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The uncertain brain: A co-ordinate based meta-analysis of the neural signatures supporting uncertainty during different contexts

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Abstract

Uncertainty is often inevitable in everyday life and can be both stressful and exciting. Given its relevance to psychopathology and wellbeing, recent research has begun to address the brain basis of uncertainty. In the current review we examined whether there are discrete and shared neural signatures for different uncertain contexts. From the literature we identified three broad categories of uncertainty currently empirically studied using functional MRI (fMRI): basic threat and reward uncertainty, decision-making under uncertainty, and associative learning under uncertainty. We examined the neural basis of each category by using a coordinate based meta-analysis, where brain activation foci from previously published fMRI experiments were drawn together (1998-2017; 87 studies). The analyses revealed shared and discrete patterns of neural activation for uncertainty, such as the insula and amygdala, depending on the category. Such findings will have relevance for researchers attempting to conceptualise uncertainty, as well as clinical researchers examining the neural basis of uncertainty in relation to psychopathology.

Keywords: Uncertainty; Decision-Making; Associative Learning; Anticipation; Anterior Insula; Amygdala; fMRI

Introduction

Environmental uncertainty is salient, as it suggests that the environment could change, and that change, whatever it may be, could carry motivationally relevant consequences (Esber & Haselgrove, 2011). Recent research suggests that biological organisms attempt to resolve and minimise uncertainty, as a means of optimising inferences and predictions about the external world, and to ultimately promote survival success (Mirabella, 2014; Peters, McEwen, & Friston, 2017). Notably, contemporary theoretical and empirical work suggests that individual differences in intolerance of uncertainty plays a central role in psychopathology, particularly anxiety and stress disorders (Carleton, 2016a, 2016b; Carlrton et al., 2012; Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994; Grupe & Nitschke, 2013; Pepperdine, Lomax, & Freeston, 2018; Tanovic, Gee, & Joormann, 2018). Grupe & Nitschke (2013, p 488) suggest that “Uncertainty diminishes how efficiently and effectively we can prepare for the future and thus contributes to anxiety.” Carleton (2016a; 2016b) posits that uncertainty itself stems from a fundamental fear, that being fear of the unknown.

Regardless of the different conceptualisations of uncertainty, a large body of empirical research has shown that animals and humans display sustained vigilance and defensive responding under conditions of uncertainty, particularly when there is potential for an aversive outcome (Davies & Craske, 2015; Dieterich, Endrass, & Kathmann, 2016; Grupe & Nitschke, 2011; Herry et al., 2007; Ran, Chen, Zhang, Ma, & Zhang, 2016; Sarinopoulos et al., 2009; Whalen, 2007). Markedly, these responses to uncertain conditions with valenced outcomes (aversive or rewarding) are exaggerated in sub-clinical populations with high intolerance of uncertainty (for review see Tanovic, Gee & Jooman, 2018) and in clinical populations with anxiety and stress disorders (Etkin & Wager, 2007; Grupe & Nitschke, 2013). The current literature has identified a number of subcortical and cortical brain regions that are engaged during the anticipation of uncertain events in healthy and clinical populations, such as the insula, amygdala, and anterior cingulate cortex, to name a few (Platt & Huettel, 2008; Nakao et al., 2012; White et al., 2014; Singer et al., 2009; Grupe et al., 2013). These regions form part of the “salience” network (Seeley et al., 2007). However, engagement of the salience network differs substantially across studies that manipulate uncertain stimuli. For example, the amygdala, insula and anterior cingulate cortex have been shown to be engaged during the processing of stimuli that predict aversive events (Etkin & Wager, 2007), whilst the insula and cortical regions such as the ventrolateral cortex are engaged during decision making under uncertainty (Platt & Huettel, 2008). The diversity of brain regions involved suggests that the processing of uncertainty varies depending on the context in which it occurs.

Given the wealth of published fMRI experiments that have examined uncertainty under different contexts (i.e. uncertainty during learning versus uncertainty during decision-making), partitioning these studies by context may reveal whether there are discrete or shared neural signatures of uncertainty in the brain. Here we aim to provide a comprehensive analysis of the extant fMRI literature on (un)certainty in healthy individuals using a coordinate-based meta-analysis. This approach is significant and timely, given (1) the lack of synthesis across the literature in conceptualising uncertainty and its neural basis, (2) the importance of identifying mechanisms related to uncertainty in psychopathology (Carleton, 2016a, 2016b; Grupe & Nitschke, 2013) using a research domain criteria (RDoC) approach (Insel et al., 2010).

Method

We adopted a data driven approach with the aim to understand the various research methods and paradigms related to uncertainty by exploring the cognitive neuroscience literature, using “uncertain” and “uncertainty” as search terms. This resulted in the identification of three broad categories of research areas investigating uncertainty (we call these categories or contexts of uncertainty): (i) Basic threat and reward uncertainty, (ii) Uncertainty under decision-making, and (iii) Uncertainty originating from associative learning. This is not meant to be an exhaustive list of contexts under which uncertainty may arise, rather an attempt to catalogue the possible contexts, given what our literature search has revealed.

