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Improved method for optical fiber temperature probe implantation in brains of free-moving rats

Stefan T. Musolino[a,b,*], Erik P. Schartner[a,c], Mark R. Hutchinson[a,b], and Abdallah Salem[b]

[a]*ARC Centre of Excellence for Nanoscale BioPhotonics and Institute for Photonics and Advanced Sensing, Adelaide, SA 5005, Australia*
[b]*Discipline of Pharmacology, Adelaide Medical School, The University of Adelaide, Adelaide, SA 5005, Australia*
[c]*School of Physical Sciences, The University of Adelaide, Adelaide, SA 5005, Australia*

ABSTRACT

Background: The localized monitoring of brain temperature is crucial to the understanding of the mechanisms underlying brain hyperthermia, such as that caused by stimulant drugs. Many animal studies investigating brain hyperthermia have utilized thermocouple electrodes for temperature measurement, however optical fiber sensors have proven to be an attractive alternative to conventional measurement techniques. Despite their advantages, optical fiber sensors in their current form have struggled to find effective use in studies involving free-moving animals.
New method: We have developed an improved optical fiber temperature probe and implantation method suitable for sensing in free-moving animals. By altering the structure of the probe, conventional guide cannulae can be used for stereotaxic implantation thus increasing ease-of-use and probe durability.
Results: The new probe structure was easily implanted and extremely durable both pre-experimentation and during sampling *in vivo*. Probe re-usability also allowed for increased experimental workflow. Rats administered MDMA showed pathological increases in brain temperature.
Comparison with existing method(s): Thermocouples commonly used for temperature measurement in deep brain structures lack the advantages offered by optical fiber sensors. Unlike our improved design, previous optical fiber temperature probes were unable to be removed from the brain of the rat without removing the dental cement affixing it to the skull. This made the probe susceptible to breakage and often resulted in the complete loss of the animal from the experiment.
Conclusions: Our fiber temperature probe and revised implantation technique can be easily employed in brain thermorecording using advantageous optical fiber sensors suitable for use in awake free-moving animals.

Keywords: Stereotaxic operation; *In vivo* optical fiber sensing; Brain hyperthermia; Rat model

HIGHLIGHTS

- Optimized method for deep brain thermorecording in awake, free-moving rats.
- Conventional technology utilized to simplify implantation.
- New probe structure minimizes risk of equipment damage before and during experiment.
- Probe capable of reuse, reducing experimental cost while improving workflow.

[*]*Corresponding author: The University of Adelaide, 30 Frome Rd, Adelaide SA 5000.*
E-mail address: stefan.musolino@adelaide.edu.au

1. Introduction

Hyperthermia is the most dangerous clinical impact of acute 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) intoxication (Kalant, 2001, Kiyatkin, 2005, Parrott, 2012) and a factor contributing to neurotoxicity (Gordon et al., 1991). It has already been established that an uncontrolled increase in brain temperature can have deleterious effects on neural cells and brain function (Brown and Kiyatkin, 2004), including disruption of the blood-brain barrier. The localized, real-time monitoring of brain temperature while under the influence of drugs such as MDMA is crucial to the understanding of the mechanisms underlying brain hyperthermia, as well as the effects of therapies targeted to alleviate these dangerous clinical symptoms.

Over the last three decades many studies investigating brain hyperthermia have utilized conventional thermocouple electrodes for temperature measurement in deep brain structures (Jiang et al., 1991, Busto et al., 1987, Brown and Kiyatkin, 2004, Kiyatkin et al., 2014). In more recent years however, optical fiber sensors have proven to be an attractive alternative to conventional measurement techniques. They provide unique advantages such as high sensitivity, immunity to electromagnetic interference, small size, robustness, as well as the ability to provide multiplexed sensing (Lee, 2003).

It has previously been shown that emission from rare-earth ions such as erbium (Er^{3+}) (Berthou and Jörgensen, 1990, Dos Santos et al., 1998, Wade et al., 1999), doped within a suitable host medium depends on temperature (Schartner and Monro, 2013). Using this information, optical fiber temperature probes based on erbium:ytterbium co-doped glass have been developed for localized temperature measurements (Schartner and Monro, 2013).

