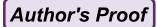
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Abstract	Big Data research is usually explorative, meaning that not all possible hypotheses are known that one may wish to test when data is made available. For the case of biomedical data this poses a significant challenge, as the originators of the data – patients or research participants – have to provide informed consent for using their data. The typically obtained "closed" or "narrow consent", i.e. consenting to use the data in a well-defined research project, is conceptually incompatible with the explorative nature of Big Data driven research. Therefore, "open" or "broad consent" is proposed as an alternative. Nevertheless, open consent cannot justify any type of data use, but requires an "information framework" that separates legitimate from illegitimate Big Data research. For example, consent is given associated with established disease categories: a patient diagnosed with early-onset Alzheimer's disease may consent to his personal medical information being used for any research enhancing our understanding of this particular disease. In our contribution, we address the question whether and how Big Data driven research may undermine this "information framework" of informed consent using the example of the Human Brain Project (HBP). Within the HBP, a Big Data infrastructure is currently being developed to access a multitude of clinical data related to brain diseases based on the conviction that many neurological and psychiatric disorders and diseases are ill-defined in terms of underlying mechanisms. We analyse the interrelation between effects of Big Data research and informed consent and we evaluate ethical and practical consequences.	

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On the Compatibility of Big Data Driven Research and Informed Consent: The Example of the Human Brain Project

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this "information framework" of informed consent using the example of the Human 20 Brain Project (HBP). Within the HBP, a Big Data infrastructure is currently being 21 developed to access a multitude of clinical data related to brain diseases based on 22 the conviction that many neurological and psychiatric disorders and diseases are ill- 23 defined in terms of underlying mechanisms. We analyse the interrelation between 24 effects of Big Data research and informed consent and we evaluate ethical and 25 practical consequences.

1 Introduction

Modern biomedical research as well as the ongoing digitalization of healthcare 28 systems is creating an enormous amount of data that has the potential to sig- 29 nificantly change our understanding of various diseases. Previous examples of 30 scientific milestones achieved through advances in information technology include 31 the steadily growing number of Internet accessible sequence databases in molecular 32 biology since the early 1980s with its emanation – The Human Genome Project. 33 Neuroscience has clearly taken a similar direction, which is illustrated by several 34 new initiatives for data sharing and common databases. Such initiatives are deemed 35 to be necessary given the massive output of this field. It is estimated that more 36 than 100,000 papers a year are published in neuroscience (Grillner 2014) – most 37 of them involving the analysis of data of various kinds, from genetic data and 38 electrophysiology measurements up to imaging and behavioural data. Compared 39 to other fields like molecular genetics, however, the large majority of neuroscience 40 data sets are still small due to the complexity of the research needed for generating 41 them.² Furthermore, data-sharing standards are often lacking. Such small data sets 42 have been referred to as "long-tail" data and may in the future become an important 43 source of new findings (Ferguson et al. 2014).

This traditional focus of neuroscience on "small science" and "small data" comes 45 increasingly under pressure due to recent "big neuroscience" initiatives (Christen 46 et al. accepted). Several Big Data projects are underway to access both small 47 and big data sets generated through research in neuroscience - a development 48 that is exemplified by the "Big Data" issue of Nature Neuroscience in November 49 2014. While many of these efforts focus on model animals, Big Data is also 50 being generated from humans. For example, the amount of openly available and 51 shared neuroimaging data has increased substantially in the last few years (Poldrack 52 and Gorgolewski 2014; Thompson et al. 2014). Even larger data sets concern 53

¹In the following, we use a wide understanding of neuroscience, including also medical fields that deal with neurological or brain diseases like neurology, neuropsychology or psychiatry.

²Examples include morphological reconstructions of neurons (which is very time-consuming), research with nonhuman primates (which is highly regulated and expensive) or neuroimaging research (which requires a costly infrastructure).

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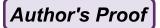
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whole-genome sequencing data and the increasing use of technologies for creating 54 large transcriptomic and epigenetic data sets from brain tissue (Shin et al. 2014). 55

In the following, we will focus on particular Big Data initiatives that are 56 integrated in the Human Brain Project (HBP). The HBP was announced in January 57 2013 as one of two flagship projects funded by the European Commission's 58 Future and Emerging Technologies Programme. The matched funding for the HBP 59 of about 1.16 billion Euros over 10 years provided by European Union (EU) 60 and partners shall enable a concerted effort to "lay the technical foundations 61 for a new model of ICT (information and communication technologies) based 62 brain research, driving integration between data and knowledge from different 63 disciplines, and catalysing a community effort to achieve a new understanding 64 of the brain, new treatments for brain disease and new brain-like computing 65 technologies" (HBP Report 2012, 3). A major goal of the project involves data 66 integration, for which the HBP is developing six ICT-based platforms dedicated, 67 respectively, to Neuroinformatics, Brain Simulation, High Performance Computing, 68 Medical Informatics, Neuromorphic Computing, and Neurorobotics (for detailed 69 information: https://www.humanbrainproject.eu/). Those platforms are intended to 70 allow sharing research data of all levels of neuronal integration (related, e.g., to ion 71 channel structures, synapse distributions, neuronal microcircuits, brain connectivity 72 patterns, or functional imaging data), methods and models (e.g., in form of computer 73 programs, respectively code) and accessing databases that contain a multitude of 74 clinical data related to brain diseases – the latter will be provided by the Medical 75 Informatics platform and is described in more detail in Sect. 4.

