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Cranial trepanation and healing process in modern patients— Bioarchaeological and anthropological implications

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Abstract

The diagnosis of cranial trepanation in the archaeological record has always been a big challenge for archaeologists. The identification is first and foremost based on the shape and edges of the opening, and in cases where the individual survived, the shape and edges resulted from both the surgical procedure and the healing process. Because of the lack of reliable data on the osseous remodelling process of the skull, it is difficult to distinguish true trepanations from some pathological or physiological defects called pseudotrepanations. Furthermore, it is challenging to investigate the post-operative survival time. The purpose of this paper was to summarize observations made on a total of 90 archaeological samples of cranial lesions interpreted as 'partially' or 'completely' healed trepanations, and compare them with 14 modern case studies. Observations made on monitoring post-operative scans of modern patients, at varying times after craniotomy, provided a preliminary timetable for the successive post-surgery bony changes in the skull, and confirmed that the process of osseous remodelling does lead to smooth and rounded edges of the profile of the opening. However, contrary to what has been observed in several archaeological case studies, none of the cases shows a complete closure of the cranial vault. The sharp vertical edges of the opening become bevelled at late stages of healing, which has to be taken into consideration when interpreting the procedures and methods in past population. By bridging bioarchaeology and medical sciences, this study adds to previous discussions on the diagnosis of healed trepanation in the archaeological record, by providing detailed descriptions of morphological changes at various healing stages, that may help archaeologists to identify ancient trepanations more accurately.

KEYWORDS

differential diagnosis, modern CT scanning records, paleopathology, positive diagnosis, post-surgery cranial bony changes, pseudotrepanation

1 | INTRODUCTION

Trepanation is a surgical procedure commonly performed on the cranium *in vivo*, which is long known to have prehistoric

origins (Prunières, 1874; Broca, 1877; Manouvrier, 1903; Lucas-Championnière, 1912). However, the issue of a reliable diagnosis in archaeological contexts remains problematic, particularly in cases that showed signs of healing. The oldest archaeological cases

diagnosed as healed trepanation date between 10,000 and 5000BC (e.g. Ferembach *et al.*, 1962; Alt *et al.*, 1997; Lillie, 1998, 2003; Alt and Jeunesse, 2006). Moreover, trepanation is a worldwide practice, as it has been identified in sites across Europe, the Middle East, Asia, Africa, Australia (e.g. Zias, 1982; Webb and Thorne, 1985; Webb, 1988; Baggieri and Giacomo, 2003; Bennike, 2003; Murphy, 2003; Han and Chen, 2007; Mountrakis *et al.*, 2011; Martin, 2013; Chikisheva *et al.*, 2014; Krivoshepa *et al.*, 2014; Slepchenko *et al.*, 2016) and the Americas (e.g. Lisowski, 1967; Sankhyan and Weber, 2001; Verano, 2003; Tiesler Blos, 2006; Nystrom, 2007; Andrushko and Verano, 2008; Verano and Andrushko, 2008; Kurin, 2013; Toyne, 2015; Verano, 2017). Current evidence indicates that trepanation had become a relatively common practice during the Neolithic period (e.g. Broca, 1876; Rakowsky and Roudenko, 1914; Pales, 1944; Dastugue, 1973; Brenot and Riquet, 1977; Jamet, 1998; Weber and Wahl, 2006; Lv *et al.*, 2013; Beyneix, 2015; Petrone *et al.*, 2015) and the Bronze Age (e.g. von Lettow-Vorbeck and Pastor Abascal, 2003; Silva, 2003; Açıkkol *et al.*, 2009; Papagrigorakis *et al.*, 2014), but the practice persisted till more recent periods, especially during the Antiquity (e.g. McKinley, 1992; Roberts and McKinley, 2003; Nikita *et al.*, 2013; Tsermoulas *et al.*, 2014) and the Middle Ages (e.g. Smrčka *et al.*, 2003; Bereczki and Marcsik, 2005; Mariéthoz and Curdy, 2005; Holck, 2008; Rubini, 2008; Fabbri *et al.*, 2012; Thompson, 2013; Simalcsik *et al.*, 2014).

In fully skeletonized specimens, the identification of trepanation is usually based on the shape and cutting profile of the cranial opening (Verano, 2016; Partiot *et al.*, 2017), resulting from both the surgical procedure itself and, if presence, any bony remodelling from the healing process. Therefore, a comprehensive knowledge of the morphological features of the cranial opening at each stage of the healing process is crucial for a differential diagnosis. However, in the absence of a reliable means of gauging the time required for osseous remodelling, it remains difficult to investigate the post-operative survival time.

Under normal circumstances on post-cranial skeletal elements in healthy adults, especially long bones, healing of fractures follows a three-stage process. The first stage is initiated by an inflammatory state with the formation of a hematoma from day 1 to day 21, which is colonized by stem cells and monocytes. The second stage, between day 2 and 3 weeks after the injury, includes the formation of a cartilaginous callus by differentiated stem cells. In the third state, this callus will then start to be ossified from the 4th week onwards, and continued to remodel until the fracture is healed, which can last for many months (Barbian and Sledzik, 2008).

However, the osteogenic activity has been reported to be less active on cranial bones compared to those of the long bones (Sevitt, 1981; Barbian and Sledzik, 2008). The long bone healing process re-establishes the bony structure through the influence of heavy and prolonged mechanical stimulation, such as walking and grasping (Buckwalter and Grodzinsky, 1999; Einhorn and Gerstenfeld, 2014; Standing, 2015). In contrast, the cranial vault is only affected by the localized impact of the temporalis and occipitofrontalis muscles through the epicranial fascia, and the indirect influence of others

muscles, such as the masseter, the splenius capitis and the trapezius (Jia-Deleglise, 2003; Standing, 2015). Thus, cranial healing and remodelling proceed differently than those observed in the post-cranial skeletal elements (Pritchard, 1946; Sevitt, 1981; Barbian and Sledzik, 2008). However, an extensive bibliographic review reveals a lack of information on the topic of timing and morphological features of post-trepanation healing, despite the antiquity of the procedure, and the routine neurosurgical operations performed today that include craniotomies. Several studies of archaeological trepanations suggested a survival time that, unfortunately, has not been supported by experimental evidence. In most cases, scholars only drew a distinction between a 'short' and a 'long' healing time, but with no substantiated arguments (Alt *et al.*, 1997; Lillie, 2003; Alt and Jeunesse, 2006; Mogliazza, 2009; Erdal and Erdal, 2011; Nikita *et al.*, 2013; Moghaddam *et al.*, 2015; González-Darder, 2016; Gresky *et al.*, 2016; Silva *et al.*, 2016; Kushner and Verano, 2017).

