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The Controlled Cortical Impact Model of Experimental Brain Trauma: Overview, Research Applications, and Protocol

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Abstract

Controlled cortical impact (CCI) is a commonly used and highly regarded model of brain trauma that uses a pneumatically or electromagnetically controlled piston to induce reproducible and well-controlled injury. The CCI model was originally used in ferrets and it has since been scaled for use in many other species. This chapter will describe the historical development of the CCI model, compare and contrast the pneumatic and electromagnetic models, and summarize key short- and long-term consequences of TBI that have been gleaned using this model. In accordance with the recent efforts to promote high-quality evidence through the reporting of common data elements (CDEs), relevant study details—that should be reported in CCI studies—will be noted.

Keywords

Traumatic brain injury (TBI); Experimental brain injury; Preclinical; Animal model; Controlled cortical impact (CCI); Common data elements (CDE)

1 Introduction

Animal models have been used to study traumatic brain injury (TBI) for over a century and they remain widely used today to better understand outcomes of brain trauma and test novel therapies [1–4]. Today, preclinical TBI researchers have the choice between several models including: weight drop injury (WDI), fluid percussion injury (FPI), blast-induced TBI (bTBI), and controlled cortical impact (CCI), the focus of this chapter. CCI was originally developed to study TBI in ferrets [5], and its desirable properties (e.g., reproducibility; control over injury parameters) have led researchers to scale the model and apply it to many other species. The original design uses a pneumatically driven piston to induce TBI, while a newer alternative added an element of portability by using an electromagnetically driven piston which is lighter in weight and negates the need for a cylinder filled with compressed N_2 gas.

The purpose of this chapter is to introduce readers to the CCI model so that thoughtful decisions can be made in their own completion of CCI research or in their consumption of the research literature. In doing so, the following will be discussed: (1) historical development, (2) key features, (3) comparison of the pneumatic and electromagnetic devices, (4) research applications, (5) relevant common data elements, as well as (6) factors

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that influence outcomes and data quality. A standard protocol will be described for pneumatic CCI in rats, along with a list of all required supplies and equipment.

1.1 History of Controlled Cortical Impact and Key Features

Animals have been used to study TBI for over 100 years, with considerable refinement of methodologies within the last three decades [1–3, 6–14]. In comparison to the many experimental TBI models available today, CCI is relatively new. It was originally developed by J.W. Lighthall and colleagues in the late 1980s and early 1990s with the goal of inducing TBI in ferrets [5, 15]. The desirable properties of CCI including the control over important injury parameters and ability to induce reproducible injury led C.E. Dixon and colleagues to scale the CCI model for use in rats during the early 1990s [16]. Since that time, CCI has been further scaled for use in several other species including mice, pigs, and nonhuman primates.

The scalability and other desirable features have resulted in CCI becoming one of the most popular and widely used preclinical TBI models. One noteworthy feature is that CCI provides quantitative control over important biomechanical parameters of TBI, in particular, the velocity, depth, and force of the tip are controlled across a wide range of contact velocities; there are also different options for tip size, geometry, and positioning, as discussed later in this chapter. Taken together, the control and customization of CCI allows researchers to address a multitude of research questions as well as scale the injury as needed to study the histopathological and functional deficits of interest. Reporting the injury parameters is of critical importance when reproducing, interpreting, and comparing published study findings, as described under the Common Data Elements heading.

A detailed protocol for inducing CCI in rats is included later, but to set the stage, a brief summary of CCI will be provided first. Traditionally, CCI is an invasive model whereby the exposed cortex is subjected to trauma following a craniectomy; in invasive CCI studies sham animals are used as controls to ensure that the results seen are not due to anesthesia and craniectomy but rather the CCI itself. Following craniectomy, the CCI device is used to transfer mechanical energy onto the intact dura mater, producing a TBI. Traditionally, the tip is pneumatically driven, though a newer model affords portability by using an electromagnetic device to drive the tip [14]. Both types of CCI allow for control over the tip depth, dwell time, and velocity; additional details about the pneumatic and electromagnetic CCI models are provided in the following section. It is also worth acknowledging that while invasive CCI remains widely used, CCI has been extended to model closed head injury [17–19] as described later in this chapter. It is also notable that even with an invasive CCI model, only one surgical procedure is necessary, as opposed to standard FPI which requires two surgeries.