Basic threat and reward uncertainty

Throughout our life we can find ourselves in situations of uncertainty that can give rise to feelings of uneasiness, such as waiting for a teacher to announce an essay grade, or a doctor to announce an outcome of a family member’s treatment. In the laboratory setting, several studies investigated such kinds of uncertainty through the anticipation of stimuli varying in predictability (usually 50/50, but also 30/70 or 20/80) and valence (positive, neutral or negative events). The events ranged from receiving a reward, an electric shock, or being presented with emotionally positive or negative pictures. The participant is typically instructed about the contingency, and the uncertainty of the event is then operationalized by a variable duration of the interstimulus interval between a cue and an emotion-relevant stimulus, or by variable onsets of the event presentation (such as 6-10, 6-12, or 2-8 seconds, see e.g. Sarinopoulos et al., 2010; Klumpers et al., 2015). We label such uncertainty originating from anticipation of an event with an unknown valence as ‘basic threat and reward uncertainty’ due to a lack of action required by the participants. The uncertainty therefore arises mainly from anticipating an unavoidable event, which doesn’t require any rule learning or decision making.

We created this conceptual category to include tasks investigating the anticipation of a stimuli with an unknown valence (e.g., Sarinopoulos et al., 2010; Schienle et al., 2010; Grupe, 2013; Klumpers et al., 2015) or an unpredictable reward (e.g., Bjork & Hommer, 2007; Gorka, et al., 2016), paradigms exploring feelings of anxiety elicited to temporally unpredictable presentations of a stimulus (e.g., Somerville et al., 2013; Shankman et al. 2014). We also included tasks involving anticipation of aversive stimuli with randomized probabilities and unpredictable administration cued by a context (e.g., Alvarez et al., 2015; 2011). Table 1 lists all the studies we included in this category.

Table 1 here

Uncertainty under decision-making

Many of our decisions and choices, such as choosing a car to buy or applying to university, involve various degrees of uncertainty and perceived risk. Such uncertainties originate when a decision is required, but the necessary information is not complete; alternatively, the outcome probability or predictability is unknown (e.g., Krug et al., 2014). This means that some decisions may be inherently risky, and a gamble is required (e.g., Cohen et al., 2006). Note that the uncertainty is being imposed on the agent by having to make a decision, not by virtue of being presented with an uncertain situation, as in basic threat and reward uncertainty. Studies in this category typically require the participant to perform a forced decision with limited information with respect to its outcome.

Various tasks in the literature are used to investigate decision-making under uncertainty, such as forced choice tasks for the most probable outcome, with a limited number of observed trials to learn, or with limited knowledge of, underlying probabilities (e.g., Krug et al., 2014; Volz et al. 2004), number or card prediction based on probability estimation (e.g., Elliott et al., 1999; Krain et al., 2008), category judgement based on limited observed trials or perceptual difficulty (e.g., Grinband et al., 2006; Seger et al., 2015), gambling tasks between low and more probable gain or high and less probable gain (e.g. Cohen et al. 2006), or reversal learning paradigms that operationalize uncertainty by requiring subjects to switch from a learned response to a different one when the contingent probabilities of the task unexpectedly change (e.g., D'Cruz et al., 2011; Robinson et al., 2010). Table 2 lists all the studies we included in this category.

Table 2 here

Uncertainty during associative learning

In everyday life we learn to associate neutral events with valenced outcomes e.g. the ping of a microwave signals cooked food, the chime on a train may warn that the doors are closing. In our literature search, we identified uncertainty originating from associative learning experiments, where the reinforcement rate between a CS+ (e.g. coloured square) and US (e.g. shock) is often unpredictable, such as 50/50, 60/40, or 80/20 (e.g., Knight et al., 2005; Straube et al., 2007). We further identified uncertainty in extinction phases of learning paradigms. Here the subjects are faced with an unpredictable omission of the US. The uncertainty during associative learning paradigms is due to the probabilistic pairing of the CS+ and US, resulting in unpredictability of valence (either shock, reward or nothing) of the CS+. This is best understood from the point of view of the agent as they internalise the unknown characteristics of the encountered environment, where an outcome (e.g. electric shock) doesn't always follow a cue. The uncertainty in associative learning is therefore different from basic threat and reward uncertainty. During associative learning the agent forms or removes a link between the CS+ and US, whilst during basic threat and reward uncertainty the agent simply tolerates an uncertain event which follows no particular pattern.

We have identified a number of studies that belong to the category of uncertainty in learning. In associative learning, paradigms with partial (i.e. <100%) reinforcement can be treated as inherently possessing uncertainty of the CS and US pairing (e.g., Knight et al., 2005), as does the extinction phase in extinction learning paradigms (e.g., Kattoor et al., 2013), and reversal learning paradigms, where uncertainty is manifested by the CS change (e.g., Li et al., 2007). We also included fear generalization paradigms; in generalization trials where increments of the CS+ (or generalization stimuli - GS) are presented, uncertainty is operationalized by the unknown pairing rule of the GS and US. Table 3 lists all the studies we included in this category.