Previous animal studies utilizing optical fiber sensors have been conducted in animals under general anesthesia (Grant et al., 2001, Chavko et al., 2007, O'Hara et al., 2005, Peterson et al., 1984, Yu et al., 2016). However, it is widely known that general anesthesia causes robust temperature decreases (>4ºC) in both the brain and in the periphery (Kiyatkin, 2005). Many processes governing neuronal activity are temperature dependent, and even small (1-3ºC) decreases in temperature affect transmitter release and reuptake that can distort the drug-induced neuronal and neurochemical effects of tested drugs (Kiyatkin, 2005, Kiyatkin, 2010). Ideally, optical fiber sensors used for *in vivo* experiments should be robust enough to withstand experimentation in free-moving animals to remove the influence of general anesthesia on the final experimental results. This motivated us to develop a portable optical fiber temperature sensor for measurement in deep brain structures in free-moving rats (Musolino et al., 2016).

The sensor we developed obtained a temperature resolution of 0.1-0.3 ºC and successfully recorded brain temperature in awake, free-moving rats, however it suffered drawbacks related to the fixation of the optical fiber within a syringe needle to accommodate stereotaxic implantation. The rigid, all-in-one implantation of the fiber fixed inside the needle made the probe susceptible to breakage during the 48 h animal recovery period post stereotaxic implantation. Breakage of the probe in this state resulted in the loss of the sensor, as well as time and resources spent replacing it. Furthermore, it resulted in of the experiment as the remainder of the broken probe stayed fixed to the skull and could not be removed without causing excessive damage.

In this study, we describe an improved method for optical fiber sensor implantation in free-moving animals. By using a revised probe structure, we have developed a fiber optic temperature probe that can utilize a standard microdialysis guide cannula for stereotaxic implantation to reduce the risk of fiber breakage prior to and during experimentation. The obtained data demonstrates that the optical fiber temperature sensor provides an efficient means of brain temperature recording in awake, MDMA stimulant administered, free-moving rats.

2. Materials and Methods

2.1. Probe fabrication

Probes were fabricated using a method described previously using sodium zinc tellurite (ZNT) glass, doped with 1 mol% erbium and 9 mol% ytterbium (Musolino et al., 2016). Co-doping with a sensitizer, in this case ytterbium, allowed for the upconversion efficiency to be significantly increased over doping solely with erbium. Temperature is monitored by observing two emission bands at 520 and 547 nm, with the ratio of these two being correlated to the temperature of the probe.

A 2-meter polarization maintaining (PM) fiber (Nufern 980XP) with connectorized patch cable was used, and 15 mm of coating stripped from the tip of the fiber. A guide cannula (BAS MD-2251, Bioanalytical Systems Inc., West Lafayette, IN, USA) was altered to house the fiber. The metal rod of the guide cannula dummy cap was removed, and the fiber was inserted in its place. The fiber was then cleaved and glued inside of the cap with approximately 4 mm of fiber protruding from the end of the cap, 2 mm of which was tellurite glass coated fiber tip (Fig.1). This fiber tip length was chosen to minimize the impact of fiber implantation on the surrounding microcirculation in tissue. This fiber was sheathed within a standard 900 µm diameter optical fiber protective sleeve. In these probes only the end-face of the fibre is sensitive to temperature, with the coating that runs on the external surfaces of the fibre having no impact on measurements.

