

Patient Registries in Cognitive Neuroscience Research: Advantages, Challenges, and Practical Advice

Lesley K. Fellows¹, Marianna Stark², Arlene Berg¹,
and Anjan Chatterjee²

Abstract

■ Neuropsychological work is the historical foundation of cognitive neuroscience and continues to be an important method in the study of the neural basis of human behavior, complementing newer techniques for investigating brain structure–function relationships in human subjects. Recent advances in neuroimaging, statistics and information management provide powerful tools to support neuropsychological research. At the same time, changing ethical requirements and privacy concerns impose increasingly high standards on the procedures used to recruit

research participants, and on subsequent data management. Shared, centrally managed research registries provide a framework for facilitating access to this method for nonclinicians, addressing ethical concerns, streamlining recruitment and screening procedures, and coordinating subsequent research contacts and data storage. We report the experience of two such registries: the patient database of the Center for Cognitive Neuroscience at the University of Pennsylvania, and the Cognitive Neuroscience Research Registry at McGill University. ■

INTRODUCTION

The scientific study of human brain–behavior relationships began in the clinic. The initial insights into the neural underpinnings of the major areas of human cognition came first from observation, and then from experimental investigation of the effects of brain injury on behavior. Such work has provided a framework both for parsing complex behaviors and for understanding how they relate to the brain (Chatterjee, 2005). Although this methodology can be traced back to the mid 19th century, it remains a foundation for cognitive neuroscience in the new millennium.

The advent of other methods, particularly functional neuroimaging, has changed the landscape of cognitive neuroscience dramatically (Fellows et al., 2005), leading some to muse in print about the continued relevance of experimental neuropsychology (Rorden & Karnath, 2004). As we and others have pointed out, lesion studies have particular inferential strengths that make them a vital complement to correlational methods such as functional neuroimaging (Fellows et al., 2005; Rorden & Karnath, 2004). As a loss-of-function method, lesion work can test whether a given region of the brain is necessary for a particular process. The dissociability of deficits after brain injury can also shed light on the component processes that make up a complex behavior.

Finally, although the type of patient-based work described here aims to address basic science questions, it is also a naturally “translational” method: The results of such studies often have immediate applicability in clinical settings.

Human lesion studies have certain strengths, but they also have important limitations. Some of these limitations are of a theoretical and inferential nature, and are intrinsic to the method (Farah, 1994; Shallice, 1988). Many others are practical, and so potentially addressable. Perhaps the major practical limitation is having access to appropriate patients with damage involving brain areas of interest, and relatedly, recruiting an adequate number of patients to provide the necessary statistical power for group studies.

Increasingly strict ethical and privacy regulations have added a new set of practical challenges to the background difficulties inherent in the study of patients with brain injury. Changing societal views have, on the one hand, led to increasingly tight restrictions on who may view an individual’s medical record, or otherwise have access to medical information. On the other hand, medical paternalism has been replaced by patient-centered medicine, which emphasizes the patient’s central, autonomous role as decision-maker in clinical and, by extension, medical research settings. Related changes in human research ethics place restrictions on how personal information collected for research purposes may be used. Typically, for example, explicit consent is

¹McGill University, ²University of Pennsylvania

needed for so-called secondary use of data that were originally collected for a different purpose.

As these societal, legal, and ethical changes have occurred, medical practice has also changed. Hospital stays are brief, patient care is more fragmented, and the patient populations being cared for in tertiary academic medical centers are increasingly complex, often with comorbidities or atypical features that make these patients less suitable for basic research.

Over about the same time frame, there have been major advances in anatomical neuroimaging, image analysis, statistical methods, and databasing, which have the potential to dramatically enhance what can be learned from traditional lesion studies. Hand-drawn sketches of brain injuries are being replaced by digital image processing techniques that facilitate increasingly sophisticated analyses of brain structure–function relationships (Rorden, Karnath, & Bonilha, 2007; Rorden & Karnath, 2004; Bates, Appelbaum, Salcedo, Saygin, & Pizzamiglio, 2003; Bates, Wilson, et al., 2003; Rorden & Brett, 2000). Magnetic resonance imaging techniques can provide not only very detailed delineation of chronic brain injury but also information about acute, and even transient, pathological changes in brain function that can be linked to changes in behavior (Hillis, 2007; Ashburner & Friston, 2000). These data can be readily stored and manipulated in digital form, and easily linked to behavioral, clinical, and demographic measures in database form.