There are certainly many ethical issues associated to data generation (e.g., animal 77 experimentation) and data sharing in neuroscience (e.g., allocation of scientific 78 credit when publishing results originating from shared data). But our focus here 79 is on the problem of informed consent when the data emerges from human subjects, 80 which researchers are required to obtain by current data protection legislation in 81 European countries. Traditionally, 3 "closed" or "narrow consent" is provided, i.e. 82 patients or research participants consent to only one or a few specific uses of the 83 data in a well-defined research project. This, however, is conceptually incompatible 84 with the nature of Big Data driven research that seeks patterns in data based on 85 hypotheses that are often not known when the data has been collected. Therefore, a 86 growing number of researchers and legislators propose "open" or "broad consent" 87 as an alternative, meaning that consent is given to using data for broader research 88 fields or – as a maximum – for any form of research (for an example in genetics, 89 see Lunshof et al. 2008). As we will outline below, such a broad consent poses 90 ethical challenges. These are increased in the case of human brain data, as such data 91

³Seen from a broader historic perspective, (closed) informed consent is a rather recent phenomenon, but can now be considered as standard at least in research settings in industrialised countries. In this contribution, we refrain from outlining the history of informed consent and of international differences in the understanding of informed consent.

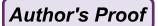


is by nature sensitive even if it does not contain healthcare information, because it 92 contains information about the organ of the mind and thus to a certain extent also 93 about the mind itself. 94

In our contribution we are particularly interested in a potential conflict that 95 is posed by Big Data research in neuroscience, especially when the research is 96 related to neurological or psychiatric diseases. On the one hand, despite the consent 97 being "open", it requires specifying *some information* about what the person is 98 consenting to; otherwise the consent cannot be called "informed". Thus, any form 99 of *informed* consent is embedded in an "information framework" that outlines the 100 general context in which the data is generated, what kind of data is actually obtained, 101 and – although not exhaustively and still in rather general terms – what kind of 102 results could be expected through analysing the data. A plausible and frequent way 103 of generating this information framework is by referring to disease categories – 104 we call this the disease space ontology. For example, a patient diagnosed with 105 early-onset Alzheimer's disease may consent to his personal medical information – 106 health record data, genetic data, neuroimaging data etc. – being used for any type of 107 research enhancing our understanding of Alzheimer's disease.

On the other hand, there is as long-standing discussion in neurology and psychiatry that many current neurological and psychiatric disorders and diseases 110 are ill-defined in terms of underlying mechanisms (Owen 2014; Thagard 2008). 111 On the example of Major Depressive Disorder representing a separate disorder 112 category according to DSM-5, there may be a different classification with a number 113 of subtypes depending on a variety of underlying biological mechanisms. Some 114 types of depressive syndromes may in fact turn out to be other disorders, whereas 115 some might turn out to be subsumed under a disease category with known causes 116 and mechanism and not just a syndrome, i.e. a heterogeneous cluster of symptoms 117 (Monroe and Anderson 2015). Taking these two developments together, it could be 118 that the standard way of providing an "information framework" through disease categories is likely to be shattered through research that necessarily relies on Big Data 120 approaches, in particular in case of brain diseases. We take this apparent paradox 121 as a starting point to explore the connection between the information framework of 122 informed consent and Big Data research that may affect this framework.

This question will be approached in our contribution from various angles. First, 124 we briefly outline the problem of neuroscience-informed disease categorisation 125 with a particular focus on psychiatric diseases. This should motivate the claim that 126 changing the disease space ontology could have an effect on the practice of giving 127 informed consent. Second, we describe in detail the current setup of data collection 128 and informed consent practice within the HBP intended to improve and change our 129 understanding of disease categories in neuroscience. In this way we want to outline 130 that significant changes with respect to our understanding of brain diseases are not a 131 mere theoretical scenario. Third, we discuss the legal problems of open informed 132 consent practices and their dependence on an information framework. In this 133 context, specific attention is paid not only to existing data protection law, but also 134 to legislation aiming at the protection of research participants (e.g. the Council of 135 Europe's Convention on Human Rights and Biomedicine). Fourth, we evaluate the 136



underlying moral justifications for upholding or transgressing certain "information 137 borders" in terms of information spheres following the proposals of Nissenbaum 138 (2004) and van den Hoven (2008). Finally, we sketch novel technological solutions for addressing this problem by referring to concepts like traceability of data use and 140 verifiable anonymisation.

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Disease Categorisation in Psychiatry from a Neuroscientific Point of View

The human brain is among the most complex structures that are object of scientific 144 investigation and it is therefore not surprising that brain diseases are hard to 145 understand. Broadly construed, neurological and psychiatric diseases can be defined 146 as disorders of the brain. There is a continuum of disorders with respect to the 147 degree of their scientific understanding. In some cases, the neurobiological cause 148 is simple and known (e.g. a specific genetic aberration on chromosome 4 in 149 Huntington's disease). Other disorders are diagnostically well-defined and there is 150 a considerable body of knowledge available regarding their underlying mechanisms 151 (e.g. neurodegeneration of dopaminergic neurons in Parkinson's disease). Yet 152 other disorders are difficult to diagnose (in particular in the early phase) and 153 competing theories are available regarding the pathophysiological mechanisms 154 (e.g., Alzheimer's disease). Finally, in many frequent disorders although neurobiological knowledge is available, but rather limited and their definitions today still rely on clinical signs, symptoms and duration (most psychiatric disorders like 157 schizophrenia or depression). In the following, we will focus on the relation between 158 disease categorisation and Big Data driven research for psychiatric disorders, as strong hopes, even promises, have been raised that those approaches can improve knowledge and subsequently therapy (Owen 2014; Wang and Krystal 2008).

According to the two most influential manuals for categorising psychiatric 162 disorders, the IDC-10 of the World Health Organization and the DSM-5 of the 163 American Psychiatric Association, the diagnosis of a psychiatric disorder rest only on clinical features, i.e. on the presence of a specified number of certain symptoms for a specified duration and the exclusion of certain specified causes, like a "organic" disease or an intoxication. The disorder concept of DSM and ICD is categorical: 167 either you have the disease or you don't – although disorder are characterised by 168 different degrees of severity, e.g. for depression. ICD-10 as well as DSM-5 do not 169 rely on underlying pathophysiological mechanisms as most of them are not known, 170 heavily debated, or can only be diagnosed post-mortem.