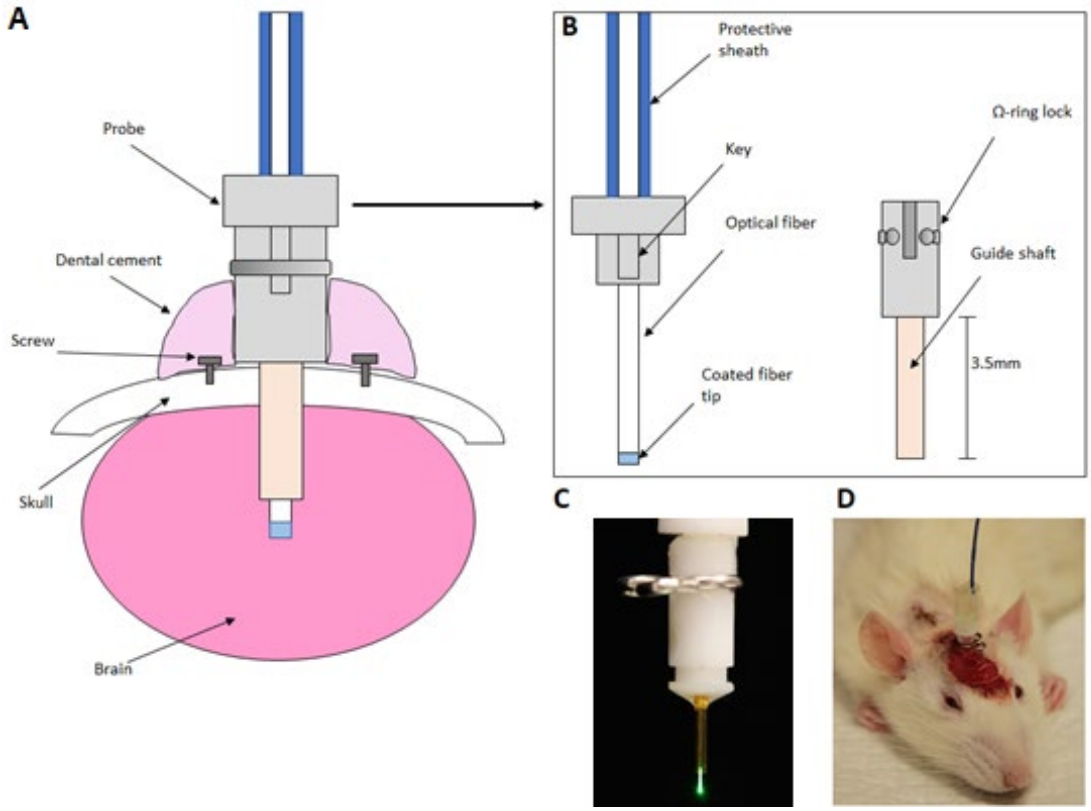

Fig. 1. **(A)** Surgical implantation of optical fiber temperature sensor. **(B)** Optical fiber temperature sensor structural components. **(C)** Photograph of the temperature sensor. **(D)** Photograph of the implanted sensor located in the striatum of an anaesthetized rat post-surgery.

2.2. Animals

Eight pathogen-free male Sprague-Dawley rats were used, weighing 270-300 g. All animals were supplied by the University of Adelaide Laboratory Animal Services (Adelaide, South Australia). Rats were housed in temperature (18–21 °C) and light-controlled (12 h light/dark cycle; lights on at 0700 h) rooms with standard rodent food and water available *ad libitum*. Ethics approval for this study was given by the University of

Adelaide Animal Ethics Committee, and all procedures were in strict accordance with the National Health and Medical Council of Australia Guidelines for the Care and Use of Laboratory Animals.

2.3. Optical fiber guide cannula implantation

Rats were anesthetized with chloral hydrate (400 mg/kg i.p.) in 0.9% saline and placed on a water-heated pad (37ºC). Once fully anesthetized, the animal's head was secured in a stereotaxic frame (Kopf Instruments, Tujunga, CA, USA). After the skull was exposed, the bregma was located and the guide cannula was implanted into the right striatum (A: +0.2 mm, L: +3.0 mm, V: -3.5 mm from bregma). All coordinates were referenced from a rat brain atlas (Paxinos and Franklin, 2004). The guide cannula was held in place using dental cement (Vertex, Dentimex BV HJ, Zeist, Netherlands) to form a robust attachment point to the skull (Fig. 1). Following the surgery, rats were given 48 h to recover. A recovery period of 24 h is considered as satisfactory for microdialysis studies, as neurotransmitter levels are stabilized and interference due to surgery and anesthesia is limited (Westerink, 2000, Esteban et al., 2001, O'Shea et al., 2005). At the end of each experiment animals were humanely killed via anesthetic overdose with chloral hydrate and brains carefully removed and stored in the freezer for future histological analysis to validate correct probe placement.

