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Ethical issues in global neuroimaging genetics collaborations

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ABSTRACT

Neuroimaging genetics is a rapidly developing field that combines neuropsychiatric genetics studies with imaging modalities to investigate how genetic variation influences brain structure and function. As both genetic and imaging technologies improve further, their combined power may hold translational potential in terms of improving psychiatric nosology, diagnosis, and treatment. While neuroimaging genetics studies offer a number of scientific advantages, they also face challenges. In response to some of these challenges, global neuroimaging genetics collaborations have been created to pool and compare brain data and replicate study findings. Attention has been paid to ethical issues in genetics, neuroimaging, and multi-site collaborative research, respectively, but there have been few substantive discussions of the ethical issues generated by the confluence of these areas in global neuroimaging genetics collaborations. Our discussion focuses on two areas: benefits and risks of global neuroimaging genetics collaborations and the potential impact of neuroimaging genetics research findings in low- and middle-income countries. Global neuroimaging genetics collaborations have the potential to enhance relations between countries and address global mental health challenges, however there are risks regarding inequity, exploitation and data sharing. Moreover, neuroimaging genetics research in low- and middle-income countries must address the issue of feedback of findings and the risk of essentializing and stigmatizing interpretations of mental disorders. We conclude by examining how the notion of solidarity, informed by an African Ethics framework, may justify some of the suggestions made in our discussion.

1. Introduction

Neuroimaging genetics, also referred to as neuroimaging genomics, is rapidly and effectively developing to combine neuropsychiatric genetics studies with imaging modalities to investigate how genetic variation influences brain structure and function. One key hypothesis is that in the case of neuropsychiatric disorders which lack definitive biomarkers, imaging provides a number of intermediate traits, or endophenotypes, that may be more proximal to the genetic substrate of the disorder than a behavioural phenotype (Thompson et al., 2010, Roiser, 2011). This closer proximity could assist in more effectively pinpointing the genes that contribute to these disorders (Thompson et al., 2010, Rose and Donohoe, 2013). As both genetic and imaging technologies improve further, their combined power may hold translational potential in terms of improving psychiatric nosology, diagnosis, treatment, and ultimately prevention of neuropsychiatric disorders (Bogdan et al., 2017).

While neuroimaging genetics studies offer a number of scientific advantages (Hariri and Weinberger, 2003), they also face various challenges (Bogdan et al., 2017). The high cost of imaging studies, for example, places limits on sample size, impacting ability to identify robust correlations (Mohammadi, 2015) and posing challenges for the replication of findings (Thompson et al., 2014). In response to these challenges, global neuroimaging genetics networks have been created to pool and compare brain data and replicate study findings. These include the ENIGMA, IMAGEN (Nymberg et al., 2013), CHARGE (Davies et al., 2015) and GIGA consortia. Formed in 2009 and building on the work of earlier international brain mapping consortia (Mazziotta et al., 2009), ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) is the oldest and largest of the neuroimaging genetics consortia, with membership currently including approximately 2,025 researchers from 45 countries across the globe (Thompson et al., 2020) (see world map of ENIGMA's working group locations, Fig. 1). ENIGMA provides a useful exemplar for considering some of the ethical issues raised by global neuroimaging genetics collaborations.

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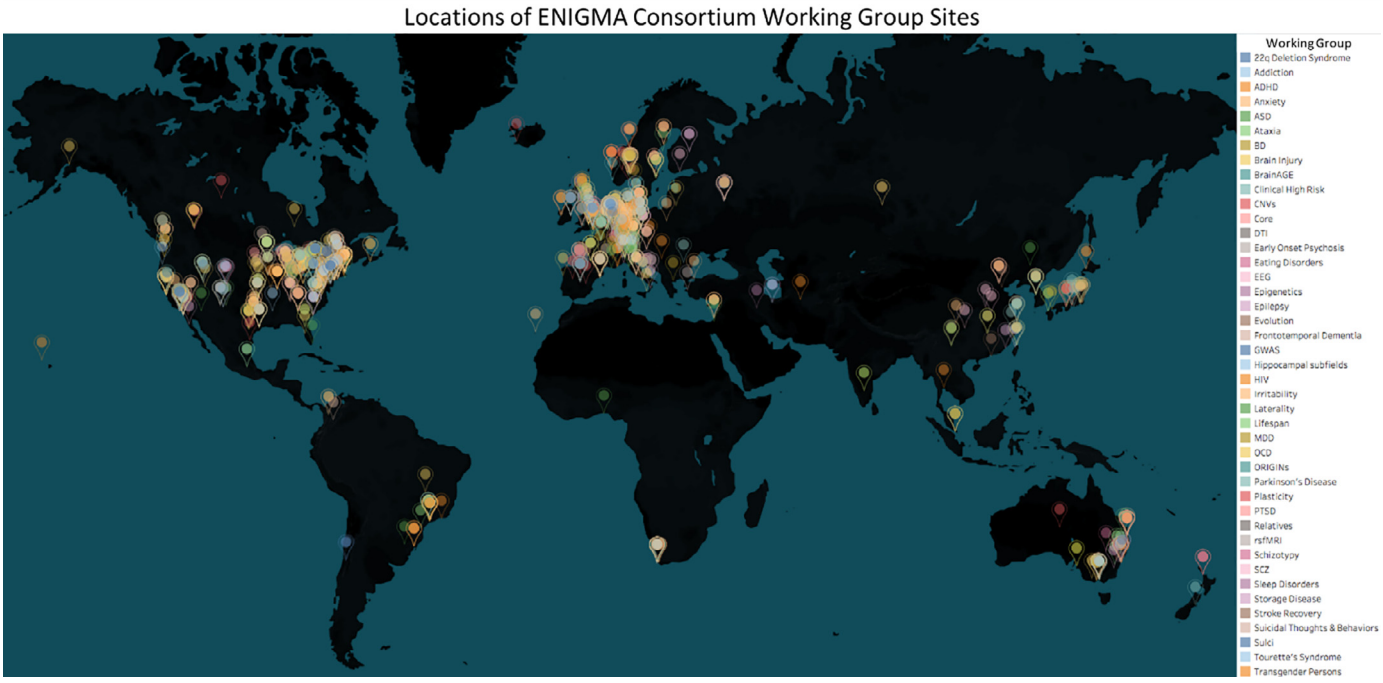

