eating disorder symptoms

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ABSTRACT

Patients with eating disorders (EDs) often present with psychiatric comorbidity, and functional and/or organic gastrointestinal (GI) symptomatology. Such multidiagnostic presentations can complicate diagnostic practice and treatment delivery. Here we describe an adolescent patient who presented with mixed ED, depressive, and GI symptomatology, who had received multiple contrasting diagnoses throughout treatment. We used a novel machine learning approach to classify (i) the patient's functional brain imaging during an experimental pain paradigm, and (ii) patient self-report psychological measures, to categorize the diagnostic phenotype most closely approximated by the patient. Specifically, we found that the patient's response to pain anticipation and experience within the insula and anterior cingulate cortices, and patient self-report data, were most consistent with patients with GI pain. This work is the first to demonstrate the possibility of using imaging data, alongside supervised learning models, for purposes of single patient classification in those with ED symptomatology, where diagnostic comorbidity is common.

Eating disorders (EDs) are complex psychiatric disorders of unknown etiology, which most commonly onset during adolescence, and often present with high rates of psychiatric and medical comorbidity. For instance, mood disorders such as depression and anxiety are thought to co-occur in up to 65% of ED presentations in adolescence [1], and up to 80% in adults with EDs [2]. Alongside psychiatric comorbidity, co-occurring medical sequelae are common in EDs. For instance, up to 94% of those with EDs report significant gastrointestinal (GI) symptomatology such as severe abdominal pain, bloating, and constipation [3]. Further still, the prevalence of suicidality in those with EDs exceeds 50% [1].

Multi-diagnostic presentations that span disordered eating psychopathology, broader psychiatric psychopathology, suicidality, and medical morbidity can be extremely difficult to treat. Such presentations are typically excluded from controlled clinical trials, and little data exist in outlining diagnostic or treatment guidelines [4]. Accurate diagnoses in such cases may be further clouded by the reciprocity between ED-related, mood-related, and medical symptomatology. For instance, ED symptoms such as self-induced vomiting, laxative abuse, and dietary restriction typically aggravate the GI symptoms, although are not necessarily the cause of GI symptoms [5,6]. In the context of comorbid ED and GI presentations, accurate diagnosis may be further clouded by marked similarities in genetic risk factors and personality traits [7].

In light of the marked difficulties surrounding accurate diagnoses in multi-diagnostic presentations, we present the case of an adolescent female who presented with a mixed diagnosis of GI pain, ED and depressive symptomology, who received several diagnoses throughout the course of her care. To assist in diagnosis, this patient underwent functional brain imaging, and her neural response to pain stimuli, alongside machine learning technology, was utilized to categorize her diagnostic phenotype. This case may offer novel insights into emerging methods for psychiatric diagnosis and personalized medicine.

1. Case study

"Anna" was a 15-year-old female with no prior psychiatric history, who self-reported a perfectionistic and anxious temperament, who exhibited a two-year history of persistent abdominal pain and nausea, early satiety, constipation and emesis after eating. She first presented to hospital at age 13, with sudden onset nausea, early satiety, abdominal pain and constipation, which resulted in consistent yet reportedly unintentional weight loss. Over a period of 8 months Anna lost approximately 22lbs, and became amenorrheic. While stating that her initial pathway into weight loss was unintentional, Anna also noted that she "secretly liked" her weight loss. At this time Anna was hospitalized, and GI examination found mild gastritis and a functional bowel disorder was suspected with functional dyspepsia, irritable bowel syndrome, gastric dysmotility, dysautonomia, and anxiety thought to be contributing to her difficulties eating. Formal psychiatric assessment resulted in a diagnosis of eating disorder not otherwise specified (EDNOS). Upon discharge Anna commenced a trial of Celexa, and a nasogastric (NG) tube was placed to assist with nutritional intake, and she was able to take all her meals orally.

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Anna was readmitted 6 months after her first admission in the context of ongoing weight loss, emesis after eating, bradycardia and amenorrhea, and continued abdominal pain, reflux, and dysphasia symptoms. She reportedly lost 6lbs in the first two weeks of school, where she reported immense stress around her grades suffering, and again reported liking her weight loss. Extensive medical examination, including upper GI series, EGD, colonoscopy, pH probe study, abdominal X-rays, and standard lab panels, revealed no remarkable findings. Anna was formally diagnosed with a somatoform disorder, anxiety disorder not otherwise specified (ADNOS), and EDNOS. With nasojejunal (NJ) tube feedings, Anna's weight stabilized but she continued to experience consistent abdominal pain and was largely food intolerant. Post-discharge, psychotherapy and biofeedback (targeted at her nausea and vomiting) were recommended, although Anna reported that these were not helpful.