Experimentation has been conducted in rats (Pritchard, 1946; Simpson *et al.*, 1953; Girgis and Pritchard, 1958), but at the best of our knowledge, data on human macromorphological features of cranial healing remain scarce. Studies on biopsies and necropsies mostly deal with repair process after burn injury (Worthen, 1971; Fabian and Sevitt, 1978; Sevitt, 1981), as well as accidental fractures (Sevitt, 1981). One study reports the osseous response following cranial gunshot wounds based on a Civil War skeletal collection stored at the National Museum of Health and Medicine, Armed Forces Institute of Pathology (Barbian and Sledzik, 2008). This collection provides detailed information regarding the nature of the injury, the survival time and any medical procedures applied to the patient. However, we argue that the timing and patterning of the osseous responses, and any resulting infection processes following a high-speed impact from a projectile are fundamentally different than those resulted from trepanation, and therefore cannot be compared directly.

In our view, the work by Nerlich *et al.* (2003) is the only study that documents the macromorphological features of craniotomies, made on healthy bone (intact or, in one very particular case, damaged after a trauma that did not result from a gunshot or a burn wound) at different stages of the healing process, based on data collected during autopsies of modern case studies. Excluding the first case study where a patient died during surgery, the paper reports on a total of 1 fractured and 9 trepanned crania of present-day individuals, who survived from a few hours to 34 years after craniotomy. All the patients had surgery in adulthood except one, who died 34 years after an operation performed at the age of three.

The first purpose of the present paper was to substantiate the results of Nerlich *et al.* (2003) by including CT scanning records to comparatively assess post-surgery cranial bony changes based on other modern cases. The sample set consists of medical post-operative CT scans of 4 living patients taken at various times after surgery to monitor the healing of their cranial lesions. This approach is advantageous in several respects. First, as the same trepanation is monitored over time on several occasions, this approach will permit a diachronic observation of the healing process, which is impossible for autopsied cases. Second, as more and more studies of

archaeological cases employ CT scanning to assess lesions (Alt *et al.*, 1997; Alt and Jeunesse, 2006; Mountrakis *et al.*, 2011; Papagrigorakis *et al.*, 2014; Tsermoulas *et al.*, 2014; Gresky *et al.*, 2016), it is imperative to explore the internal structure of the craniotomy margins in modern cases.

The goal of this paper was, first, to provide a critical review of what defines a 'healed trepanation' in archaeology, according to the observed macromorphological features of cranial lesions. Second, the dynamic observation of the healing process on modern cases will allow the describing of specific macroscopic signs of healing in their orders of appearance. The improvement in the chronological resolution of the post-operative healing process in modern individuals, and the identification of the presence or absence of these macroscopic signs on archaeological cases will improve our positive and differential diagnosis of healed trepanation.

2 | MATERIAL AND METHODS

The materials involved in the critical review of what defines a 'healed trepanation' in the anthropological literature came from an extensive literature review and consisted of 90 archaeological cases of cranial openings. These cases come from 46 references, and are either interpreted as 'partially' or 'completely' healed trepanations (Appendix S1). These cases are selected according to three criteria: first, all cases are identified in adults as healed trepanations through positive or differential diagnosis, using macroscopic, radiographic or microtomodensitometric analysis; second, samples are reasonably well preserved; and lastly, accessibility of the illustrations of the lesions. As the 90 case studies covered a wide chronogeographical framework (from the Neolithic to the Contemporary Period in Europe, Asia, America, Oceania and Africa), we considered them representative of the general morphological variability observed in most cases of healed trepanations in past populations.

The dynamic observation of the healing process on modern cases used to discuss the diagnosis of healed trepanations in past population is based on post-operative CT scans from four present-day patients from the Hôpital Pellegrin in Bordeaux, France. We performed a retrospective cohort study of patients who underwent at least one craniotomy and post-operative CT scan for different brain lesions. All data were gathered and analysed following the guidelines set by the hospital's ethics committee.

Medical data acquired by industrial medical CT equipment (BRILLIANCE 40, Phillips©) of thirty patients were analysed, only data from four adults are discussed in this study, since they were the only ones to have underwent at least two CT scans after the surgery. In these four cases, the bone flaps removed were reinstated after the surgery. The post-operative images were analysed using a picture archiving and communication system (PACS) on a workstation by one of us (ED) at the Hôpital Pellegrin.

A sample of images of craniotomies are gathered from the four individuals, over a total of nine different post-operative states, ranging from 4 days to 5 years after surgery. As the CT scans come from

TABLE 1 Information on the CT scans of the modern cases studied in our sample

Cases	Time after surgery	Sex	Age (in years)	Location of the craniotomy
P1a	+5 days	F	[45-50]	Temporal
P1b	+39 days			
P2a	+4 days	F	[55-60]	Frontal
P2b	+35 days			
P3a	+7 days	F	[75-80]	Temporal
P3b	+5 months			
P3c	+20 months			
P4a	+10 days	M	[55-60]	Parietal
P4b	+59 months			

Note: Time after the surgery, sex and age of the patients, and the locations of the craniotomy.

the post-operative follow-up of four patients, intra-individual observations of healing could be observed in two or three stages (Table 1). In order to grant anonymity, the age of the patients at the time of the surgical intervention is given in half-decades. The post-surgical treatment consisted of prescribing painkillers that is not known to have any impact in the healing process. Furthermore, the hospital records documented that none of these individuals took post-surgical antibiotic treatment. Two-dimensional observations are made on the remodelling of the external and internal structures of both the bone flap and the cranial vault. Nonmetric observations focused on specific sections of the cranial vault adjacent to the opening, of the bone flap and of the space between the bone flap and the vault. Intra-individual observations of different CT scans were made at the same location, using multiplanar reconstruction (MPR). Because the configuration of the scanners for such post-operative examinations is specifically adapted to the exploration of soft tissues (soft tissues window), a retrospective observation of bony tissues on CT scans involves adjustments that have unfortunately reduced image resolution (bone window). This technical constraint explains the rather poor quality of certain images that we have procured. However, note that this does not prevent a reliable assessment of the macroscopic bony structures during the healing processes.

