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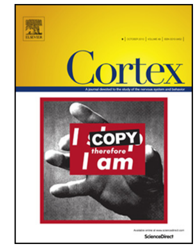

Research report

State of belief, subjective certainty and bliss as a product of cortical dysfunction

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ABSTRACT

Introduction: Ecstatic seizures are focal epileptic seizures which are fascinating from a phenotypical point of view as they include intense positive affect, feelings of heightened self-awareness and enhanced well-being. They have been previously suggested to arise in the anterior insular cortex, although strong arguments are still lacking.

Methods: We describe the cases of two new patients with ecstatic seizures. Their evaluation included a careful history, encouraging the patient to provide significant details about their ictal symptoms in order to better understand the origin of the sense of bliss and support the hypothesis of an insular involvement according to the current stage of knowledge. Ictal electroencephalographic and blood flow studies complemented these data in one patient.

Results: The comprehensive description of the ictal ecstatic symptoms by the two patients has brought out an unfamiliar sense of absence of doubt which was at the basis of a feeling of meaningfulness and certainty. The ictal single-photon emission computed tomography (SPECT) showed an increased blood flow maximal at the junction of the right dorsal mid-insula and the central operculum.

Conclusions: The unveiling of an ictal sense of certainty during ecstatic seizures might imply, in the light of current knowledge, a defect in the system processing prediction errors within the framework of generalized predictive coding mechanisms of the brain. Accumulative evidence has recently highlighted a crucial role of the anterior insular cortex in this system, particularly in the detection of mismatch/conflict between prediction state and outcome. Abnormal activity related to epileptic seizure in a structure prevents its normal activity: in the anterior insula, it could prevent the detection of prediction errors, and thereby prevent the feeling of ambiguity (and the associated negative emotional component), leading to a blissful state which could be close to the deeper states of meditation.

1. Introduction

During recent years there has been growing evidence for the role of the insula in many important cognitive processes and particularly in dealing with uncertain/ambiguous information. It was first recognized as the main cerebral structure behind our sense of global interoception, generated at every moment via the processing of various sensory external and

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internal stimuli (Craig, 2009). An integrative model of the role of the anterior insula in feelings and processing uncertainty in the context of decision making has been proposed (Preuschoff et al., 2008; Singer et al., 2009). The insular cortex seems indeed to integrate external sensory and internal physiological signals with computations about their uncertainty. This integration is expressed as a dominant feeling state that modulates social and motivational behavior in conjunction with bodily homeostasis. As we are going to show in this paper, the role played by the anterior insula in processing uncertainty could be of major importance to account for the "ecstatic" symptom.

The first ecstatic epileptic seizures that we can recognize throughout the literature are those of Dostoevsky, in his correspondence and also attributed to some of the characters of his novels, as the Prince Mychkine in "The Idiot". Ecstatic seizures consist of a feeling of bliss, associated with a sense of high self-awareness and a physical sensation of global well-being (without any sexual feeling). The ecstatic seizures have been suggested to originate in the insular cortex (Picard and Craig, 2009) because (i) the anterior insular cortex is the best candidate region that may explain concomitant feelings of heightened self-awareness (Craig, 2009; Modinos et al., 2009; Critchley et al., 2004), enhanced well-being (Craig, 2003) and intense positive affect; and (ii) ictal single-photon emission computed tomography (SPECT) performed in two patients have shown increased blood flow in the anterior insula (Picard and Craig, 2009; Landtblom et al., 2011).

The present study reports the phenomenologic description brought by two new patients with a high power of introspection, intelligence, and level of vocabulary, which helps to dissect the cognitive process leading to the ecstatic feeling.

2. Patients and results

2.1. *Patient 1*

A 17-year-old Swiss apprentice farmer suffered from epileptic seizures from the age of 15 years.

He experienced an extremely pleasurable state of consciousness during his seizures. He felt a deepening awareness of the situation or conversation going on around him, a sudden clarity. It was as if he clearly understood everything, especially if he happened to be in the midst of a discussion with several people. He grasped it all simultaneously. Things suddenly seemed self-evident, almost predictable (yet without the feeling of knowing the future).