1.2 Controlled Cortical Impact Types

1.2.1 Pneumatic Controlled Cortical Impact—The pneumatic CCI device (Fig. 1) was the first to be developed and it remains the most commonly used today. For these reasons, the pneumatic model will be emphasized in this chapter with a brief discussion on how it differs from the electromagnetic alternative. A standard pneumatic CCI device features a

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small bore (19.75 mm) reciprocating a double-acting pneumatic piston with a 50 mm stroke length. The piston is used to drive a tip of a desired size and geometry into the neural tissue (or in some cases the intact skull) to induce brain trauma. The cylinder is held by a crossbar which can be stereotaxically adjusted for variable mounting positions allowing the tip to be either aligned vertically or angled with respect to the brain. The velocity of the piston is monitored by a sensor and can be controlled to promote uniform injury across test animals. Researchers using the CCI model are able to control the depth, duration (a.k.a. dwell time), and velocity of injury as well as choose what size and shape of tip to use.

1.2.2 Electromagnetic Controlled Cortical Impact—The electromagnetic CCI device (Fig. 2) is very similar to the pneumatic model and also uses a stereotaxic frame for adjustability. The electromagnetic CCI devices are considered to be more portable due to their lighter weight. Another similarity is the availability of tips with varying sizes and geometry (e.g., flat, beveled, round). Generally speaking, tip scaling correlates with animal size; for example, 3 mm tips are commonly used for mice, 5–6 mm tips for rats, 10 mm for nonhuman primates, and 15 mm for pigs. Depending on the vendor, the device may come with a variety of tips. Alternatively, there may be additional tips available to purchase separately. Some researchers have also modified tips based on their unique research needs with one group using vulcanized rubber from a lacrosse ball to cover the tip [19]. A list of commercial vendors who sell both electromagnetic and pneumatic CCI devices is included in Table 1.

1.3 Applications of Controlled Cortical Impact

1.3.1 Closed Head Injury—Though originally CCI was developed as an invasive TBI model, it has been more recently adapted to study closed head injury (CHI) including repeated concussions. CHI models have become an area of increased research emphasis as the risk to individuals who are in the military or those involved in various athletic activities is further appreciated. The aforementioned strengths of CCI make it a popular choice for researchers studying CHI [17–19]. Applications of CCI to study CHI include a study modeling sports-related concussions [19]. In this study, the researchers combined elements of CCI with elements of Marmarou's impact acceleration model in an attempt to enhance control over clinically relevant variables. For example, a foam pad was placed under the rodent to limit rotational acceleration and instead promote linear acceleration. In this study, more deficits were observed after repeated TBI than a single TBI, as assessed using a battery of neurobehavioral tests including measures of cognition, memory, and sleep [19].

1.3.2 Long-Term Outcomes—The high survivability of CCI makes it a good choice for studying the long-term changes associated with TBI. Available evidence suggests that CCI results in chronic and progressive changes. For example, one study which assessed the test animals up to 1 year post-TBI reported ongoing deficits including progressive tissue loss and ventricular expansion [20]. In addition to the aforementioned histopathological consequences, there are several chronic behavioral deficits that have been reported. For example, after CCI (vs. sham) memory and learning deficits have been found to persist into the long term as assessed using the MWM [21–35]. Notably, persistent MWM deficits are more rarely reported in other models, including lateral FPI [36, 37] and medial FPI [38].

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Long-term deficits in motor function have also been reported, as assessed using the foot fault test [22, 34, 39, 40], whereas the authors of this chapter were only able to find one FPI study reporting long-term motor deficits using this measure [41]. That is to say that CCI is a good choice when researchers are interested in exploring long-term motor and memory symptoms after brain injury. Conversely, no CCI studies were identified where motor deficits on the inclined plane task were reported, though such deficits have been reported after lateral FPI [42]. Similarly, no CCI studies were identified where chronic deficits in reversal learning were reported, although this has been reported in several lateral FPI studies [36, 37, 43]. A detailed review of long-term outcomes for the major experimental TBI models is available to interested readers [44].

