Phases in the decision to request euthanasia and brain structures involved

Jose M. Trejo-Gabriel y Galán, Adrián Alacreu-Crespo, Esther Cubo-Delgado

Introduction. Euthanasia laws do not mention as an obstacle brain diseases other than dementia that damage circuits involved in decision-making.

Development. Narrative review of the stages of the decision to request euthanasia and the brain areas involved. The amygdala, the cingulate and insular cortex, and different parts of the prefrontal lobes are activated during decisions with similarities to that of requesting euthanasia.

Conclusions. When an injury or malfunction of any of the structures involved in making decisions is known, a specific evaluation should be made of the influence it may have on the competence of the patient to request euthanasia.

Key words. Amygdala. Competence. Decision making. Euthanasia. Neuropsychology. Prefrontal lobe.

Neurology Departement. Hospital Universitario de Burgos. Burgos (J.M. Trejo-Gabriel y Galán, E. Cubo-Delgado). Laboratory of Cognitive-Social Neuroscience, Psychobiology-IDOCAL. Facultad de Psicología. Universidad de Valencia. Valencia, Spain (A. Alacreu-Crespo). IGF. Université de Montpellier (A. Alacreu-Crespo). CNRS-INSERM and Department of Emergency Psychiatry and Acute Care. Hospital Lapeyronie. CHU Montpellier. Montpellier, France (A. Alacreu-Crespo).

Correspondence:
Dr. Jose M. Trejo Gabriel y Galán. Servicio de Neurología. Hospital Universitario de Burgos. Av. Islas Baleares, 3. E-09006 Burgos.

E-mail:
jtrejogyg@gmail.com

Accepted:
14.12.21.

Competing interests:
None declared.

How to cite this article:
Trejo-Gabriel y Galán JM, Alacreu-Crespo A, Cubo E. Phases in the decision to request euthanasia and brain structures involved. Rev Neurol 2022; 74: 61-5. doi: 10.33588/rn.7402.2021416.

Versión española disponible en www.neurologia.com

Introduction

Euthanasia laws in general, including the recently approved in Spain, exclude people with dementia [1,2]. However, to assess the validity of a request for euthanasia or assisted suicide, diseases that may damage the circuits involved in decision-making should also be taken into account. Therefore, we review in a simplified way these circuits, the structures that are part of them, the decision stages, and interventions that may help the patient at each stage.

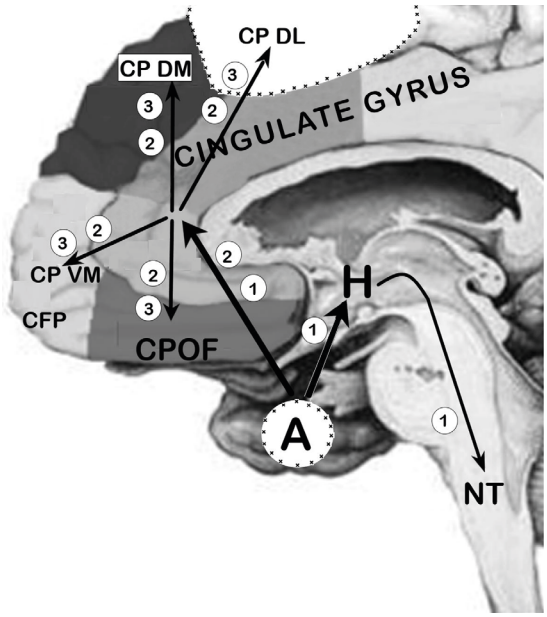
Development

We have made a narrative review of the brain structures that participate in complex decisions with some characteristics of the decision to request euthanasia and also reviewed the diseases of these structures that can therefore influence the request for euthanasia. A decision consists of choosing between 2 or more options after considering that it will lead to different consequences either in the short or long term [3]. Decisions are made to obtain a reward or to escape from an aversive stimulus. Euthanasia belongs to this second group of decisions since the patient decides to escape from unbearable physical or psychological pain. We have divided this decision-making process into three successive stages: perception of an 'afferent' stimulus or situation, cognitive-emotional processing, and 'efferent' response (final decision). Unlike simple or conditioned reflex responses, in each of the three stages the cognitive and emotional processes that operate are complex and variable depending on the environment and the subject, so that in similar situations, decisions may not be the same. What we know about how different brain structures participate in decisions is extrapolated from animal models, from subjects with lesions in these brain areas, and from brain imaging and metabolic studies in healthy subjects. The process of deciding on euthanasia has some peculiarities compared to other previous decisions of the individual: the 'afferent' situation, in general a progressive disease, is new and overwhelmingly aversive, the mental processing does not lead to a solution given the incurability of the disease and a mistaken decision cannot be ammended once euthanasia is performed.