Fig. 1. World map of locations of ENIGMA's working groups (Thompson et al., 2020).

The ethical implications elicited by imaging genetics call for what Tairyan and Illes describe as "an expanded neuro-space" (Tairyan and Illes, 2009). This refers to "the ethics environment generated by the complex interaction of genetics, neural systems and behaviour" (Tairyan and Illes, 2009). Their analysis was the first to address issues raised by this confluence of genethics and neuroethics and aimed to serve as a point of departure for further discussion. While the number of neuroimaging genetics studies has increased considerably since their paper in 2009, there have been surprisingly few subsequent discussions devoted specifically to ethical issues in this area. Furthermore, to our knowledge, there have been few discussions in the literature of the ethical issues raised by global neuroimaging genetics collaborations in particular. While considerable attention has been paid to ethical issues in genetics, imaging, and multi-site collaborative research respectively, it is worth considering the implications of the convergence of these distinct areas.

We begin our discussion with an overview of neuroimaging genetics. We then focus on ethical issues in two areas. **First, we discuss benefits and risks of global neuroimaging genetics collaborations**. While there are numerous possible ethical issues in this area, we limit our discussion to two aspects that have potential for both benefit and risk: (1) the potential of global neuroimaging genetics collaborations to enhance relations between countries and address global mental health challenges, and concerns about inequity and exploitation associated with such collaborations, and (2) benefits and risks posed by data sharing. **Second, we discuss the potential impact of neuroimaging genetics research findings in low- and middle-income countries (LMICs)**. Here we discuss the issue of feedback of findings and the risk of essentializing and stigmatizing interpretations of mental disorders arising from neuroimaging genetics studies. Throughout our discussion, where low-resourced contexts are discussed, we take African contexts as our point of departure. **We conclude by examining how the notion of solidarity, informed by an African Ethics framework, may justify some of the suggestions made in our discussion.**

2. An overview of neuroimaging genetics

The field of neuroimaging genetics is approximately twenty years old. Initial studies followed the single variant approach, focusing on associations between candidate genes, with known functions, and neural systems (Bookheimer et al., 2000) (e.g., the effects of variants of the catechol-O-methyltransferase (*COMT*) gene on brain structure and function in conferring risk for schizophrenia (Hariri and Weinberger, 2003, Hashimoto et al., 2015). While initial candidate studies indicated the heritability of brain measures (Jansen et al., 2015), they were hampered by small effect sizes, difficulties in replicating findings, and concerns of publication bias (Bogdan et al., 2017, Mufford et al., 2017), and indeed many apparently promising findings have since been abandoned or refuted (Border et al., 2019, Jahanshad et al., 2017). With the ability to sequence the entire genome, the single variant approach was largely replaced by genome wide association studies (GWAS). From neuroimaging data such as MRI, DTI and resting state functional MRI, it was possible to derive "objectively measurable", quantitative traits or markers to increase the power of GWAS (Potkin et al., 2009). However, these studies were still underpowered due to small sample sizes (Bogdan et al., 2017, Thompson et al., 2014). This led to the formation of collaborative neuroimaging genetics consortia, such as ENIGMA, and the adoption of a meta-analysis approach, which combines results across different research sites in order to increase statistical power.

Currently, ENIGMA comprises 51 working groups, 32 of which are focused on neurological and psychiatric disorders (Thompson et al., 2020). To date, the consortium has produced the largest structural MRI studies of major depressive disorder (MDD) (Schmaal et al., 2017), schizophrenia (van Erp et al., 2016), bipolar disorder (Hibar et al., 2018), obsessive-compulsive disorder (Boedhoe et al., 2017), attention deficit/hyperactivity disorder (Hoogman et al., 2017), posttraumatic stress disorder (Morey et al., 2017), epilepsy (Whelan et al., 2018), 22q11.2 deletion syndrome (Sun et al., 2018), substance use disorders (Mackey et al., 2019), and autism spectrum disorders (van Rooij et al., 2018), combining data from more than 50 000 individuals. The findings of these studies indicate quantitative differences in brain structure and function, which can assist in identifying the nature and magnitude of those differences, despite the absence of "objective laboratory diagnostic test[s]" (Bearden and Thompson, 2017). These studies also indicate commonalities among certain disorders (e.g., MDD, schizophrenia and bipolar disorder are all associated with deficits in hippocampal volume (Opel et al., 2020)) which are consistent across the globe

(Koshiyama et al., 2020), as well as important differences between disorders (Bearden and Thompson, 2017). There are also working groups focusing on a range of methodological issues and approaches (Bearden and Thompson, 2017).