3 | RESULTS

3.1 | Three types of 'healed trepanation' in the anthropological and archaeological literature

Despite the abundance of archaeological cranial lesions identified as 'healed trepanations' in published literature (Appendix S1), our review highlights the criteria to define what constitute as 'healing' are inconsistent across these sources. Three main types are commonly reported in these studies (Figure 1), herein refer to as type A, type B and type C, respectively. Type A is the most common sign of healing described in anthropological/archaeological studies (85%). This type

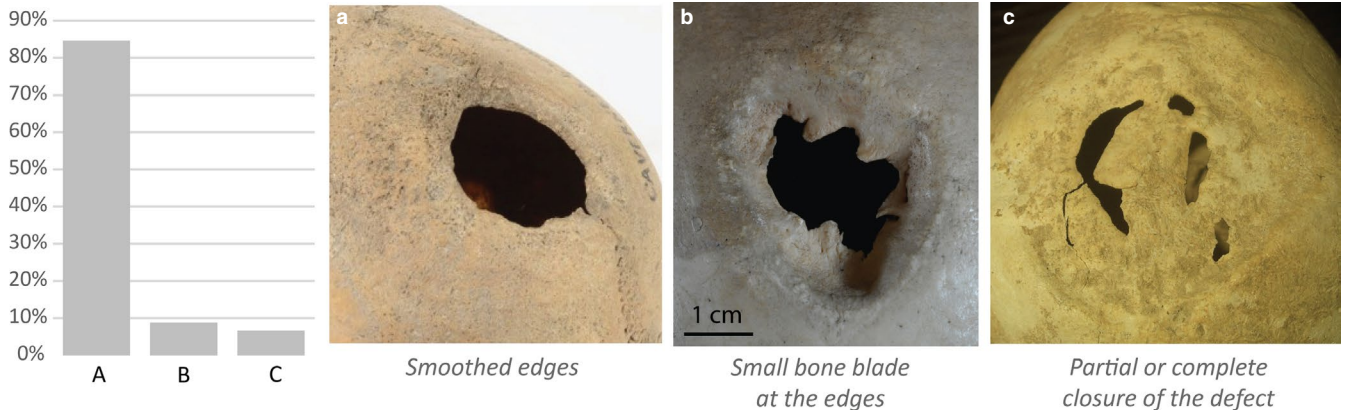


FIGURE 1 Three main macromorphological features of 'healed trepanation' according to anthropological literature (90 archaeological cases from 46 references reviewed). Type a: smoothing of the edges and loss of the typical bony layering; example: ©MNHN-Domenech HA-24442; type b: limited concentric projection of new compact bone at the edge of the lesion, particularly along its lower contour and without closure of the opening; example: ©MNHN-HA-19210, published in Thillaud (1996, p.154); type c: partial or near-complete closure of the opening with a newly formed compact bone plate from the tabula interna; example: ©Musée de la Régence, Neolithic case of Ensisheim (France) published in Alt *et al.* (1997) and Alt and Jeunesse (2006)

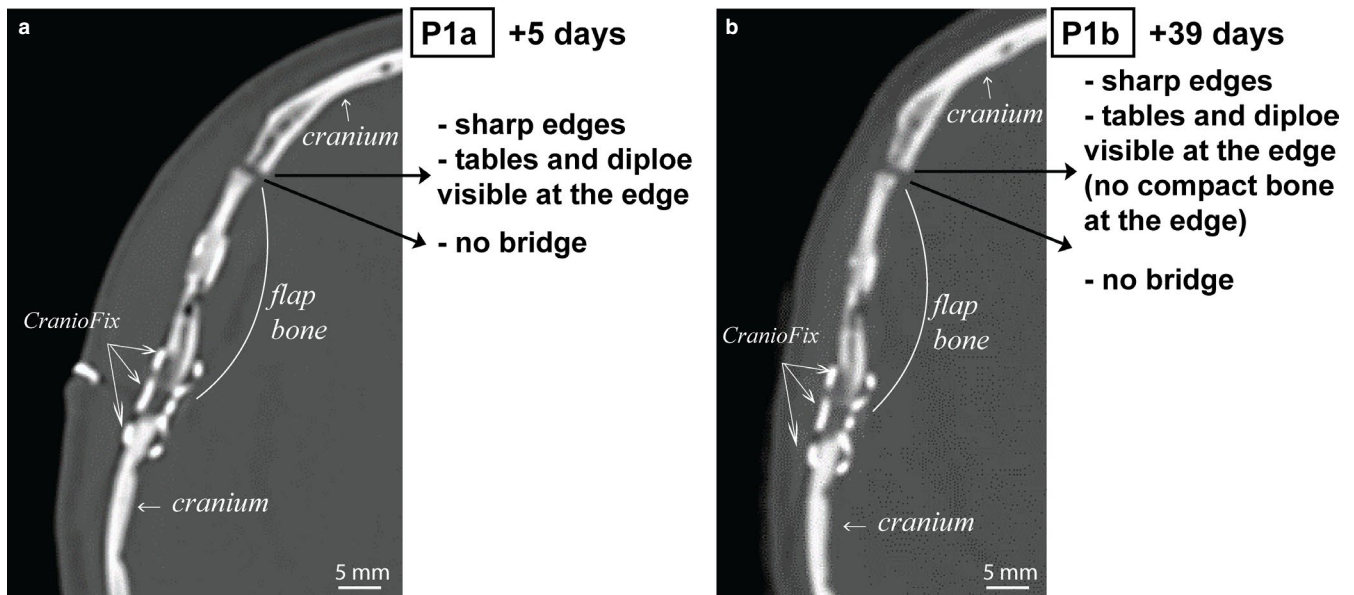


FIGURE 2 Craniotomy performed on the right temporal bone of an adult female between the ages of 45 and 50 years. (a) Case P1a: 5 days after surgery; (b) Case P1b: 39 days after surgery

of trepanation is usually defined by a smooth edge and the loss of the typical bony layering at the cross section (Figure 1a). In this case, the ectocranial margins are generally bevelled. The contours of this type of lesion range from rather linear to only slightly irregularly shaped, but are still largely well defined. Type B is observed less often (9%). It corresponds to the presence of a limited concentric projections of new compact bone in the form of bone spurs at the edge of the lesion, particularly along its lower contour, without closure of the opening (Figure 1b). Lastly, type C (6%) is lesions with partial or a near-complete closure of the opening, with newly formed compact bone plate from the tabula interna (Type C: Figure 1).

According to the literature reviewed, the differences between these three macromorphological types of lesions can almost be

invariably attributed to a differential survival time. Types A and B are often described as 'partial healing' or 'healing in progress', while type C is often qualified as 'completely healed' (Rogers, 1938; Guy *et al.*, 1989; Alt *et al.*, 1997; Lillie, 2003; Verano, 2003; Alt and Jeunesse, 2006; Han and Chen, 2007; Andrushko and Verano, 2008; Nikita *et al.*, 2013). Within this general categorization, variations of morphological details among the published specimens are commonly interpreted as specifically intervention-dependent. For example, different surgical techniques employed to open the cranial vault, such as 'scraping' or 'grooving', could affect the angle of the inclination of the edge, and thus resulted in different healing patterns (Broca, 1877; Lucas-Championnière, 1912; Lisowski, 1967; Kenesi, 2001; Thomas, 2011).