Afferent phase

The first part of the 'afferent' phase begins when symptoms of the disease are perceived, which elicit fear without awareness of what the threat is, as the diagnosis of a specific disease has not yet been communicated. Initially, the amygdala (the 'fear nucleus' in the depth of the temporal lobe) is acti-

Figure. Structures involved and phases in the decision to request euthanasia.



Structures: A: amygdallar nucleus; H: hypothalamus; NT: brainstem nuclei of the autonomic nervous system; CP DM: dorso-medial prefrontal cortex; CP DL: dorsolateral prefrontal cortex (not visible in sagittal section); CP VM: ventro-medial prefrontal cortex; CP OF: orbito-frontal prefrontal cortex; CFP: frontopolar cortex. Decision phases: 1. 'Afferent' phase; 2. 'Processing' phase; 3. 'Efferent' phase (firm decision). Simplified diagram showing only some connections between the marked areas. Figure with Creative Commons BY license, modified [27].

vated and through it the lateral hypothalamus [4] (with activation of sympathetic nerves) (Figure) and also activates the hypothalamic paraventricular nucleus (with corticotrophin and consequently cortisol discharge to the bloodstream). This prepares the body for a 'fight or flight' response, but not being possible to respond effectively to an incurable disease, the activation is permanent and exhausts the patient [5], which can in turn worsen the disease. When the physician communicates the diagnosis and prognosis to the patient the unconscious fear of the unknown decreases, hence the importance of a complete information communicated that should be in phases to facilitate its acceptance by the patient [6]. But upon receiving the news of an incurable disease, a fear of something known but unsolvable becomes conscious, while the amygdala activates the cingulate cortex [7] (Figure). Not all subjects will experience the same, because according to past experiences, different patterns will be stored in the amygdala, which, activated by current experience, will trigger fear [8] and therefore the amygdala and its projection to the cingulate gyrus (Figure) are the main structures involved in the 'afferent' phase of the decision. Left or bilateral amygdalar lesions eliminate not only learned fear responses but also innate fear responses [7]. Such lesions may be due to the very selective of the amygdala but infrequent Urbach-Wiethe disease [9] or to temporal lobe lesions that encompass the amygdala such as herpes simplex or autoimmune encephalitis, resection of the temporal lobe for treatment of refractory epilepsy, strokes, trauma or tumors (Table). Lesions of the cingulate gyrus occur in infarcts in the territory of the anterior cerebral artery, in aneurysms of the anterior communicating artery and in tumors. If there is a cingulate lesion, the conscious discomfort characteristic of fearful situations will not be felt. Although anxiety / fear and its consciousness can also be non-adaptive and pathological, they have a protective physiological function, the absence of which could lead to underestimating the severity of the decision of requesting euthanasia, aspects that have not been sufficiently studied. The physical suffering that most frequently leads to requesting euthanasia is pain, and the disease cancer, responsible for 70% of euthanasias [10]. Other aversive physical stimuli can be inferred from the symptoms of the diseases for which euthanasia is requested. Neurological diseases are the second group of diseases for which euthanasia is requested, particularly amyotrophic lateral sclerosis, stroke, multiple sclerosis, Huntington's disease, and Parkinson's disease [1]. In them, the aversive situation is the loss of mobility or its control, of speech or language, and in incipient dementia, the fear of cognitive worsening. Cardiovascular and pneumological diseases with their manifestations of dyspnea and consequent mobility limitation are the third cause of request for euthanasia. Blindness and deafness are less frequent reasons. But when patients who request euthanasia are asked why they do so, they do not usually mention symptoms (except when in pain) but instead the repercussions of the disease on their lives, with phrases that have in common the word 'loss' (loss of independence, of quality of life, of desire to live, of dignity or loss of control) [11]. While experiencing loss or grief, additionally to the cingulate, the insular cortex is activated [12]. The latter is dysfunctional in suicidal patients and has special relevance in the processing of both physical and psychological pain, whose intensity is known as the main determinant of suicide attempts [3,13]. Stroke, tumors, or encephalitis frequently damage