Anna was re-hospitalized after a suicide attempt approximately 9 months later, in the context of persistent nausea and emesis. She reported a gradually declining mood, and had begun to experience depressive symptomatology (i.e., persistent sadness, crying, anhedonia, difficulty sleeping, difficulty concentrating, hopelessness, and suicidal ideation), and ongoing low appetite and restricted food intake. Anna was hospitalized for 1 week to ensure her safety, although recorded another serious suicide attempt 1 week after this discharge. Subsequently she was hospitalized for 5 months due to prolonged suicidality and frequent non-lethal self-harm (i.e., scratching). During this admission Anna was formally diagnosed with major depressive disorder, somatoform disorder not otherwise specified, and EDNOS, with a differential diagnosis of ADNOS. During this hospitalization, and with engagement in (i) group, (ii) individual, and (iii) family therapy, alongside (iv) psychotropic medication (i.e., Celexa, Remeron, Zyprexa), Anna's self-harm, suicidal ideation, and "collapsing" spells resolved, and her depressive symptoms abated. However, her nausea and vomiting also persisted despite multiple medication trials (i.e., Maalox, Nexium, carafate, milk of magnesia, senna-S, esomemprazolem Zofran, Erythromycin). She was discharged to outpatient providers after placement of a gastro-jejunal (GJ) tube, without a clear primary psychiatric diagnosis, and took part in a neuroimaging session approximately 2 weeks later.

2. Methods

2.1. Experimental pain paradigm

Anna underwent a well-validated pain anticipation paradigm that our group had previously administered to healthy control women (HCW; N = 23); women with major depressive disorder (MDD; N = 15); women with gastrointestinal pain due to irritable bowel syndrome, Chron's, and ulcerative colitis (GIP; N = 12); and women recovered from anorexia nervosa (RAN; N = 12) [8–10]. This paradigm consists of an anticipation phase (to cue either high pain, low pain, or uninformed pain) and a stimulus administration phase (either high pain; [6 sec; 47.5 °C] or low pain [6 sec; 45.5 °C]), and has been previously described by our group [8–10].

2.2. Psychological assessment

Anna completed a semi-structured clinical interview, Beck Depression Inventory-2 (BDI-2) [11], Spielberger State-Trait Anxiety Inventory (STAI) [12], Pain Catastrophizing Scale (PCS) [13], and Toronto Alexithymia Scale (TAS-20) [14].

2.3. fMRI protocol

Anna completed two fMRI runs (412 brain volumes/run) in a 3.0 Tesla GE Signa EXCITE scanner, which followed the exact same parameters as our previously published protocols for this pain anticipation paradigm [8–10].

2.4. fMRI statistical analysis

All imaging data were analyzed with the Analysis of Functional NeuroImages (AFNI) software package (1) as in prior studies (2), using the same analytic procedure as outlined in our previous studies of pain anticipation [8–10]. In order to protect against inflated family-wise error rates (3) we followed procedures currently recommended by the developers of AFNI (4, 5).

2.5. Support vector machine

Using age as a covariate, we created pain-related brain activation masks in the 23 healthy control women who previously performed the same task, characterizing brain response to high versus low pain, and anticipation of high versus low pain. Using these functional masks, brain activation patterns within the insula during anticipation and experience of high pain conditions were extracted from each subject in each diagnostic group who had previously completed the same task (GIP = 12; MDD = 15; RAN = 12; Anna). The insula is implicated in pain anticipation and perception, EDs, depression and GI symptoms due to its pivotal role in interoception, emotion, and homeostasis [8–10,15,16], and this region was therefore an excellent candidate for our classification aims. These activations were used in Structured Vector Machine (SVM; R package: e1071; www.r-project.org) to determine the predicted diagnostic classification for Anna. The SVM classifier was created on the GIP, MDD, and RAN groups, and subsequently Anna was classified according to her brain activation. An additional SVM was performed using subjects' responses on behavioral measures (PCS, TAS-20, STAIY-trait, and BDI-2). The SVM classifier was created on the GIP, MDD, and RAN groups, and Anna was classified according to her responses on psychological measures.

3. Results

3.1. Clinical and behavioral measures

Table 1 shows Anna's ratings on several psychological measures, alongside ratings from comparison groups.