Between the publication of DSM IV (released in 2004) and DSM-5 (released in 172 May 2013) it was hoped that the new DSM-5 would advance the field considerably 173 with respect to two issues: integrating dimensional approaches (i.e. use constellation 174 of symptom dimensions instead of categories for example for the diagnosis of 175 personality disorders) and integrating neurobiological criteria (genetic, molecular, 176 neuroimaging) for making diagnoses. Suggestions in this direction were intensively 177



discussed by the DSM-task force of the American Psychiatric Association over several years. At the end, however, none of these conceptual changes were included in DSM-5. This was largely because it was felt that neurobiological knowledge was not (yet) reliable enough, but also due to the fact that the DSM is much more than a medical nosology: it also serves a central societal role by providing the basis for mental health care and thus is conservative in nature as changes would immediately affect millions of patients and carefully balanced systems of providers and consumers.

This missing integration of neurobiological knowledge frustrated many mental 186 health scientists. In fact, 3 weeks before the official release of DSM-5, Thomas 187 Insel, at that time director of the National Institute of Mental Health (NIMHM),⁴ the largest research institute for mental health in the western world, launched a 189 considerable attack on DSM-5 by declaring in his blog that "the weakness (of DSM-190 5) is its lack of validity. Unlike our definitions of ischemic heart disease, lymphoma, 191 or AIDS, the DSM diagnoses are based on a consensus about clusters of clinical 192 symptoms, not any objective laboratory measure. In the rest of medicine, this would 193 be equivalent to creating a diagnostic system based on the nature of chest pain or the 194 quality of fever. Indeed, symptom-based diagnosis, once common in other areas of 195 medicine, has been largely replaced in the past half century as we have understood 196 that symptoms alone rarely indicate the best choice of treatment" (Insel 2013). 197 The apparent lack of availability of reliable biomarkers for mental disorders was 198 explained by Insel as a conceptual rather than as an empirical problem: it would be 199 equivalent to rejecting the usefulness of the electrocardiogram (ECG) as a diagnostic 200 tool, only because many patients with chest pain do not have ECG changes. In fact it 201 was the ECG which allowed differentiating chest pain due to specific heart problems 202 from other forms of chest pain, i.e. the tool helps to categorise the disorders by 203 measuring physiological processes. And, according to Insel, the same should be 204 done in psychiatry by "collecting genetic, imaging, physiological, and cognitive 205 data to see how all the data – not just the symptoms – cluster and how these clusters 206 are related to treatment response" (Insel 2013). Such an approach is only possible 207 using Big Data techniques, as we will outline in the next section.

In fact, the NIMH started a research program some years ago which is now 209 known under the name Research Domain Criteria (R-DOC; Morris and Cuthbert 210 2012). The basic idea of this approach is to achieve a dimensional characterisation 211 of mental illness as mentioned above in order to discover, refine or reclassify 212 mental disorders. For this purpose, it is suggested to study diseases based on a 213 two-dimensional grid based on current neurocognitive and molecular approaches 214 and knowledge. One dimension consists of five core domains of mental functioning 215 ("systems") that have been determined by consensus conferences of active scientists 216

⁴Interestingly, in particular with respect to the increasing role of ICT for (mental) health, Thomas Insel announced in September 2015 after 13 years serving as director of the NIMH that from November 2015 on he will move to Alphabet, the umbrella organization of Google in order to help to develop mobile health technologies.

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from the field, i.e. systems for negative valence, positive valence, cognition, social 217 processes and arousal. Each of these domains has subdomains, e.g. the system for 218 negative valence comprises the subdomains active threat ("fear"), potential threat 219 ("anxiety"), sustained threat, loss and frustrative non-reward. The other dimensions 220 refer to levels of organisation on which the constructs within the domains can be 221 measured: from genes, molecules, cells, circuits, physiology, to behaviour, self- 222 reports, and paradigms. By filling this 2-dimensional grid with scientific results, 223 it will, in the long run, be possible to characterise mental disorders on a sound 224 empirical basis and detect patterns leading to the discovery of new disorders or 225 reclassification of new ones. These discussions on a new understanding of mental 226 disorders as disorders of neurocognitive domains are also referred to as the "third 227 wave of biological psychiatry" (Walter 2013).

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However, for this approach to being realised, a revolution, or at least a reform 229 of disease concepts is required. It also would entail Big Data neuroscience on 230 mental health: only if you have obtained enough high dimensional data from many 231 domains of many subjects together with clinical data, this approach might become 232 successful. But standard DSM-based research uses the (not-so) gold(en) standard 233 of symptom-based categories and will thus make no progress. Therefore, Insel has 234 announced that the NIMH will in the future not fund research based on "old" still 235 gold-standard disease categories, but rather RDOC-oriented, dimensional research. 236 To take a simple example, it would not fund neurobiological research on alcohol 237 addiction, but rather neurobiological research on impulsivity as a contributor to 238 alcohol drinking.

But what would such a change induce on the level of actual researchers who have 240 to interact with patients and research subjects and obtain their informed consent for 241 using their data? Consenting to the use of data in research obviously requires a basic 242 understanding on the context in which the data has been generated and in which it 243 is likely to be used. Lay people like patients usually do not have the competences 244 needed to assess the detailed hypotheses of research in which they are involved, e.g. 245 when they are asked to participate in a clinical trial for testing a new medication. 246 Although such detailed information is not required, as the main interest of the patient 247 probably is to obtain information on possible health risks and benefits – this type 248 of information is still presented in a context framed by the disease from which 249 the patient is suffering. Taking the simple example from above, a patient with a 250 severe drinking problem would probably expect that the research in which he is 251 involved relates to alcohol addiction and not to some research on impulsivity, as 252 the person may consider impulsivity (to some degree at least) as a legitimate aspect 253 of his personality. Thus, the specific disease along with a laymen understanding of 254 what, e.g., a depression or Alzheimer's dementia involves, is crucial for putting the 255 informed consent into a context.

