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Could COVID expand the future of addiction research? Long-term implications in the pandemic era

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Abstract

Background/Aims: The COVID-19 pandemic has significantly impacted face-to-face research. This has propelled ideas and plans for more remote styles of research and provided new perspectives on conducting research. This paper aimed to identify challenges specific to conducting remote forms of experimental addiction research, although some of these challenges apply to all types of addiction research.

Argument: The impact of the COVID-19 pandemic has led to important lessons for future addiction research. Although remote research has been conducted for decades, little experimental research has been performed remotely. To do so require a new perspective on what research questions we can ask and could also enable preferential capture of those who may be more reluctant to engage in research based in clinical settings. There may, however, be crucial factors that will compromise this process. We illustrate our argument with three real-world, ongoing case studies centred on gambling behaviour, opioid overdose, and cannabinoid psychopharmacology. We highlight the obstacles to overcome to enable more remote methods of study.

Conclusions: The future of experimental research and, more generally, addiction research, will be shaped by the pandemic and may result in advantages, such as reaching different populations and conducting addiction research in more naturalistic settings.

KEYWORDS

Addiction, cannabis, COVID-19, gambling, opioids, research

INTRODUCTION

The COVID-19 pandemic has resulted in face-to-face research being either paused or significantly changed to protect against transmission of the virus. This has ignited discussions on how remote research might be feasible and adopting methodological approaches that would have previously been regarded as only relevant for future studies, or deemed impractical or unsafe. Although some research has returned

to pre-pandemic state, generally, new explorations into addiction research have been triggered. Therefore, if we are to consider taking our work to participants' homes, or other remote locations, might it involve compromises? We argue that much can be gained from this new direction and will provide important lessons for future studies.

As researchers with a special interest in experimental research, our work has been particularly impacted by the pandemic restrictions. This has forced us to reflect on our work from a perspective that is somewhat novel to our research (although not to the wider field). Many areas of addiction research have already conducted research

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remotely (e.g. collecting data via telephone) because of the pandemic [1]. Others have been conducting research remotely for decades via telephone questionnaires or interviews, among other remote methods, (e.g. remotely delivered contingency management in individuals with opioid use disorder or mobile phone-based smoking interventions) [2–5].

Remote forms of addiction research will undoubtedly offer a number of advantages in the future. However, experimental research is particularly challenging to conduct remotely, mainly because of its uncertainty in collection of outcome measures as well as safety and practical aspects that are usually addressed by the controlled clinical settings, in which they normally take place. Therefore, our main focus for this paper is on case studies involving experimental addiction studies. We present a number of general areas for consideration, before using ongoing case studies from live research in three areas (gambling, cannabis and opioid overdose) to highlight how these changes can offer benefits and challenges for remote experimental research.

GENERAL ETHICAL, MORAL, AND LEGAL CONSIDERATIONS

Addiction research, as all research, needs to be conducted legally, ethically and morally—to explore areas of the addiction field that yields a greater understanding of addiction and its related harms, but doing so within the bounds of the law, and to ensure the safety, wellbeing, dignity of participants—with a genuine scientific justification. Researchers require ethical approval for their study protocols, local Research and Development (R&D) approvals to ensure the study is sponsored by the local research institution and appropriate indemnity insurance, should a participant be harmed by the research. Furthermore, because addiction research often involves the administration of drugs with abuse liability, the research needs to take additional precautions, especially ethical considerations whereby the research should not encourage or condone illegal activities or expose the participant to potential legal consequences. In the case of experimental research when drugs are administered to participants, the researchers are required to seek exemptions from the law in the form of licences from government bodies. Such licences vary by country, but in the United Kingdom (UK) the licences are issued by the Home Office—and include licences for storage, handling and administration to participants.

Since the COVID-19 pandemic, moving addiction research online and into peoples' homes happened relatively seamlessly for some studies and approval bodies were accommodating for research into the effect of COVID-19: indeed, in some instances, ethical approval was granted within days of applying. However, studies to explore the effects of illegal drugs may face significant challenges. Even when researchers wish to study the effects of a drug that a participant regularly takes, it may still pose legal and ethical challenges. First, researchers may be seen as incentivising illegal behaviours by asking volunteers to participate, especially if participants are provided with reimbursements. Second, although researchers are studying drug use