1.4 Species Used

One of the assets of the CCI model is that it can be translated to induce experimental TBI in many species. This is accomplished by scaling the injury parameters so as to maintain the percent of brain volume deformed in relation to total brain volume taking into account desired extent of injury to address the research questions. In order to induce CCI in large animals (e.g., pigs), modifications may be necessary to ensure the piston is high enough. Table 2 provides a summary of the various species that CCI has been applied to including injury parameters commonly used in each species.

1.4.1 Rat—Graded TBI can be easily produced in rats using the CCI model. Indeed, the effects of CCI are well categorized in rats where it has been found to result in diverse histopathological and functional changes consistent with what occurs in clinical TBI cases, including but not limited to: blood–brain-barrier disruption, derangements in blood flow and pressure, axonal injury, inflammation, and edema. It is also worth noting that functional symptoms of TBI (e.g., deficits in learning, memory, and motor function) can be assessed using neurobehavioral testing, which is well characterized in rats. For example, memory is readily assessed using the Morris Water Maze (MWM), Barnes Maze, or Novel Object Recognition (NOR) task; whereas motor function can be assessed using the Beam Balance Task, Beam Walking Task, Rotarod Task, and Wire Grip Task.

1.4.2 Mouse—Shortly after translation of CCI from ferrets to rats, the model was further extended to mice [45–47]. Refinement of CCI in mice has paralleled the increasing application of genetically modified mice to TBI research to explore the role of genes and gene products in brain injury recovery [48]. Generally speaking, to scale CCI down for mice entails decreasing the injury depth to adjust for the relatively thinner cortex in mice compared to rats. Though slightly less well categorized, a plethora of behavioral testing strategies are available for use in mice including the MWM, NOR, and BBT [31, 33, 49, 50].

1.4.3 Pig—To adequately address some research questions, larger, more human-like brains are needed, necessitating the use of a pig or other large mammal models. The main difference from the rat and mouse models is the considerably larger impactor tip and greater depth to which the neural tissue is deformed (*see* Table 2). In one study, CCI was scaled to induce TBI in piglets; injury parameters were chosen after adjusting for differences in brain morphology (e.g., size and dimensions) in the study's test animals [51]. As with rodent

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models of CCI, when pigs are used the histopathological changes mirror what is seen in TBI patients, including but not limited to, deranged blood flow and changes to vasculature, ongoing neurodegeneration via a number of mechanisms, and edema. To date, pig models have been used to add to the evidence surrounding TBI biomechanics [52] and as part of an effort to identify clinically relevant biomarkers of underlying brain injury [53]. However, despite these efforts there is a relative dearth of normative data specific to pigs when compared to rodents [54]. Additionally, behavioral testing is less well characterized in pigs and not to mention more challenging to perform due to their larger size and relative intelligence.

1.4.4 Nonhuman Primate—An alternative to the pig model is the nonhuman primate model of CCI, which is typically applied over the frontal cortex [55]. As with the other models, the histopathological changes reported after nonhuman primate CCI mimic what is seen clinically, including but not limited to edema, macrophage accumulation, and neurodegeneration. Nonhuman primates play a critical role in establishing the safety of novel therapies before translation to humans. Notably, due to the increased ethical considerations, care requirements, and cost, a relatively limited number of research institutions have primate research facilities. Consequently, nonhuman primate studies represent only a small fraction of TBI studies. Indeed, the use of nonhuman primate models is only justified when there are major factors that prohibit the use of a less sentient animal.

1.5 Special Considerations, Problems, and Troubleshooting

High-quality CCI research relies on thoughtful study design and careful execution. A few important confounders that have been empirically studied will be addressed as follows. When appropriate, troubleshooting strategies will be noted.

1.5.1 Tip Geometry—Commercially available tips come in round or beveled flat shapes of various sizes. When CCI was developed in ferrets, round tips were used [5, 15]; though still in use, beveled flat tips have become the norm [47, 48, 56–59] and are especially preferred for mouse CCI. Despite convention, little empirical research has tested the effects of tip geometry on outcomes. In one study, Pleasant and colleagues compared flat vs. rounded tips in a mouse (C57BL6J) model; they found more extensive cortical hemorrhage and neuronal loss (proportionally) with flat tips. The rate of neocortical loss was faster with flat tips, with a plateau in neurodegeneration 20 h earlier than rounded tips (4 h vs. 24 h) making the latter a more desirable choice when studying secondary injury cascades in the subacute period [60].