Table 3 here

Literature search and selection criteria

The search was conducted to include papers published before June 2017. We used the following search terms in the Neurosynth database: “uncertainty”, “anticipation”, “conditioning”, “extinction”, “reversal”. In citation searches from Google Scholar and PubMed we added “fMRI”, or “associative learning”, in addition to the above-mentioned terms and their combinations. We identified 170 publications.

After selection based on the information contained in the abstract, individual publications were examined for our inclusion and exclusion criteria. The inclusion criteria for uncertainty manipulations in the selected categories were (1) physically healthy participants with no prior history of brain injury or neurological illness, (2) fMRI image acquisition during anticipation of an uncertain stimulus; or before decision or gamble based on incomplete information; or before US was administered or omitted. In the case of associative learning, we only accepted publications with partial reinforcement rate (ranging from 30% to 80%). (3) Reported activation foci in statistical contrasts of uncertainty manipulation: uncertain vs certain, uncertain vs baseline, low uncertainty vs high uncertainty, or CS+ vs CS-. The exclusion criteria were (1) dual task studies as there was insufficient literature to cover this category, (2) studies that did not report simple statistical contrasts but instead opted to use more complex models (such as Bayesian models and prediction error models), and (3) analyses that did not report regions outside of their a priori regions of interest. Since we did not include unpublished material, this review may be biased.

The publication search was performed by the second author and double-checked by the first author. In total, we were left with 87 publications.

Data analysis

Reported foci locations (in x y z coordinates in MNI or Talairach) of the appropriate contrasts (i.e. uncertain vs certain, uncertain vs baseline, low uncertainty vs high uncertainty, or CS+ vs CS-) were gathered from each study, these were then transformed into MNI space where necessary using the convert foci tool in GingerALE (utilizing the Lancaster transform). We used the activation likelihood estimate (ALE) algorithm (Eickhoff, Laird, Grefkes, Wang, Zilles, & Fox, 2009), a kernel based method, to identify voxels activated by uncertainty under each domain. The ALE method was selected due to its: (1) wide use in the literature, (2) similarity to other kernel based methods and (3) efficient computation time (Samartsidis, Montagna, Nichols, & Johnson, 2017). We used a cluster forming threshold with a cluster level inference of $p < .05$ and a false discovery rate of $p < .01$ (GingerALE version 2.3.6). We set the number of permutations to 5000 per analysis. We created a map for each of the three categories using FMRIB Software Library (FSL) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

We performed an analysis similar to the one described above to identify clusters activated by certainty (vs uncertain conditions) that served as a control. This further offers a method to rule out that neural signatures of uncertainty are not also present during situations of certainty. Overlapping brain areas in the uncertain and certain contrast would suggest little specificity of brain areas for uncertain/certain states. For this analysis, we created a map of the opposite contrasts to those used above. This was represented in the decision-making literature as certain vs uncertain, in associative learning as activations associated with CS- (contrast CS- vs

CS+), and in the basic threat and reward uncertainty literature as safe/aversive vs uncertain.

Results

Individual category analyses for uncertainty

Altogether the database included 1212 activation foci from 87 experiments involving 2132 participants (see Fig 1). Of the total, table 4 reports experiments used in the three categories.

We created maps to investigate the neural signatures of uncertainty for each category separately. Partly replicating the analysis reported above, the analyses of the three identified categories revealed overlapping clusters (see Fig 2) in bilateral anterior insula for all categories: basic threat and reward uncertainty, decision-making, and associative learning. The dorsal anterior cingulate cortex, right caudate, and bilateral amygdala, were only found in the associative learning category (Additional non-overlapping clusters of activation found in the separate domains are displayed in table 5).

Table 4 and 5 here

Figure 1 here

Figure 2 here

Individual category analyses for certainty

The database was smaller than our “uncertain” database as most studies did not report contrasts of certainty, including 270 activation foci from 35 experiments involving 836 participants (see Table 6).

We used ALE to identify voxels that were activated under all examined categories for the certain contrasts. The analysis didn’t reveal any significant clusters independently in each category, or common to all identified categories. Figure 1 shows a map of the activation foci, with some cluster trends in ventromedial and the dorsomedial prefrontal cortex.

Table 6 here

Discussion

In the current coordinate-based meta-analysis of brain activation foci from published fMRI experiments, we examined the neural basis of uncertainty during different contexts (i.e. basic threat and reward uncertainty, decision-making under uncertainty, and associative learning under uncertainty). Our findings revealed that the brain is more generally active under conditions of uncertainty versus certainty. Furthermore, we identified a common role for the bilateral anterior insula in all three categories of uncertainty. The dorsal anterior cingulate cortex, right caudate, and bilateral amygdala were only found in the associative learning category. These results are further supported by the lack of overlapping brain areas activated during uncertain and certain contrasts, suggesting differential activity for situations of uncertainty over certainty. No brain regions were found to be systematically engaged during certainty relative to uncertainty across studies. Taken together these findings suggest that there are shared, as well as discrete patterns of brain activation for uncertainty during different contexts.