Neuroimaging genetics combines two highly complex and distinct approaches to identifying and understanding disease pathways, each of which faces its own technical challenges. The development of non-invasive imaging modalities has yielded increasingly sensitive *in vivo* study of the neuroanatomy of neurological and psychiatric disorders. Caution has, however, been called for regarding the findings of such studies (Weinberger and Radulescu, 2016), given that MRI signals are susceptible to numerous confounding variables including weight, fitness, alcohol, drug and nicotine use, stress levels, and mental state, as well as artifacts such as head movement and breathing (Mufford et al., 2017, Weinberger and Radulescu, 2016).

Progress has also been made in deepening understanding of the genetic basis of psychiatric disorders (Sullivan et al., 2018). GWAS, and, more recently, whole-exome sequencing studies (WES) have played a key role in identifying common genetic variants that contribute to complex disease risk. However, given the small effect sizes of most risk variants, GWAS require large samples of cases and controls. Despite their widespread use there is also scepticism regarding the ability of case-control GWA studies to adequately explain the genetic basis of common complex diseases (McClellan and King, 2010). A major hurdle that has faced association studies is the issue of missing heritability (Manolio et al., 2009); a disorder such as schizophrenia, for example, is approximately 80% heritable but a large Psychiatric Genomics Consortium (PGC) study of schizophrenia, demonstrated that common variants only accounted for approximately 30% of the heritability (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014, Rhoades et al., 2019).

Consortia such as ENIGMA have made major advances in establishing the genetic architecture of neuroimaging phenotypes (Satizabal et al., 2017, Hofer et al., 2019, Grasby et al., 2020). In addition to the studies mentioned above, an ENIGMA study that included GWAS data from over 40 000 individuals identified 45 significant loci that impact subcortical structures in the brain involved in movement, learning, memory and motivation (Satizabal et al., 2017). A more recent study of over 50 000 people – from 60 worldwide cohorts – discovered over 200 genetic loci associated with cortical gray matter thickness and surface area (Grasby et al., 2020). These genetic markers significantly overlapped with loci that confer genetic risk for insomnia, ADHD, and Parkinson's disease. These findings have implications for a deeper understanding of the causes of differential brain development and pathways of neuropsychiatric dysfunction. Still, neuroimaging genetics studies are typically characterized by small effect sizes[1] (Bogdan et al., 2017, Hashimoto et al., 2015). However, further research as well as the development of new models and methods will continue to address these challenges (Grasby et al., 2020, Smeland et al., 2018, Franke et al., 2016, van der Merwe et al., 2019).

3. The benefits and risks of global collaborations in neuroimaging genetics

There is a growing body of literature that addresses ethical issues in global research collaborations involving multiple sites and institutions in both high-income countries (HICs) and low- and middle-income countries (LMICs) (Parker and Bull, 2009, Schroeder et al., 2018) as well as ethical challenges associated specifically with genetics research in the context of such collaborations (de Vries et al., 2011, Munung et al., 2017). We build on these discussions by examining how the combination of neuroimaging and genetics adds to the ethical complexity. In this section we look at two ethical issues that are internal to such collaborations: the benefits and risks of collaborations and data sharing, respectively.

3.1. Science diplomacy and collective problem solving

The challenges facing humanity require global effort and collaboration between nations (Schroeder et al., 2018). Recognition of this has been a major driver in global mental health (Patel and Prince, 2010). A benefit that is sometimes overlooked in global scientific collaborations is the way in which they are able to build and enhance diplomatic relations and transcend political conflicts between nations. Science diplomacy is defined as "the use of scientific collaborations among nations to address the common problems facing … humanity and to build constructive international partnerships" (Fedoroff, 2009). The value of scientific cooperation was highlighted during the Cold War with concerted efforts of Soviet and American scientists working on a vaccine for the polio virus (The Editors, 2017). In the context of twenty-first century conflicts between nations, scientific collaborations may be a way of bridging political conflicts between nations. With representation from 45 countries, some of which have minimal diplomatic ties, membership in a consortium such as ENIGMA is a way of, at the very least, keeping channels open between nations.

Scientific collaborations are not only constructive in terms of building diplomatic relations between conflicting nations, they also facilitate expertise-sharing. This leads to a more constructive form of collective problem solving whereby results are considered from different perspectives and disciplinary backgrounds, enabling innovative insights and approaches to be developed. In addition to these benefits, scientific collaborations have the potential to facilitate connections between HICs and the poorest nations across the globe and to build capacity in the latter (Fedoroff, 2009, Zewail, 2010). For example, while the majority of ENIGMA sites are located in North America, Europe and Australia, the consortium also has members in the Middle East, Russia, and in LMICs in Asia, including India, and South America. While there are African members, the continent is conspicuously underrepresented. This is unsurprising, however, given the scarcity of MRI scanners in Africa (Ogbole et al., 2018), and in particular, the lack of high field strength scanners suitable for research purposes (Spottiswoode and Carey, 2008).