This context also affects the moral significance of diseases. A disorder caused by 257 a genetic factor (e.g. Huntington's disease) is associated with specific types of moral 258 problems (e.g., related to inheriting the disease) that are not perceived to be present 259 in neurodegenerative disorder. Some brain disorders are associated with a stronger 260 stigma than others (e.g. schizophrenia versus epilepsy). Yet some disorders are 261

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understood to be clearly "brain based" (e.g., Parkinson's disease), whereas others 262 are much more associated to "external" (e.g., social or cultural) causes, although it 263 is likely that changes in the brain play an important role in the disease course (e.g., 264 anorexia nervosa) - and such "external causes" involve a different responsibility 265 relation (e.g. by avoiding certain social settings or by generating an imperative 266 to change certain societal aspects through policy interventions). Consenting to use 267 data related to one disease may thus mean something different than consenting to 268 contribute data related to another disease or to broader spectrum of diseases relevant 269 to specific domains of functioning.

If now a research program is installed that seeks connections between neuronal 271 diseases that lay people consider rather different, should they be informed on these 272 possible links? For example: should a Parkinson's disease patient be informed that 273 analysing her data may help to understand schizophrenia or depression – and in 274 this way implicitly given her some reason to suspect that she might suffer also 275 from one those diseases? Actually, the re-conceptualised disease space ontology 276 may look very different compared to the disease space that frames the current social 277 handling of these diseases in terms of physician-patient relation, health insurance, 278 or stigmatisation. Here, we try to sketch possible ethical consequences of such a 279 change in the disease space. But before that, we outline the actual possibility that 280 such a change could happen (Sect. 4) and the current legal setting related to informed 281 consent (Sect. 5).

Data Collection, Informed Consent and the Human Brain **Project**

Every day, an impressive amount of data related to brain health and disease are 285 produced in clinical and research establishments across Europe. Usually, these data 286 are in the format of descriptive clinical data, laboratory results or brain images 287 that serve to help medical decision-making. They are viewed mostly only once 288 before being archived on departmental or laboratory servers for a finite number of 289 years. This mass of data constitutes an enormous research resource that is currently 290 largely unused. Though the data are collected at different sites, it has now been 291 demonstrated that the variance introduced by analysing data from multiple imaging 292 platforms or clinical chemistry laboratories is much smaller than the variance that 293 is attributable to the disease (Stonnington et al. 2008). In other words, variability 294 through differences in methodological practice can be controlled. This fact suggests 295 an opportunity to use archived data for the pathophysiological, anatomical and 296 medical studies on a population basis. This is a major motivation of the data 297 integration strategy of the Human Brain Project (HBP) in the medical informatics 298 platform.

Recent advances in computing and commercially available algorithms for feder- 300 ating data from local databases that work unobtrusively in the background in real 301

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time make such a project practicable and cost-effective. The Medical Informatics 302 platform of the HBP proposed an initial programme based on federation of data 303 related to brain diseases to establish feasibility, sharing protocols, data usage 304 agreements, access protocols and other issues. This idea represents a quantum leap 305 from the path trodden out in the past by successful database initiatives such as 306 the Alzheimer's Disease Neuroimaging Initiative (ADNI, see www.adni-info.org), 307 which is used by many researchers world-wide although it is much smaller in scope 308 and more expensive because the technology was not available at the time of its setup. 309

From an ethical point-of-view, the mass of brain health and disease related 310 information collected in hospitals, clinics and research establishments is grossly 311 underused at present, which represents an extraordinary waste of resources. With 312 advances in modern information technology, especially in terms of massive data 313 storage and access to hardware, analysis tools and data mining techniques, these 314 data can be used to carry out a range of studies of social and medical importance. 315 The range of possible investigations is enormous, if the data can be systematised 316 and intelligently mined. The main goal of the Medical Informatics platform of 317 the HBP is to federate and integrate clinical and basic science research together 318 with information technology and establish new ways for open access to shared 319 aggregate data in order to ask hypothesis driven questions, to mine data, to carry 320 out epidemiological, genetic and other surveys. But certainly, the question emerges 321 whether the practice of large-scale access to this data is compatible with the 322 informed consent given by the patients from which this information emerges. We 323 will come back to this point later and we first outline the technical procedures of 324 data collection.

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The complexity of clinical data especially in the field of neuroscience makes 326 evident the need for a coherent framework for integrating the multiple temporal and 327 spatial scales of data to facilitate its interpretation. Ongoing large-scale projects 328 (e.g., ENIGMA, Human Connectome Project, Allen Brain ATLAS, GENSAT) 329 demonstrate that brain imaging data capturing in vivo anatomical and functional 330 information about the brain can serve as a backbone for developing a viable 331 framework for research data integration. From a clinical perspective, the more 332 prominent examples are the recent developments in the neuro-epidemiology of 333 dementia based on differential patterns of cortical atrophy associated with cognitive 334 decline; the development of biomarkers from analysis of scans and subsequent 335 cognitive outcome or neuro-pathological examination; population wide genetic 336 association with in vivo pathology studies, as demonstrated by image-derived brain 337 tissue characterisation.

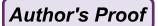
To give a very specific example that illustrates what could become possible, 339 there is a pressing demographic and economic need to answer questions about 340 the preclinical stage of dementia, in particular the incidence and natural history of 341 pathological change, early detection and diagnoses based on brain measures rather 342 than behavioural expression, and how to monitor the rate of pathological brain 343 changes on sufficient numbers of people such that the results are generalizable. The 344 repercussions of the results will be important because there is preliminary evidence 345

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to suggest that the dementias can be differentiated by early distribution of brain 346 atrophy. It should therefore be possible to identify purer cohorts of the different 347 dementia-associated diseases than is now possible to identify, and to test and develop 348 new specific disease-modifying drugs. This type of research could eventually lead 349 to a new classification of dementia-associated diseases that is quite distinct from 350 today's understanding. This would be an example of a re-conceptualized disease 351 space through Big Data research.