In summary, human lesion studies remain a vital pillar of cognitive neuroscience in the 21st century, and modern imaging, statistical, and data management methods can address some of the practical challenges of this work. However, the fundamental challenge of participant recruitment and access remains, and modern ethics and privacy considerations add further constraints. Here, we describe a research registry system designed to efficiently address this challenge; similar responses to these constraints have been reported in support of clinical neuropsychological research (Schwartz, Brecher, Whyte, & Klein, 2005). The registry system provides an organizational structure; a set of recruitment, access, and retention procedures; and a data management framework to support cognitive neuroscience research in brain-injured participants. We describe the implementation of this system at the University of Pennsylvania (UPenn) and McGill University, and discuss the advantages and drawbacks of this approach (Table 1).

REGISTRY ORGANIZATION

The structure of both registries is similar because the McGill registry was modeled on the one developed at the UPenn's Center for Cognitive Neuroscience. Both are conceived of as a shared research resource. The linchpin of the organizational framework is a dedicated coordinator who plays a variety of roles. The coordinator is, in turn, supervised by a clinician–researcher, who, in

Table 1. Current Challenges for Human Lesion Studies

<i>Accessibility</i>	Making patient-based research methods available to nonclinicians
<i>Autonomy</i>	Putting participants at the center of research participation decisions
<i>Information management</i>	Respecting modern privacy policies
<i>Ethics</i>	Recruiting while respecting confidentiality rules, specifying uses of collected data
<i>Efficiency</i>	Harnessing information technologies to optimize data management
<i>Scale</i>	Achieving an adequate sample size to support modern image analysis techniques, and to study behaviors with large individual differences in the normal population
<i>Sustainability</i>	Investing in infrastructure and personnel, and establishing recruitment and retention procedures that can be sustained over the long time frame required for such work

both cases, happens to be a neurologist. There are advantages to the person in the supervisory role being a clinician, preferably in the clinical neurosciences: Such a position facilitates communication with other referring physicians (most often neurologists, neurosurgeons and physiatrists). Residents are also more likely to alert the database coordinator about relevant cases when they have an already-established relationship with the supervising clinician.

The coordinator's duties include identifying and subsequently recruiting potential research participants, obtaining informed consent for their participation in the registry, and then gathering the relevant background information about these participants, including performing a screening neuropsychological evaluation and accessing available clinical neuroimaging. These data are maintained in a computerized database. Only the coordinator has access to identifying and contact information. Individual investigators can view a more limited set of information within the database (e.g., lesion location, basic demographic and clinical information, results of screening tests) in order to select potential candidates for a specific research project. The coordinator serves as the contact point between investigators and registry participants. She or he informs the registry participant of the opportunity to participate in a particular study. If the patient is interested, the coordinator then arranges

the study visit with the investigator and maintains records about the frequency and duration of study visits, and, in general terms, the nature of the study.

The coordinator's "go-between" role serves several crucial functions. First, it protects the privacy of registry participants to the fullest extent possible. Investigators have access only to anonymized clinical information until the point the patient agrees to participate in their study. Second, it improves the informed consent process by reducing the likelihood of coercion: The person obtaining initial consent for participation in a given study is the coordinator, a (relatively) neutral party, rather than the investigator or the patient's personal physician. Third, it puts a human face on what might otherwise be a rather soulless bureaucratic mechanism for tracking research subjects. Patients get to know the coordinator, and vice versa. Among other benefits, this relationship allows the coordinator to gauge the appropriate intensity of a given participant's involvement in research. This is done explicitly by asking how often a patient is willing to be contacted, and implicitly, by being sensitive to changes in their life circumstances and to the kinds of demands that might be placed on individual participants if they meet inclusion criteria for several ongoing investigations.