3.2. fMRI results

3.2.1. Pain anticipation

Fig. 1 shows Anna's brain activation during the anticipation of painful heat stimulus. Significant activation was observed within right anterior cingulate and left posterior cingulate cortex during pain anticipation that followed an informed cue conditions (both low and high). In the uninformed cue condition, much broader significant whole brain activation was observed, specifically within bilateral anterior insulas, anterior cingulate and prefrontal cortices, as well as temporal regions (see Table 2).

3.2.2. Pain experience

Fig. 1 shows Anna's brain activation during administration of painful heat stimulus. Significant activation was observed within contralateral anterior insula cortex and adjacent inferior frontal gyrus, anterior cingulate, and regions within the prefrontal cortex

Table 1
Demographic and psychological variables for "Anna", in the context of those recovered from anorexia nervosa (RAN), those with depression (MDD), those with gastrointestinal problems (GIP), and healthy control women (HCW).

	Anna	HCW (n = 23)	GIP (n = 12)	MDD (n = 15)	RAN (n = 15)
Demographics (Mean ± SD)					
Age	15	24.7 ± 6	17.3 ± 1.2	27.7 ± 9.4	29.1 ± 7
Psychological Variables (Mean ± SD)					
BDI-2	16	2 ± 3	11.8 ± 9.8	28.4 ± 9.1	4.2 ± 4.3
PCS	25	6.8 ± 6.8	25.8 ± 11.5	25.4 ± 14.5	6.6 ± 7.5
TAS	56	33.4 ± 7.4	50.7 ± 10.2	56.5 ± 11.8	37 ± 9.4
STAIY – STATE	52	23.9 ± 3.5	35.4 ± 11.1	51.1 ± 9.8	28.4 ± 7.3
STAIY – TRAIT	46	24.7 ± 3	39.3 ± 12.4	58.3 ± 6.8	27.9 ± 7

BDI-2 – Beck Depression Inventory 2; PCS – Pain Catastrophizing Scale; TAS – Toronto Alexithymia Scale; STAY – Spielberger State/Trait Anxiety Inventory; Ant – anticipation; Unpl – Unpleasantness.