2.4. Drug treatments

Prior to saline (10ml/kg, i.p) or MDMA (10 mg/kg, i.p) administration at t=0 on the experimental day, ambulatory rats were pre-treated with 3 doses of saline (10ml/kg, i.p) following a therapeutic drug pre-treatment schedule. On the experimental day rats were gently restrained as the dummy cap was removed from the guide cannula and the temperature probe inserted into the striatum. Brain temperature recording was started shortly after probe insertion at 9am (time -120), and the last saline pre-treatment injection administered at 10.30am (time -30). The temperature recordings taken between time -120 and time 0 were used to establish baseline brain temperature levels. At 11am (time 0), rats received either saline (10ml/kg, i.p) or MDMA (10 mg/kg, i.p) after which brain temperature was recorded for a further 4 h until the end of the experiment. National Instruments LabVIEW software was used to simultaneously record both the upconversion emission from the fiber probe, as well as the ambient temperature from a resistance temperature detector (RTD) (Fig. 2). A high ambient room temperature of 29 °C was maintained for the duration of the experiment.

2.5. Data analysis

Significant brain temperature differences between control and MDMA-treated groups were evaluated using two-way ANOVA with Bonferroni's post-hoc test. $P < 0.05$ was considered statistically significant.

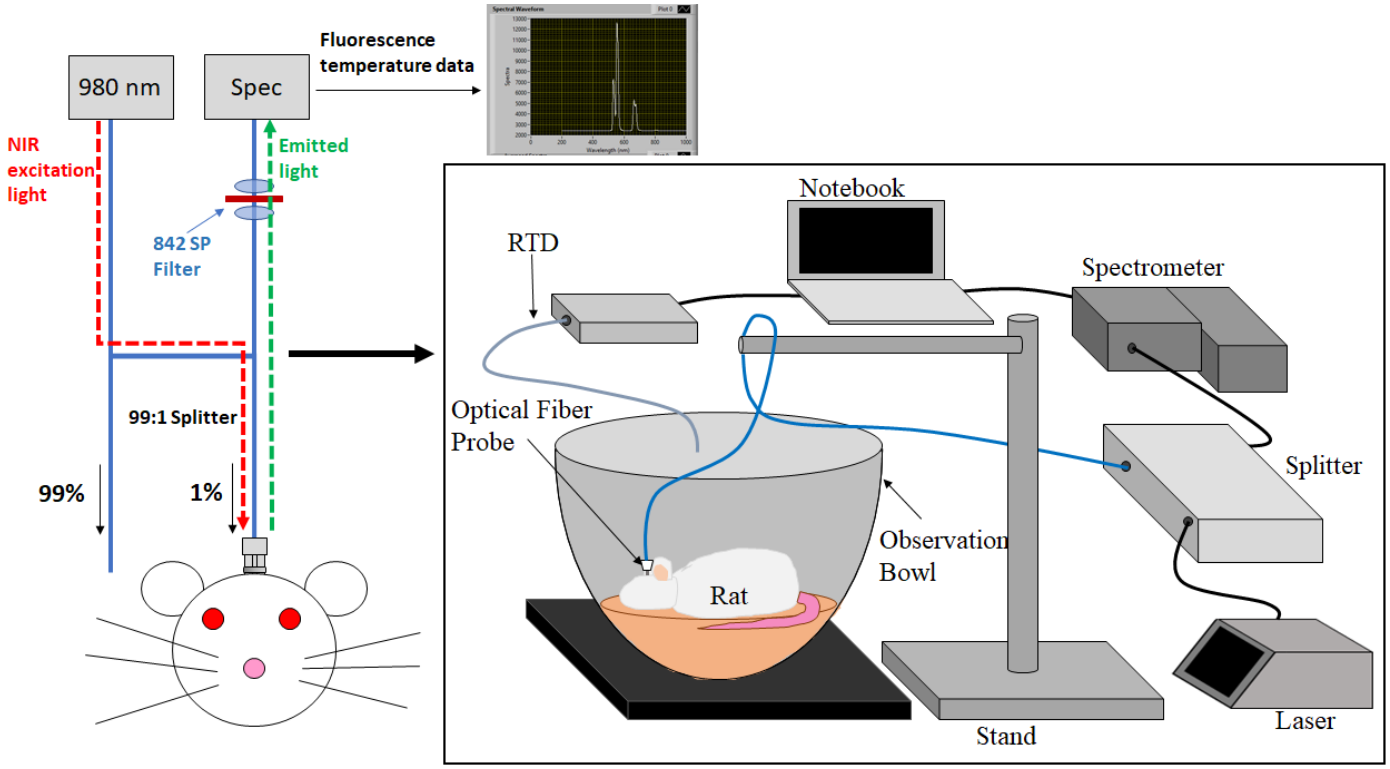

Fig 2. Experimental setup for in vivo temperature measurement using portable optical fiber temperature sensor. A 980-nm wavelength excitation light is used, and the emitted light of 524-nm and 547-nm are acquired with a spectrometer.