3.2 | Intra-individual stages of the healing process in modern cases monitored by CT scans

The cases studied in the present study are referenced with the patient number (e.g. P1, P2, etc.), followed by reference for the postoperative scan (e.g. P1a: first postoperative examination of patient n°1). None of the cases selected has shown any macroscopic inflammatory reaction that is suggestive of infectious pathological changes, even at early post-operative stages P1a, P2a, P3a and P4a (Table 1). We searched for signs of bone healing such as variations in bone thickness at the opening, bone remodelling, merging of bone fragment, formation of bone spurs, bone bridge or bone blade, or the closing of the opening.

The first case study (P1) corresponds to a craniotomy performed on the right temporal bone of a female between the ages of 45 and 50 years. The removed bone flap, which had been partially fragmented during surgery, has been replaced with a medical cranial fixation system (*CranioFix*®, *Aesculap*®, Tuttlingen, Germany) (Figure 2). After five post-operative days (P1a), the thickness of the vault at the opening is at 4.1 mm, and the bone flap and the vault are separated anteriorly by a space of 1.5 mm. No obvious osseous remodelling is observed, there is no smoothing of the edges, and the diploe is visible in cross section (Figure 2a). No distinct macroscopic changes can be observed after 39 post-operative days (P1b). The thickness of the vault at the opening has not decreased. The bone flap and the surrounding bone tissue are still separated anteriorly by a space of 1.5 mm, and no bone bridge is observed between them. Several millimetre-sized bone fragments of the flap resulting from the surgical procedure also do not show any apparent change (Figure 2b).

The second case is that of a craniotomy performed on an adult female between the ages of 55 and 60 years (Table 1). The cranial opening is located on the frontal bone (Figure 3), which is why the

site of the opening is substantially thicker than the site of the P1 opening described before, and the vault thickness ranges between 7.3 and 12.7 mm. The bone flap has been precisely re-inserted into the cranial opening so that the gap from the vault edge is only between 1 and 2 mm in size. Similar to P1, in this case, no macroscopic sign of bony reaction is observed after four post-operative days (Figure 3a), or over a month (Figure 3b). Despite the proximity of the flap and the vault edges, the gap between the vault and the bone flap did not show any sign of closing up, and there is no bone bridge formed at this stage.

The third case, P3, corresponds to a craniotomy performed on the left temporal bone of an adult female between the ages of 75 and 80 years (Table 1). The bone flap was partially fragmented during surgery, and was replaced with the bone flap and by the patient's own microresidual bone powder (Figure 4). The bone flap was re-positioned close to the edge of the vault, with a gap ranging from less than 1 mm to 3 mm, and is in certain areas in direct contact with the vault. Seven days after the surgery (P3a), the thickness of the vault is measured to be 4.9 mm just next to the aperture. The smaller fragments of the bone flap are clearly discernible, showing no sign of osseous reaction (Figure 4a). After five post-operative months (P3b), signs of healing can be observed (Figure 4b). The edges of the vault, and of the bone flap itself, have become smooth. Several distinct bone bridges between the cranial vault and the bone flap are now present, even if this does not correspond to a complete reconstitution of bony continuity, as structural fusion is still ongoing. Also, the fragmented parts of the bone flap still show limited merging. Another image showing a different angle of the opening at the same stage of healing for P3b (Figure 5a) shows surgically related lesion (a hole 2 mm in diameter in the neighbouring bone close to the edge of the lesion). This hole is partially healed after 20 post-operative months (Figure 5b). Nonetheless, at this stage there are no

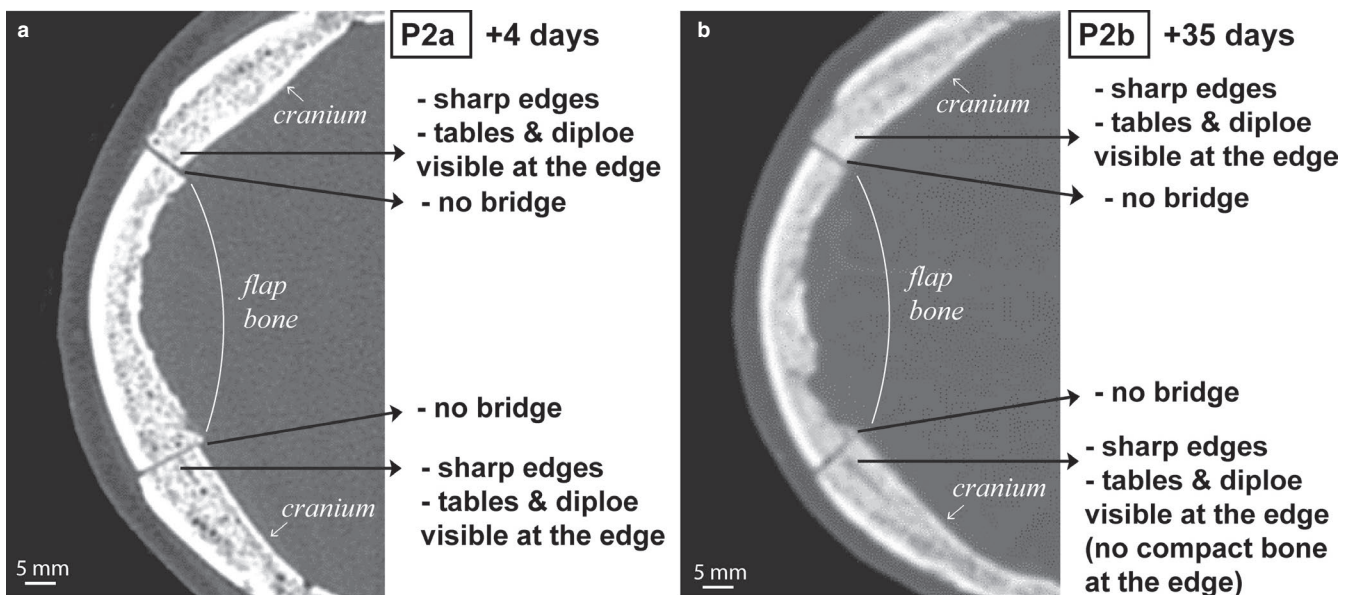


FIGURE 3 Craniotomy performed on the frontal bone of an adult female between the ages of 55 and 60 years. (a) Case P2a: 4 days after surgery; (b) Case P2b: 35 days after surgery