1.5.2 Anesthesia—Overall, careful choice of whether to use anesthesia and what anesthesia regimen to use is critical. In deciding, researchers should consider the study goals, along with established guidelines for the treatment of research animals. Empirical evidence shows that differences in outcomes of TBI are associated with various anesthesia agents; notably, isoflurane results in less hippocampal damage than fentanyl as well as fewer behavioral deficits [61]. Another study found that preinjury isoflurane had neuroprotective effects [62]. It is hypothesized that fentanyl contributes to neural suppression, whereas isoflurane reduces excitotoxicity and promotes blood flow [54]. Ketamine also demonstrates

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neuroprotective properties via antagonism of *N*-methyl-D-aspartate (NMDA) receptors [63]. Halothane has also been reported to have neuroprotective properties after contusion injuries [64]. Use of neuroprotective anesthesia can obscure deficits in performance in all anesthetized groups. For fentanyl, the concern is that the resulting neural suppression could worsen performance and may obscure treatment effects in a drug study.

Despite these concerns, the overwhelming majority of CCI studies use anesthesia, commonly isoflurane. Volatile gases (e.g., isoflurane, halothane) are often preferred due to their relatively short half-life compared to long-acting options (e.g., pentobarbital), facilitating evaluation of righting reflex shortly after anesthesia discontinuation [16]. Typically a high dose (e.g., 4 %) is used to induce anesthesia followed by a reduced maintenance dose (*see* Subheading 4). Anesthetized animals should be monitored to ensure consciousness is not regained during surgery. Assessments like the toe pinch can be used to assess sufficiency of anesthesia in accordance with institutional and national policies. One recent study of repetitive closed head injury used unanaesthetized mice that were instead comfortably restrained to avoid the confounding effects of anesthesia on TBI outcomes and promote clinical relevance [19].

Commonly encountered problems surrounding anesthesia are summarized later. First, if animals are intubated and the animal is fighting the ventilator, changes in tube placement may alleviate the problem. Also, if consciousness is regained, then the anesthesia induction system should be checked to ensure that the anesthesia is set to the appropriate level and there are no leaks in the tubing. It is also important to consider that if gaseous anesthesia is used, specialized laboratory equipment is required including appropriate ventilation and scavenging systems to ensure the safety of personnel; isoflurane detection systems are available to monitor exposure.

1.5.3 Craniectomy and Sham Procedure—Researchers typically produce craniectomy using a pneumatic or electric drill, although a handheld trephine is sometimes used. Efforts to reduce heat production during the craniectomy can help reduce potential confounders, and sterile saline can be applied to the craniectomy site to reduce the temperature if the procedure is prolonged. Since anesthesia and craniectomy can result in behavioral and functional changes it is important that when invasive CCI is used control animals be exposed to sham. Empirical evidence shows that craniectomy results in inflammation and lesions regardless of whether a trephine or electric drill is used, as compared to naïve rats (anesthesia only). However, lesions were largest and behavioral deficits were most severe in animals that received their craniectomies using a drill [65]. Craniectomy location also affects outcome with midline craniectomy leading to more sagittal bleeding [16] than parasagittal craniectomy [66, 67]. Bilateral craniectomies have been used to enhance lateral movement of tissue and produce subsequent bilateral cortical contusions [68, 69]; producing bilateral craniectomies is also a good way to train individuals on the procedure. Details regarding the control group should be provided in publications [65], including any bleeding, mortality, inconsistency across animals, etc.

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2 Materials

2.1 Animals

A strength of the CCI model is that it can be used in many species. In much of our work, adult male Sprague Dawley rats (280–320 g; Charles River Labs, Raleigh, VA, USA) are used; thus, this protocol is specific to Sprague Dawley rats. Our animals are routinely housed in a climate-controlled room with a 12 h light/dark cycle and are regularly monitored by the Department of Laboratory Animal Research.

2.2 Anesthesia

- Induction Dose: 4.0 % isoflurane in 2:1 N_2O:O_2.
- Maintenance Dose: 2 % delivered in 2:1 N_2O:O_2.