The use of data mining – the technological precondition for restructuring the 353 disease space – involves the extraction of patterns from large sets both for scientific 354 and business related queries. The use of this technique has exploded in the last 355 few decades in many fields in biomedicine, as outlined in Sect. 2. Considering 356 the remarkable advances in biomedical imaging technology and analysis, data 357 mining offers new opportunities capitalising on the ability to extract characteristic 358 features from abundant and diverse information about human (patho-) anatomy and 359 physiology. The creation of disease-specific neuroimaging data repositories (ADNI, 360 ENIGMA, IMAGEN) represents first attempts to use advanced neuro-informatics 361 methodologies for databases of clinically relevant information. Although offering 362 standardised data processing of anatomical brain images, these databases serve 363 mainly as repositories rather than frameworks for data mining on clinical neuro- 364 science grounds. Data mining approaches are aimed at making use of the large 365 data set in order to extract main predictors that explain variance in the data. An 366 understanding of the nature and extent of inter-subject variation is critical for the 367 characterisation of the neural basis of cognitive processes in healthy subjects and the 368 changes that cause abnormal functioning. Data mining approaches build upon the 369 decomposition of inter-individual differences to create meaningful classifications of 370 subjects and predictions of continuous variables such as behaviour or performance. 371 The principal hypothesis is that characteristic distributions of variability of the 372 structure of the brain and its connectivity patterns will be of diagnostic value through 373 identification of disease discriminative patterns.

The Medical Informatics platform of the HBP (see www.humanbrainproject.eu/ 375 medical-informatics-platform; Frackowiak and Markram 2015) is building on a 376 concept for data federation that allows mining all available resources without the 377 need to directly access the original data. Rather than copying, downloading and 378 mirroring data, the current set-up focuses on locally creating data aggregates, which 379 provide a summary of the available data at a particular site. These aggregates are 380 feature-specific and can be queried by the end-user in the form of double-aggregated 381 data. At no instance is there access to individual-specific data, which could open the 382 possibility for data misuse and identification of a given person. The combination of 383 simple database language queries and advanced methodological tools for statistical 384 inference and learning allows harvesting the aggregated data, binding multiple 385 sources of information and extracting characteristic features to answer domain- 386 specific questions. This is a dynamic process that aims to create clinical generative 387 models of specific diseases. As more data is gathered models can be re-evaluated 388 and refined to answer more subtle questions.



The processing of the data to extract features for aggregation is performed 390 locally within the secured systems of hospitals based on the availability of powerful 391 algorithms able to handle vast amounts of data. Several issues surrounding big data 392 analysis on the Medical Informatics platform of the HBP need consideration in 393 relation to data protection. Legally binding laws enforced by the EU authorities 394 stipulate that responsibility for the data and its ownership is transparent (see 395 also Sect. 5). Although our framework does not allow accessing individual data, 396 current laws and regulation apply to data transfer, data processing and data security 397 and the Human Brain Project has to ensure that data management is compliant 398 with data protection law. This also means that beyond strict procedures for data 399 anonymisation, data preparation for mining should be restricted to well-defined 400 workflows that prevent data miners from identifying specific individuals or from 401 uncovering confidential information. This protection of privacy is – from an ethical 402 point of view - the uncontroversial part of the problem. It is also in the focus of 403 current legislation, as we outline below. But our question is, whether privacy is the 404 only and main concern of Big Data driven research in neuroscience. 405

4 Legal Issues of Open Consent and Its Information Basis

The prevailing Data Protection Law applicable in all EU Member States is mainly 407 based on European legal guidelines. Debates over the minutiae of a new EU Data 408 Protection Regulation (anticipated to be passed around 2016) are fully underway. 409 Particularly the question of how this new Law will affect the use of personal data in 410 a scientific context is one of the main aspects in need of clarification. However, there 411 is a large consensus that the mere, indiscriminate adoption of general data protection 412 standards for scientific work could pose an unnecessary and unjustified restriction 413 of the freedom of research. 414

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Furthermore, specific problems arise regarding the practical implementation of 415 so-called informed consent. Originally developed as a bioethical principle, the 416 notion of informed consent can be found in many documents of international 417 and national law (e.g. the Council of Europe's Convention on Human Rights and 418 Biomedicine) today and has thus become an integral part of the Positive Law. In 419 'classical' research projects such as in clinical trials it has been shown, however, 420 that providing (too much) information to the research subject can occasionally lead 421 to the opposite effect of what the informed consent aims at; excess of information 422 can leave the concerned party unable to make a (truly) informed choice after all. This 423 problem exacerbates in Big Data driven research areas as outlined above: one cannot 424 effectively communicate the potentially enormous range of testable hypotheses to 425 patients. Therefore it has to be examined which models of informed consent can

⁵An overview on the legislation procedure is available here: http://ec.europa.eu/justice/data-protection/

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be used or further developed, that protect research participants on the basis of legal 427 compliance and yet do not disproportionately restrict the efficiency of research.

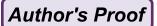
However, integrating informed consent into Big Data driven research also 429 touches upon the question whether or not the concept as such leads to an adequate 430 protection of research participants. Especially with regard to other contexts, e.g. 431 establishing so-called bio-banks, it was and still is discussed, if informed consent in 432 its classic understanding is sufficient to protect the rights and interests of research 433 participants in a sufficient manner (D'Abramo 2015; Hofmann 2009).

Due to the complexity and high dynamics of modern biomedical research, it is 435 stressed that research participants may not realise the full implications of giving 436 their consent. While agreeing to the use of their samples or test results for 'the 437 purpose of research', participants may have a lack of understanding what exactly 438 that vaguely phrased expression means (Cordasco 2013). Therefore, in a legal 439 context, the restriction of the range of the informed consent has been consistently 440 demanded. A restriction may be imposed with regard to a certain time frame (e.g. 441 informed consent is given for a time period of 5 or 10 years, in combination with 442 the obligation to newly clarify the purpose of the use of the elevated personal data 443 in order to attain a renewed consent of the participants) or regarding a factual aspect 444 which would restrict the given informed consent to a particular project or to the 445 research of a specific disease pattern.