that a participant engages in regardless of the research, researchers might potentially be held responsible should the participant be harmed by the drug use on this occasion. This would require the researchers to have safety procedures in place in case there is an adverse event—difficult if the research is done remotely. Third, should the researchers wish to conduct a randomised controlled trial remotely, perhaps the most ambitious form of remote research, significant legal and ethical barriers need to be overcome. To our knowledge, such research has not yet been attempted, and ethics committees and licencing boards are unlikely to know how to deal with such a request. A hypothetical Home Office licence for a participant to use an illegal drug (provided by the researchers) in their home may prove difficult as the licence would grant permission for the person to effectively break the law during a prespecified time (the experiment), and to that effect legalising the drugs the participant may have in their home. This may be politically sensitive because it could be viewed as policy makers are condoning drug use or drug possession by permitting such research. Last, it could be argued that observing participants over video call when they are engaged in illegal activities (using drugs) should be avoided because confidentiality cannot always be assured with all video call software.

RESEARCH ACCESSIBILITY

The adaptations and innovations implemented in research protocols as a result of COVID-19 have the potential to both increase and reduce research accessibility. For researchers, lockdown provided both challenges and opportunities. One ongoing challenge facing researchers, particularly those working with groups traditionally harder to reach, is participant access. Lockdown ensured that people were in one place, most of the time. The convenience of participating from home may assist recruitment, and lead to lower attrition for studies that require multiple sessions. This is exemplified in a study by Neale et al. [1] looking at the experience of rough sleeping during the pandemic. The 'Everyone in' initiative to temporarily house all street homeless during lockdown resulted in a large number of homeless individuals being in the same place. Researchers were able to initiate and maintain contact with previously homeless individuals via telephone in the accommodation rooms, therefore, enabling access previously difficult to maintain. Furthermore, a necessary shift toward online data collection enabled participants who may not otherwise have been included in on-campus research, thereby increasing research accessibility and reducing inequalities that disadvantage those with additional commitments such as caring or work responsibilities. The lack of geographical restrictions could improve the diversity of participant samples, which can increase the generalisability of findings. However, although predominantly online research may reduce some existing inequalities, digital exclusion may disadvantage other groups. Some individuals do not have the required broadband access to adequately run studies, or may not have the necessary technical knowledge to access online research. Although some of these problems can be averted through considered research design, some

digital exclusion will doubtless remain; therefore, researchers will need to consider this when adapting research for the post-pandemic era.

FURTHER METHODOLOGICAL CHALLENGES

The disruption to face-to-face research, although bringing a number of new benefits and opportunities, such as increased research accessibility, also presents researchers with new challenges. The challenges can vary depending on research methodology. For example, in qualitative research, although interviews are possible via online or telephone interviews, the capacity to build a relationship between researcher and participant is reduced. Furthermore, it is possible that language barriers can be amplified, and the lack of non-verbal cues can hinder understanding, particularly with non-native English speakers, or those with hearing difficulties. Researchers will also face practical challenges in the post-pandemic era; some studies require equipment, ranging from something simple such as a heart rate monitor, to something more advanced, such as an MRI scanner. Although it will be possible to adapt equipment use and study protocol for some research, others will necessarily remain lab based. A further practicality of remote research to consider is the delivery and subsequent return of equipment, such as oximeters and virtual reality (VR) headsets to the host research facility. Equipment will need to be posted or couriered to participants, and participants may need to be offered incentives to return equipment. This would place an additional financial consideration on budgets; therefore, additional funding contingencies would need to be put in place. Additionally, some fundamental research procedures are also more challenging when done remotely such as obtaining informed consent and issuing participant payments, while maintaining compliance with General Data Protection Regulation (GDPR) regulations. Such procedures will need to be refined for the post-pandemic era.

SAFETY CONSIDERATIONS

Some aspects of safety, both of participant and researcher, may be compromised when conducting research remotely. This is particularly relevant to experimental drug studies where the clinical setting, often within a hospital, is preferred because of the presence of safety provisions, the presence and expertise of clinical staff and the proximity of emergency medical services. These important safety aspects are minimally present in someone's home or a remote setting. This is not to suggest that remote, experimental studies cannot be conducted safely. However, safety issues must be addressed in a way that is still adequate, meanwhile still fulfilling the aims of the research. For example, in some cases, it may be required that researchers remain outside of the home/remote setting for the duration of study and be located at a close

proximity to the remote setting (e.g. within a vehicle outside) but this could be implemented by use of live capture of vital signs and video-call software, thereby minimising physical contact with participant, except where it is absolutely necessary. Even an issue as minor as lack of mobile signal on a researcher's phone may require extra planning. Although these types of issues may seem trivial, they become crucial when faced with a potentially life-threatening adverse event. The case studies in this paper are concrete examples of the varied issues that can arise in remote studies.