Environmental uncertainty is salient as it suggests that something could change, which may have motivationally relevant consequences (Esber & Haselgrove, 2011). It is probable that the brain is geared towards minimising uncertainty, in order to optimise predictions about potential future outcomes, and to make the appropriate actions and decisions about choices (Mirabella, 2014; Peters et al., 2017). Indeed, our results from the coordinate-based meta-analysis revealed far more brain foci for the uncertain versus certain contrasts, compared to the reverse contrasts. In addition, our findings suggest that activation in brain regions overlap across contexts with uncertainty, and reveal discrete activation patterns for specific contexts with uncertainty. Such results suggest that uncertainty may engage the relevant brain mechanisms, depending on how generalised or specific the mechanism is for a given context. For example, the anterior insula has been suggested to be part of the salience network and has been implicated in anticipation (Grupe et al., 2013), and interoception and bodily feedback (Craig, 2010; Seeley et al., 2007; Seth, Suzuki, & Critchley, 2012). Across contexts with anticipation of uncertain outcomes, the anterior insula may become more engaged in order to tag the salience signalled by the anticipation of an uncertain event in relation to the internal state of the self. In another example, the amygdala and dorsal anterior cingulate cortex have been implicated in the associative learning of threat (Fullana et al., 2016). The pairing of a conditioned stimulus and unconditioned stimulus is more salient when the pairing is uncertain (partially reinforced, 50%), as it suggests the pairing may be unstable, risky or subject to change. Therefore, during uncertainty in an associative learning context, the amygdala and dorsal anterior cingulate cortex are engaged to prepare for the processing of a potentially different outcome i.e. the CS may or may not be reinforced (Shackman & Fox, 2016; Shackman, Salomons, Slagter, Fox, Winter, & Davidson, 2011).

In general, our findings support the majority of brain regions proposed by previous literature on uncertainty (Platt & Huettel, 2008; Nakao et al., 2012; White et al., 2014; Singer et al., 2009; Grupe et al., 2013). However, the analysis does not provide support for the involvement of prefrontal regions such as the orbitofrontal cortex (Mushtaq et al., 2011; Grupe et al., 2013) or other subcortical regions such as the bed nucleus stria terminalis (Lebow & Chen, 2016; Shackman & Fox, 2016) in the processing of uncertainty for any of the identified categories. It should be noted that some of the clusters found were substantially bigger than others. For example, the clusters for the insula, anterior cingulate cortex and caudate were much larger than those found in amygdala. This could be due to these regions having more involvement in the processing of uncertainty. However, the size of the clusters is more likely to be due to there being more individual variation in structure and function. Activation in smaller structures that have been implicated in uncertainty such as the bed nucleus stria terminalis and subthalamic nucleus may have not been detected or systematically reported because of small activation extent due to the structures' size.

Here we examined a coordinate-based meta-analysis on data from healthy participants. Interestingly, a number of the brain regions (e.g. amygdala, insula and dorsal anterior cingulate cortex) identified in this study have been suggested to play an important role in anxiety and stress disorders (Etkin & Wager, 2007; Grupe et al., 2013; Tanovic, Gee, Joormann, 2018). Due to greater sensitivity to future threat uncertainty in sub-clinical and clinical populations (for reviews see, Carleton, 2016a; Carleton, 2016b), we would expect to see more systematic involvement of these regions identified for contexts with uncertainty, as well as more shared overlap of brain regions across contexts with uncertainty. Particular disorders may be related to greater neural activation in all uncertain contexts (e.g. generalized anxiety disorder), whilst other disorders may be related to a particular uncertain context (e.g. associative learning for obsessive compulsive disorder, post-traumatic stress disorder, and specific phobias). Further work is needed to elucidate whether this would be the case, given the importance of uncertainty in psychopathology, and the current research domain criteria (RDoC) framework used to identify biosignatures related to mental health disorders.

It may be possible that some of the brain regions reported here which have been implicated in uncertainty were in fact active due to a different common denominator of all analysed studies rather than uncertainty, such as negative affect or anticipation. However, it is likely that is it the combination of these factors. For example, if it was solely anticipation, we should have observed similar neural profiles for anticipating an uncertain and certain event. Furthermore, the results may have been dominated by the associative learning under uncertainty literature that focused on uncertain threat, which was substantial, compared to the decision making and basic threat and reward uncertainty literature. To rule out possible common denominators, future work should aim to partition different levels of uncertainty, types of uncertainty and valence across multiple contexts e.g. sustained uncertain threat, momentarily uncertain threat, sustained uncertain reward etc.

Due to a lack of any overlapping clusters found in the analysis for certainty, the neural signatures of certainty may be more variable and occur in distinct neural systems during different tasks or for different stimuli. It is also likely that due to the limited number of studies reporting certain contrasts including certainty vs uncertainty, clusters have not appeared in our analysis due to low power (e.g. certainty-specific contrasts were reported in 35 out of 87 experiments). This possibility is hard to rule out, since the literature reporting brain correlates of certain states is limited. However, it may also be that the states of certainty are rarely achieved both in real life or experimental research. Perhaps, experimental approaches that use a continuum from uncertain-certain may provide more promising results in determining brain regions that are involved in states of certainty.