However, the approaches of restricting either the temporal or the factual context 447 of informed consent fail to work even with regard to small-scale projects: a renewed 448 informed consent can usually not be obtained due to research participants moving 449 away or dying in the meantime. Furthermore, the maintenance of an address register 450 would not only go beyond the scope of time effort, but also be a great financial 451 burden to any project and may actually generate new privacy risks due to problems 452 in securing this information from unauthorized access.

A restriction of the informed consent to a certain factual context is problematic as 454 well, because Big Data research aims for a cooperation and combination of different 455 projects, and not for individual projects. In addition, undertaking a follow-up project 456 would be made impossible for the researcher who got the informed consent in the 457 first place. Lastly, the restriction to only one specific disease pattern is problematic 458 as well due to the difficulty of insufficient clarity and changing definitions and 459 understandings of a certain disease – as we have outlined in detail in Sect. 3.

Regarding the reasons mentioned above, jurisprudence represents a general 461 permissibility of a 'broad consent' which is of unlimited time and enables largely 462 unrestricted factual research. As far as some legal systems assume an inadmissibility 463 of a 'general consent', this concept deals with the consent given by a third person 464 to carry out any kind of legal action and cannot be compared with the approach 465 and content of a 'broad consent' (see for the case of biobanks: Serepkaite et al. 466 2014). The latter does not mean that contributors of genetic material or data do 467 not obtain any rights. Personal rights and data protection laws as well as privacy 468 issues obviously have to be respected. Therefore, the current legal understanding 469 of the problem of Big Data driven research focuses on demanding technological 470 solutions that ensure that privacy and data protection are respected, mainly through 471



aggregation and anonymization techniques or – more generally – privacy-by-design 472 approaches. This intermediate conclusion from a legal point of view leaves open 473 two questions: First, are these technologies actually able to protect the privacy 474 of the research participant? And second, what are the deeper moral reasons and 475 possible effects of ethical significance when such a new 'broad consent' regime is 476 implemented? We will now focus on the second question.

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5 Ethical Issues of Changing the 'Information Framework'

When assessing the problem of informed consent in a Big Data context, a historical 479 perspective is helpful. The notion of informed consent has been put in the centre of 480 bioethical considerations after one of the darkest episodes in the history of medical 481 research – the horrific experiments carried out by doctors on concentration camp 482 victims in Nazi Germany. In the Nuremberg trials of 1947, the requirement that 483 "The voluntary consent of the human subject [to medical research] is absolutely 484 essential" has been formulated for protecting the participant from harm. These 485 requirements strongly influenced the Declaration of Helsinki, that later underwent 486 several revisions, in particular related to the notion of informed consent (Carlson 487 et al. 2004). Despite these changes, the 'moral core' of informed consent in the 488 bioethical common-sense-understanding is protecting the individual from involun- 489 tarily incurred harm. From that perspective, the ethical question is, whether Big 490 Data driven research backed by 'broad consent' could create additional harm for 491 the subject – i.e. harm not directly related to the research intervention itself (e.g., 492 the risks of some imaging techniques, which certainly are part in the information 493 procedure when obtaining informed consent), but to long-term outcomes of the 494 research. As the current legal discussion described in Sect. 5 demonstrates: the focus 495 of the discussion is almost exclusively on privacy breaches as the main harm that 496 could result. For example, one wants to avoid that the genetic data of a person with 497 Huntington's disease made available for research can lead to a re-identification of 498 this person, thereby harming this (still healthy) person in her social setting, e.g., by 499 provoking a dismissal from her job.

We certainly do not dispute that this kind of harm is of relevance in Big Data 501 driven research – and the main ethical question here is whether the technological 502 solutions for preventing such harm actually will do their job. This aspect will be 503 further discussed in Sect. 7. But we suggest two further issues that need ethical 504 consideration: First, the necessity of broad consent for Big Data driven research 505 may pose additional problems that have harm-implications. Second, broad consent 506 is associated with other (positive) ethical values than harm-prevention that may help 507 to make Big Data research more ethical. We will now discuss these two issues in 508 more detail.

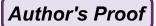
The first issue relates to the point that providing informed consent requires 510 informing the patient on the intervention that will generate the data. On the one hand 511 this concerns information on the direct risks and consequences of the intervention 512

itself. For example, in case of a MRI scan of the brain, issues like technical risks (e.g., implants) or incidental findings have to be discussed. This part of the informed 514 consent procedure is not affected by a subsequent use of the data in a Big Data 515 context. On the other hand, the patient has to be informed at least to some degree 516 on the potential use of the data. If the informed consent is broad, this degree will 517 be quite unspecific, but still needs some framing. Patients are unlikely to accept an 518 explicit formulation like 'You agree that your personal data will be used for any 519 kind of application'. Thus, a framing in two respects will be necessary: First, one 520 has to induce trust in the patient that harm through privacy breaches will effectively 521 be prevented. Second, some factual framing will be needed. Probably the broadest 522 kind of factual framing is that the data will be used for *research* purposes (and, e.g., 523 not sent to a wellness company such that they can tailor new commercial offers for 524 patients with similar diseases). More likely is, however, a (at least implicit) framing 525 that the data will be used for research related to the medical condition of the patient. 526 But why is such a framing necessary? 527

The reason for this is - as we suggest - that information frameworks play a 528 decisive role for giving moral meaning to the world we live in. This insight can 529 be partly attributed to the idea of spheres of justice, introduced in 1983 by the 530 philosopher Michael Walzer, which proposes that societies consist of different social 531 spheres (e.g., medical, political, market, family and educational) each defined by 532 a different type of good that is central to that particular sphere. These different 533 types of goods (e.g., medical treatment in the medical sphere, political responsibility 534 and public office in the political sphere) and the meaning and significance they 535 have in each of these spheres, have their own associated criteria, principles and 536 mechanisms concerning their distribution and allocation. In order to prevent mixing 537 up distributional criteria and goods from different spheres (and prevent, e.g., 538 allocating seats in parliament on the basis of financial assets, family relationships 539 or health condition, or making one's ranking on a waiting list in health care 540 dependent on family relationships or college degrees) these spheres have to be kept 541 separated. This idea implies amongst other things that the distribution of access to 542 particular goods tracks the sphere's specific normative considerations (e.g., 'need' 543 in the medical sphere, 'democratic election' in the political sphere). Goods have 544 to be distributed along the mechanisms of the corresponding sphere and goods 545 from different spheres ought not to influence each other in terms of distribution. 546 Put differently, this means that the exchange of goods between spheres has to be 547 "blocked"; Walzer talks about "blocked exchanges" and the "art of separation".