Case study 1: gambling behaviour and virtual reality

This study uses a slot-machine task delivered in fully immersive VR to assess the impact of specific within-game constructs such as near-misses on persistent gambling behaviour. In a purpose-constructed VR lab, participants complete a range of cognitive assessments (on paper) and, assuming inclusion criteria are met, then perform two tasks (one gambling, one non-gambling) in fully immersive VR, before completing further paper assessments. The virtual environment is calibrated to the research space, which includes a mock 'gambling zone', including a bar stool and a fruit machine case. This set-up allows the researcher to retain full experimental control of the environment in which the behaviour to be studied is performed, while increasing ecological validity in task delivery. The outcome sequence in the tasks can also remain under researcher control to ensure consistency across tasks and study conditions.

In the 'at-home' version of these studies, tasks that are currently programmed in Unity and delivered via a desktop personal computer (PC) and a VR headset, would be transferred to a mobile platform, and could be delivered via inexpensive VR headsets such as the Google cardboard, which could easily be posted to the participant's house. Study protocol documents, consent forms and paper assessments completed could be completed online, with simple step-by-step instructions provided. Although developing the capability to take part in this study at home would increase the physical accessibility of the study, it would exclude those not able to either access online content, or download a VR based app onto a smartphone. Furthermore, the VR experience would not be as immersive (i.e. missing the tactile stimulus), and the researcher would lose the experimental control afforded by in-lab studies. Furthermore, on completion of the study, to ensure ethical compliance, participants are subject to a post-test debrief to ensure the task has not triggered cravings to gamble: if cravings are induced by the study, protocols are in place to manage this. However, the protocols are based on immediate assessment in a face-to-face context—not immediately and easily possible when the study is delivered remotely.

Overall, it would be possible for this study to move online and be delivered remotely, provided significant technological and methodological adaptations were introduced.

Case study 2: opioid overdose in heroin-assisted treatment

This study focusses on the effects of varying doses of pharmaceutical heroin (diamorphine) on respiratory function to better understand overdose risk. This study measures a variety of physiological markers of respiratory depression in response to diamorphine injected at different doses within a clinical research facility. These markers are obtained by measuring pulse oximetry, carbon dioxide, airflow and neural respiratory drive via electromyography of parasternal intercostal muscles. The study allows participants to self-administer their dose in as realistic and usual way as possible [6]. Participants recruited for this study are those on diamorphine/heroin maintenance treatment who, as part of their ongoing treatment, are prescribed 'take-home' doses of diamorphine and typically administer their own medication at home.

As part of the 'at-home' version of this study, participants would not experience any change to their usual drug self-administration. Furthermore, it is certainly possible to conduct screening and physiological monitoring while also implementing robust safety procedures in a participant's home or non-hospital setting, but these come with some caveats. Nonetheless, an experimental at-home study of heroin overdose represents a new opportunity to examine drug administration in the very environment that participants will be using, potentially providing the most naturalistic environment possible for this type of study. However, issues pertaining to safety of the participants require even more careful consideration. Losing proximity to an emergency department means that adaptations must be made to the study design. For example, we decided that, at least initially, a dose escalation or dose increase to the study drug should not take place in the 'at-home' context. Additionally, to facilitate a potential emergency intervention, the 'at-home' study would require the presence of a study doctor either in the home or close by as described in the 'Safety Considerations' section. Other issues such as the transportation of bulky equipment and its security are issues that also need consideration. Each physiological measure in the study has its own device and they are all connected together via a separate device to one laptop. All in all, this study can be conducted in the home of participants and without disruption to participants' treatment or usual drug administration.

Case study 3: cannabinoid psychopharmacology

These studies usually require volunteers to attend experimental visits at a research facility where they are initially screened by a study doctor for medical or psychiatric conditions, and given urine drug/pregnancy screen to ensure the study does not put a pregnancy at risk and no other psychoactive drugs are present that might interfere with the research. Blood samples and vital signs are collected throughout the session to monitor plasma levels of drug during the course of the day and what physiological responses these are associated with. Normally the main outcome

measures include standardised cognitive assessments, psychological questionnaires and clinical interviewing to assess the psychotic-like effects cannabis may have on some individuals. The careful screening of participants, presence of experienced research and clinical staff, a calm and distraction-free space and the availability of rescue medication (usually benzodiazepines) ensures participant safety and the integrity of the data collected.