A limitation of the current meta-analyses is that we may have missed other categories of uncertainty with an imaging literature due to there being a smaller number of studies or a publication bias. For example, there is a growing literature on the role uncertainty in inhibitory control (Chikazoe et al. 2009; Zandbelt and Vink 2010). In these studies, some of the cues are certain as they indicate that go-signals are never followed by a stop-signal, whereas other cues are uncertain as they indicate that go-signals may or may not be followed by a stop-signal. Notably, some of the brain areas reported to be differentially engaged in these tasks overlap with the current meta-analysis findings i.e. anterior cingulate cortex. Future research should aim to examine the role of uncertainty on inhibition, as inhibition may be an important process for counteracting uncertainty (Mirabella, 2014).

We opted to subdivide uncertainty by context in order to make less assumptions about what uncertainty is, given the number of different definitions of uncertainty in the literature. However, the subdivision of uncertainty by context may only reflect a sub-set of the types of uncertainty. There are other ways that uncertainty could have been divided i.e. the difference between an uncertain outcome of known "risk" and one with an uncertain outcome where the probabilities are "ambiguous".

In the current study we included older fMRI studies with smaller samples sizes, as GingerALE alters the full width half maximum of foci depending on sample size (Fox, Laird, Eickhoff, Lancaster, Fox, Uecker, & Ray, 2013). However, as previously noted there is a reporting bias in fMRI studies with smaller sample sizes (David et al., 2013). Therefore, to address this issue we have included an alternative analysis without studies with smaller sample sizes (see Supplementary Material). It is important to note that the current coordinate based meta-analysis focused on fMRI data primarily from 1.5 and 3 tesla MRI scanners, which have their own methodological problems (Turner, 2016). With the advancement of higher resolution MRI imaging (Martino et al., 2018), other imaging technologies such as magnetic resonance spectroscopy, and functional connectivity research, in the near future we will be able to examine the function and structure of brain networks in relation to uncertainty in more depth and detail.

In summary, the current co-ordinate based meta-analysis attempted to synthesise the available fMRI evidence for the processing of uncertainty. The results suggested that overall the brain is more active during uncertainty versus certainty, and that there are shared and discrete patterns of neural activation depending on the type of context where uncertainty occurs. The findings further support and bring together modern conceptualisations of uncertainty, and will be critical for clinical researchers making the leap to understand the neural basis of uncertainty in relation to psychopathology.

Conflict of interest

The authors report no conflict of interest.

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Table 1

Studies included in the basic threat and reward uncertainty dataset

Study	Year	N(F)	Category	Task
Alvarez et al.	2015	40(20)	Basic threat uncertainty/Context	Context cued shock with randomized interval
Alvarez et al.	2011	18(8)	Basic threat uncertainty/Context	Context cued shock
Bjork et al.	2007	20(10)	Basic reward uncertainty	Cued or uncertain anticipated stimuli
Dalton et al.	2005	17(0)	Basic threat uncertainty	Cued anticipated shock
Drabant et al.	2011	51(51)	Basic threat uncertainty	Cued or uncertain anticipated shock
Gorka et al.	2016	37(27)	Basic reward uncertainty	Slot machine
Grupe et al.	2013	43(22)	Basic threat uncertainty	Cued or uncertain anticipated stimuli
Jensen et al.	2003	11(5)	Basic threat uncertainty	Cued anticipated stimuli
Klumpers et al.	2015	99(0) & 69(47)	Basic threat uncertainty	Cued anticipated shock
Klumpers et al.	2010	23(11)	Basic threat uncertainty	Cued anticipated shock
Motzkin et al.	2014	19(8)	Basic threat uncertainty	Cued or uncertain anticipated stimuli
Nitschke et al.	2006	21(11)	Basic threat uncertainty	Cued anticipated stimuli
Sarinopoulos et al.	2010	40(18)	Basic threat uncertainty	Cued or uncertain anticipated stimuli
Schienle et al.	2010	30(30)	Basic threat uncertainty	Cued or uncertain anticipated stimuli
Seidel et al.	2014	25(13)	Basic threat uncertainty	Cued or uncertain anticipated shock
Shankman et al.	2014	19(13)	Basic threat uncertainty	Countdown to event
Somerville et al.	2013	55(32)	Basic threat uncertainty	Countdown to event/unpredictably occurring event
Yoshimura et al.	2014	15(9)	Basic threat uncertainty	Countdown to event
Zaretsky et al.	2010	16(9)	Basic threat uncertainty	Rating of emotion