Walzer's work has been applied to the realm of information systems by Nissenbaum (2004) and Van den Hoven (2008). Nissenbaum coined the term *contextual* 550 *integrity* of social spheres, whereas spheres are defined through the expectations and behaviour of actors that differ per sphere. In order for contextual integrity and 552 sphere separation to be achieved, the type of information that is revealed and the flows between different parties have to be appropriate for the context. 554

Within the broader privacy debate, the challenge of Big Data is that information 555 produced within these spheres (health, politics, criminal justice, market) travels 556 much faster and is more difficult to control than in the traditional offline world. 557



So we face a set of phenomena that threaten the integrity of social spheres and the 558 cultural and social meanings expressed in them, including our values. Of course 559 the boundaries between spheres are to a certain extent relative to time and culture. 560 and not carved in stone forever, but it is important to note that every age, society and 561 culture does in fact draw and treat these boundaries – construed as sets of constraints 562 on the flow of information – as of high normative relevance.

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Going back to our example, this also means that broad consent should respect 564 these boundaries. The point is that providing broad consent for using data can 565 transgress these boundaries in ways that generate indirect harm for the person 566 who provides the data even in cases when privacy is fully respected. For example, 567 researchers emerging from fields completely unrelated to the disease condition of 568 the patient may use the (aggregated and anonymized) data to check for connections 569 between health conditions and credit rating; resulting finally in a policy that prevents 570 the patient in future to obtain certain bank credits. This would be considered a breach 571 of a boundary between two social spheres with quite different moral regimes: the 572 health sphere on the one hand and the economic sphere on the other hand. Other 573 researchers may use the data in a way that finally results in a genetic test that allows 574 testing foetuses – and in this way offer the option of abortion to the future parents. 575 Such a development may be against core-values of the patient when she reads about 576 this type of research in the newspapers, as she realises that her data may have played 577 a role in this research. In this case, personal boundaries between acceptable and 578 unacceptable applications of scientific research are breached. Yet other researchers 579 may – based on research that includes the anonymised data of the patient – come to 580 the conclusion that some sub-form of a neurological disorder (actually the condition 581 from which the patient suffers) is associated with another disease that has a much 582 stronger social stigma – and the patient is finally confronted with social exclusion 583 resulting from the public dissemination of this reconceptualised disease space.

The underlying problem of these still hypothetical cases is that through broad 585 consent, the consenting person risks that his data finally leads to research result 586 that transgress important moral boundaries of this person or of society in general. 587 The person contributes to a "new world" which he personally rejects. Thus, the 588 question emerges how broad consent can be made compatible with respecting these 589 boundaries.

Answering this question involves the insight that requiring consent is not merely 591 an act to protect a person from unwanted harm – the classic understanding of 592 informed consent. But it also involves requiring an explicit agreement to contribute 593 to something that the person considers to be a valuable goal. Consenting is an act 594 of autonomy that has a positive motive (e.g., compassion) and is backed up by 595 some understanding of fairness (e.g. that the resulting research is not leading to 596 unjustified discriminations). Understanding consent as such an active act entails the 597 notion of responsibility in two ways: First, the consenting person trusts that the 598 researcher will deal responsibly with this data – both with respect to preventing 599 privacy breaches as well as with respect to the goal of the study. Second, the 600 consenting person may to some degree be set in a position to control the usage of the 601 data. Although it will probably be an exception that the person herself would like 602 to track the usage of her data, one may consider a model of "data stewardship", i.e. 603 an institutional setting that (as a representative of the data provider) allows tracking 604 data usage and regularly report on how the personal data of people has contributed 605 to research. Both ensuring trust and responsibility will have to be "materialised" 606 through technological solutions that function and that can be understood by both 607 the users of Big Data technologies as well as those who provide the (Big) data. 608 Whether these technologies are available is the topic of the next section.

6 Technological Ways of Securing Open Consent

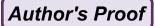
A major technological problem related to this aim of enhancing trust and responsibility is that current anonymisation practice does not take the informational 612 self-determination of the data subject into account. Since in most cases the data 613 releaser is held legally responsible for the anonymisation (for example, this happens 614 in official statistics), the releaser favours global anonymisation methods, where he 615 can make all choices (methods, parameters, privacy and utility levels, etc.).

When asked to provide data and consent, the subjects must hope there will 617 be a data protector who will adequately protect their privacy in case of release. 618 Whereas this hope may be reasonable for data collected by the public health care 619 system or more generally by (democratic) administrations, it may be less founded 620 for private surveys (data collected by pharmaceutical companies or by any other 621 private company). Indeed, a lot of privately collected data sets end up in the hands of 622 data brokers (U.S. Federal Trade Commission 2014), who trade with them with little 623 or no anonymisation. Hence, there is a fundamental mismatch between the kind of 624 subject privacy (if any) offered by data releasers/protectors and privacy understood 625 as informational self-determination: usually, the subject is not given control on how 626 her data is protected.