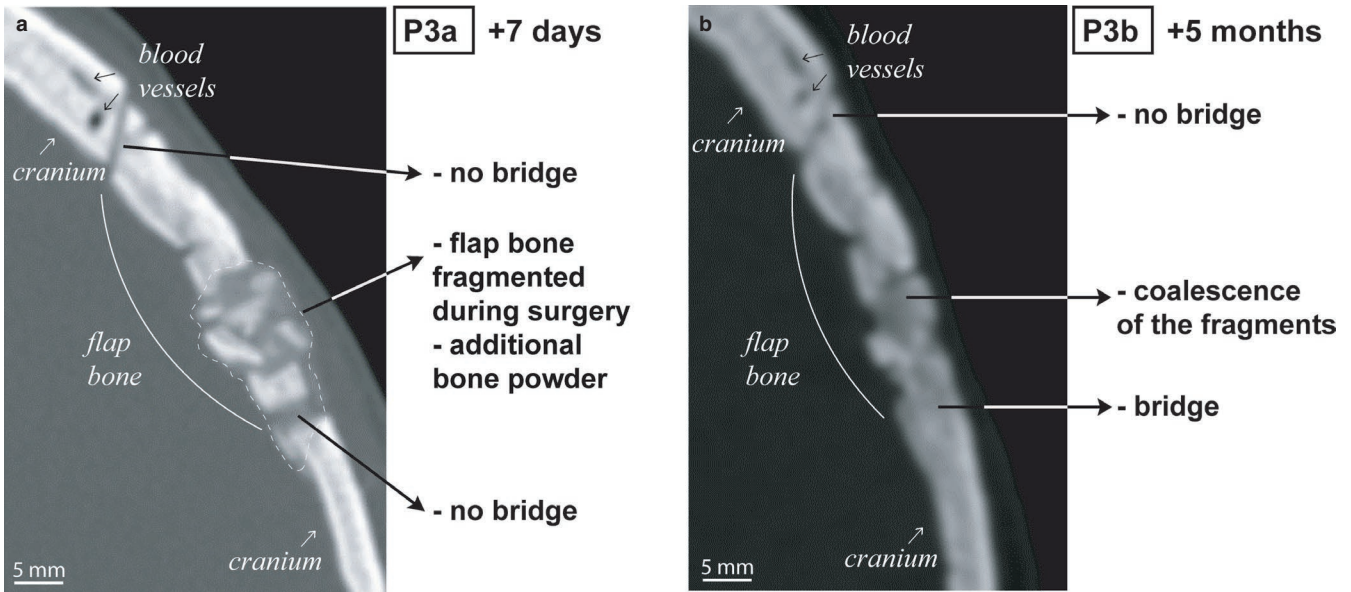


FIGURE 4 Craniotomy performed on the left temporal bone of an adult female between the ages of 75 and 80 years. (a) Case P3a: 7 days after surgery; (b) Case P3b: 5 months after surgery

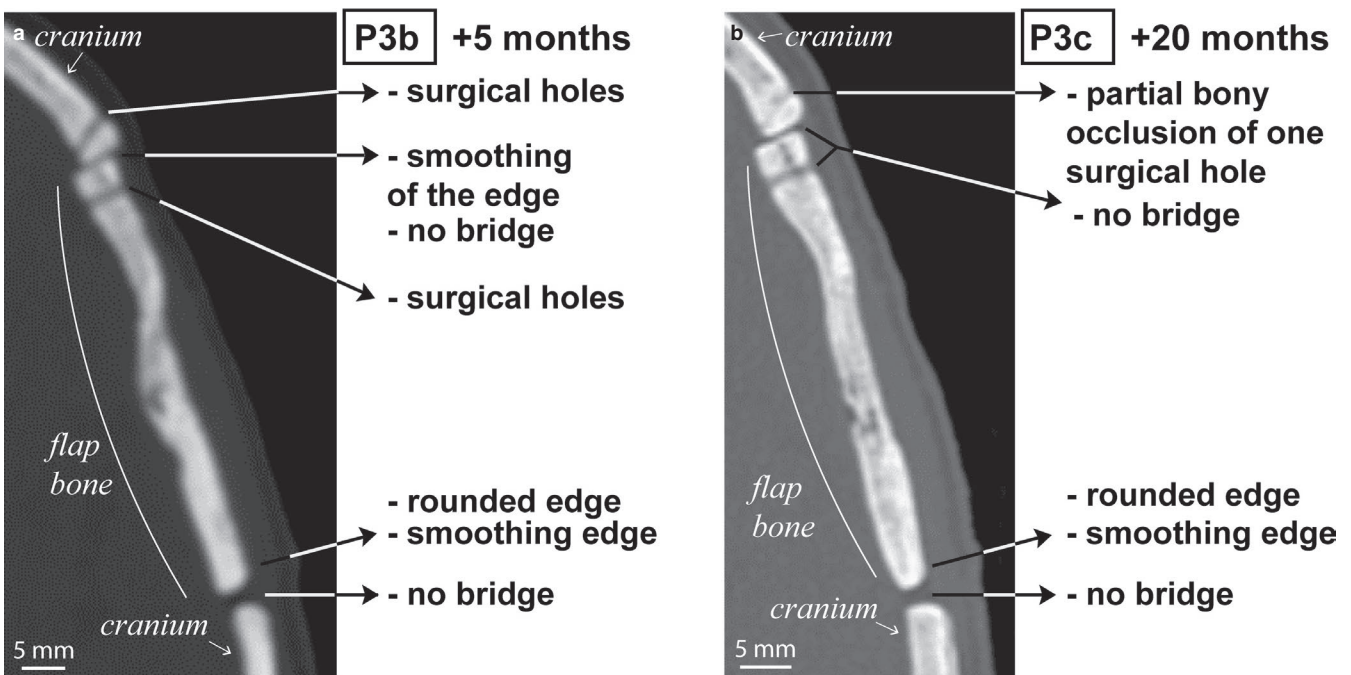


FIGURE 5 Craniotomy performed on the left temporal bone of an adult female between 75 and 80 years. (a) Case P3b: 5 months after surgery; (b) Case P3c: 20 months after surgery

major changes compared to the scan performed on the same patient 14 months earlier (Figure 4 vs Figure 5b). The smooth shape of the edges is comparable between the two stages, the surrounding vault next to the aperture is still 4.9 mm thick, and no bone bridge is present between the flap and the vault, which are still separated by a gap of 1–3 mm.