Insofar as neuroimaging genetics studies have long-term potential to contribute to improved understanding and treatment of neuropsychiatric disorders, the underrepresentation of African participants in such studies is a potential source of health inequity. The gap between developing nations, and Africa in particular, and developed nations in the research and treatment of mental illnesses has been emphasized previously (Sankoh et al., 2018, Demyttenaere et al., 2004). Such disparities also exist within nations, with many indigenous populations and racial-ethnic minority populations experiencing inequitable access to mental healthcare (McIntyre et al., 2017, Cook et al., 2017). This gap and recognition that a lack of access to mental health care constitutes a violation of the fundamental human right to mental health has been pivotal in motivating global mental health (Patel and Prince, 2010, Patel et al., 2018). The research gap has also been highlighted in genomics research (Martin et al., 2018). Genomics studies have mostly been conducted in HICs and, even within these countries, have predominantly included participants with European ancestry, therefore, any insights, predictive ability or potential clinical utility gained from these studies may be limited to these populations (Martin et al., 2018). The same concern holds for the need for knowledge of the effects of ancestry-specific variants on the brain (Tairyan and Illes, 2009). Addressing global inequities in mental health will require not only increasing the number of scanners on the African continent but also investing in the infrastructure capable of supporting such equipment and the requisite expertise to operate it.

While global science collaborations have the potential to address global health inequities, such collaborations have also been identified as contexts of potential exploitation of LMICs or 'ethics dumping'

[1] There are exceptions e.g., variants in the APOE $\epsilon 4$ gene and copy number variants (CNVs) which may have substantial effect sizes (Sønderby et al., 2018, Ulfarsson et al., 2017, Sun et al., 2018).

(Schroeder et al., 2018). The latter refers to the tendency of researchers or institutions in HICs to take advantage of a lack of ethics oversight and governance structures in low-resourced countries in order to undertake or export research, (e.g. clinical trials), that would be either illegal or ethically untenable in their own countries (Schroeder et al., 2018, Hawkins and Emanuel, 2008). While exploitation of LMICs may not be intentional, there is a risk of inadvertent exploitation. This may be due to a lack of awareness on the part of HIC researchers or institutions of relevant contextual information such as salient cultural factors or localized ethical challenges.

In order to safeguard against both intentional and unintentional exploitation, equity in international research has become a driving force (Parker and Bull, 2009, Schroeder et al., 2018). This includes creating awareness among researchers of the potential for exploitation and the need for contextual sensitivity, capacity building of ethics oversight and research ethics committees in such countries, and the introduction of "compliance mechanisms" (Schroeder et al., 2018). Examples of the latter include implementing sound ethics frameworks for governance and best practice of research in LMICs (see (Yakubu et al., 2018)), introducing and developing national guidelines, and by funders and institutions adopting and enforcing codes of conduct. The Global Code of Conduct for Research in Resource-Poor Settings was introduced with the explicit purpose of counteracting ethics dumping and encouraging equitable relationships between HIC and LMIC researchers and institutions (Global Code of Conduct for Research in Resource-Poor Settings, 2018). It comprises 23 articles, or recommendations, founded on the principles of "fairness, respect, care and honesty" (Global Code of Conduct for Research in Resource-Poor Settings, 2018). Respecting these four principles forms the basis of a foundation of trust between stakeholders in collaborative research and is more likely to ensure that research is equitable.

An approach used by ENIGMA, to ensure equity and diversity of geographic and cultural representation in their projects, is to have working groups and other aspects of collaboration led by scientists from a range of different countries. For example, one of the ENIGMA working groups is led from Russia and there have been regular workshops in Moscow and Siberia (Namazova-Baranova et al., 2017, ENIGMA-Skoltech International Workshop, 2016). Another recent ENIGMA initiative led by investigators in an LMIC country is the 'India ENIGMA Initiative for Global Aging and Mental Health', which involves large-scale data collection in Bangalore, India. A key goal of the project is to train emerging and established scientists in India, with targeted biostatistical and imaging workshops to bolster capacity and training in setting up international projects (John et al., 2019). A related biobanking effort by the c-VEDA consortium in India (cveda.org) has led to a coordinated study of brain development in adolescence across 7 sites. A key goal of this effort is to study effects on the brain of environmental risk factors that may be specific to emerging societies, including "exposure to nutritional stress, environmental neurotoxins and culturally dependent forms of psychosocial stress" (Zhang et al., 2020).

3.2. Data sharing: Equity and privacy

With the formation of global neuroimaging consortia involving multi-site collaboration, neuroimaging studies have been able to participate in big data research with the collection, storage, analysis and sharing of vast swathes of information about human behaviour, health and disease (Smith and Nichols, 2018). Big data science is an efficient and cost-effective way of acquiring, integrating and disseminating knowledge (Murdoch and Detsky, 2013). In biomedical research, it has long-term potential for considerable improvements in health care outcomes (Luo et al., 2016). While sample sizes of individual imaging studies remain small, meta-analytic approaches, as used by ENIGMA, enable the sharing and pooling of a large amount of analyzed data from numerous studies conducted across sites, using standardized protocols that enable cross-site harmonization of methods (Thompson et al., 2014).

