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Abstract: Data sharing in autism neuroimaging presents scientific, technical, and social obstacles. We outline the desiderata for a data-sharing scheme that combines imaging with other measures of phenotype and with genetics, defines requirements for comparability of derived data and recommendations for raw data, outlines a core protocol including multispectral structural and diffusion-tensor imaging and optional extensions, provides for the collection of prospective, confound-free normative data, and extends sharing and collaborative development not only to data but to the analytical tools and methods applied to these data. A theme in these requirements is the need to preserve creative approaches and risk-taking within individual laboratories at the same time as common standards are provided for these laboratories to build on.

Response to Reviewers: Sunday 17 December 2006

Dear Profesor McDougle

Thank you for your mail of 5 December in regard to our paper "Offering to Share: How to Put Heads Together in Autism Neuroimaging" submitted to JADD. We're very happy to learn that the manuscript is acceptable pending our addressing the reviewers' suggestions.

Reviewer #1 called the paper well written and thoughtful, and had no criticisms. We have considered Reviewer #1's suggestion as to the subtitle, and in fact discussed this issue more generally prior to our original submission. Although we do recognise that "How to Work Together in Autism Neuroimaging" has value in being more straightforward and literal, at the same time we value the memorability of putting heads together literally (for data sets) and metonymically (for scientists' thoughts), a turn of phrase which we think makes a position paper such as this more likely to be noted and kept in mind. Absent specific objections, therefore, we have some degree of preference for sticking with the title as is.

Reviewer #2 called the paper well reasoned, thorough, and excellent as written. This reviewer stated that their only substantive criticism was that the link between the paper's discussion of the current state of autism imaging collaboration and the proposed project outlined in Table 2 seemed disjointed, and the proposed study outline therefore would be better framed as a future study spurred by the consensus that we have described, and discussed under its own subheading. We agree, and have moved these details from the legend of Table 2 to the new subsection "Instantiating the protocol in future studies" and augmented them, whilst taking care not to add too much to the paper's total length.

Reviewer #2 also highlighted some typographical issues, which we've addressed by checking all spellings and making changes where indicated. All spellings are canonical British English spellings.

Lastly, Reviewer #2 suggested changes to our table of phenotyping measures. Since age is readily computed from date of birth, we opted not to clutter the table with age as a separate item. We've added race in addition to our existing entry of ethnicity. Instead of the reviewer's suggestion of `type of education,' we've added the more general term `intervention history.'

We had specified the WAIS-IV in order to be forward-thinking, but as we've now learnt that the WAIS-IV remains about two years in the future, we've changed this to WAIS-III. We thank Reviewer #2 for catching a transcriptional error which had substituted "One Word Repetition" for "Nonword Repetition"; this error has been corrected. In addition, the author responsible for the phenotype battery (N.J.M.) has given the table a final, detailed review and inserted a few additions in the areas of attention, executive function, and memory.

We thank you and the reviewers for your time and insights, and we hope that these alterations render the paper acceptable for publication. We look forward to your response.

Best regards

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Offering to Share:

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Running head: Sharing in Autism Neuroimaging

Abstract

Data sharing in autism neuroimaging presents scientific, technical, and social obstacles. We outline the desiderata for a data-sharing scheme that combines imaging with other measures of phenotype and with genetics, defines requirements for comparability of derived data and recommendations for raw data, outlines a core protocol including multispectral structural and diffusion-tensor imaging and optional extensions, provides for the collection of prospective, confound-free normative data, and extends sharing and collaborative development not only to data but to the analytical tools and methods applied to these data. A theme in these requirements is the need to preserve creative approaches and risk-taking within individual laboratories at the same time as common standards are provided for these laboratories to build on.

Key words: imaging, MRI, PET, morphometry, segmentation, data sharing

Offering to Share: How to Put Heads Together in Autism Neuroimaging

The Problem

Tracing the behaviourally defined syndrome of autism to its neurobiological roots poses a difficulty since autism is heterogeneous in terms of its detailed symptom profiles (Ronald et al., 2005), genetic and environmental antecedents (Veenstra-Vanderweele et al., 2004) and developmental mechanisms (Belmonte et al., 2004a). Because autism in this regard may be an amalgam of many unknown conditions, it seems a foregone conclusion that behaviourally ascertained groups of subjects contain large amounts of unmodelled variance, and that the relation between group size and statistical power is a steep one (Coon, 2006). This problem of sample size in the context of heterogeneous conditions is particularly acute in the domain of brain imaging, where costs are great and small samples are therefore more accepted and more usual. A solution seems clear in principle: the many small data sets collected by various investigators ought to be pooled into one large data set for analysis. Several obstacles, though, make such data sharing easier said than done. These obstacles are scientific, technical, and social – but not insurmountable.