ETHICAL CONSIDERATIONS

The registry is not a research project, but rather, a tool to support research projects. Consequently, the consent document describes in very general terms the kinds of research that registry participants may become involved in, and focuses instead on what kind of information will be collected in the registry, who will have access to that information, and how that information will be used. In establishing such a registry, it may be important to consider how wide a range future projects may cover, particularly in terms of the demands placed on participants. Will future projects be limited to noninvasive behavioral studies, or are functional imaging, event-related potential, transcranial magnetic stimulation, or genetic studies also possibilities? What about treatment studies? Local institutional review boards may require that this full range be specified in detail during the consent process, or that participants be asked to indicate their willingness to be contacted for different kinds of studies. It is important to be clear (both to participants and to ethics oversight committees) that registry participants are consenting only to be informed about future research opportunities, and are completely free to accept or decline participation in any particular study.

Participants with brain damage may have difficulty providing fully informed consent due to the very cognitive deficits that make them eligible for participation, and these issues need to be addressed in compliance with the standards of the local institutional review board. Although neither of the registries described here

currently enrolls children younger than 18 years, this population also requires particular attention to ethical and consent issues.

The possibility of using such registries as recruitment sources for treatment studies raises an interesting issue: If the treatment has a measurable effect on performance, then the participants would be different from other, untreated registry members, presumably making them ineligible for participation in future basic research studies. Treatment studies may also place greater demands on patients in terms of time and effort, and potentially expose them to greater risk, all of which might influence their ability or willingness to participate in basic research. On the other hand, patients may be more willing to be listed in the registry if it means they will have the opportunity to participate in treatment trials. Given the limited state of current treatments for cognitive impairments after brain injury, these are relatively minor concerns at the moment, but they may well become more important considerations in the medium term.

A further question to consider when planning a registry is how wide a range of investigators will have access to it. Is it open to a specific list of researchers, to those affiliated with a specific institution or center, or to any researcher anywhere in the world? Currently, both registries described here limit access to those affiliated with the center or institution at which they are based. Access by nonaffiliated researchers can be undertaken in collaboration. This has the advantage of more-or-less capping the intensity of database use, and means that the same institutional review board will approve individual studies.

Although the registry is primarily a research support tool, as the database associated with it grows, it may become a resource for research in its own right. That is, research questions could be answered by analysis of the data routinely collected about registry participants. Two steps need to be taken to permit this to occur: First, consent documents must make clear that the data collected may be used for this purpose in the future, the so-called "secondary use." Second, it may be worth thinking about potential secondary-use applications when deciding which clinical, demographic, and neuropsychological information to acquire.

A final consideration for the consent process is germane both to the registry consent, and the consent documents for the individual research studies that will draw participants from the registry. This relates to the direction of information flow between the registry database and individual research projects. Various models are possible: At one extreme, researchers draw information from the registry, and return only the minimum information needed for smooth functioning of the registry service, such as the frequency and duration of an individual's participation in a particular study. At the other, all data collected in the course of all experiments completed by a given participant are eventually linked back to the registry database. The latter model would

provide a particularly rich dataset for secondary-use purposes. Currently, both registries function somewhere between these extremes. Individual investigators return information to the database about the experimental tasks they have administered. If these included standard measures that might be useful to other researchers in the future, these results are added to the database. Of course, this requires that the researcher obtain consent for this type of data sharing. Finally, addition of informal observations made by individual investigators to the primary database can be extremely useful. For example, noting that a particular participant fatigues quickly is helpful in planning subsequent studies.

RECRUITMENT

Potential participants can be identified in a variety of ways, limited primarily by privacy considerations. Clinician referral is the main mechanism of recruitment at both sites. Clinicians who care for patient populations of potential interest (such as stroke, tumor, surgically treated epilepsy) are asked to mention the registry to appropriate patients, and if the patients are interested in hearing more about the program, to pass their contact information to the registry coordinator. Where confidentiality policies permit, this process is facilitated by having the coordinator screen charts, generate a list of patients who might be candidates, and then provide that list to the relevant clinicians to aid in the recruitment process. A brochure explaining the registry can also be a helpful recruitment aid; this is often sent to patients after the initial telephone contact.