While some form of data sharing is a prerequisite for multi-site collaboration, it elicits ethical concerns related to equity, privacy, informed consent and governance (Vayena and Blasimme, 2018). We discuss the first two areas of concern. Data sharing is ethically justified by the principles of justice and beneficence (Bezuidenhout and Chakauya, 2018). More specifically, it has the potential to rapidly advance scientific progress as it enables widespread use of data by a range of scientists from different disciplines, it facilitates "collaboration, transparency, …, reproducibility" and accountability in science (Milham et al., 2018) and reduces unnecessary effort and waste of resources associated with the replication of data sets Figueiredo 2017. For these reasons, science funders strongly support data sharing and scientific journals are increasingly asking for data to be deposited in an open access database at the time of publication (Gewin, 2016, Policy on data, software and materials management and sharing, 2017).

Despite widespread support by researchers (Kessler, 2018) and benefits that address the reproducibility crisis in science (Baker, 2016), among others, data sharing poses technical and ethical challenges. Specialized expertise is required to store, manage and analyze data which may be initially costly for laboratories to implement (Figueiredo 2017). Multi-site collaborations, in particular, may struggle with technical challenges regarding different institutional regulations and requirements pertaining to data sharing (Boland et al., 2017). These may include: Material Transfer Agreements (MTAs) and Limited Data Use Agreements (DUAs); the General Data Protection Regulation (GDPR) in Europe; differences in consent forms regarding sharing of data or derived data, conditional on other oversight (e.g. bilateral IRB assent); and MoUs for collaboration that address data access. Moreover, data acquired from clinical populations may impose additional constraints and limits on data sharing which require consideration. More fundamentally, however, data sharing challenges traditional conceptions of intellectual ownership (Alter and Gonzalez, 2018). A common concern by scientists is that they fear being "'scooped' with their own data" (Alter and Gonzalez, 2018), or that their data will be misused or misinterpreted (Figueiredo, 2017).

Investigators in LMICs may be at particular risk regarding some of the above concerns. The formation of the African Open Science Platform initiative (AOSP) in 2016, with the aim of furthering open science and research collaboration in Africa, indicates clear support for the ethos of data sharing (African Open Science Platform. April, 2019). That said, LMIC researchers experience challenges that pose obstacles to their participation in the open science movement. In particular, LMIC and HIC researchers differ in their access to resources, technical support and infrastructural provisions (Bezuidenhout and Chakauya, 2018). LMIC researchers may, for example, face problems such as slow or intermittent internet speeds, outdated software and/or hardware and power disruptions; challenges which are not experienced in HICs (Bezuidenhout et al., 2016). Discussions that engage with challenges experienced in data sharing in HICs are therefore not likely to be portable to LMICs. This is evident in the fact that because most discussions of data sharing have taken place in HICs, they have focused on challenges arising from differences between kinds of data as opposed to differences between research contexts (Zewail, 2010). In keeping with surveys conducted in HICs which have investigated perceptions of benefits and risks of data sharing among scientists (Stuart et al., 2018), a survey from 13 sub-Saharan African countries showed that scientists recognise data sharing to be a way of increasing the "impact and visibility" of their research (Bezuidenhout and Chakauya, 2018). However, sub-Saharan scientists differ from their HIC counterparts in also regarding data sharing as a way of supporting "future *personal* connections" with known and trusted colleagues, rather than with strangers (Bezuidenhout and Chakauya, 2018). Fears of scooping and misuse were equally present in this cohort, particularly given concerns that research takes longer in LMICs and researchers produce fewer publications on average.

This information has important implications. If greater uptake of open science and data sharing is to be encouraged in LMICs as a scien-

tific good, the consortium approach is clearly one of the ways in which this can be achieved, given the value placed on trust and established connections among LMIC scientists. Four elements of ethical data sharing in LMICs have been proposed: "assessing the value of sharing" by engaging with all stakeholders; "minimizing harm" to participants and populations; "promoting fairness and reciprocity" by protecting the interests of local researchers and ensuring that research is relevant to the health needs of communities; and developing trust between all stakeholders (Bull et al., 2015). Moreover, priority must be given to further research of broad consent procedures, devising governance models and data sharing policies, and capacity building (Bull et al., 2015).

In terms of incentivizing data sharing at an individual level, consortia should address scooping concerns with solutions tailored to LMIC researchers and the challenges specific to their contexts. Certain consortia have successfully implemented embargo periods so that scientists have sufficient time to publish before their data is released (Parker et al., 2009). "Embargo flexibility" entails tailoring embargo agreements to the requirements of researchers and their disciplines and recognizes the "right of first use" of their data (Roche et al., 2014). In ENIGMA, for example, the sharing of data with other members is entirely optional, but the maximum use of the data is facilitated, subject to any prevailing terms of consent regarding data use, data security requirements, subject to oversight of appropriate IRBs and any international agreements. Insofar as they stipulate how data are able to be used, data usage agreements (DUAs) are helpful in protecting the interests of researchers and participants, however, in the context of multi-site collaborations and multiple agreements, if DUAs are excessively complex, this increases the administrative burden and may impede progress (Sarwate et al., 2014). Another way in which data sharing may be incentivized is by ensuring co-authorship on all derived papers.