3. Results

3.1. Effect of MDMA at high ambient temperature

Using our improved technique, we found that changes in brain temperature caused by differential drug treatments were clearly identifiable. Fig. 3 shows that when administered at high ambient temperature a saline drug treatment caused no significant increase in striatal brain temperature at any time point compared to baseline temperatures ($p > 0.05$). The mean basal temperature of saline treated rats was 36.34 °C ± 0.13 and this remained steady with no significant fluctuation for the duration of the experiment.

However, MDMA administration at high ambient temperature caused significant increases in striatal brain temperature. Fig. 3 shows that striatal temperature was significantly increased at 30 minutes post-MDMA administration ($p < 0.0246$) compared to the saline controls ($p > 0.05$), and this peaked at 90 minutes post-MDMA ($p < 0.0001$). The MDMA-induced elevated striatal temperature was maintained for the majority of the 4-h observation period, however significant temperature differences ceased at 156 minutes post-MDMA ($p > 0.05$).

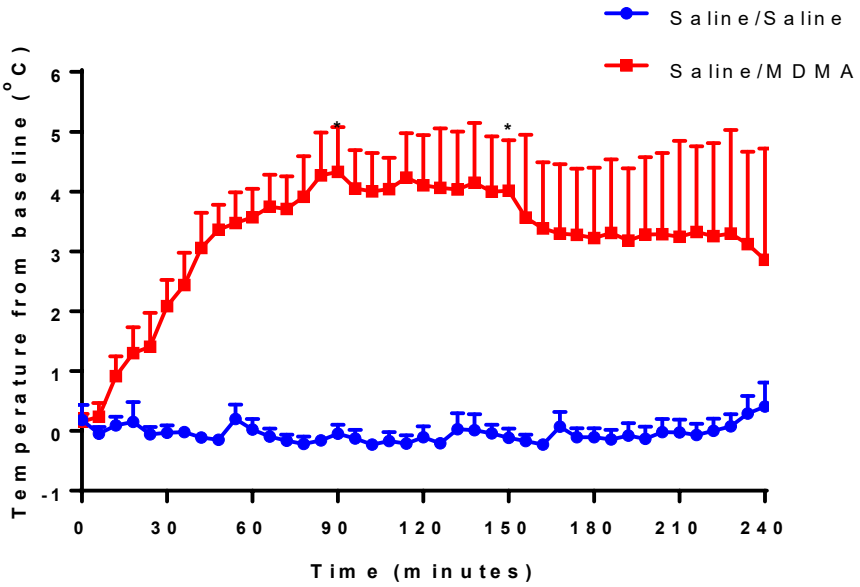

Fig 3. *In vivo* results for fluorescence brain temperature probes in saline/saline (n=4) and saline/MDMA treated rats (n=4) at high ambient temperature (29 ºC). Temperature data is averaged across all trials at 6-minute intervals. Error bars show the standard error in the mean. * indicates where animals died prematurely.