The focus of recruitment will vary across registries, and over time, depending on the needs of the investigators making use of the registry. This situation can become a counterproductive vicious circle if a potential user queries the database, finds few subjects appropriate for their planned study, and so abandons the study. This prevents a specific study from being carried out, but also makes it unlikely that future work in that area will be attempted. Both registries encourage a more constructive approach, in which the recruitment mechanisms are adjusted to support the specific project. This works best when it is interactive: when the researcher specifies the patient population of interest, but also works with the coordinator (often in conjunction with the neurologist supervising the registry) to determine how that population can be accessed. Clearly, this process is more cumbersome than when appropriate patients are already listed in the registry, but it still has advantages over the ad hoc recruitment methods that would have been used to solve this problem in the past. First, the registry provides an experienced person as well as established procedures to undertake the recruitment, and second, the process will result in a new population being added to the registry, facilitating future research in this area. Indeed, where multiple investigators make use of the reg-

istry, this form of investigator-initiated recruitment will result in a particularly rich and relevant resource over time.

This flexibility means that patient recruitment in both databases does not follow rigid inclusion and exclusion rules: Recruitment can be syndrome-based in one area (e.g., McGill's registry recruits patients with acquired aphasia, regardless of lesion site or sites), and neuro-anatomically driven in another (e.g., identifying patients with damage to a specific region within the frontal lobe, regardless of clinical symptoms). Similarly, patients are generally included in the registries even if they meet what might be considered "relative" exclusion criteria (e.g., a past history of drug or alcohol abuse, or of depression). This information is flagged in the database, and investigators can then decide for themselves if a given patient is eligible for a particular study. This heterogeneity of inclusion and exclusion criteria is the practical result of meeting the needs of many investigators. It is worth noting that this lack of consistency may have implications for secondary-use studies, depending on their specific designs.

Recruitment is the rate-limiting step in the development and use of such registries. It requires sustained effort and takes time. A sense of the expected time course can be gained from Figure 1, which shows accrual to both registries since their inceptions. This figure shows only those subjects actually enrolled in the database, comprising the 10–20% of potential participants who are found to be eligible, interested, and available to participate. Thus, for every patient enrolled in each registry, 5 to 10 more were identified as possible candidates, but excluded at various stages of the screening process.

RETENTION

Given the "front end" investment of time and resources in recruiting patients, once they are enrolled in the registry, minimizing dropout becomes crucial. We have identified a number of factors that seem to be important

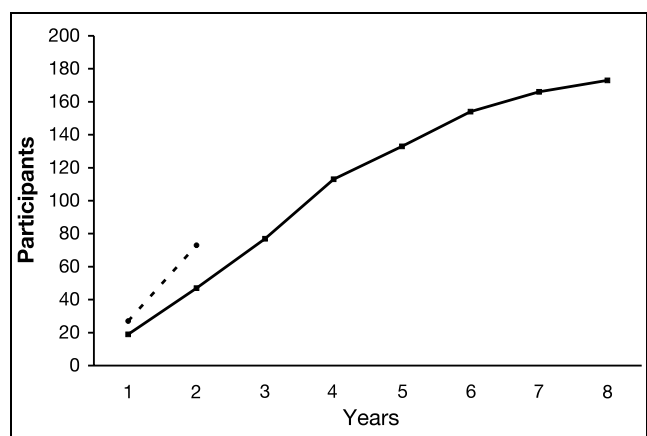


Figure 1. Cumulative recruitment into the UPenn (solid line) and McGill (dashed line) registries since inception, by year.

in this regard. As mentioned, the relationship between the patients and the database coordinator puts a human face to the process, which we suspect is a critical factor. This connection is strengthened through intermittent contact with all registry participants, including those who may not have recently participated in any specific study, such as through holiday cards.

Continuity of the coordinator position is important here; this is not a position to fill with a series of temporary employees, or part-time student help. In addition, clearly explaining the purpose of this kind of research breeds loyalty to the enterprise. When patients understand the contribution they are making, they are often remarkably generous with their time and effort. (This is perhaps particularly the case when patients are no longer able to carry out their usual occupational or social roles because of their brain injury.) The purpose of the research can be made concrete by providing intermittent summaries of the research being done through the registry. At UPenn, a biannual newsletter is sent to all registry participants. The newsletter provides an update on recent findings, publications and presentations, profiles of the investigators involved, and information about ongoing projects. Feedback about this newsletter from registry participants has been overwhelmingly positive.