Abbreviations: N, number; F, female

Table 2
Studies included in the decision-making dataset

Study	Year	N(F)	Category	Task
Bhanji et al.	2010	14(7)	Probability	Prediction task
Cohen et al.	2005	16(7)	Probability	Gambling task
Crtichley et al.	2001	8(2)	Probability	Card prediction task
Elliott et al.	1999	5(2)	Probability	Prediction task
Feinstein et al.	2006	16(8)	Probability	Card prediction task
Hosseini et al.	2010	40(3)	Probability	Prediction task
Hsu et al.	2005	16(3)	Probability	Gambling task
Huettel et al.	2005	12(3)	Probability	Confidence decision task
Jung et al.	2014	24(8)	Probability	Number estimation
Koch et al.	2008	28(17)	Probability	trial and error based probabilistic learning
Krug et al.	2014	64(27)	Probability	Decision task based on estimated probability
Paulus	2001	12(2)	Probability	Prediction task
Payzan-LeNestour et al.	2013	18(9)	Probability	Decision task based on estimated probability
Schlösser et al.	2009	12(0)	Probability	Decision task based on estimated probability
Volz et al.	2003	16(5)	Probability	Decision task based on estimated probability
Volz et al.	2004	12(7)	Probability	Decision task based on estimated probability
Banko et al.	2011	16(6)	Task difficulty	Category judgement
Callan et al.	2009	14(7)	Task difficulty	Driving decision task (turning)
Grinband et al.	2006	10(5)	Task difficulty	Category judgement
Li et al.	2012	20(13)	Task difficulty	Category judgement
Limongi et al.	2016	16(9)	Task difficulty	Prediction task with temporal uncertainty

Mestres-Missé et al.	2016	22(11)	Task difficulty	Perceptual decision task
Seger et al.	2015	16(12)	Task difficulty	Category judgement
Simmons et al.	2007	14(10)	Task difficulty	Perceptual decision task
Causse et al.	2013	15(?)	Field specific - aviation	Flight decision task (landing)
Cools et al.	2002	13(8)	Reversal learning	Probabilistic reversal-learning task
D'Cruz et al.	2011	15(9)	Reversal learning	Probabilistic reversal-learning task
Hampshire et al.	2012	19(0)	Reversal learning	Probabilistic reversal-learning task
Robinson et al.	2010	16(5)	Reversal learning	Probabilistic reversal-learning task

Abbreviations: N, number; F, female

Table 3

Studies included in the associative learning dataset

Study	Year	N(F)	Category	CS	US	Reinforcemen
Buchel et al.	1999	11(5)	Learning	Tone	Tone	50%
Buchel et al.	1998	9(2)	Learning	Face	Tone	50%
Delgado et al.	2008	12(6)	Learning	Coloured square	Shock	60%
Delgado et al.	2011	15(7)	Learning	Colour	Shock	33%
Greening et al.	2015	20(11)	Learning	Tone	Shock	50%
Harrison et al.	2015	55(38)	Learning	Coloured sphere	Noise	50%
Harrison et al.	2017	57(37)	Learning	Coloured sphere	White-noise	50%
Hu et al.	2013	25(8)	Learning	Coloured square	Shock	50%
Knight et al.	2005	9(5)	Learning	Tone	White-noise	80%
Linman et al.	2011	24(13)	Learning	Colour	Shock	62.50%
Maier et al.	2012	17(11)	Learning	Picture	Shock	50%

Moessnang et al.	2013	29(15)	Learning	Odour	Odour	60%
Olsson et al.	2007	11(0)	Learning	Colour	Shock	60%
Straube et al.	2007	12(10)	Learning	Symbol	Shock	50%
Haritha et al.	2012	25(16)	Learning/anticipation	sound tone?	White-noise	30%
Labrenz et al.	2016	49(25)	Learning/anticipation	Shape	Rectal distension	completely random
Andreatta et al.	2015	24(13)	Extinction	Context	Shock	60%
Dunsmoor et al.	2007	18(11)	Extinction	Tone	White-noise	Ext. data only
Ewald et al.	2014	26(17)	Extinction	Context & light	Shock	Ext. data only
Feng et al.	2014	29(?)	Extinction	Coloured square	Picture	63%
Gottfried et al.	2004	16(9)	Extinction	Face	Odour	50%
Hermann et al.	2016	46(0)	Extinction	Context & light	Shock	63%
Icenhour et al.	2015	48(24)	Extinction	Visual cue	Rectal distension	75%
Iidaka et al.	2009	18(0)	Extinction	Face	Voice	50%
Kattoor et al.	2013	19(?)	Extinction	Shape	Rectal distension	75%
LaBar et al.	1998	10(5)	Extinction	Coloured square	Shock	Ext. data only
Lang et al.	2009	21(7)	Extinction	Context/colour	Shock	50%
Milad et al.	2007	14(8)	Extinction	Context & light	Shock	60%
Morriss et al.	2015	21(12)	Extinction	Colour	Noise	Ext. data only
Phelps et al.	2004	11(6)	Extinction	Coloured square	Shock	35%
Reinhardt et al.	2010	20(0)	Extinction	Coloured square	White-noise	50%
Seyhlmeyer et al.	2010	32(20)	Extinction	Face	White-noise	25%
Morris et al.	2004	12(?)	Reversal learning	Face	White-noise	33%
Schiller et al.	2008	17(9)	Reversal learning	Face	Shock	30%

Dunsmoor et al.	2011	14(7)	Fear generalization	Face	Shock	62% acq. 66 gen.
Greenberg et al.	2013	25(25)	Fear generalization	Shape	Shock	50% acq. 50 gen.
Lissek et al.	2014	20(11)	Fear generalization	Shape	Shock	80% acq. 33 gen.
Onat et al.	2015	29(0)	Fear generalization	Face	Shock	30%