2.3 Supplies and Equipment

1. Homeothermic heating system (Harvard Apparatus, MA, USA).
2. Stereotaxic frame.
3. Isoflurane.
4. Cylinders of compressed N_2O and O_2 for isoflurane delivery.
5. Cylinder of compressed N_2 to drive pneumatic tip.
6. Anesthesia chamber.
7. Gas scavenging system.
8. Cannula for intubation.
9. Laryngoscope to assist with intubation, if necessary.
10. Animal trimmers.
11. Pneumatic drill with drill bits.
12. Compressed air for drill.
13. Betadine.
14. Sterile drape.
15. Cotton-tipped applicators.
16. Gauze.
17. Saline-filled syringe.
18. Sterile surgical instruments (scalpel; scissors; periosteal elevator; microdissecting forceps; rongeurs; bulldog clips, etc.).
19. Temperature probe and associated readout (Harvard Apparatus, MA, USA).
20. MouseOx Plus, blood oxygenation monitoring system, and associated readout (Starr Life Sciences Corp., PA, USA).

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21. Suture kit.
22. Pneumatic CCI device (Pittsburgh Precision Instruments, PA, USA).
23. Tip of desired size and shape.

3 Methods

1. Before starting the surgeries, ensure the CCI device is in good working order. Does the piston fire freely? Is the impact velocity and dwell time consistent with what is set?
2. Place the rat in an anesthesia chamber and induce anesthesia with 4% isoflurane in a 2:1 mixture of N_2O:O_2; ensure the animal is sufficiently anesthetized using a toe pinch test.
3. Intubate the rat.
4. Place the anesthetized animal in a stereotaxic frame and secure the incisor and ear bars to keep the animal secure throughout the surgery.
5. Adjust the anesthesia to the maintenance dose of 2 % isoflurane (*see* **Note** [1]).
6. Assess the animal's level of alertness using the toe pinch test for suppression of pedal response (or another similar test) to ensure sufficient anesthesia is being delivered.
7. Use the hair trimmers to shave the rat's scalp moving both with and against the grain.
8. Use a sterile drape to cover the animal such that the only opening in the drape is directly over the exposed scalp.
9. Use gauze and antiseptic solution (e.g., Betadine) to scrub the scalp and prepare the surgical site.
10. Use a scalpel to make a midline incision (*see* **Note** [2]).
11. Separate the muscle from the skull using the periosteal elevator and microdissecting forceps.
12. Reflect the skin and fascia to expose the underlying skull and scrub the surface of the skull with a cotton-tipped applicator.
13. Use pneumatic drill (hooked up to a compressed air cylinder) to create a craniectomy. Center the craniectomy between the sagittal suture and coronal ridge with the borders near the lambda and bregma for unobstructed tip clearance (*see* **Note** [3]).

[1]Traditionally, the authors of this chapter use a maintenance dose of 2% isoflurane in a 2:1 mixture of N_2O:O_2 titrating up the dose if the animal is showing signs of regaining consciousness.
[2]The incision made in our lab is approximately 20 mm long for rats (shorter for mice).
[3]The authors strive to make consistent craniectomies that are approximately 6 mm in diameter to facilitate clearance of a 5 mm diameter tip.

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14. If necessary, use rongeurs to elongate the craniectomy until it is large enough to accommodate the impactor tip; carefully lift away the resulting bone flap, so as to avoid dura breech (*see* **Note** [4]).

15. To ensure that the tip is centered over the craniectomy site, manually extend the shaft on the CCI device and gently lower the impactor tip so that it lightly and briefly touches the exposed dura mater.

16. With the piston statically pressurized and in the full stroke position, zero the tip to the cortical surface.

17. Carefully withdraw the tip and adjust the piston assembly to the desired impact depth based on the research goals and study protocol (*see* **Note** [5]).

18. Induce injury by actuating the CCI device; discontinue the anesthesia (*see* **Note** [6]).

19. Close the surgical site using sutures or another method. Apply topical anesthetic (e.g., lidocaine) to the surgical site to minimize discomfort.

20. Remove the rat from the stereotaxic frame and extubate.

21. Complete any assessments desired in the immediate postinjury period (e.g., righting reflex latency) and postsurgical monitoring.