the insula (Table). But euthanasia and suicidal behaviors, in addition to the intensity of suffering, depend on the ability to overcome it (resilience), which seems to improve with physical exercise and training in coping strategies, instruments that the professional can use at this stage, in addition to the mentioned, complete information and pain management. In practice, the subject repeatedly feels his symptoms and situation, processes them and feels them again, so that the afferent and processing stages become inseparable.

Table. Common neurological diseases of the temporal or prefrontal lobe.

Amygdalar lesions (in temporal lobe)	Prefrontal lobe, cingular and insular gyri lesions
Herpes simplex encephalitis	Severe cranioencephalic trauma
Autoimmune encephalitis	Frontal-temporal dementia
Resection of the temporal lobe for treatment of refractory epilepsy	Infarction in the territory of the anterior cerebral artery
Benign or malignant tumors of the temporal lobe	Subarachnoid hemorrhage due to aneurysm of the anterior communicating artery
	Benign or malignant frontal lobe tumors
	Ischemic leukoencephalopathy of frontal location
	Isular injury due to stroke, tumor or herpes simplex encephalitis

Processing phase

Human decisions are influenced by the aforementioned 'fight or flight' response mediated by fast subcortical circuits, response that depends on how the 'afferent' situation has been 'marked' by the amygdala and the autonomic nervous system [14]. But these influences will be modulated in the specific circuits to plan and decide: the prefrontal lobes. These are activated when the terminal patient foresees his future life and weighs decisions to improve his situation, but unlike in previous adversities, he/she will not be able to make the current or future repercussions of the disease disappear whatever he/she does. This can inhibit any adaptive behavior, as it happens in experimental animals that cannot avoid punishment in the 'learned helplessness' paradigm [15], an experimental model of depression in which the activity of the lateral nucleus of the habenula is increased [16]. In fact, the most frequent reason why patients in palliative care centers want their life to end as soon as possible is not pain, but hopelessness or awareness of the futility of their actions to avoid the repercussions of the disease, to which sometimes depression is added [17,18,19]. The prefrontal and cingulate cortex are necessary to perceive pain as suffering, since pain continues to be perceived but is no longer interpreted as suffering after prefrontal or cingulate lobotomy [20]. The feelings of dignity and meaning are based on self-awareness, which activates the frontopolar cortex of the prefrontal lobe, especially on the right side [21]. Thus, health professionals can help these patients by acknowledging the value of their past, present and future life. Also, by means of the prefrontal lobe the subject can plan [22] what to do in the time left before his death and about its circumstances. The subject will feel more control over his life, and if he decides to request euthanasia it will be later and not out of desperation. Diseases that damage the prefrontal lobe, whether traumatic, degenerative, vascular, infectious or neoplasic (Table) will interfere with decision-making. A socially based motive that people requesting euthanasia mention is 'being dependent' or 'being a burden to others'. The perception of social rejection activates the orbito-frontal and ventro-medial prefrontal cortex, in anatomical continuity with the cingulate cortex, which is instrumental in the awareness of emotions (Figure). Subjects with a fatal disease such as cancer usually go through five successive psychological phases [23]: denial, anger, negotiation, sadness and acceptance, and not reaching this last phase can lead to request euthanasia early on. We could speculate in a simplistic way that during the denial and anger phases the activation of the amygdala and the autonomic nervous system predominates, during sadness the cingulum and insula activation, while in the negotiation and acceptance phases the prefrontal lobe is the most active. If during the processing stage the subject finds no alternative but to die in order to alleviate a suffering for which he does not have sufficient resilience, he will go to the last stage of requesting euthanasia.