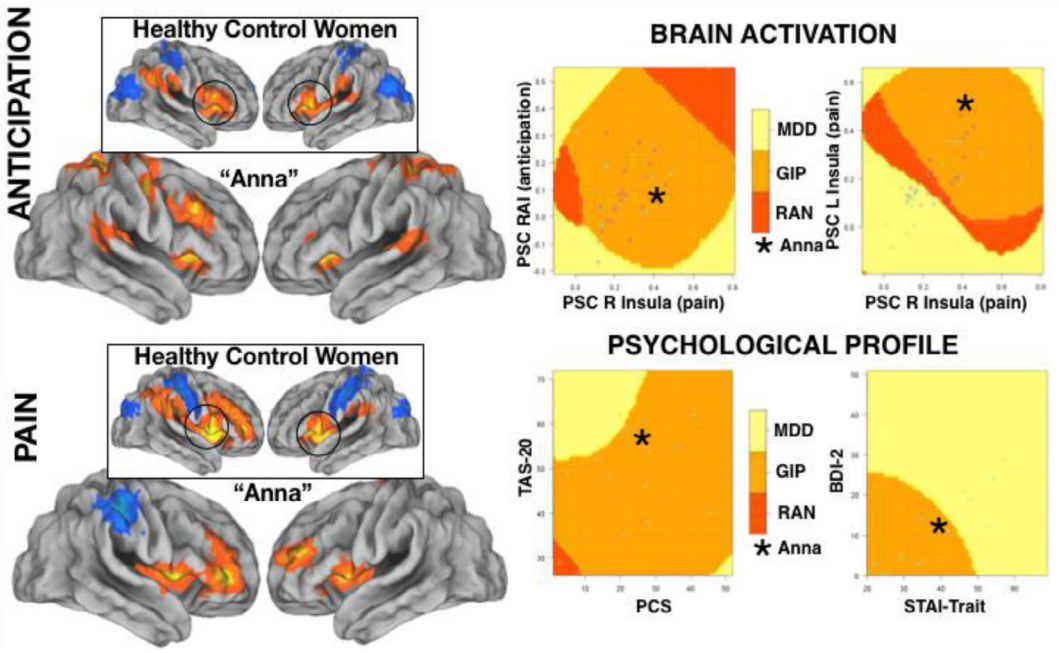

Fig. 1. Left: Anna's whole brain activation during an experimental pain task (comparable activation pattern in healthy control women is shown for comparison). Right: Support Vector Machine classification plots Based on both, insula activation during pain anticipation and experience (*top panel*) (Log-Likelihood (df = 4) = 14.288, p < 0.001) and psychological measures (*bottom panel*) ((Log-Likelihood (df = 4) = 53.626, p < 0.0001), Anna (*) was classified as an individual with gastro-intestinal pain (GIP) (RAN – recovered anorexics; MDD – major depressive disorder; PSC – percent signal change; RAI – right anterior insula; TAS- 20 – Toronto Alexithymia Scale; PCS – pain catastrophizing scale; BDI-2 – Beck Depression Inventory-2; STAI-Trait – Spielberger State-Trait Anxiety Inventory.

during administration of a low pain stimulus. During administration of a high pain stimulus, much broader significant brain activation was observed, specifically within bilateral insula cortices, anterior cingulate cortex, right thalamus, and several regions within precentral gyrus and cerebellum (see Table 2 for details). In addition, significantly decreased activation was observed within the inferior parietal lobule during the administration of the high pain stimulus.

3.3. SVM results

3.3.1. Brain activation

We performed SVM based on a priori insular activation extractions in each diagnostic group in each subject. Diagnosis (GIP, RAN, MDD) was identified with 56% accuracy (Log-Likelihood (4) = 14.288, p < 0.01) and Anna was classified as belonging to GIP (see Table 3, Fig. 1).

3.3.2. Psychological variables

We performed SVM based on psychological measures in each diagnostic group in each subject. Diagnosis (GIP, RAN, MDD) was identified with 84% accuracy (Log-Likelihood (4) = 53.626, p < 0.001) and Anna was classified as belonging to GIP (see Table 3, Fig. 1).

4. Discussion

This case illustrates the application of functional neuroimaging and machine learning technology to augment diagnostic practice in a single patient with overlapping GI, ED and depressive symptomatology. More specifically, we (i) describe brain activation patterns during somatic pain anticipation and experience, and (ii) utilize a machine learning approach, informed by prior sample classifications, to inform the best diagnostic fit for a single patient based on objective neural and psychological data. We found, both objectively (i.e., brain response) and subjectively (i.e., psychological profile), that Anna's profile was consistent with individuals with GI pain and less so with women with depression or anorexia nervosa. SVM models created on our prior sample size were more sensitive to depression than to anorexia nervosa, thus our findings suggest that depression can be ruled out more conclusively and

Table 2
Anna's brain activation during pain anticipation and receival.

Pain Anticipation	Volume	Talairach			t-stat
		X	Y	Z	
Informed Cue Anticipation					
Right Medial Frontal Gyrus/ACC	2176	1	3	57	2.3
Left Posterior Cingulate Cortex	1280	0	−31	26	2.2
Uninformed Cue Anticipation					
Right Medial Frontal Gyrus/ACC	18432	1	−12	57	2.4
Right Cuneus	5120	1	−83	12	2.2
Left Superior Temporal Gyrus	4480	−54	−30	13	2.2
Right Anterior Insula	4032	39	19	7	2.3
Right Cerebellum	3584	4	−48	−15	2.2
Right Superior Temporal Gyrus	3264	46	−35	16	2.2
Left Postcentral Gyrus	2496	−24	−39	58	2.2
Right dorsolateral Prefrontal	1792	37	19	34	2.2
Right Precentral Gyrus	1408	40	−8	45	2.3
Left Anterior Insula	1280	−36	22	7	2.1
Right Superior Parietal Lobule	1280	22	−47	61	2.2
Pain Receival					
Low Pain					
Left Superior Frontal Gyrus/ACC	3840	0	9	58	3
Right Anterior Insula	3456	44	16	5	3
Right Inferior Frontal Gyrus (BA 46)	3200	40	40	8	2.9
Right Inferior Frontal Gyrus (BA 9)	2176	46	4	33	3
Right Middle Frontal Gyrus	2176	39	25	34	2.9
High Pain					
Right Thalamus	18752	1	−17	13	3.2
Left Medial Frontal Gyrus/ACC	7424	−1	2	57	3.2
Right Insula	6464	46	6	6	3.2
Left Insula	6336	−41	11	8	3.2
Right Inferior Parietal Lobule	4608	42	39	13	3.2
Right Inferior Frontal Gyrus/dlPFC	4224	42	39	13	3.2
Left Middle Frontal Gyrus/dlPFC	3200	−34	45	23	2.9
Left Cerebellum	2368	−37	−52	−36	3.1
Right Cerebellum	1280	36	−47	−32	3.1

Table 3
Structured Vector Machine results for brain-based and behavior-based classifications.