While the ethical concerns associated with data sharing are not unique to imaging genetics, brain and genetic data represent fundamentally personal and potentially sensitive information about human beings. A frequently voiced ethical concern regarding data sharing is therefore the impact it may have on the privacy of research participants. While consortia such as the PGC use mega-analysis approaches, ENIGMA has primarily used meta-analysis (Thompson et al., 2014). The meta-analysis approach addresses privacy concerns, to a large extent, and is in line with ethical guidelines and legal restrictions in certain countries regarding the sharing of personal data of participants (Thompson et al., 2014). This approach is also ethically commendable as site members retain ownership of their data and are responsible for protecting the privacy of participants. That said, the risk of privacy breaches remains because despite the fact that summary statistics shared through meta-analysis contain deidentified information, various methods have been used to demonstrate that participants may be reidentified from pooled data (Homer et al., 2008, Schadt et al., 2012, Gymrek et al., 2013). However, it has been argued that de-identification or ensuring anonymity equates with ensuring that the likelihood of matching "a correct identity to a record in a dataset is very small" (El Emam et al., 2015).

De-identification of data is primarily aimed at protecting the personal information associated with individual research participants. However, a related concern associated with population studies, which could be intensified in the case of neuroimaging genetics studies, is that the disclosure of potentially sensitive information about particular populations or communities could have negative implications for such populations (de Vries et al., 2012). A well-documented example of this occurred with the publication of a comparison between the genome sequence of a member of the 'Khoisan' people, "the oldest known lineage of modern human" and "a Bantu from Southern Africa" (Schuster et al., 2010). The study aimed to deepen understanding of genetic diversity by investigating and comparing common variants. What was problematic about this study was the unsubstantiated and unrelated inferences made in an additional paper, published with the study and supposedly based on it. This paper contained information and cultural inferences that San community leaders found to be "private, pejorative, discriminatory and inappropriate" (Chennells and Steenkamp, 2018). The exploitative nature of this study and the negative implications for the population in question of sharing what was deemed to be information of a "sensitive and private nature" highlights the importance of community engagement prior to and during research and the need for adequate, contextually informed, assessment of possible risk (Chennells and Steenkamp, 2018). Certain studies, e.g. population-level neuroimaging genetics studies of cognitive performance, that may be subject to misinterpretation, require ethical safeguards to be put in place (Gray and Thompson, 2004, Gray and Thompson, 2004a). Such ethical safeguards include: securing the consent of target groups via "appropriate representatives", full disclosure to participants of the study's aims, the option to withdraw and have one's data destroyed or removed from databases, and appropriate care taken with descriptions and communication of findings (Gray and Thompson, 2004).

A few observations can be made from our discussion that are relevant for global collaborations. First, given the contextual challenges and implications associated with data sharing, it is unlikely that a one-model or standardized approach to governance will be appropriate. To minimize risk and ensure maximum benefit for all concerned, data sharing approaches must be adaptable for diverse research contexts (Nicol et al., 2019). Second, to address privacy concerns and balance them with the importance of data sharing, greater consideration is needed of the views of all stakeholders, including research participants themselves. Various studies have investigated privacy concerns of research participants regarding both deidentified and open genomic data sharing in various HICs (Shah et al., 2019, Goodman et al., 2017, McGuire et al., 2011). However, as there have been limited studies of this kind in LMICs (Parker and Bull, 2015), further work is needed in this context.

4. The potential impact of neuroimaging genetics research findings in LMICs

Over and above internal issues associated with the collaborative process, the findings generated by neuroimaging genetics collaborations have wider implications for research participants, their families and their communities. We next examine dilemmas associated with feedback of findings and the risk of essentializing and stigmatizing interpretations of imaging genetics research.

4.1. Feedback of findings

By participating in neuroimaging genetics studies, research participants are contributing to knowledge of the pathogenesis of neuropsychiatric disorders. If this research yields findings that have clinical potential, it may ultimately lead to long-term collective benefits for persons with such disorders. However, given that participation will not produce direct benefits for participants, there is, arguably, an obligation to recognise their contributions by providing any benefits that are reasonably possible. This is in keeping with a recognition of the importance of reciprocity which has gained traction as a protective mechanism in research (Tindana et al., 2019, Maiter et al., 2008, Trainor and Bouchard, 2013). One way of ensuring that participation is beneficial to participants is to provide feedback of findings where appropriate (National Academies of Sciences Engineering and Medicine 2018, Illes et al., 2006). In the case of experimental results there is agreement that only "high quality research results" (Botkin et al., 2018) or those that are "clinically … valid, and reliable" (National Academies of Sciences Engineering and Medicine 2018) should be shared with participants.