3.2 Post-operation

After the operation, animals recovered quickly and resumed eating and grooming after awakening and were allowed free movement around the observation bowl during the recovery period. All animals were closely monitored over the following 48 hours to ensure no damage was done to the guide cannula. Some animals scratched at the guide cannulae area however none were able to remove the guide cannula or open the Ω-ring lock on the guide shaft. The implantation of guide cannulae independent of the sensor ensured no damage was done to the sensor during the recovery period prior to experimentation. Conversely, previous probe implantation methods resulted in probe breakage prior to experimentation on 9 of 15 occasions (Fig. 4). Post-experiment, animals were sacrificed, and the temperature probe removed from the guide cannula for later reuse. Guide cannulae were then removed from the skull.

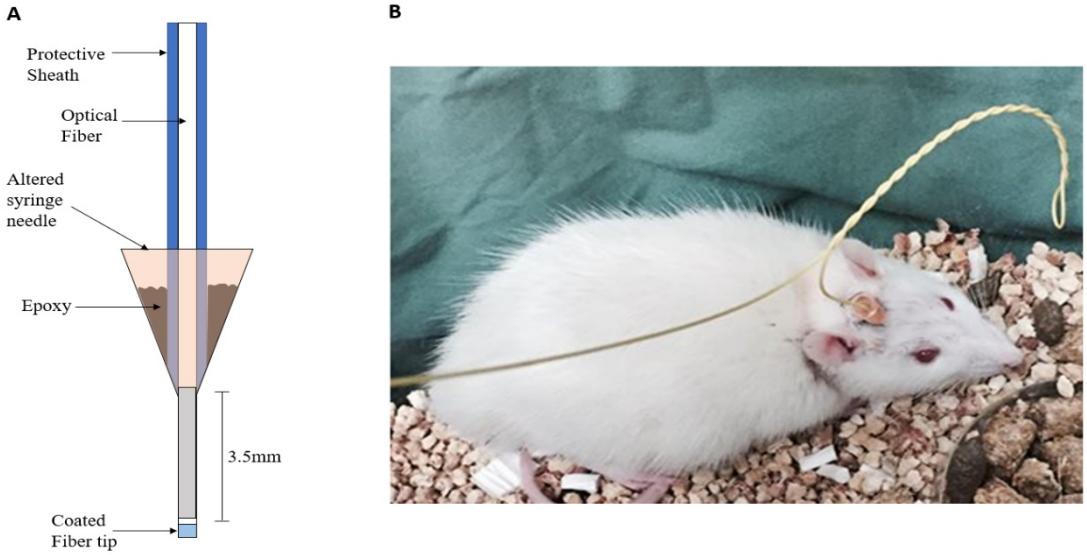

Fig 4. (A) Previous model temperature sensor structural components. (B) Photograph of implanted previous model temperature sensor implanted within a live rat. Movement of the animal during the overnight recovery period lead to excessive fiber twisting resulting in probe breakage.

3.3 Probe Durability

On the experimental day the temperature probe was inserted successfully through the guide shaft without damaging the probe tip (Fig. 5A). Bending and twisting of the probe was observed throughout MDMA experiments, however this did not result in probe breakage on any occasion. Removed brains displayed only a small hole indicating that animal movement during the experiment resulted in no lateral movement of the probe within the guide shaft (Fig. 5B). Post experiment, *in vitro* probe calibration tests revealed that no significant difference in overall probe signal intensity between pre-implant and post-implant probes, indicating no damage to the sensor occurred during the experiment (Fig. 5C). Post-experiment calibrations also displayed no significant difference in FIR-generated temperature values between pre-implant and post-implant probes, indicating probes were capable of reuse after removal (Fig. 5D).

The separation of temperature sensor from the implant housing allowed for multiple animal implantations per week requiring only one calibrated sensor for data collection. This facilitated increased experimental throughput on consecutive days due to reduced fiber fabrication time. Previous methods required one calibrated sensor per animal, limiting experimental output due to necessary fiber re-fabrication periods post-experiment. The ability for easy probe removal post-experiment also significantly cut time and resources costs associated with fabricating new sensors for following experiments. This also removed the potential for probe tip damage during cannula removal from the skull following data collection.