It is also important to ensure that investigator–users, and their research staff, conform to a standard set of practices so that the experience of registry participants is uniform across all studies. One bad experience can lead to a participant withdrawing from the registry entirely, having an obviously negative impact on the resource as a whole. Both sites have documents outlining policy in this regard. These includes standard approaches to compensating participants for their time and effort. They also stipulate commonsense recommendations regarding professional behavior, dress, and what to do if a medical emergency occurs. The UPenn database makes this material available on their Website, and has an annual, mandatory training session for research assistants, students, and others wishing to recruit through their registry. Such a session is particularly useful for students and research assistants, whose only relevant experience may be participating in or conducting behavioral experiments in healthy undergraduate students.

These measures seem to be effective: Although registry attrition due to illness, death, or patients moving away is inevitable, withdrawal at the patient's request is uncommon (1–2 patients/year at both sites).

SCREENING

Once participants are recruited and consent, some form of screening assessment is carried out. The optimal extent of this screening is a matter of debate, and varies across the two sites. On the one hand, more detailed screening provides better service to end-users of the

registry, allowing investigators to select their study population precisely, cutting down on the background evaluations that need to be done as part of a particular study, and enhancing the registry database's secondary use capabilities. On the other hand, longer screening takes additional time, effort, and money, and with the best of intentions, may still not meet the requirements of particular studies. Furthermore, all registry participants undergo screening, but only a subset will actually participate in further research, making intensive screening assessments potentially inefficient.

Both registries described here compromise with a relatively brief intake session, which includes consent, collection of demographic and medical information, details of the neurological history, and a screening neurological/neuropsychological assessment. At UPenn, the main instrument has been the Mattis dementia rating scale, which provides a brief (and standardized) assessment of major cognitive domains, although one that is not particularly specific for the deficits commonly seen after focal brain injury. A new battery, the Philadelphia Brief Assessment of Cognition (PBAC), is under development and will be used as the screening instrument. At McGill, a computerized screening battery is being piloted, intended to screen for focal deficits while minimizing the expertise required of the person administering the battery. At both sites, the coordinator carries out the screening. In general, these screening batteries have the dual aims of identifying cognitive deficits that may be of research interest, and documenting the presence or absence of other, potentially confounding deficits.

DATA MANAGEMENT

The information collected in the screening assessment is entered into secure, computerized databases. These databases have two levels of accessibility: the coordinator has full access, including identifying and contact information, whereas investigators are limited to viewing deidentified information only. The main practical issues surrounding the database are to ensure appropriate security and to use consistent terminology particularly for fields which are very likely to be searched by investigators (e.g., site of damage, symptoms, signs).

Neuroimaging data are also stored in digital form wherever possible, although at the moment neither registry has integrated these data, in full, directly in the database. Improved handling of lesion data is a goal of both sites. Ideally, lesion data could be directly searched and visualized as images, rather than filtered through cumbersome labeling. Efforts to develop these tools are ongoing.

FUNDING

These registries are conceived of as shared, cooperative research tools. As such, they present particular funding

challenges. Unlike some shared research resources, where costs can be recovered through a per-use charge, registries require sustained support regardless of intensity of use. This is particularly true when the registry is first being established; even with energetic recruitment efforts, it may be 2 or 3 years before the registry is of sufficient size to viably support multiple users. Although the costs associated with such a project are relatively low, they are continuous. Beyond basic computer resources, there are few equipment costs; the bulk of the financial requirement is for salary. Such “human-powered,” long-term research resources are often ill-served by traditional grant structures.

In principle, individual users should be able to eventually cover the costs of patient registries through grant support: If anything, the registry is a more efficient mechanism for recruitment than traditional, ad hoc methods that would be funded through investigator-initiated grants. An established registry also strengthens grant applications by ensuring the feasibility of recruiting brain-damaged subjects. Institutional support to start the database is extremely helpful as the entire program requires steady funding over time to be useful, regardless of short-term intensity of use or short-term grant success. Per-use charges can recoup some of the costs, particularly those associated with screening, and perhaps neuroimaging. At UPenn, the first investigator to see a new patient bears the cost of the screening visit. In addition, those making use of the resource contribute to other costs as possible, depending on their expected use, and their level of grant support. Every new grant that proposes to use the database is required to budget for personnel salary costs. At McGill, the consortium of researchers supporting this resource makes a more-or-less fixed annual contribution to its upkeep, including costs associated with the initial screening visit. The Montreal Neurological Institute also provides support.