While neuroimaging genetics studies currently generate data with population-level significance, imaging may detect the presence of incidentalomas (asymptomatic tumours or other abnormalities) or other incidental findings (e.g. aneurysms) unrelated to the research question, that may have clinical significance (Illes et al., 2004, Buchman and Illes, 2010). Where such incidental findings deliver reliable, clinically

actionable information, there is a moral obligation to deliver such results in our opinion. Analogous considerations hold in genetics research. However, systematic reviews indicate that the prevalence of malignancy in incidentalomas is less than 5% for brain incidentalomas (O'Sullivan et al., 2018). This creates a dilemma regarding the sharing of such information, given the negative outcomes of overdiagnosis (Chojniak, 2015). In particular, sharing such information may cause acute anxiety for participants, leading to unnecessary treatments and overburdening health care systems (O'Sullivan et al., 2018).

These risks and burdens are likely to be intensified in collaborative research involving studies in LMICs. Moreover, standardized approaches to feedback developed in HICs are unlikely to be appropriate or implementable in such contexts (Sullivan and Berkman, 2018, Ortiz-Osorno et al., 2015). A finding that is actionable in a HIC may not be actionable in a resource-strained context. A protocol-by-protocol approach has been suggested as a more appropriate way of responding to the challenges of feeding back findings in areas such as genomics research which are subject to continual change and a lack of certainty (Weiner, 2014). This approach would also seemingly address contextually specific feedback challenges. While it is recognized that collaborations must seek to balance the need for consistency in research and ethics practices across the network with appropriate response to diversity in local contexts (Parker and Bull, 2009), feedback approaches that differ across sites, on the basis of access to healthcare resources, risk exacerbating inequities and are therefore unjust. However, providing feedback of an actionable finding in a context where access to requisite treatment and care is lacking is equally problematic. This seemingly intractable dilemma may require falling back on a nuanced, contextually informed, calculation of the benefits and harms of disclosure and a provision of alternative benefits where potential harms of disclosure are likely to be excessive (Sullivan and Berkman, 2018).

4.2. Essentialism and stigma

While there is much overlap between the ethics generated by genetic and brain research respectively, the latter arguably elicits qualitatively distinct concerns (Roskies, 2007, Illes and Racine, 2005). This is predominantly attributable to the tendency to regard the mind and the brain as constitutive of highly valued, metaphysical concepts such as personal identity, the self, free will and moral capacity. It is also the basis of the premise that the ethical and philosophical issues generated by brain research and interventions are sufficiently unique, in comparison with other areas of medical research and practice, to treat neuroethics as a distinct area of focus, in its own right. Moreover, the mind and the brain are inextricably related in such a way that it is easy to see how an essentialist view of the brain arises. In the absence of brain function there can be no higher-order mental function. Neuro-essentialism, makes a leap beyond this observation and espouses the view that psychological states and experience are best explained with reference to brain states and function and that psychiatric disorders are disorders of the brain (Schultz, 2015). On such a view the mind is synonymous and reducible to the brain.

Genotypes, their expression in observable brain morphology, and phenotypes, form a complex, non-linear causal chain that is impacted by environmental interactions. In comparison with brain morphology, genes are possibly more causally distant from neuropsychiatric phenotypes (Roskies, 2007). Despite this distance, genethics must contend with its own distinct ethical issues. Awareness of the relatively stable, heritable and fundamentally unique nature of the human genome is also likely to lead to essentialist views (Kong et al., 2017, Dar-Nimrod and Heine, 2011). Genetic-essentialism refers to the tendency to overestimate the genetic basis of behaviour, traits, health and disease, while downplaying the role played by environment (Phelan et al., 2013). Studies, mostly conducted in HICs, indicate that information about genes and the brain is frequently interpreted through an essentialist lens (Parrott et al., 2012, Gould and Heine, 2012). Given that imaging genetics studies are explicitly focused on the relationship between genes and the brain in conferring risk for neuropsychiatric disorders, it is easy to understand how communication about this research may be interpreted by participants and communities in essentialist ways. What is therefore, arguably, unique in neuroimaging genetics research is how the confluence of these two areas that are particularly susceptible to essentialist interpretations may heighten risk for various misinterpretations (Tairyan and Illes, 2009).

This is important because essentializing interpretations are problematic insofar as they support other reductionist views. First, essentialism generally entails oversimplifying or reducing something that is complex in its cause, structure or function, e.g. understanding mental disorders purely or predominantly in terms of a biological model rather than acknowledging psychosocial determinants. Second, essentialism can lead to determinism which, in this context, is the view that if mental disorders are caused by genotype and neurophysiology, factors over which we have little to no control, there is little to no room for agency. Determinist interpretations also impact assessments of risk or probability with the result that information about risk may be regarded as implying more certainty than is warranted (Illes and Racine, 2005, Palk et al., 2019) This can engender a sense of powerlessness or fatalism (Shen et al., 2009). Third, and connected with the previous points, essentialist interpretations of neuroimaging genetics findings may exacerbate stigma towards mental disorders (Tairyan and Illes, 2009, Illes and Racine, 2005). This could be the case if beliefs about mental disorders as being 'in the genes and the brain' lead to the view that persons with such disorders, and their relatives by association (Catthoor et al., 2015), are inherently different. This risk is considerable, given the high levels of stigmatization of mental disorders in particular regions of the globe (World Health Organization, 2018).