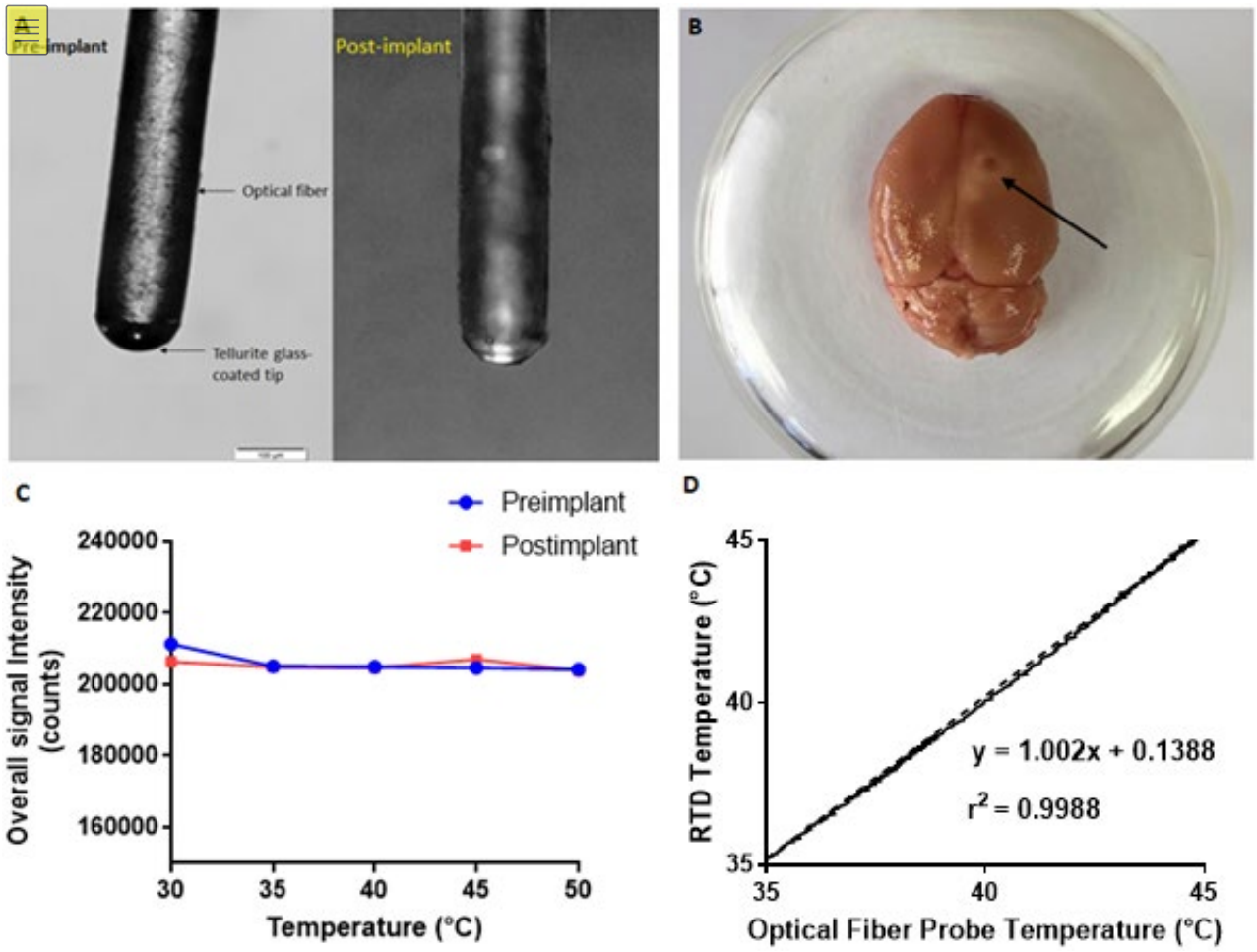

Fig. 5. (A) Microscopic photograph of the temperature sensor and tellurite glass-coated tip pre and post brain implantation. **(B)** A small hole indicating where the probe was inserted. **(C)** *In vitro* overall signal intensity results for brain temperature probes pre and post implantation. **(D)** Linear regression curve of optical fiber temperature probe post-implantation and RTD. Optical fiber probe temperature data expressed utilizing pre-implant calibration values.