22. Keep the test animal in a holding cage until it is able to fully recover from anesthesia, as evidenced by the return of spontaneous locomotion.

23. Once the animal has fully recovered, return it to the animal housing room and resume normal husbandry.

24. Continue to administer analgesic in accordance with institutional and government guidelines for pain management in laboratory animals.

4 Common Data Elements

The National Institute for Neurological Diseases and Stroke (NINDS) has published a set of common data elements (CDEs) for experimental TBI research including details surrounding the animals used (e.g., species, strain, commercial supplier), demographics (e.g., age, sex), metrics (e.g., weight), animal husbandry, and outcome assessment(s) used (e.g., timing of assessment, measures). Beyond the CDE's generic to all experimental TBI models, the NINDS recognizes a set of CDEs specific to CCI research. The CCI-specific CDEs include, but are not limited to craniectomy size, tip (size, shape, angle, rigidity), and injury parameter settings (depth, dwell time, velocity). Researchers are encouraged to review the current list of CDEs during study planning, grant writing, and dissemination of findings to promote comparison of studies and the conduct of high-quality research [70].

[4]It is common practice to discard the bone flap rather than attempt to reattach it, as this can lead to secondary injury (e.g., increased intracranial pressure).
[5]In our lab, we induce moderate TBI using a 5 mm tip to deform the neural tissue of a rat to a depth of 2.8 mm at a velocity of 4 m/s.
[6]Depending on the preference of the researchers and the method used to close the surgical site, anesthesia can be discontinued before or after wound site closure.

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5 Conclusion

CCI is one of the best characterized models of experimental TBI and it remains a popular choice for studying the physiologic and functional deficits that occur acutely and chronically following TBI. Traditionally, CCI is an invasive model that is preceded by craniectomy, but recently the model has been applied to study concussion and other types of closed head injury. The original CCI model was pneumatically driven but more recently, an electromagnetic alternative has been introduced which provides increased portability.

Researchers employing the CCI model should give care and attention to study design and selection of injury parameters. Control over important confounding variables (e.g., hypothermia, hyperthermia) is critical to adequately address the research questions. The first step is to thoroughly explore the literature to consider how various injury parameters have panned out with respect to histopathological and functional consequences in the past. Researchers are also encouraged to conduct pilot work in order to tailor the experimental design (e.g., injury parameters, tip size, anesthesia type) and subsequently facilitate addressing the research goals. Pilot research also provides a valuable opportunity to ensure that the device is in proper working order and is calibrated.

This chapter introduced the CCI model including a brief overview of its development and extension to various species and research applications. A list of required supplies and equipment was provided as well as a detailed protocol for pneumatic CCI in rats. Discussion of confounding factors and troubleshooting methods were briefly discussed. Lastly, the importance of CDEs was extolled and exemplars of CDEs specific to CCI were noted. This introductory chapter will enable readers to be thoughtful consumers of publications describing CCI research and have the requisite knowledge needed to design and conduct a CCI study.

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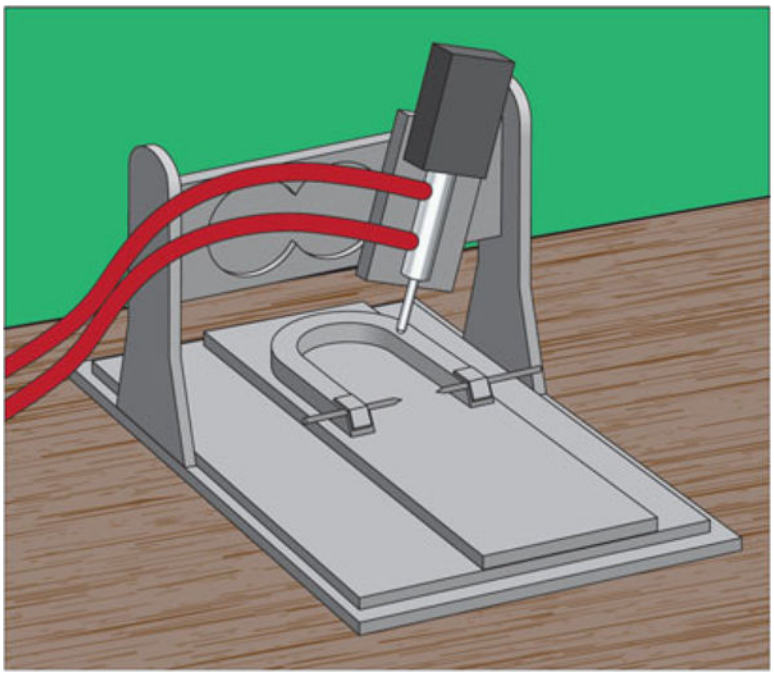

Fig. 1.