While he knew where he was and what he was doing, he did not want to interrupt the experience by talking. At the same time, very often he felt a taste, pleasant but nothing more (gustatory hallucinations). He could not compare this taste with any taste he knew. During the seizure, he could not "be located in time". It was as if time stopped. For him, these seizures lasted at least 40 sec while his family members could say it lasted 1–3 sec. These seizures were all triggered by a pleasant context. It could be an interesting discussion with several people with whom he liked to talk. In this case, the significance of all parts of the discussion suddenly became completely clear, as if a sudden incredibly clear understanding and meaningfulness of the whole discussion was offered to him. Other triggering factors were nice things that he could see, hear or think about. It could be when he saw "a tractor with the harvest, nice photos, a nice color, a flower, a nice landscape, a bird singing, grazing animals, branches that move with the wind, a beautiful woman", or on the occasion of a kiss, a caress, a nice thought about someone, a hope….

At the beginning of his epilepsy history, he suffered from more severe focal seizures, without any clear triggering factor, starting with a very strange bad taste, unsimilar to any existing taste, a vestibular illusion and hypersudation, followed by a loss of consciousness with oral automatisms (chewing movements) and then a tonic seizure of the face and upper limbs, with prolonged post-ictal confusion.

Magnetic resonance imaging (MRI) showed a tumor suspicious of a ganglioglioma in the right temporal pole beside an arachnoidal cyst (Fig. 1A). An 80 sec-seizure with ecstatic symptoms (the patient seemed struck by a sudden thought) followed by a loss of consciousness with left hemifacial dystonia and then oro-alimentary automatisms was recorded. Ictal electroencephalogram (EEG) showed rhythmic 12 Hz activity in the right anterior temporal area, with a diffusion in the homolateral frontal region, followed by delta slow waves in the bilateral frontotemporal regions and then a right anterior temporal flattening at the end of the seizure. A moderate tachycardia was observed from the beginning of the clinical

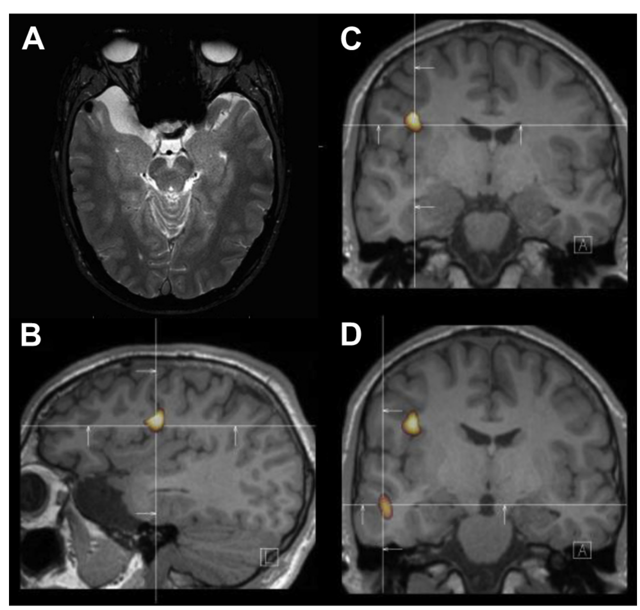

Fig. 1 – Cerebral MR and ictal SPECT images of patient 1. (A) Gradient echo T2* axial MR image showing a small round (hypointense) tumor in the right temporal pole and a neighboring arachnoid cyst. (B–D) Ictal/interictal technetium-99m HMPAO (^{99m}Tc-HMPAO) SPECT subtraction using BRASS analysis program. The software allows automatic fitting of brain perfusion scans and subtraction; (B) sagittal image, (C–D) coronal images, showing an increased blood flow maximal at the junction of the right dorsal mid-insula and the central operculum. (D) A cluster of increased blood flow was observed in addition within the right temporal pole, close to the tumor.

seizure. PET using ^{18}F-Fluoro-deoxyglucose (FDG) showed a focal hypometabolism in the temporal pole, mesial and anterior lateral temporal lobe and anterior insula on the right side. Interictal SPECT and ictal SPECT using technetium-99m hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) were performed. Subtraction using the Brain Registration and Analysis Software Suite (BRASS) analysis program, with automatic fitting of brain perfusion scans on the MRI image showed a significant ictal hyperperfusion at the junction of the right dorsal mid-insula and central operculum, and in the right anterior temporal region (Fig. 1B–D).