4. Discussion

Until recently, the approaches to measure brain temperature *in vivo* has been limited to thermocouple electrodes, which lack many of the benefits provided by light-based sensing. This led us to develop an optical fiber based temperature probe capable of recording brain temperature within an ambulatory rat (Musolino et al., 2016). Although this sensor achieved localized temperature measurement within deep brain structures, its durability before and during experimentation was not satisfying. Therefore, we developed an improved optical fiber temperature probe with increased durability that utilized a more conventional stereotaxic implantation and insertion technique.

This new optical fiber temperature probe and altered implantation method provided many advantages at all stages of our experiments compared to previously used probe designs. The ease of surgical implantation was greatly increased, as guide cannulae used with the new probe interacted more smoothly with the stereotaxic equipment during surgical implantation compared to the previous probe's altered syringe needle housing. Furthermore, the separation of the sensor from the guide cannula allowed for significantly increased probe durability during the recovery period post-surgery. Many experiments utilizing previous probes ended prematurely due to probe breakage pre-experimentation. Unlike the improved design, previous probes were non-removable from the brain of the rat without first removing the dental cement affixing it to the skull. This made the probe extremely susceptible to breakage when left unattended during overnight recovery. Most probes were either snapped due to excessive twisting caused by animal movement or gnawed through by the animal, resulting in the complete loss of the experiment. New probes were fabricated with the capacity for removal after surgical implantation to remedy this issue. This removability and reusability feature allowed for multiple animal implantations whilst requiring only one temperature probe for all brain thermorecording. This feature drastically reduced the time and resources spent fabricating new sensors after each failed experiment and allowed experiments to take place in parallel increasing experimental workflow.

Using our improved method, we found that a dose of MDMA (10 mg/kg, i.p.) administered at high ambient temperature (29 ^{o}C) induced a long and modest hyperthermia in some animals, while others showed extremely high pathological increases in brain temperature values compared to their saline controls. MDMA under these warm conditions was excessively toxic, resulting in lethal over-heating of brain tissue (>42 ^{o}C) in two tested animals. This mortality rate is notable as the commonly accepted LD_{50} for intraperitoneally injected MDMA in the rat is 49 mg/kg (Hardman et al., 1973). Our results support previous data that high ambient temperatures exacerbate the MDMA-induced hyperthermic response (Gordon et al., 1991, Malberg and Seiden, 1998, Seiden and Sabol, 1996). It is well known that the brain is the most temperature sensitive organ in the body and even small deviations in temperature can have profound negative impacts within the brain (Schiff and Somjen, 1985), thus an effective means of localized thermometry is required to better assess and understand these impacts.

Optical fiber sensors should compete with more established neural recording techniques such as thermocouple electrodes, however these new sensors do not always appeal to users already accustomed to these mature technologies (Lee, 2003). We have developed a new probe that utilizes an implant procedure identical to that of conventional microdialysis techniques, complete with a fully portable optical setup (Musolino et al., 2016) to accommodate an ease of transition from conventional techniques to the advantageous optical fiber sensing. These fiber sensors also have the potential for multiplexing with other sensors to measure other chemical properties, or for simultaneous imaging and sensing to be done using the same fiber (Li et al., 2018).

Future investigations will use this method of brain thermorecording to assess the therapeutic effects of treatment drugs in animals suffering from acute MDMA intoxication. This improved method of temperature measurement in the brain should allow for an improved understanding of the hyperthermic effects of stimulant drugs, as well as the therapeutic effects of the drugs used to alleviate their dangerous clinical symptoms.

We believe that our novel temperature probe and revised implantation technique can be employed to make brain thermorecording using optical fiber sensors in awake free-moving rats easier, more reliable, and more reproducible in future neurological studies.

Conflicts of interest

None.

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