HEALTHY CONTROL PARTICIPANTS

Although recruitment of brain-injured participants ought to be the major challenge in carrying out lesion studies, it sometimes seems that recruiting healthy, age-matched control participants is even harder. The procedures and tools that support the patient registries are readily adaptable to healthy controls, and both McGill and UPenn have companion registries for this purpose. This results in efficiencies for both participants and investigators. Participants have already been recruited and screened, and do not need to scan the classifieds for research opportunities, or submit to repeated assessments with standard instruments. For investigators, a quick search in the database can identify potential participants according to demographic or neuropsychological variables, allowing rapid recruitment of a matched control sample.

OUTCOMES

The purpose of a database registry is to facilitate research. Effective facilitation should be reflected in its use by investigators, presentations, publications, and grant support. At UPenn, eight faculty make use of the registry; at McGill, six faculty are actively using this new resource, and a further eight have committed to supporting the project with the intent of future use. Investigators using the UPenn registry have generated 35 presentations at meetings and 22 peer-reviewed publications over the 8 years of its existence, and that work has been supported by more than 20 externally funded grants. Although these measures are not “outcomes” in any controlled sense, they support the view that such databases can be a rich resource in facilitating research.

DISCUSSION

It is unfortunate that the colorful phrase “experiment of nature” is often applied to human lesion studies, with the attendant implication of an effortless, if haphazard, enterprise. Although the lesions themselves “just happen,” the experiments do not. As with any experimental method, this kind of enquiry rests on a set of procedures and techniques. We argue that the evidence that can be gleaned from lesion studies is important in understanding human brain–behavior relationships, and that improving the procedures and techniques in support of this method will enhance the quality and applicability of this work to cognitive neuroscience as a whole. The experience reviewed here indicates that research registries are a useful mechanism for supporting this kind of research, and for making it accessible to a wider community of investigators. We have tried to identify the important elements of success, and to point out pitfalls and potential difficulties. The framework we describe is certainly not the only means of achieving this goal, but we hope that it will provide a starting point for others interested in establishing this kind of registry, and encourage those who have taken different approaches to solving these problems to share their expertise.

The registries described here are cooperative resources at the level of single institutions; extending this cooperation across multiple sites would have advantages. In theory, this could further shorten recruitment times, permit group studies of patients with lesions in rarely injured locations, and increase sample sizes across the board (with the latter particularly important for supporting newer voxel-based analysis methods). On the other hand, it also would add further complexity to issues of consent, accessibility, and funding, and might reduce the likelihood of independent labs replicating crucial results. Nonetheless, multi-site collaboration is increasingly commonplace in clinical studies of rare conditions, for example, in pediatric oncology (Reaman, 2004). The organizational procedures found

to be effective in such collaborative clinical research settings could be adapted to support multisite cognitive neuroscience research.

Although full multi-site collaboration may take time to establish, other levels of collaboration might be worth considering in the shorter term. At a minimum, these could include sharing tools, data management methods, and recruitment approaches. The collaborative use of particular screening instruments across sites could support interesting secondary-use studies in larger samples with a minimum of coordination.

Research registries or other mechanisms to identify research subjects are a necessary step in lesion work, but there are other challenges. Recent and ongoing work addresses appropriate experimental design and statistical analysis (Kimberg, Coslett, & Schwartz, 2007; Rorden et al., 2007; Crawford, Garthwaite, Azzalini, Howell, & Laws, 2006; Stuss et al., 2005; Bates, Appelbaum, et al., 2003; Bates, Wilson, et al., 2003). The statistical approaches and image analysis tools developed for functional imaging are potentially applicable, or adaptable, to address these challenges, particularly as sample sizes increase. Creative experiments that take advantage of the strengths of the lesion method, bolstered by these tools and resources, will continue to shape our understanding of human brain-behavior relationships. The development of such registries would provide access to lesion methods for cognitive neuroscientists, many of whom tacitly regard “cognitive neuroscience” as synonymous with functional neuroimaging. Our hope is that wider familiarity with and use of data from lesion studies will continue to advance our understanding of brain-behavior relationships and impose important constraints on inferences made in functional neuroimaging studies.

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Reprint requests should be sent to Lesley K. Fellows, Montreal Neurological Institute, Rm. 276, 3801 University Street, Montreal, QC, Canada H3A 2B4, or via e-mail: lesley.fellows@mcgill.ca.

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