Finally, the last case, P4, corresponds to a craniotomy performed on the left parietal bone on an adult male between the ages of 55

and 60 years (Table 1). In this case, the bone flap has undergone recalibration before reinserted. A gap 2 mm up to 2 cm wide remains between the flap and the edge of the vault. In posterior position, the gap is 7.9 mm wide (Figure 6). The bone flap and the vault are both 6 mm thick. After 10 post-operative days (P4a), the sharp edges of the cross sections are still clearly visible, and no macroscopic remodelling can be observed on the vault or the bone flap (Figure 6a). Five years later (P4b), while the edges of both the bone flap and the

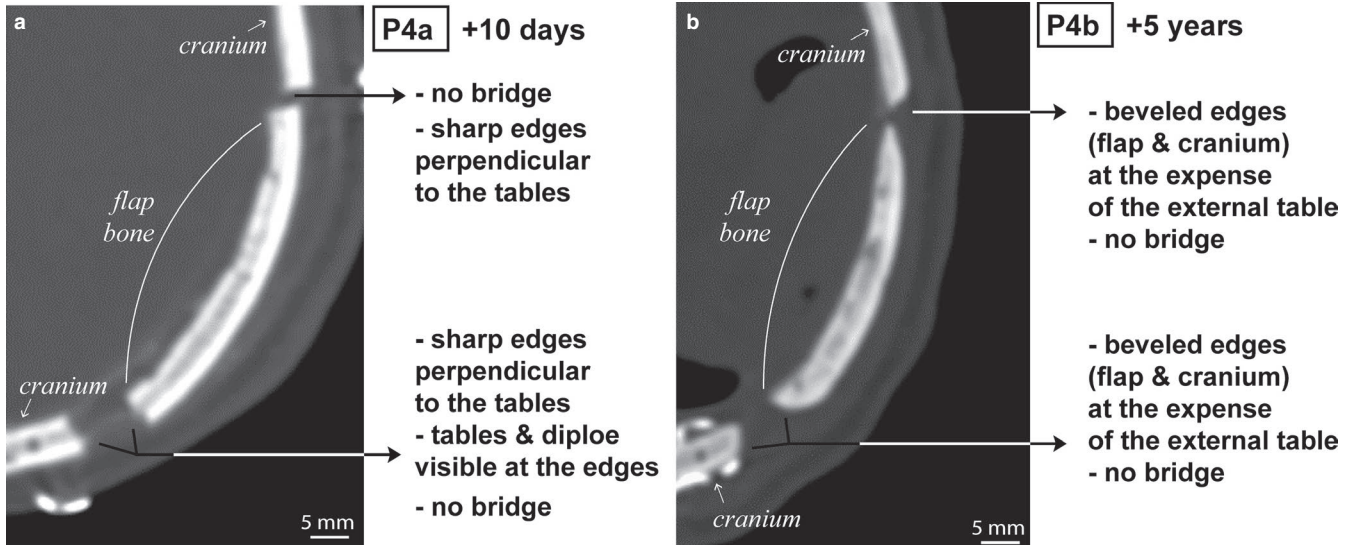


FIGURE 6 Craniotomy performed on the left temporal bone of an adult male between the ages of 55 and 60 years. (a) Case P4a: 10 days after surgery; (b) Case P4b: 5 years after surgery

cranial vault are thinner than 6 mm and reveal a bevelled shape appearance, bony continuity between the two elements is still lacking, with persistence of a relatively large empty space between them, up to 9.5 mm in some places (Figure 6b).

3.3 | Time-related bony reactions and synthesis of the macromorphological features in modern cases

The sample of CT scan images of nine post-operative stages from four modern patients adds critical information to the study performed by Nerlich *et al.* (2003), which consists of data generated from 10 autopsied individuals (Table 2). The cases from the study of Nerlich *et al.* (2003) are referenced with the number of the autopsied patient (e.g. N1: examination of patient n°1). Note that in some cases, the bone flap removed was reinstated after the surgery. In the P samples, the bone flaps were always replaced, but the distance between the cranial vault and the flap is variable, from less than 1 mm (P3) to a gap of around 2 or 3 mm (P1, P2) and to circa 1–2 cm (P4). This variability permits observations to be made under a variety of healing conditions. In the N samples, the situation of the bone flap is only described for 4 cases: it is reinserted close to the skull (1–3 mm) in 3 of them, and not reinstated in the last case (Table 2). In addition, the case N6 refers to an individual who had not undergone a typical trepanation, but had suffered a traumatic cranial fracture. By means of reconstructive surgical intervention, the bone fragments damaged were replaced shortly after the traumatic episode (Nerlich *et al.*, 2003). As no bone has been extracted, the remodelling process observed in N6 has to be compared to the others with caution.

To allow a clearer comparison, we have divided the modern case studies into three main post-operating periods (Table 2): an early period comprised between few hours and 10 days after trepanation

($n = 8$), a median period comprised between about 1 month and 20 months ($n = 6$), and a late period comprised between 4 and 34 years ($n = 5$). The first macroscopic signs of healing observed in the samples occurred during the median post-operative period. The case P1b shows a *terminus ante quem* at 39 days post-surgery, before which no macroscopic sign of healing is observed. The case P3b constitutes a *terminus post quem* at 5 months post-surgery, after which osseous remodelling can be observed. If including the case of N6, the timeline for *terminus post quem* could be refined to starting at around at 2 months post-surgery.

The osseous signs of healing can be identified through different macromorphological features. All healed cases show smoothed and rounded edges, with the loss of the diploe structure at the opening margins, where it is replaced by a layer of compact bone. In certain cases, bone bridges or merging of the fragments occurred. The extensive merging of cranial fragments is portrayed in case N6. Similarly, in cases N7, N8, and N10, where the removed bone flap has been reinstated, there was partial reunion to the vault margin (Nerlich *et al.*, 2003). Case P3 has undergone a specific surgical procedure to stimulate focal osteogenesis (*supra*), which has led to the merging of the bone flap fragments, and the development of bone bridges between the flap and the vault. Another specific morphological feature of healing is documented through the healing process of case P4 (Figure 6a,b). This process shows the remodelling of the vault and bone flap edges, which is initially sharp and vertical, into a bevelled-shape profile at the expense of the external table.