2.2. Patient 2

Patient 2 is a 39-year-old American philosopher, which implies high introspective capacities. He started to suffer from epilepsy at the age of 18 years and seizures ended abruptly when he was 21, allowing a discontinuation of antiepileptic medication at the age of 23. Cerebral MRI was normal. He had two types of seizures. The first consisted of auditory musical hallucinations ("*loud, unconnected snippets of music playing*"), which were accompanied by feelings of terror or intense sadness. Over the course of the next several weeks, the seizures tended to be confined to these unpleasant feelings. Some months later on, he also began having ecstatic seizures, while the seizures with a strong negative emotional content disappeared.

A few years ago, the patient wrote a description of his feelings during his former seizures.

Excerpts concerning the unpleasant emotional seizures:

"A sense of dread and sadness became overwhelming during the seizures. My thoughts would transform into paranoia and repetitive suicidal ideations. My beliefs during these spells were often frightfully specific; any thought, whether it concerned the surrounding environment or any other subject, would be coopted by the seizure. If someone was in the room or if nobody was in the room, their presence or absence would confirm only the worst thoughts. Any thought, no matter how harmless the topic might seem, would immediately be transformed by the seizure into the premise of a terrifying scenario." "Strangely, these thoughts, although totally convincing, always faded into obscurity when the spell was over. After a few minutes had passed, I knew quite clearly that these beliefs were totally false."

Excerpts concerning the ecstatic seizures:

"Every detail of my perceptions was every bit as accurate as they ever are."

"In dramatic contrast to the ordinary way of experiencing one's surroundings, during my seizures, all of these boundaries would suddenly be erased. Although all my judgments of shape, size, color, texture, and so on would remain totally unchanged, the evaluation of my environment would undergo a sudden transformation. Everything would be joined together into one whole, as if every single thing in my surroundings were deliberately placed by an artist with the goal of composing a photograph. This would result in a sense of vividness which derived, not from any dramatic hallucination or visual "trick", but from the fact that each object in my visual field was emphasized, so to speak, by everything else. When these boundaries are erased, a second phenomenon begins - ***all the ordinary facts about the environment seem suddenly to become infused with certainty and a sense of inevitability****."*

"One often has (what is sometimes called) an "aha!" moment when we can suddenly explain several puzzling facts simultaneously with the same answer. ***The sense that I had when I was experiencing some of these seizures was not unlike a continuous series of profound "aha!" moments.*** *Although nothing around me seemed to have changed in any concrete way, every observation of my surrounding environment seemed to "make sense" in this way. It is the sense, as I mentioned before, that one might have when admiring an expertly composed painting or photograph – each detail seems to be the way it is for a reason, even if that reason is difficult to articulate or seems only to float at the very edge of one's consciousness.*

"The great consilience, coherence, and vividness of everything in the world seemed to demand an explanation of its organization. And the explanation was immediate and completely convincing – some mind or purposive agency was at the root of the world's organization. This was a conviction that was both incredibly vague and totally compelling. Speaking as someone who is not normally given over to such beliefs – I am an atheist who happens also to be a professor specializing in logic – these beliefs are wildly out of character for me. ***But, looking back on these experiences, I am struck by two features of these beliefs, which I now believe may be related. First, they were absolutely immune to any rational doubt; indeed, they seemed not even to be possible candidates for any such doubt. Second, they seemed – perhaps ironically, given my earlier statement – to have many of the same features as the most justified, and rationally derived beliefs that a person could possibly hold****. For instead of merely being justified by one or several other considerations or observations, these seemed to be irrefutably supported by literally everything in the world. Literally everything that I could experience seemed to cohere with, and lend support to, the belief that there was some sort of agency behind it all. The level of apparent organization possessed by everything in the world simply demanded such an explanation."*

Both patients described a tremendous feeling of well-being and confidence during their ecstatic seizures. They felt no dissociation/detachment, no sexual feelings or any kind of "rush". Both described that time did seem to move very slowly, as if every moment was stretched out over a long period of time. Neither of the patients had used street drugs prior to having seizures.