Diagram depicting a standard pneumatic CCI device (without the associated cylinder of compressed N_2 gas). Depending on the research goals, researchers can choose the ideal tip (e.g., size, geometry) and injury parameters (e.g., depth, dwell time, velocity)

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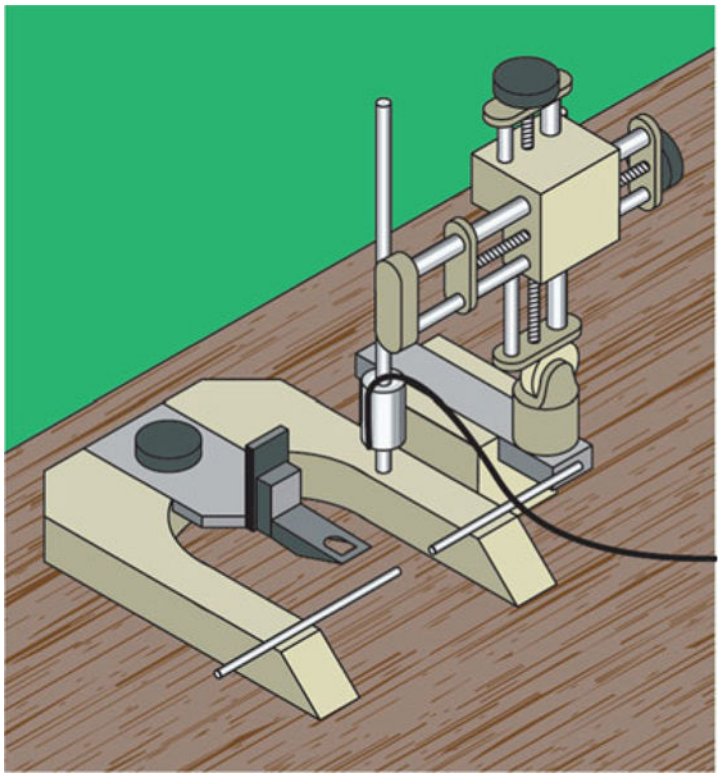

Fig. 2.

Diagram depicting a standard electromagnetic CCI device. As with pneumatic CCI, the tip and injury parameters can be adjusted. Unlike with the pneumatic model, the tip is driven by an electromagnetic actuator negating the need for N_2 gas

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Table 1

Commercially available pneumatic- and electromagnetic-CCI devices

CCI Type	Company	Model
Pneumatic	Precision Systems and Instrumentation	LLC TBI-0310 Impactor
	Pittsburgh Precision Instruments	Pneumatic Powered Controlled Cortical Impact Device
	AmScien Instruments	Pneumatic (Cortical) Impact Device (Model: AMS 201)
Electromagnetic	Leica	Impact One Stereotaxic Impactor for CCI
	Hatteras Instruments	Pinpoint PCI3000 Precision Cortical Impactor

Suppliers and models are listed for commonly used pneumatic- and electromagnetic-CCI devices

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Table 2

Commonly used CCI parameters for various species

Species	Injury site	Crani. size (mm)	Tip diameter (mm)	Velocity (m/s)	Dwell time (ms)	Depth (mm)
Mouse	Parietal Cortex	4–5	3	4–6	50–250	0.5–2
Rat	Parietal Cortex; Midline	6–8	5–6	4	50–250	1–3
Primate	Frontal Lobe	11–12	10	3.5	150	7
Pig	Frontal Lobe	15–18	15	2–4	50–400	12

For each species, injury details commonly used are provided including injury site, craniectomy size, tip diameter, velocity, dwell time, and depth

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