The scientific obstacles are matters of sample heterogeneity, which complicate the comparability of separately ascertained groups. This heterogeneity is both longitudinal and cross-sectional. Longitudinally, especially given autism's nature as a developmental disorder, measurements can be expected to change over the course of maturation and aging (Carper et al., 2002; Aylward et al., 2002). (The inconsistency of recent findings on the size of the amygdala at various ages is a case in point (Baron-Cohen et al., 2005).) The consequent need to

control and account for age particularly hampers retrospective efforts to combine separately ascertained samples. Cross-sectionally, autism's multiplicity of symptom profiles and neurobiological mechanisms makes it imperative to correlate imaging with other measures of potential endophenotypes, heightening the demand for large data sets which can be fractionated according to such measures. In addition, autism is much more common in males than in females, and sex differences extend to symptom profiles (McLennan et al., 1993) and possibly to mechanisms (Baron-Cohen et al., 2005), making it important to factor out sex as a variable, and magnifying the problem of sample size in the case of the smaller, female subgroup.

The technical obstacles concern comparability of raw and derived data across scanners (Jovicich et al., 2006; Han et al., 2006) and analytical methods, as well as the problem of storage and retrieval of images and related subject variables. Adherence to fixed acquisition strategies is complicated by variables such as the radiopharmaceutical ligand chosen for a receptor of interest in PET, or the type of coil used in MRI or the type of crystal in PET. Such factors and their associated tradeoffs make it difficult and inadvisable to require absolute standards in very basic parameters such as MRI pulse sequence or PET attenuation correction method. Even within individual studies, the pressure to adopt newer instruments is a well-known difficulty in longitudinal approaches. In addition to these sources of variance in raw data, differences in analytical procedures including methods of segmentation and measurement of tissues and structures introduce variation in derived measures. Finally, once the data are acquired and analysed, an informatics challenge exists in the databasing

problem of storing and retrieving brain images (Van Horn et al., 2004) and related subject information (Scahill & Lord, 2004).

These scientific and technical obstacles are well defined, and strategies can be and have been devised to solve them. On a more abstract level, though, prospects for data sharing are affected at least as much by social and cultural obstacles (Koslow, 2000). A reward structure in which proposals are rated as to likelihood of success and ranked against each other encourages productive competition, but often at the cost of potentially productive cooperation and speculation. Investigators become biased towards 'safe' approaches driven by preconceived and conservative hypotheses, rather than 'fishing expeditions' that take advantage of the data-mining capacity of information technology. Furthermore, instead of being shared freely, observations collected during these studies often are guarded zealously. As a result, what's best for an individual investigator doesn't always coincide with what's best for science. Though it is easy enough to get all the stakeholders to agree in principle that this is a poor state of affairs, finding agreement on how to change it is more problematic. Solutions imposed from the top down are likely to evoke opposition, or at least lack of support, since such methods do not involve the expertise and concerns of the individual scientists who are affected. A solution is most effective when all the people affected have been afforded an opportunity to participate in defining it (Ury, 1993). The field of autism research, and individual investigators within autism research, need a structure that preserves competition's benefits to scientific innovation (and to individual advancement), but also facilitates cooperative and speculative research that otherwise would be impossible.

Successes

A strategy for collecting, maintaining, and distributing shareable brain images in the context of autism research can take inspiration from similar efforts in normative and clinical populations. The Biomedical Informatics Research Network (BIRN) is developing technical infrastructure and policy to support sharing of biomedical data, with a subgroup focusing specifically on morphometric data. Collaborative MRI morphometric studies of depression, Alzheimer's disease, and mild cognitive impairment are used as test cases for the development and application of analysis pipelines and strategies for data archiving and retrieval (Jovicich et al., 2005) The project applies the grid computing model (Peltier & Ellisman, 2004), in which computer networks function as links not only to data storage facilities but to computational facilities, and the data analysis pathway is supplied to users not as downloaded software to be run locally but rather as a network-based service.

The International Consortium for Brain Mapping (ICBM) (Mazziotta et al., 2001) is a prospective study of 7000 normal subjects with the goal of creating a probabilistic atlas of the human brain, one that describes not only normal anatomical location but also normal anatomical variation. The ICBM has structured itself in a way that promotes – and indeed demands – solution of problems of data exchange and interoperability. The group deliberately selected centres with different scanning hardware and computing systems, so that data processing and archiving could not depend on any particular scanner characteristics or single data format. Rather than specifying any specific pulse sequence or other fundamental parameters related to scan acquisition, quality control is implemented in terms of derivative

properties such as tissue segmentability. The benefits of competitive innovation are combined with a cooperative structure in which individual laboratories are free to develop their own algorithms for each stage of a pipeline of data processing, and these competitive solutions are then compared and evaluated by an impartial judge. The winning methods then become part of the standard ICBM processing pipeline, whilst individual laboratories remain free to supplement this standard approach with their own methods. Here again, the model of grid computing applies: raw scans can be uploaded to the ICBM web site, where the standard processing pipeline can be applied to each.