In the 'at-home' version of these studies, the blinded study drug and rescue medication could be couriered to the participant's home, along with urine/pregnancy tests and a portable vital signs monitor (all of which will be collected from the participant after the experiment). Instructions for how to self-administer the study drug and urine tests can be given to the participant by the researchers live via video call. Online platforms can be developed for the delivery of cognitive tasks and psychological questionnaires. Clinical interviews to investigate the psychotic-like effects of cannabis can be done using video call after the participant is no longer intoxicated. Such a study might not be able to incorporate the same level of safety procedures, and so the study population may need to be restricted to more experienced users or the dose of the drug may need to be reduced, at least initially, to minimise the risk of adverse effects. Researchers may still be required to develop further safety protocols as described in the 'Safety Considerations' section'. Furthermore, the quality of cognitive test data may not be assured as the participants' home may not provide a distraction-free environment nor would the researcher be there to assist the participant with questions or if the participant becomes confused. Last, collection of blood samples would be challenging as blood samples often need to be centrifuged within minutes of collection.

KEY LESSONS LEARNT

The usual experimental set-up in the studies described here crucially allows researchers to retain experimental control of the study environment and procedures. However, although there are obstacles that overlap within each of the three case studies that need to be overcome, we conclude that it is possible to conduct these studies remotely. Furthermore, there are associated advantages. Special attention is needed regarding the quality of collected data to ensure comparability to that collected in the laboratory. The benefits and compromises, challenges and opportunities that manifest in different ways across different research fields require careful consideration.

Advantages to remote research

1. An advantage to remote research is comparing laboratory versus naturalistic settings. Although laboratory-based experiments allow the researchers to retain full experimental control (e.g. environment, dosage, outcome sequences, etc.), it can be argued that remote research delivered to the individual in a naturalistic setting (e.g. their own home) will create an environment where the individual is more likely to act more naturally.

2. Remote research increases accessibility of research in some respects; those who are unable to travel to a research site, will be able to complete research conducted purely online. In this respect, remote research is beneficial and increases real-world relevance and generalisability.
3. There is a protective benefit for researchers and participants during a global health pandemic. A perhaps obvious advantage of remote research is the ability to conduct research without face-to-face interaction, thereby preventing transmission of a highly contagious virus. This is particularly relevant to drug users who may potentially be at increased risk of respiratory-related conditions.
4. There is an issue of cost and funding. Although there may cost saving benefits in conducting research remotely, with regard to, for example, renting a room, travel, etc., there are other costs relating to procurement of digital devices that may have additional funding requirements.

Areas that require compromise or further consideration:

1. How much experimental control can be compromised to allow increased ecological validity? Furthermore, less is known regarding data quality of remote cognitive/biological studies. Further information on quality of remotely collected data is required.
2. We must make sure to also consider those who do not have the right or sufficient technology, or adequate connectivity to complete online studies, which might constitute a form of digital exclusion. Although some low-cost alternatives such as Google cardboard VR headsets are available, some other required technology cannot be used remotely (e.g. MRI scanners). How can we balance accessibility and practicality?
3. Arguably the most important considerations centre on safety, of both the participant and the researcher. Studies that require administration of substances such as cannabis and heroin are conducted in the laboratory under strict protocols, with emergency procedures and safety measures in place. Although some safety measures can be implemented if a researcher attends to the remote research site, less can be done if the remote research requires self-administration. Furthermore, risks for researchers are increased if working alone and entering, for example, a stranger's house.
4. Protocols such as emergency response teams on alert and researcher safety protocols can be developed to mitigate safety risks, but these risks, although reduced, are not removed. Therefore, what increase in risk is acceptable to facilitate remote research?

CONCLUSIONS

Many aspects of addiction research are likely to revert back to how they were before the pandemic. Many lessons will have been learned from this challenging time that may expand the reach of addiction research and be more resilient against future disruption. Although

remote experimental research may experience initial barriers and teething problems, we believe pursuing innovative experimental designs will bear fruit in the long-term.

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J.S. is a researcher and clinician who has worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments from whom his employer (King's College London) has received honoraia, travel costs and/or consultancy payments: this includes, last 3 years, MundiPharma, Camurus and Accord and trial medication supply from Camurus. J.S.'s research is supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. J.S. is an NIHR Senior Investigator. For a fuller account, see at <http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx>.

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