Herein, we summarize several of the main macromorphological features of cranial remodelling in modern cases observed through CT scans and direct observation between 4 days and 34 years after surgery (Figure 7). In the particular context of an accurate re-positioning of the bone flap or fragmented cranial bones, merging of the pieces and formation of bone bridges may start to occur after the second post-operative month. Otherwise, the smoothing/rounding

TABLE 2 Information on the cases studied in the present study and in the study of Nerlich *et al.* (2003)

Cases	Age of the patient at the time of surgery (in years)	Time after surgery	Post-operative periods	Macroscopic healing signs	Situation of the bone flap
N2	41	+few hours	Early	No	<i>Not specified</i>
P2a	[55-60]	+4 days		No	Re-positioned (closely to the cranium)
P1a	[45-50]	+5 days		No	Re-positioned (closely to the cranium)
N3	35	+6 days		No	<i>Not specified</i>
N4	33	+7 days		No	<i>Not specified</i>
P3a	[75-80]	+7 days		No	Re-positioned (in punctual contact with the cranium)
N5	86	+10 days		No	<i>Not specified</i>
P4a	[55-60]	+10 days		No	Re-positioned (to distance to the cranium)
P2b	[55-60]	+35 days	Median	No	Re-positioned (closely to the cranium)
P1b	[45-50]	+39 days		No	Re-positioned (closely to the cranium)
N6	76	+2 months		Yes ^a	Fractured elements preserved in strict contact after trauma
P3b	[75-80]	+5 months		Yes	Re-positioned (in punctual contact with the cranium)
N7	23	+12 months		Yes	Repositioned
P3c	[75-80]	+20 months		Yes	Re-positioned (in punctual contact with the cranium)
N8	70	+4 years	Late	Yes	Re-positioned (closely to the cranium)
P4b	[55-60]	+5 years		Yes	Re-positioned (to distance to the cranium)
N9	42	+6 years		Yes	<i>Not specified</i>
N10	68	+6 years		Yes	Re-positioned (closely to the cranium)
N11	3	+34 years		Yes	Extracted (large opening preserved)

Note: Age at the time of the surgery, post-operative time, healing signs, and situation of the bone flap. N-cases: cases from Nerlich *et al.* (2003); P-cases: cases from Partiot *et al.*, present paper.

^aNot trepanation, but fracture.

of the edges (initially sharp), and the bevelling of the margin's profile (initially vertical) appear to be two distinct osseous remodelling features that occur at different stages of the healing process. The first occurs after 5 months of the surgical procedure, the second after

5 years. While none of the lesion show signs of complete healing, the process of which the edges developed a bevelled-shape profile is, according to our modern series, the only feature that occurs at a 'late' post-operative period. Thus, 'complete healing' can be considered

FIGURE 7 Synthesis of the main macroscopic cranial osseous remodelling in modern cases of trepanation. P: CT-data, present study; N: direct observations, Nerlich *et al.* (2003)

	Smooth/Rounded edges and loss of diploic bone structure															
	P2a	P1a	N3	N4a	N4a	P1b	N6?	P3b	N7	P3c	N8	P4b	N9	N10	N11	
	0	0	0	0	0	0	X	1	1	1	1	1	1	1	1	
	Coalescence or bridge between cranium fragments or flap and cranium (if nearby)															
	P2a	P1a	N3	N4a	N4a	P1b	N6?	P3b	N7	P3c	N8	P4b	N9	N10	N11	
	0	0	?	?	X?	0	0	1	1	1	1	X	?	1	X	
	Beveling of the edges															
	P2a	P1a	N3	N4a	N4a	P1b	N6?	P3b	N7	P3c	N8	P4b	N9	N10	N11	
	0	0	?	?	?	0	X	0	?	0	?	1	??	??	?	
	Closure of the trepanation defect when flap absent or far from the margins															
	P2a	P1a	N3	N4a	N4a	P1b	N6?	P3b	N7	P3c	N8	P4b	N9	N10	N11	
	0	0	?	?	?	0	X	0	0	0	0	0	?	?	0	
	4	5	6	7	10	1	2	5	12	20	4	5	6	34		
	days					months		mths		mths		yrs		yrs		
	Early postoperative period					Median postoperative period					Late postoperative period					
	surgery															

when a layer of compact bone covers the diploe at the site of affliction, where the edges appeared to be smooth and, occasionally, show osteophytes or bone spicules (Chege, *et al.*, 1996; Weber and Wahl, 2006; Kushner and Verano, 2017).

In the future, this healing timeline can be benefited including records of individuals of more age groups and both sexes, to account for greater interindividual variability.

4 | DISCUSSION

4.1 | Variability of healing time and remodelling patterns

Modern surgical cases have to be compared to archaeological cases with caution. Having said that, observations from modern medical practices can improve our understanding of cranial vault healing processes in archaeological context and, more specifically, of trepanation. First, despite the advances of modern surgical techniques, current postoperative monitoring of patients does not include any medication that would directly affect the healing processes. Hence, in an ideal scenario where no infection is present, the difference in the bone remodelling timelines between those of modern and ancient patients would be limited. Second, the reinstatement of bone flap in modern patients has not been documented yet in archaeological records. However, following our observations, that condition is not always a fundamental obstacle, since the flap-cranial bone gap in modern cases can be very wide (up to 2 cm) due to the recalibration of the bone flap. This practice is a factor that certainly affects the remodelling processes, as shown by patient P3b, where distinct bone fragments began to merge, and the formation of a bone bridge can be observed (Figure 4). Nevertheless, in the four other cases where the bone flap was reinstated, there was minimal contact between the respective crania and the reinstated bone flaps. Thus, the observations of the healing processes of these cases should be reasonably comparable to a trepanation without bone flap

reinstatement, making them appropriate for preliminary comparison to the archaeological cases.

However, several conditions must be considered in order to use these medical observations for the improvement of the analysis of the archaeological record. First, the healing process timing for ancient trepanations must be discussed by considering the location of the opening in the vault, its size, and if any impact was made to the dura mater (Verna *et al.*, 2002; Gosain *et al.*, 2003; Cooper *et al.*, 2010). Death, is for example, more common when the trepanation was performed in the cranial musculature regions (Verano and Andrushko, 2008).

The preservation of the dura mater, which is the primary source of osteogenic cells (Cooper *et al.*, 2010), is imperative for the patient's survival and healing. Individual biological responses may also introduce variability in the healing timing, as local bone structure or pathology or individual repair capabilities may hasten or delay the healing process (Frost, 1989; Anzelmo *et al.*, 2015; García Gil *et al.*, 2016). Significant variations in the thickness and density also exist between the cranial vault bones, especially in the external cortical layer, and local differences for the healing potentials have been reported (Peterson and Dechow, 2003). These variations may be related to local differences in mechanical microenvironments, and may influence the speed of bone repair. Last, but not least, the age and sex of the patient is a crucial factor to take into account, because cranial vault thickness, histomorphology, vascularization and physiological repair capabilities differ greatly over one's lifetime, and particularly with biological events such as female menopausal process (Anzelmo *et al.*, 2015; García Gil *et al.*, 2016). The healing capacity of the calvaria is reported to be inversely proportional to age, and appears to decrease rapidly after 1 year of age (Gosain *et al.*, 2003; Bonda *et al.*, 2015; Feroze *et al.*, 2015).

