



The preclinical data forum network: A new ECNP initiative to improve data quality and robustness for (preclinical) neuroscience



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Preclinical Data Forum Network

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Received 3 February 2015; received in revised form 25 April 2015; accepted 25 May 2015

KEYWORDS

Reproducibility;
Robustness;
Relevance;
Quality assurance;
Neuroscience;
Pre-clinical

Abstract

Current limitations impeding on data reproducibility are often poor statistical design, underpowered studies, lack of robust data, lack of methodological detail, biased reporting and lack of open data sharing, coupled with wrong research incentives. To improve data reproducibility, robustness and quality for brain disease research, a Preclinical Data Forum Network was formed under the umbrella of the European College of Neuropsychopharmacology (ECNP). The goal of this network, members of which met for the first time in October 2014, is to establish a forum to collaborate in precompetitive space, to exchange and develop best practices, and to bring together the members from academia, pharmaceutical industry, publishers, journal editors, funding organizations, public/private partnerships and non-profit advocacy organizations. To address the most pertinent issues identified by the Network, it was decided to establish a data sharing platform that allows open exchange of information in the area of preclinical neuroscience and to develop an educational scientific program. It is also planned to reach out to other organizations to align initiatives to enhance efficiency, and to initiate activities to improve the clinical relevance of preclinical data. Those Network activities should contribute to scientific rigor and lead to robust and relevant translational data. Here we provide a synopsis of the proceedings from the inaugural meeting.

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1. Introduction

Reproducibility of research findings and data quality are the pillars of the scientific method. In addition, in industrial pharmaceutical research and development (R&D) programs, data reproducibility, robustness and relevance are key drivers for decision making. Yet recent studies suggest that reproducibility of published data and data quality in research, including neuroscience, is low (Table 1). The inability to reproduce published findings has scientific, financial, legal and ethical implications and has been raised as a major concern amongst industrial and academic scientists, editors, publishers and public organizations (e.g., Couzin-Frankel, 2013; Dolgin, 2014; Landis et al., 2012; Macleod et al., 2014; McNutt, 2014; Motulsky, 2014; Munafo et al., 2014; Prinz et al., 2011; Steckler, 2015; Steward and Balice-Gordon, 2014). A number of contributing factors have been proposed, including inadvertent errors, poor experimental design, biases, and biological variability, to name a few.

To improve data reproducibility, robustness and data quality in the neuroscience field, a network was formed under the umbrella of the European College of Neuropsychopharmacology (ECNP), which will focus on preclinical research in the precompetitive space of the brain disease research (see <http://www.ecnp.eu/projects-initiatives/ECNP-networks/ECNPNetworks/Preclinical-Data-Forum-Work.aspx>). The goal of this network is to establish a forum to collaborate, exchange and develop best practices, with members from academia, pharmaceutical industry, publishers, journal editors, funding organizations, public/private partnerships and non-profit advocacy organizations from the US and Europe. Specifically, we expect that the open exchange of information about our colleagues' successes and failures to reproduce published data would save time, resources and animals. Sharing best practices should improve scientific rigor, lead to robust and relevant translational data, improved biomarkers, and eventually enhance trust in our data. Importantly, those are relatively simple, but achievable, steps with high and immediate impact on daily research activities both in academic laboratories and pharmaceutical industry. Moreover, the lessons learned from these activities are also of high interest to publishers, editors, funding and advocacy organizations.

The network met for the first time in Berlin in association with the 27th ECNP Congress in October 2014. Key objectives for that meeting were (1) to evaluate the factors affecting reproducibility, robustness and relevance in data generation, (2) to identify what prevents different stakeholders from sharing data and (3) to identify potential working mechanisms that could help to address some of the challenges related to transparency in data reporting and analysis. Herewith, we provide a synopsis of proceedings from this meeting.

2. Factors affecting data reproducibility, robustness and relevance

The issue of low data reproducibility was clearly highlighted in reports from companies like Bayer and Amgen, having

Table 1 Challenges for data reproducibility and quality.

Frequency of occurrence	Outcome	Source
1.97%	Of scientists self-reported data fabrication, falsification or modification at least once	Fanelli, 2009
31%	Of animal studies on neurological disorders showed evidence for excess statistical significance, suggesting bias	Tsilidis et al., 2013
34%	Of scientists self-reported questionable research practices	Fanelli, 2009
54%	Of resources published were not uniquely identifiable in published biomedical studies, making replication difficult	Vasilevsky et al., 2013
55%	Of MD Anderson Cancer Center scientists experienced at least one incidence of being unable to reproduce published data	Mobley et al., 2013
57%	Of neuroscience studies found to have low statistical power ($\leq 30\%$), hence low reliability	Button et al., 2013
57%	Of internal study protocols were amended after statistical review at Astra Zeneca - would figures from published studies be comparable or possibly even worse?	Peers et al., 2014
65%	Of published data (oncology, women's health, cardiovascular) were inconsistent with internal data at Bayer	Prinz et al., 2011
72%	Of scientists reported questionable research practices by colleagues	Fanelli, 2009
78%	Of studies in social sciences with null results remained unpublished	Franco et al., 2014
85%	Of resources have been estimated to be wasted in science	Chalmers and Glasziou, 2009
0%	Of out of more than 100 compounds previously suggested to be potential ALS drugs found active in an ALS mouse model if standardized study design was used	Perrin, 2014

substantial difficulties to reproduce internally what has been reported in the public domain (Begley and Ellis, 2012; Prinz et al., 2011) - experiences shared by many scientists working in other pharmaceutical companies and academia.