3. Discussion

According to the description of the two patients of the present study, the cognitive phenomenon underlying the ecstatic symptom is a sense of "clarification"/"certainty" in relation to the present moment. The thought is devoid of any doubt, of any feeling of ambiguity, throughout the seizure. This analysis of the ecstatic feeling by these two patients is concordant with more common descriptions by previous patients of "complete fixation of the mind on the present moment without escape toward the past or the future" and of "absence of any problem, questioning or doubt".

Can the feeling of certainty reported by both patients explain a blissful state, and can it be related to an insular location?

Uncertainty, defined as a lack of information about an event, is a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing. The unavailability of information is treated as a negative characteristic of the environment.

For an optimal homeostasis (i.e., energy-efficient maintenance of our health), basic principles of self-organization are based on the imperative to minimize surprise (maximize evidence) associated with sensory states, by actively sampling the environment, and the imperative to minimize uncertainty about the inferred causes of that input, by making inferences about future states with the greatest possible precision or certainty (Friston et al., 2012). For this purpose, our brain makes use of a generalized predictive coding, which includes prediction error processing and leads to prediction error correcting mechanisms (see Fig. 2). An integrative computation of predictive and current states (or events) occurs continuously. The processing of prior beliefs about future states allows the uncertainty of posterior beliefs to be minimized: by an updating, posterior beliefs about the hidden states become progressively more confident and outcome tends to shrink to the expectation.

There is accumulating evidence for a role of the anterior insula in generalized prediction error coding. Besides its recognized role in interoception (Critchley et al., 2004; Craig, 2009) and in self-reflection processing (Modinos et al., 2009), a crucial role of the anterior insula in (emotional, sensory, …) state prediction/anticipation and in processing uncertainty in the context of decision making has been highlighted (Ploghaus et al., 1999; Nitschke et al., 2006; Singer et al., 2009). Functional imaging experiments in healthy participants have shown activation in the anterior insula both in the case of anticipation of resolution of uncertainty or risk (risk implying known alternatives, consequences and probabilities) and in the processing of risk prediction error, that is tracking of how accurate one's forecast was relative to outcome (Bossaerts, 2010). The anterior insula would act as a comparator between a predicted (anticipated) state and the upcoming outcome (« feedback »), that is the actual, experienced state (Fig. 2). In short, the anterior insula seems to be engaged in « signaling that we do not understand », i.e., that there is ambiguity. This role of the anterior insula in computation of predictive states and prediction errors allows for error-based learning. As an example, such a prediction-learning scheme, based on predictive coding and error processing mechanisms, helps for visual recognition in the visual cortex (Rao and Ballard, 1997, 1999), or, in the case of affect processing, by indicating continually how (in)accurate my certainty about the feeling state was, the comparator (the insula) helps to update the predicted state such that future predicted states will be more accurate (Singer et al., 2009). This model also applies to risk processing (Kuhnen and Knutson, 2005; Rushworth and Behrens, 2008). During gambling tasks, the anterior insula has been shown to encode the risk prediction when waiting for the outcome of a risky decision and to reflect the risk prediction error once the outcome was known, by acting as a comparator between predicted risk and realized risk (Preuschoff et al., 2008; Singer et al., 2009). The time course is consistent with a role in rapid updating. Brain activity during risk prediction and risk prediction errors was shown to be located in the very anterior part of the bilateral insulae, more dorsal for the prediction than for error processing (Preuschoff et al., 2008; Tang et al., 2011).

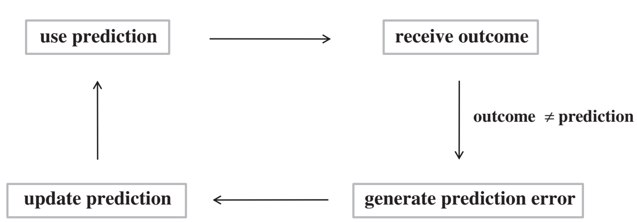

Fig. 2 – Brain mechanisms of online prediction updating by prediction error processing [scheme derived from possible role of dopamine neurons in error driven learning (Schultz, 1998)]. For each future state, the brain uses prediction, i.e., prior beliefs about future states. After receiving the experienced outcome, it compares outcome with prediction and generates prediction errors, allowing it to update future predictions. These mechanisms of predictive coding, aimed at adapting behavior, may be applicable across different modalities, whether in the context of sensory perception, interoceptive perception, affect, reward, risk,… In case of ecstatic seizures, we hypothesize that the dysfunction of the anterior insula would prevent the generation of errors. This would be tantamount to a state in which outcome = prediction, leading to unchanged prediction and to an unchanged behavior, and possibly a blissful state if long lasting.