Efferent phase

In the 'efferent' phase of the request for euthanasia, the patient only sees a perverse crossroad: euthanasia or intolerable suffering impossible to avoid. The lack of mental flexibility can prevent him from looking at other alternatives that, while not solutions to the disease, can make the time left worth living it. Also, the impulsive patient may want to quickly escape the aversive situation through euthanasia. Frequently, lack of flexibility and impulsivity go hand in hand when there is a malfunction of structures involved in decision-making such as

the ventral prefrontal cortex (more when it is the right) and its connections with the nucleus accumbens, the amygdala and the striatum [24]. Since 'mental rehearsals' of decisions are made in the processing phase, the structures that are involved then are also activated in the final decision. There are brain diseases without macroscopic structural damage in which impulsivity is increased. This is the case of Parkinson's disease treated with dopamine agonists and Gilles de la Tourette's disease in which there is dysfunction of subcortical dopamine circuits. Also, of impulse control disorders included in mental illnesses, such as pathological gambling, kleptomania, trichotillomania, excoriation disorder, intermittent explosive disorder, pyromania and oppositional disorders, defiant behavior, attention deficit- hyperactivity and antisocial personality. Psychiatric patients can have additional dysfunctions to impulse control that can interfere with conscious, free and reflective decisions, which is why their requests for euthanasia are only accepted in the Netherlands and Belgium. The amygdala protects against decisions that are harmful to our body such as suicide or euthanasia through fear of harm, which in injuries of the amygdala could be reduced. But it is diseases that damage the prefrontal lobe (Table) that can most easily lead to 'non-reflective' decisions of any kind [25], which can include the request for euthanasia, and prefrontal deficits can go unnoticed in a conventional interview. Making a parallel with survivors of suicide attempts, these subjects make riskier decisions, without aversion to losses and in a more impulsive way [26]. This type of faulty decision-making can be measured by the specific Iowa Gambling Test that measures prefrontal functioning, and in which people with suicidal behavior have low scores [13]. A patient with an injured orbitofrontal cortex may make riskier and / or impulsive decisions, since this area of the prefrontal lobe will not be able to exercise its controlling function consisting of deferring an immediate reward (in this case the relief of suffering) when there is a greater subsequent punishment (death) [25]. Finally, when the competent patient has made a firm decision to request euthanasia, the doctor, even if he/she does not agree with it or does not participate in the process, can only show respect and empathy.

One limitation of this review is that, because it does not seek to answer a single question, it cannot be systematic. For the sake of clarity and brevity, the description has been simplified, omitting some of the experimental data and connections between the brain structures mentioned.

Conclusions

In the process of requesting euthanasia, the amygdala, cingulate cortex, and insula are initially activated, followed by different areas of the prefrontal lobe that are responsible for conscious evaluation, planning, and decision-making. In cases of suspected malfunction of these structures, a specific neuropsychological assessment is advisable to assess whether the patient is competent to make this irreversible decision.

References

1. Steck N, Egger M, Maessen M, Reisch T, Zwahlen M. Euthanasia and assisted suicide in selected European countries and US states: systematic literature review. Med Care 2013; 51: 938-44.
2. Ley Orgánica 3/2021, de 24 de marzo, de regulación de la eutanasia. «BOE» núm. 72, de 25 de marzo de 2021, p. 34037 a 34049. URL: https://www.boe.es/eli/es/lo/2021/03/24/3. Last consultation date: 02.04.2021.
3. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neurosci 2005; 11: 1458-63.
4. Gupta R, Koscik TR, Bechara A, Tranel D. The amygdala and decision-making. Neuropsychologia 2011; 49: 760-6.
5. Peters A, McEwen BS, Friston K. Uncertainty and stress: why it causes diseases and how it is mastered by the brain. Prog Neurobiol 2017; 156: 164-88.
6. Calzada Sierra DJ. Algunas consideraciones bioéticas en el abordaje de los pacientes con esclerosis lateral amiotrófica. Rev Neurol 2001; 32: 952-7.
7. Iversen S. Emotional states and feelings. In Kandel ER, ed. Principles of neural science. 4 ed. New York: Mc Graw Hill; 2000. p. 982-97.
8. Damasio AR. Toward a neurobiology of emotion and feeling: operational concepts and hypotheses. The Neuroscientist 1995; 1: 19-25.
9. Siebert M, Markowitsch HJ, Bartel P. Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. Brain 2003; 126: 2627-37.
10. Emanuel EJ, Onwuteaka-Philipsen BD, Urwin JW, Cohen J. Attitudes and practices of euthanasia and physician-assisted suicide in the United States, Canada, and Europe. JAMA 2016; 316: 79-90.
11. Chapple A, Ziebland S, McPherson A, Herxheimer A. What people close to death say about euthanasia and assisted suicide: a qualitative study. J Med Ethics 2006; 32: 706-10.
12. O'Connor MF. Immunological and neuroimaging biomarkers of complicated grief. Dialogues Clin Neurosci 2012; 14: 141-8.
13. Alacreu-Crespo A, Olié E, Seneque M, Béziat S, Guillaume S, Costa R, et al. Decision-making skills moderate the relationship between psychological and physical pain with suicidal behavior in depressed patients. Psychother Psychosom 2019; 88: 190-1.
14. Damasio AR, Tranel D, Damasio H. Somatic markers and the guidance of behaviour: theory and preliminary testing. In Levin HS, Eisnberg HM, Benton AL, eds. Frontal lobe function and dysfunction. New York: Oxford University Press; 1991.
15. Yan HC, Cao X, Das M, Zhu XH, Gao TM. Behavioral animal models of depression. Neurosci Bull 2010; 26: 327-37.
16. Li B, Piriz J, Mirrione M, Chung C, Proulx CD, Schulz D, et al. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. Nature 2011; 470: 535-9.