Although there are some fraudulent studies out in the field, intentional misconduct is not seen as the major issue at hand. Most scientists conduct experiments with the best intentions in mind and one has to be careful that a discussion on reproducibility does not become an uncomfortable and threatening subject for many excellent scientists. The debate on reproducibility needs to be conducted in a professional and ethical manner which pays careful attention to its consequences (Steckler, 2015).

There is ample evidence that technical issues are the major drivers. Studies are under-powered, do not follow appropriate blinding and randomization procedures, contain overtly flexible study designs (e.g., insufficiently defined endpoints), use poor statistics and demonstrate an over-reliance on *p*-values (Ioannidis, 2005; Motulsky, 2014). Within publications there is insufficient methodological detail, reporting of small effect sizes, highly variable data, or adoption of a biased reporting strategy that fits a hypothesis, with incomplete reporting or failure to report negative results at all - issues that were also identified by the Network as major contributors to the low reproducibility of data. A number of suggestions and guidelines have been published to improve this situation (e.g., ARRIVE guidelines, 2011; Begley and Ioannidis, 2015), but are limited in scope as long as authors do not have to adhere to such standards. Moreover, it is important to realize and acknowledge that low reproducibility is an inherent feature of science especially when highly unexpected findings ('discoveries') are made, as the positive predictive value of those studies is often very low (Franco et al., 2014; Ioannidis, 2005; Tsilidis et al., 2013). While those are issues that have a high impact on data reproducibility, they have the added advantage that they can be identified and potentially corrected by appropriate actions such as training and education (Ioannidis, 2014). Already the development of an upfront statistical analysis plan that takes into account power, type 1 error and consideration of the probability that a given experiment indeed leads to a true finding (the positive predictive value of a study) would greatly enhance the usefulness of the data generated and of the conclusions derived from these results. It may be even more important to see whether data are robust (i.e., whether a finding/concept can be observed under different conditions), as this may give an idea about the biological relevance of a finding. Ultimately, it can be expected that improved reproducibility and robustness of data will also facilitate the development of more valid biomarkers which are urgently needed for the development of novel therapies for many brain disorders (Anderson and Kodukula, 2014; Morgan et al., 2012).

3. Factors impeding data sharing across stakeholder groups

If there is so much concern in the field and if so many people struggle to reproduce others' data, why does it seem so

difficult to more widely share source data and detailed information in publications? Knowing that the sharing of such information eventually saves time, money, research tools and animals, it is difficult to argue against such practice. In fact, a number of journals explicitly ask their authors to also submit the data that underlie the reported results, to make materials used in publication available and to provide all the information required to successfully conduct a published experiment (e.g., the British Medical Journal; Groves (2010)). However, the degree of enforcement of this varies, as does compliance, and individuals may be reluctant to share their source data because those data may be seen as their intellectual property or as the main assets securing an individual's own career success. While many factors, especially the 'human factors', may be to certain degree understandable, there are precedencies where sharing of raw data has been successful. A laudable example is the Human Genome Project where the positive value of the availability of raw data is evident and acknowledged by the scientists involved (<http://genomicsandhealth.org/>). Maybe it is initiatives like this that can be consulted to take some lessons learned for the broader neuroscience community as well.

Also, this is not just an academic issue as industry is often hesitant to freely share source data as well, again, because of the notion that competitive space should be protected, there may be corporate rules and regulations preventing open data sharing, as well as legal restrictions and ethical aspects that may have to be taken into consideration (e.g. if consent from patients that allows sharing of those data is lacking). But while there seem to be differences amongst company policies with respect to data sharing, it also seems evident that several companies became more open over recent years and are willing to make data public, which is a positive development (<http://www.technologyreview.com/news/529046/big-pharma-opens-up-its-big-data/>; <http://www.jnj.com/news/all-johnson-and-johnson-announces-clinical-trial-data-sharing-agreement-with-yale-school-of-medicine>).

There are additional technical and non-technical hurdles when it comes to sharing of source data. Not only authors use many different formats of data which poses a technical challenge to share those data, but data repositories have to be curated and sustained. While the current publishing practice for many journals requires data deposition, only a few community endorsed repositories exist (e.g., GenBank (<http://www.ncbi.nlm.nih.gov/genbank/>) or the RCSB Protein Data Bank (<http://www.rcsb.org/pdb/home/home.do>)) and many data types do not have designated repositories. Even more important, there does not seem to be a consensus across the scientific community what the best approach for data sharing should be. Should the repositories be managed/controlled by the publishers, is it a responsibility of the funding agencies to provide financial support, or should such data repositories be organized by the scientific community?