These variations are to be taken into consideration regarding the present investigation, which mostly focuses on advanced patients (older than 40 years of age), with an exception of N11. This case described an individual surviving a craniotomy at the age of 3, which did not show any closure 34 years after surgery. Thus, this case

underlines the polyfactorial character of the cranial healing process. Although further studies are necessary to characterize interindividual cranial healing variability, we observed that around one post-operative month, there is very little difference in terms of degree of healing between P1 and P2, despite their substantial difference in bone thickness to start with. The observations of both P and N samples deny the possibility of any closure of wide and empty gap. There is no restoration of bony continuity observed in the cranial vault, as shown in the late stage of post-operative period, where the gap is not filled despite having a bone flap in close proximity to the edge of the vault.

Moreover, these observations are supported by the results of current innovative therapy researches on bone reconstruction. Even when an inert biocompatible support favourable to bone regrowth is used with optimal cellular conditions, bony continuity restoration appears to be limited. The possibility of bone formation by colonization of the edge cells is then about a centimetre from each edge, and therefore often insufficient for larger bone loss (Chiron and Brouchet, 2017).

4.2 | Interpreting the shape of the trepanation: contribution to positive and differential diagnosis of archaeological trepanations

The application of our findings to archaeological cases addresses the variability of the opening procedures in past populations, since the interpretation of the procedures and methods for cranial opening is based often from the lesion shape, sharpness of the profile and the slope of the edges. In archaeological contexts, three techniques are often considered: *drilling*, *scraping* or *cutting-grooving* (Lisowski, 1967; Campillo, 1984; Chege *et al.*, 1996; Hibon, 2004; Erdal and Erdal, 2011; Thomas, 2011; Gresky *et al.*, 2016). Moreover, different types of tool are assumed to be used throughout history, for example during Neolithic and Middle Age (stone scrapers, stone or metal chisel, arrowhead or even dagger). So far, only one archaeological instrument, the Peruvian *tumi*, has been positively identified as a tool dedicated to this operation (Goodrich, 2014). Currently, it is not known whether technical differences in trepanation protocols or the tool itself would affect the bone remodelling patterns.

According to our bibliographical review, the most common feature described in archaeo-anthropological literature (Type A: fig. 1 and S1 Table) is that of bevelled edges, interpreted as a trepanation made with the scraping technique. However, our findings show that bevelling edges appear with the healing process. The procedure analysis of type A openings must now consider this particular healing process, which is the inclination of the edges.

The interpretation of the type B trepanation may also be subject to discussion, since the *drilling* procedure (Lisowski, 1967; Hibon, 2004; Erdal and Erdal, 2011; Gresky *et al.*, 2016) may represent a confounding factor. As the procedure may lead to the appearance of bone discontinuities along the trepanation edges of the internal

table (cf. Type B: fig. 1), it can lead to misinterpret the projections as newly formed bone spurs (Sevitt, 1981). Interpretations of this type has therefore to be made cautiously and on a case-by-case basis.

Finally, the interpretation of the type C trepanation as complete healed trepanation with closure of the opening must be re-evaluated. What is usually interpreted as large, newly formed bone blade indicative of healing and post-surgery survival may result instead from osteolytic processes or developmental defects. For these features in particular, a differential diagnosis should consider preferentially the large number of defects caused by pathological, physiological or even taphonomical processes, reported as pseudotrepanation (Stewart, 1971; Stewart, 1975a; Stewart, 1975b; ÓDonnabhain, 2003; Partiot *et al.*, 2017; Sparacello *et al.*, 2018). For example, we suggest that the diagnosis of the Neolithic case of Ensisheim (illustrated as type C: fig. 1), as a healed trepanation with the complete closure of a wide opening (Alt *et al.*, 1997; Alt and Jeunesse, 2006), should be challenged, in particular by considering osteolytic factors such cerebrospinal fluid leakage. Only a precise re-examination of the original Ensisheim skull would allow providing an alternative diagnosis.

5 | CONCLUSIONS AND FUTURE DIRECTIONS

Despite the long history of the surgical practice of cranial trepanation, very little is known about the cranial vault healing process and its timing. This lack of information has significantly hampered archaeologists from reliably diagnosing trepanation among archaeological samples. The present study incorporates CT scanning records of modern patients to comparatively assess post-surgery cranial bony changes, and provides data to help analyse the shapes of the cranial openings in archaeological cases. Our results have demonstrated that macroscopic reactions may occur early after surgery. The merging of the bone pieces and formation of bone bridges between close fragments may start to occur after the second post-operative month. The smoothing/rounding of the edges (initially sharp) occurs after 5 months post-surgery, whereas a bevelling of the margin's profile (initially vertical) occurs only after 5 years. None of the cases shows any complete closure of the cranial vault, and new bone formation appears to be very limited in adults.

These particular findings highlight how the inclination of the margins of a healed trepanation may be related to the healing process of the bevelling of the edges, and not only to the cranial opening technique, which now has to be taken into consideration when interpreting the procedures and methods in past population. Moreover, the results already challenge the usual binary categorization made in archaeological literature of 'partially healed' and 'completely healed' trepanations (Types B and C). The results from this study suggest that archaeological lesions with partial or nearly complete closure of the opening with a compact bone blade, formerly described as 'completely healed' trepanation, should be more suitably redefined as 'pseudo-trepanations'.

In the future, we hope to expand our collection to incorporate records of individuals of all ages and both sexes to account for greater interindividual variability in order to improve our understanding of the healing timeline and the respective macroscopically characterizations of pathological reactions that may occur, according to medical data, very early after surgery. This supplementation of other records and the better understanding of the biological variability of the healing processes could lead to a scientific reassessment of post-survival time in past populations. While the reason for *in vivo* cranial trepanation since the Neolithic period remains ambiguous, this perspective would offer an insightful glance into the social conditions of past societies, including aspects such as sanitary conditions, the efficacy of therapeutic treatments and many more.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

CP, AT and ED acquired the data and analysed the data. CP and AT drafted the manuscript with input from ED, CJ, AL, DL and BM. All authors gave final approval for publication.

DATA AVAILABILITY STATEMENT

Post-operative scans are available for study on request at the Centre Hospitalier Universitaire, Hôpitaux de Bordeaux, France.

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