Abbreviations: N, number; F, female; ext., extinction; acq. acquisition; gen., generalisation

Table 4

Summary of experiments used for uncertainty contrasts

Domain	N experiments	N	Activation foci
Basic threat and reward uncertainty	20	668	239
Uncertainty in decision making	29	519	337
Uncertainty in associative learning	38	870	612
All categories	87	2057	1188

Abbreviations: N, number

Table 5

Activation clusters from uncertain contrasts independent categories analysis

Region	Side	Cluster volume (mm^3)	Weighted centre[a] (x,y,z)
Basic threat and reward uncertainty			

Anterior insula	R	536	39, 18.2, 1.7
Anterior insula	L	352	-32.7, 22.9, 4.4
Uncertainty under decision-making			
Anterior insula	L	312	-31.4, 21.5, 3.1
Anterior insula	R	88	34.9, 23.5, -.2
Uncertainty during associative learning			
Anterior insula	R	2472	36.1, 21.6, -1.5
Anterior insula	L	1672	-33.1, 20.8, -.1
Caudate	R	424	11.4, 7.8, 3.1
Anterior cingulate cortex	R	168	5.7, 21.8, 31
Amygdala	L	40	-22, -6.4, -13.6
Amygdala	R	8	26, -2, -16

Abbreviations: R, right; L, left. a All co-ordinates are displayed in MNI (Montreal Neurological Institute) space.

Table 6
Summary of experiments used for certainty contrasts

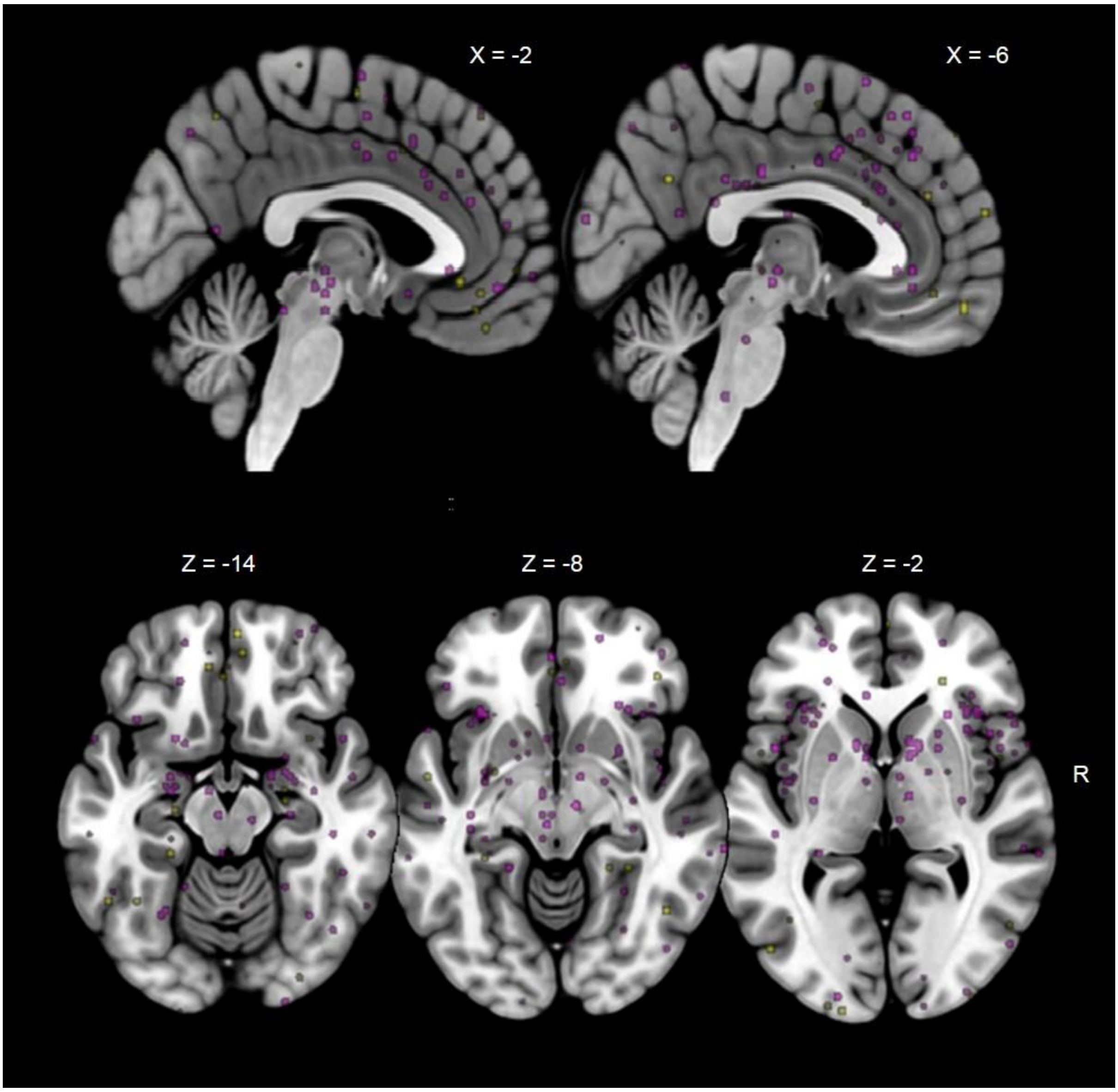
Domain	N experiments	N	Activation foci
Basic threat and reward uncertainty	9	235	63
Uncertainty in decision making	9	157	84
Uncertainty in associative learning	17	444	123
All categories	35	836	270