To empower the data subject, Domingo-Ferrer and Muralidhar (2015) proposed 628 a permutation-based paradigm of data anonymisation. They showed that any 629 anonymisation method is functionally equivalent to permutation plus (perhaps) a 630 small amount of noise. In a nutshell, if one compares the ranks of the values 631 of each original and each anonymised attribute, one finds that the effect of any 632 anonymisation method is to change the ranks to some extent, which can be viewed 633 as a permutation (see Domingo-Ferrer and Muralidhar (2015) for more details and 634 a running example). Based on this, they defined a new privacy model, called (d, v, 635 f)-permuted privacy that is verifiable by the subject. When given the anonymised 636 data set by the data protector, each subject can check how much the values in her 637 record have been permuted and whether this permutation is sufficiently protective. 638

Just allowing the subject to verify protection may not be enough or even worse 639 than not allowing verification if the subject is left unsatisfied with the level of 640 protection provided. An unsatisfied subject may refuse to answer and/or to give 641 consent the next time the data collector approaches her. A more constructive 642 alternative would be to allow the subject to take care of the anonymisation of 643

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her own data record (local anonymisation, e.g. Song and Tingjian Ge 2014). In 644 the context of the HBP, in some cases it may be viable for patient subjects to 645 use their personal devices (e.g. smartphones) to conduct local anonymisation. For 646 example, if a patient is being continuously monitored through sensors connected 647 to her smartphone while at home, clearly all data being collected can be locally 648 anonymised by her smartphone.

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Beyond assuming a well-informed subject with some basic knowledge of the 650 implications of anonymisation, a problem of local anonymisation is that the subject 651 must anonymise her record without seeing the records of the other subjects. Hence, 652 the subject cannot know whether the anonymisation she is applying will permute 653 the values of her record enough with the values of the other subjects. To play it 654 safe, each subject is likely to add a lot of noise to her values, which results in an 655 anonymised data set with too poor utility.

In Soria-Comas and Domingo-Ferrer (2015) collaborative anonymisation has 657 been proposed as a synthesis alternative that seeks to empower the subjects while 658 preserving data set utility as in the case of centralised anonymisation for the 659 same privacy level. The idea is that subjects generate the anonymised data set 660 in a distributed and collaborative manner. Neither the data collector nor subjects 661 gain more knowledge about the confidential information of a specific subject than 662 disclosed by the anonymised data set.

Let us analyse the motivations of a rational subject to engage in collaborative 664 anonymisation. Rationally, she will only contribute to form an anonymised data set 665 if the benefits she obtains compensate her privacy loss:

- A subject without any interest in the research made possible by the data being 667 collected is better off by declining to contribute (privacy prevails). Note, however, 668 that subjects may have indirect interests, like expecting a potential benefit from 669 the research conducted with the data (better healthcare, better life conditions, 670 etc.) or simply satisfying a philanthropic inclination.
- A subject without privacy concerns can directly supply her data without any 672 anonymisation requirements (potential benefit prevails).
- A subject who is interested in the research made possible by the data but has 674 privacy concerns should prefer the collaborative approach to both the centralised 675 and the local approaches because: (i) It outperforms centralised anonymisation 676 by offering privacy with respect to the data collector; (ii) it outperforms local 677 anonymisation because it yields less information (utility) loss and hence enables 678 better research.

Collaborative anonymisation leverages the notion of co-utility (Domingo-Ferrer 680 et al. 2015), which refers to protocols (interactions) designed in such a way that 681 the best strategy for a rational selfish player to attain her goal is to help some 682 other players to attain theirs. Co-utile protocols make mutual help self-enforcing. 683 In anonymisation of individual data, the privacy protection obtained by a subject 684 positively affects the protection that others get. In other words, when masking the 685 identity of a subject within a group, none of the subjects in the group is interested 686 in making any of the other subjects re-identifiable, because that makes her own data 687

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more easily re-identifiable. In this sense, we can say collaborative anonymisation 688 is co-utile. Specifically, Soria-Comas and Domingo-Ferrer (2015) give a co-utile 689 protocol to achieve k-anonymity in a collaborative way. k-Anonymity is a privacy 690 model in which each subject in indistinguishable within a group of k subjects when 691 looking at the released data set.

While the above (d, v, f)-permuted privacy model can allow a patient/subject to 693 verify how well her data have been anonymised, and local/collaborative anonymi- 694 sation can give the subject full control on the anonymisation process, privacy is not 695 all a patient may need, as mentioned in Sect. 6. Being able to track the usage of 696 her data is a complementary (and probably more ambitious) requirement. In fact, 697 for some types of data used in HBP, anonymisation may be unfeasible because the 698 data is inherently identifying and cannot be altered to make it less identifying (e.g. 699 this is the case of genetic data or even human brain scans); for such data, all the 700 patient could be promised by the researchers/collectors is to keep track of who 701 accesses it and how it is used (the data stewardship mentioned in Sect. 6). Such 702 tracking is addressed by the so-called provenance technologies. Provenance refers 703 to the chain of successive custody (including sources and operations) of information 704 (or even hardware equipment). The current practice of information provenance is 705 rather rudimentary and still far from being dependable enough. The good side 706 is that there are many sectors interested in improving provenance technologies: 707 beyond healthcare research and HBP, the banking sector, the software industry and 708 the cybersecurity sector are important fields where tracking information usage is 709 very important. Hence, substantial research efforts are underway: technologies have 710 been demonstrated for annotation in scientific computing, for provenance-aware 711 data storage (automatically tracking accesses, downloads, etc.), for building tamper-712 resistant chains of custody, for pedigree management (tracking the source of data), 713 etc. (See Chapter 9 of U.S: Homeland Security 2009 and references therein).

Conclusion 715

In conclusion, we suggest that a broader ethical focus would allow understanding the 716 ethics of Big Data driven research not solely as an issue of upholding the privacy of 717 the individual who consents to her data being used, but also as a matter of individuals 718 that decide to contribute to a positive goal and thus would like to be put into a 719 position such that they can trust that they are indeed making the world a better place. 720 This requires generating an understanding on how Big Data research may affect the 721 ontology upon which consent decisions are based (e.g., disease ontologies) as well 722 as the underlying, morally significant boundaries. This also requires developing and 723 integrating technologies in Big Data research that empowers the subject so that she 724 really is in control of what happens to her data before it is released. This should 725 enable her to give her data and her consent in conditions that are more compatible 726 with informational self-determination.



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On the Compatibility of Big Data Driven Research and Informed Consent: The...

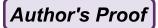
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AUTHOR QUERIES

- AQ1. Please confirm the corresponding author and affiliation details.
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