Activation in the anterior insula can generate emotional negative arousal or anxiety in case of anticipation of negative outcome, anticipation of uncertain outcome, or in case of mismatch between anticipated and actual state (Wu et al., 2012; Knutson and Greer, 2008; Gray et al., 2007; Sarinopoulos et al., 2010). In decision making under risk, the activation of the anterior insula was also reported to scale the magnitude of unfairness, when using an ultimatum game experiment (Sanfey et al., 2003) or skewed gambles (Wu et al., 2012).

Some authors have suggested a role of the insula in the generation of intuitive, « feeling-based » decision making, or intuitive beliefs when not enough information about outcomes is available (Pushkarskaya et al., 2010). Thereby De Ridder et al., who postulated that brain's main function is to reduce environmental uncertainty, suggested that phantom percepts observed in the case of sensory deafferentation relate to a filling in, through the activation of the insula, in order to reduce uncertainty, to make sense of the world (De Ridder et al., 2012). In the same way, Harris et al. (Harris et al., 2008) stated that the human brain is "a prolific generator of beliefs, as personhood is largely the result of the capacity of a brain to evaluate new statements of propositional truth in light of countless others that it already accepts" (Harris et al., 2008). They suggested that the final acceptance of a statement as "true" or its rejection as "false" relies particularly on the anterior insula and that the insula constitutes an important region mediating belief, disbelief and uncertainty. Kapogiannis et al. even showed that disagreeing with religious statements engaged bilateral anterior insulae (Kapogiannis et al., 2009).

The concept of insight is very close to that of certainty. Insight involves problem solving that happens all-of-a-sudden through understanding the relationships of the various parts of a problem rather without a process of trial and error. It is a sort of acute deduction. Insight solutions are commonly called "aha!" moments. Archimedes provided the archetypal story of the "aha!" moment when he discovered the principle of displacement and then ran down the street shouting ''Eureka!'' (Aziz-Zadeh et al., 2009). Here, patient 2 described his ictal symptoms as a succession of "aha!" moments. The anterior insula, classically shown to signal "that we do not understand", that there is ambiguity, has also been involved in this diametrically opposed situation. A functional MRI (fMRI) study using a verbal task (anagrams) showed an early bilateral insular activation during insight solutions (Aziz-Zadeh et al., 2009).

In ecstatic seizures, our hypothesis is that the comparator between the predicted state and the actual state (anterior insula) no longer functions. As patients with ecstatic seizures have a feeling of clarity, certainty, and of full understanding of self, others and the environment, it seems that the predicted states are preserved, as well as the (sensory) feedback of the upcoming outcome, which is necessary to elicit prediction errors. Yet a dysfunction at the level of the comparator will inhibit information processing and thus preclude any mismatch detection between predicted state and actual state. It is expected that the integrated feeling state including close predictive and current feeling states (with very low feeling prediction errors) will be experienced as emotional confidence. Thus a dysfunction of the anterior insula could explain the feeling of meaningfulness, a sort of « clairvoyance » or almost anticipation reported by patient 1 (« without it being a sensation to know the future »). By blocking the generation of mismatches, the seizure would block negative emotions and negative arousal arising from predictive uncertainty. The long-lasting state without any mismatch, with the preservation of unchanged prediction for several seconds, is a sort of plunge into contemplation, and can be close to the confidence and serenity state observed in meditative states, experienced as blissful in the deeper states (Aftanas and Golocheikine, 2001).