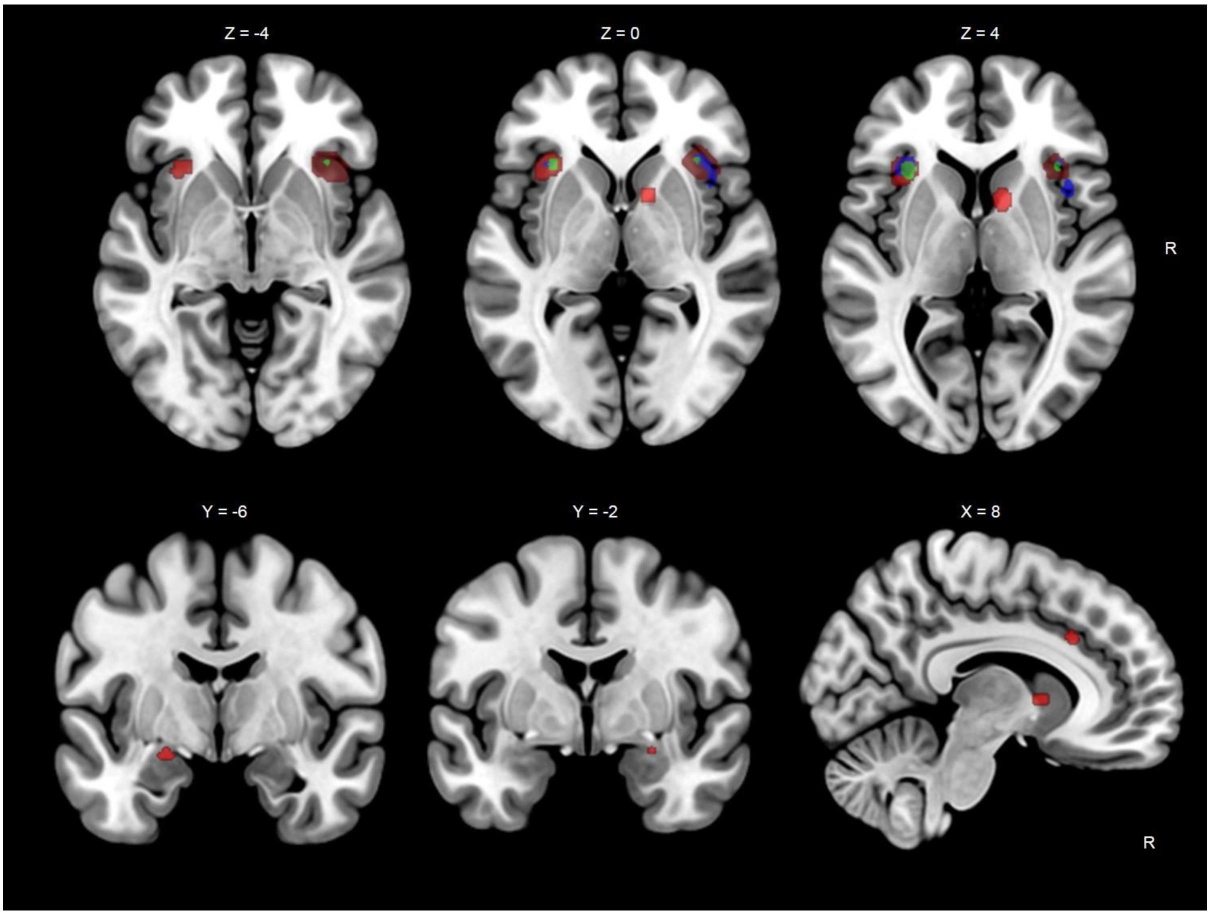
Abbreviations: N, number

Figure Captions

Figure 1. Foci from uncertain and certain contrasts across all three categories. Purple foci represent co-ordinates for the uncertain contrasts, and yellow foci represent co-ordinates for the certain contrasts. Co-ordinates in MNI space. R = Right.

Figure 2. Results from the co-ordinate based meta-analyses of contexts with uncertainty. Substantial overlap across all three categories was observed in the bilateral anterior insula. Whilst, decision making and associative learning under uncertainty revealed discrete activation in the anterior cingulate cortex, amygdala, and right caudate. Blue represents basic threat and reward uncertainty, green represents decision making under uncertainty and red represents associative learning under uncertainty. Co-ordinates in MNI space. R = Right.


X = -2
X = -6
Z = -14
Z = -8
Z = -2
R


Z = -4
Z = 0
Z = 4
R
Y = -6
Y = -2
X = 8
R