17. Dees MK, Vernooij-Dassen MJ, Dekkers WJ, Vissers KC, van Weel C. 'Unbearable suffering': a qualitative study on the perspectives of patients who request assistance in dying. J Med Ethics 2011; 37: 727-34.
18. Breitbart W, Rosenfeld B, Pessin H, Kaim M, Funesti-Esch J, Galietta M, et al. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA 2000; 284: 2907-11.
19. Chochinov HM, Wilson KG, Enns M, Lander S. Depression, Hopelessness, and suicidal ideation in the terminally ill. Psychosomatics 1998; 39: 366-70.
20. Freeman W, Watts W. Pain of organic disease relieved by prefrontal lobotomy. Proc Roy Soc Med 1946; 39: 445-7.
21. Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. Annu Rev Psychol 2002; 53: 401-33.
22. Manes F, Sahakian B, Clark L, Rogers R, Antoun N, Aitken M, et al. Decision-making processes following damage to the prefrontal cortex. Brain 2002; 125: 624-39.
23. Saracino RM, Rosenfeld B, Breitbart W, Chochinov HM. Psychotherapy at the End of Life. Am J Bioeth 2019; 19: 19-28.
24. Clark L, Cools R, Robbins TW. The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. Brain Cogn 2004;55: 41-53.
25. Schiebener J, Brand M. Decision making under objective risk conditions-a review of cognitive and emotional correlates, strategies, feedback processing, and external influences. Neuropsychol Rev 2015; 25: 171-98.
26. Cáceda R, Durand D, Cortes E, Prendes-Alvarez S, Moskovciak T, Harvey PD, et al. Impulsive choice and psychological pain in acutely suicidal depressed patients. Psychosom Med 2014; 76: 445-51.
27. Northoff G. Brain and self - a neurophilosophical account. Child Adolesc Psychiatry Ment Health 2013; 7: 28.

Fases en la decisión de solicitar la eutanasia y estructuras cerebrales involucradas

Introducción. Las leyes de eutanasia no mencionan como obstáculo las enfermedades cerebrales diferentes de la demencia, pero que dañan los circuitos involucrados en la toma de decisiones.

Desarrollo. Revisión narrativa de las etapas de la decisión de solicitar la eutanasia y las áreas cerebrales involucradas. La amígdala, la corteza cingulada, la ínsula y distintas partes de los lóbulos prefrontales se activan durante decisiones con similitudes a la de solicitar la eutanasia.

Conclusiones. Cuando se conoce una lesión o mal funcionamiento de alguna de las estructuras involucradas en la toma de decisiones, se debe realizar una evaluación específica de la influencia que pueda tener en la competencia del paciente para solicitar la eutanasia.

Palabras clave. Amígdala. Competencia. Eutanasia. Lóbulo prefrontal. Neuropsicología. Toma de decisiones.