A second data transparency issue is the hesitation to make public the negative data or data from reproduction attempts. This may be related to the academic perceptions that those data may be of low value, or to fear that such data sets may be seen as a reflection on the inability of the researcher to conduct proper studies. Along the same lines, some journals are reluctant to publish these type of data as

such data may be perceived to be less novel or reliable, although some journals have now started to explicitly invite authors to submit such studies. Despite these - real or perceived - hurdles, there was unanimous agreement amongst the network participants that a forum to share data from reproduction studies, negative data and source data is of high importance.

4. Landscape of available data sharing platforms

A preliminary analysis of available information technology platforms for data- and knowledge-sharing in the area of neuroscience conducted by the Preclinical Data Forum Network yielded a plethora of options for different applications, for example, publication-sharing platforms such as Academia.edu, ResearchGate.net and SciRef.com, knowledge integration platforms such as the NIH-funded Neuroscience Information Framework (NIF) (Gardner et al., 2008) and NeurolexWiki (Larson and Martone, 2013), Allen Brain Atlas (<http://www.brain-map.org>), and the cloud-based data repositories such as TranSmart™ (Szalma et al., 2010). The funding organizations see the clear need for data storage and sharing mechanisms. The EU Innovative Medicines Initiative (IMI), for example, developed a knowledge management system capable of hosting all data for the programs receiving IMI funding, called the European Translational Information and Knowledge Services (eTRIKS; <http://www.imi.europa.eu/content/etrips>). Similarly, the Organization for Economic Co-operation and Development (OECD) has invested in the establishment of the International Neuroinformatics Coordinating Facility (INCF) with funding from 17 countries to develop collaborative infrastructure and promote the sharing of data and computing resources (www.incf.org). Nevertheless, at this time no data management platform exists for sharing of *preclinical neuroscience data*. Setting up such a platform to allow scientists from academia and industry to exchange and discuss data in a precompetitive spirit is a need also recognized by ECNP and will be a key activity of the future network, with the goal to learn from each other's successes and failures and to avoid unnecessary duplication of efforts.

Another important outcome of the network meeting in Berlin was the agreement that there is a clear educational need not just around issues related to reproducibility and data integrity, but more generally in training investigators in best practices for scientific research. In the USA, this is a strong focus area for the National Institutes of Health (NIH) that work to raise the community awareness for the issue of poor data reproducibility and to enhance formal training of young scientists (Collins and Tabak, 2014). For example, NIH recently announced the funding opportunity and solicited applications for the development of training modules for graduate students, postdoctoral fellows, and beginning investigators specifically designed to enhance data reproducibility (see more at: <http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-15-006.html>).

In a joint effort, our network will also develop an educational program aligned with NIH activities specifically geared towards the needs of the preclinical neuroscience community.

Furthermore, it was realized that a forum should be created that would allow the publication of data from replication attempts or of negative data. Taking this view from the network members, some publishers took action and started to establish novel journals or sites where such work could easily be shared with the wider scientific community (e.g., SpringerPlus, Replication Studies in Neurosciences, <http://www.springerplus.com/about/update/RepStudNeuro>).

However, a 'cultural change' would probably be the most important step forward. What is needed is a scientific society that embraces open exchange of information, including the exchange of source data, that is rewarded for sharing quality data instead of 'hot' data, and that shares experimental detail and resources to allow others to replication and move on. For this to happen, all stakeholders - scientists in academia and industry, publishers, and funding agencies - will need to come together on these issues, to insure that replication and robustness is as high a priority as innovation.

It remains to be seen how initiatives like the new ECNP network on data robustness will evolve and what they eventually will contribute to the field of neuroscience. As such, the Network may serve as a future advisory board on the conduct of preclinical studies for neuroscience R&D, both for its members as well as e.g. members of other ECNP Networks and beyond. In addition, the value of preclinical data in view of clinical relevance should be addressed. Thus, while not a current focus, it can be expected that the network will eventually expand into the clinical space, especially to cover the translational interface between preclinical and the clinical research. ECNP members who want to become active in our network can apply to join (<http://www.ecnp.eu/~media/Files/ecnp/Projects%20and%20initiatives/Network/Guideline%20for%20applications%20to%20become%20a%20member%20of%20an%20ECNP%20Network.pdf>) and thereby help to shape their own future. Evidently, we must make an effort to improve the robustness and clinical relevance of our data and the time for this is now.

Funding

The ECNP Preclinical Data Forum Network receives financial support from ECNP.

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Conflict of interest

Thomas Steckler is a full-time employee of Janssen Research & Development and an Editor at Springer Publishers. Anton Beshpalov is a full-time employee of Abbvie. Katja Brose is an Editor at Cell Press and an employee of Elsevier. Martien Kas, Magali Haas and Elena Koustova have no interests to declare.

Acknowledgments

None.

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