SVM	Predicted	Actual			Specificity
		RAN	GIP	MDD	
fMRI	RAN	3	1	2	50%
	GIP	4	6	0	60%
	MDD	5	5	13	57%
	Sensitivity	25%	50%	87%	56%
	"Anna"		X		
Behavior	RAN	8	0	0	100%
	GIP	2	9	0	82%
	MDD	0	3	15	83%
	Sensitivity	80%	75%	100%	86%
	"Anna"		X		

Notes: fMRI:Log-Likelihood (df = 4) = 14.288, $p < 0.001$; Behavior:Log-Likelihood (df = 4) = 53.626, $p < 0.0001$.

with greater confidence than anorexia nervosa symptoms. However, our confidence in the diagnostic classification is bolstered by relatively high sensitivity and the concordance of the imaging and behavioral models.

To our knowledge, this is the first reported case in which neuroimaging data and machine-based learning have been used to augment diagnostic practice in multidiagnostic ED patients. Precision medicine; an important goal in the ongoing evolution of psychiatry, is predicated on the detection of reliable and objective markers of illness psychopathology, which may aid in the diagnosis and personalized treatment of psychiatric illness [17]. Neurocircuit function in particular has been earmarked as an important facet of precision medicine in psychiatry, and the use of neuroimaging data in concert with machine learning approaches may offer important contributions to diagnostic practice in the context of EDs, where self-reported symptom denial and several overlapping psychopathologies are common.

Strengths of this study include the novel use of fMRI and machine learning technology to classify a complex psychiatric and medical presentation. Important limitations relate to the case study design, and further validation of these methods is warranted in more diverse presentations. Further, this methodology can only match individual patients to diagnostic groups who have previously undertook the same experimental paradigm. Thus, to be more broadly effective, a broader array of patients undertaking the same experimental paradigm are needed. Notwithstanding these limitations, the use of neuroimaging to guide clinical decision-making by generating single patient level classifications is an important step as our field advances towards precision medicine.

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Riluzole-induced recurrent pancreatitis

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ABSTRACT

Riluzole is the only drug approved for the treatment of patients with Amyotrophic Lateral Sclerosis (ALS). It is well tolerated, being the most frequent adverse effects asthenia, nausea and reversible increase of liver enzymes levels. Severe adverse effects are extremely rare. We report for the first time, two patients with sporadic limb-onset ALS who developed recurrent acute pancreatitis (AP), with portal vein thrombosis as complication, during treatment with riluzole. We suggest that AP should be considered as a probable rare and severe side effect of treatment with riluzole in patients with ALS. We believe that in patients who develop AP during treatment with riluzole, its withdrawn may prevent recurrent AP and should be discussed with patients.

1. Introduction

Riluzole is a neuroprotective drug that inhibits glutamatergic neurotransmission in motor neurons, but other protective actions are probably involved [1]. Currently, it is the only drug approved for the treatment of patients with Amyotrophic Lateral Sclerosis (ALS). Riluzole is a reasonably safe drug. The most frequent adverse effects are asthenia, nausea and reversible liver enzymes levels elevation [1].

We report recurrent pancreatitis in two ALS patients associated with riluzole treatment.

2. Case report 1

A 56-old-year man was diagnosed with upper limb-onset sporadic ALS (probable disease, revised El Escorial criteria), following 7 months of progressive weakness. He had history of arterial hypertension treated with ramipril and no history of alcohol consumption, hypertriglyceridemia or gallbladder stones. Generic riluzole was prescribed.

Three months after starting riluzole he was admitted to the emergency department due to abdominal pain, nausea and vomits. The diagnostic workup, including amylase levels and abdominal CT findings, established the diagnosis of necrotizing acute pancreatitis (AP). There was no evidence of biliary obstruction. The AP was moderately severe and associated with pseudocysts and portal venous thrombosis. The patient recovered and the treatment with riluzole was re-started, respecting patient decision following discussion about potential risks. ALS progressed slowly, affecting bulbar region and lower limbs. Five years later the patient was again admitted with a mild AP, with rapid recovery. However, two months later, the patient developed severe recurrent AP, determining admission in the intensive care unit. He died two weeks later after various medical complications.

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