Some neuropsychiatric conditions include an intolerance to uncertainty. Neuroticism, characterized by the tendency to experience negative emotional states, demonstrated greater right anterior insula activation during decision making, even when the outcome of the decision was certain (Feinstein et al., 2006). The corresponding "subjective uncertainty" seemed to be due to a response latency for certain decisions which approached the response latency for uncertain decisions, in such a way that the brain could interpret certainty as uncertain. In anxiety disorders, the intolerance of uncertainty is a hallmark of the inability of patients to tolerate the sensations that are evoked by ambiguous situations. Several studies pointed to altered insular function being a feature of many of the anxiety disorders, with a heightened activity in the anterior insula during processing of certain kinds of salient stimuli in individuals prone to anxiety (Paulus and Stein, 2006). In case of mismatch between predicted state and actual state, enhanced anterior insula activity may even correlate with the interpretation of neutral stimuli as threatening, evoking anxiety and avoidance behavior (Paulus and Stein, 2006). In one study the neural signal in (mid-)insula was shown to increase with increasing intolerance to uncertainty during an affective ambiguity task (Simmons et al., 2008). Obsessive compulsive disorder (OCD), a disorder specifically characterized by a greater subjective experience of doubt, could constitute the state opposite to that observed during ecstatic seizures. Interestingly, an altered pattern of insular activity in OCD patients was shown to correlate with exaggerated prediction error signals and/or greater autonomic arousal during cognitive control, compared to healthy subjects (Cocchi et al., 2012). In an error-eliciting interference task, OCD patients showed greater activation in left anterior insula and frontal operculum across all errors (Stern et al., 2011). These functional findings have a morphometric correlation: OCD patients with predominant checking symptoms have a significantly larger gray matter volume in the anterior insular cortex bilaterally (Song et al., 2011; Nishida et al., 2011).

Finally, the ictal involvement of the insula in both patients of the present study was further suggested by the accompanying ictal symptoms. Patient 1 described gustatory hallucinations. The primary gustatory cortex has been located within the anterior insula, at the caudal section of the anterior dorsal insula according to some studies (Small, 2010), or at its junction with overlying frontal operculum and the dorsal mid-insula and overlying rolandic operculum (Veldhuizen et al., 2011). While activation of the insula has been traditionally linked to aversive stimuli and negative emotions like disgust (Wicker et al., 2003), the stimulation of the insula may induce gustatory sensations (Ostrowsky et al., 2002), as the "goût curieux", disagreeable taste, reported in one case (G.B.) by Penfield and Faulk (Penfield and Faulk, 1955).

Patient 2's auditory illusions/hallucinations may also implicate the temporo-insular region. Auditory responses were shown to represent 10% of the evoked responses during stimulations of insular (and circuminsular, i.e., temporo-opercular) regions (Penfield and Faulk, 1955), and particularly its ventral part (Isnard et al., 2004).

The first seizures of patient 2 were associated with horrible feelings, at the extreme opposite of ecstatic seizures in terms of emotion. Such alternating unpleasant and ecstatic symptoms have already been reported in some patients (Stefan et al., 2004; Williams, 1956). This could be due to an opponent organization with mutual inhibition between right and left anterior insula, so that the balance between the two sides may be crucial for induction of positive or negative emotions (Picard and Craig, 2009).

4. Conclusions

Both patients in the present study spontaneously described a feeling of "certainty" during ecstatic seizures. We suggest that abnormal insular activity during an epileptic seizure may prevent any prediction error processing, or ambiguous information processing, generated by the insula. This could give the patient an impression of a link between all perceptions with a logical thread, creating a (morbidly constructed) complete clarity and coherence. While ambiguity and uncertainty are unpleasant and have been characterized as an aversive state which can cause stress (Sarinopoulos et al., 2010) that people are motivated to reduce (Bar-Anan et al., 2009), a state of certainty may promote a sustained feeling of serenity, an experience that we do not usually have the opportunity to know in our normal lives. This could lead to a spiritual interpretation in some individuals.

In conclusion, these cases lead to novel suggestions on the link between ecstatic seizures and the processing or absence of processing of ambiguous information, which could be further investigated in the future by designing decision making tasks that involve risk and uncertainty. More generally, these observations raise questions about the possible link between the prediction error processing brain mechanisms and the proneness to happiness.

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