The causes of stigma associated with mental disorders and the way in which it is manifested differ across the globe, but within Africa its sources are generally consistent and identifiable. High levels of stigma are predominantly attributed to fear and hostility arising from culturally informed beliefs regarding the aetiology of mental disorders, e.g., beliefs about spiritual causes such as witchcraft, demonic possession, retribution or the view that symptoms and behaviours are deliberate or indicate weakness or incorrigibility (Egbe et al., 2014, Kapungwe et al., 2010, Gureje et al., 2005, Shibre et al., 2001, Shah et al., 2017, Opare-Henaku and Utsey, 2017, Palk and Stein, 2020). External factors and notions of responsibility thus play an important role in stigmatizing ascriptions in these contexts. Stigmatizing beliefs about external or spiritual causes are challenging to address because they can be reconciled with information about the biological basis of mental disorders, by extending the perceived causal chain to encompass the latter. Moreover, addressing different, culturally informed, explanatory models of disease requires sensitivity.

In terms of a connection between responsibility and stigma, biological or genetic models of mental disorder may lead to more acceptance because they have a tendency to feed into essentialist, determinist interpretations or, at least, to less blame and, ultimately a decrease in stigma. However, a systematic review of 33 studies conducted in both HIC and LMICs that focused on this question found that in most cases, biogenetic explanations of mental disorder did not increase acceptance (Angermeyer et al., 2011). Findings also confirm that stigma, manifested as a desire for social distance, is mostly informed by perceptions of "dangerousness and unpredictability" (Angermeyer et al., 2011, Kvaale et al., 2013). These findings were echoed in a meta-analysis of 26 studies which found that neurobiological explanations were also associated with increased stigma, reflected in an increased desire for social distance from individuals with mental disorders (Loughman and Haslam, 2018). However, findings also indicated that responses to biogenetic explanations were impacted by culture and the nature of the disorder in question (Angermeyer et al., 2011). In non-Western contexts, negative stereotypes may be more strongly informed by perceptions of

responsibility. It is important, therefore, that discussions of genetic neuroimaging findings highlight the importance of a non-reductionistic and non-essentialist perspective, in order to counter such views. This is also important when scientists relay findings to the media (Racine et al., 2005, Racine et al., 2006), which often adopts an essentialist perspective.

5. Concluding remarks – African ethics perspectives as a resource

We conclude with some suggestions informed by ethical perspectives that are prevalent in sub-Saharan Africa. We use the term African ethics simply for ease of reference, while noting the diversity of normative perspectives found on the African continent. In the same way that there is no definitive Western ethics, there is no singular African ethics. However, there are certain themes that are sufficiently prevalent, that descriptions of African perspectives as largely communitarian or Western perspectives as predominantly individualist are coherent. Insights drawn from these themes may be a useful resource for thinking through some of the challenges that we have highlighted.

Communitarianism is a widespread worldview that recognizes and derives normative implications from the relational nature of human existence. African communitarian perspectives are informed by the underlying view that personhood is, and should be, relationally constituted and maintained. The way one relates with others is therefore fundamentally important; social values such as harmony, good will, connection, interdependence, accountability, and reciprocity are guiding ideals (Metz, 2007). The ethos of a communitarian position and its associated ideals is well captured by the notion of solidarity. The value of solidarity as a necessary addition to the dominant bioethics paradigm has also been recognised in global health ethics discussions (Benatar et al., 2016, Tosam et al., 2018, Andoh, 2011).

As an intrinsically relational value, solidarity is a powerful ideal. It is grounded by the premise that respecting and cultivating connections is good as an end, in itself, rather than as a means to an end. While the ability of an appeal to values, principles or ideals to address some of the issues we have discussed may be limited; the addition of a relational notion, such as solidarity, to the dominant bioethics paradigm has great potential to address some of the internal issues associated with collaborative research that we have highlighted. In global collaborations aimed at improving health, an emphasis on solidarity is in keeping with recognition of the historical context that has led to global health inequities and justifies an obligation to redress these by supporting and building the capacity of researchers and institutions in low-resourced contexts. In the context of neuroimaging genetics studies, solidarity would justify investment in the infrastructure, equipment, and skill necessary to achieve greater representation of low-resourced contexts. ENIGMA has done this, for example, by mentoring a range of individuals in these contexts. Cultivating solidarity in collaborative research will lead to stronger, more equitable, connections between researchers and sites. An ethos of solidarity is also congruent with reciprocity-based approaches to research that is mutually beneficial for stakeholders and responsive to local needs. Solidarity also justifies inclusivity and genuine participation of local communities and populations in ensuring this latter requirement.

Our aim in this paper is to draw attention to both the opportunities and heightened risks posed by the convergence of neuroimaging and genetics, and the need for appropriate caution in global collaborations. Our discussion has not aimed to be exhaustive; there is an abundance of literature addressing the areas we have highlighted. We emphasize that concerns for stigma and equity are key ongoing ethical challenges for neuroimaging genetics collaborations. Here we have provided a theoretical approach based on the framework of communitarianism as a resource to discuss such challenges, and we offer a number of practical recommendations to decrease stigma and increase equity.

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Author statement

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