The NIH MRI Study of Normal Brain Development (Evans, 2006) is another prospective study of normal neuroanatomy. MR scans and spectroscopy data are collected at six participating centres with uniform acquisition parameters, and these raw data are uploaded to a central database maintained by a single coordinating centre. Tissue segmentation and anatomical parcellation are performed at the coordinating centre, using components of the ICBM analysis pipeline. Intensity histograms of the raw images are corrected for magnetic field inhomogeneities which vary from centre to centre, and comparability of derived measures is evaluated for many brain regions – a difficult issue since systematic contrast differences within the raw data can translate to systematic differences in derived measures such as cortical thickness. The study's large sample will serve as a resource for involvement of the wider MRI research community, and enables correlative morphometric studies between anatomical regions, the anatomical analogue of functional connectivity measures.

In addition to large-scale normative studies, precedent exists for application of MRI data

sharing strategies to specific diseases. In 2002, the Tourette Syndrome Association (TSA) convened a neuroimaging workshop, out of which grew the TSA International Neuroimaging Consortium. The Consortium was built on the model established by the TSA Consortium for Genetics and, therefore, could take advantage of an existing collaborative network and subject database. The Consortium's initial focus is to add structural imaging to the genetic data already available. Later, after technical and sociological obstacles have been addressed, functional imaging may be added.

Imperatives

The past few years' surge of interest and activism has autism poised to become a major focus of biomedical research. Whatever institutional structures are developed for this activity will affect it for many years, and therefore it is crucial to manage these so that they facilitate discovery and do not retard it.

Embracing non-hypothesis-driven resources

Funding agencies must recognise that in the age of data-mining technology, a deserving proposal need not be exclusively driven by a specific hypothesis. Studies that aim to establish collaborative resources and to explore unforeseen correlations within these data are valuable even without – and in some cases especially without – *a priori* knowledge of the directions in which the data may lead. Many research questions of great relevance to neuropsychiatric and neurodevelopmental disorders – perhaps the majority of questions in imaging – cannot be answered with the comparatively tiny samples attainable by individual laboratories, and therefore demand such collaborative resources. To restrict our attention to hypothesis-driven

studies with narrow research backgrounds would be to deny the informatics advances of the twenty-first century. Accordingly, study sections must stop focusing exclusively on replying to specific hypotheses, and consider prioritising proposals that establish bioinformatics resources applicable in hypothesis generation and testing. This resource-driven approach is already considered valid in the case of tissue banks, and it makes sense to extend it to collections not of physical brain tissue but of virtual brain images. In this context of informatics resources, divergence of research interests and approaches can be regarded as a potential asset, not as a liability. With regard to autism in particular, where heterogeneity is such a significant consideration, logical methods of subgrouping will allow more intelligent querying of genetic and phenotypic data. A great deal of information can be mined from the conjunction of genetic information with neuroanatomical, behavioural, and other phenotypic data – even though such integrative proposals all too often are derided as 'underpowered' by reviewers familiar with only one facet of the work. The conservative, hypothesis-driven approach of waiting for narrowly focused experts to ascertain a specific genotypic or phenotypic signal, and only then commencing exploration of possible genotype-phenotype correlations, is no longer the only productive strategy. To hasten progress in autism research, funding agencies must augment this focus with strategies that sweep up a breadth of observations. This imperative holds especially in the current funding climate, in which competition is keen and funding agencies may be tempted to seize on narrow and outdated criteria to exclude proposals from further consideration. The Human Genome Project, for instance, never would have begun had it had to pass the scrutiny of a traditional study section.

Combining imaging with genetic, biochemical and behavioural assessments

A basis for such correlative work on autism already exists, in the form of the Autism Genetic Resource Exchange (AGRE) (Geschwind et al., 2001). As of this writing, AGRE contains data from more than 1100 families, and is accessed by more than 135 researchers. AGRE provides the highest quality of standardised data, and is the source for over a third of the data in the Autism Genome Project. The resemblance of this picture to the state of the TSA Consortium for Genetics in 2002 bodes well for a similar extension of AGRE to neuroimaging, and we suggest that one of the first projects of a collaborative autism neuroimaging network might be to image either the existing AGRE population or a new, younger cohort that would be recruited prospectively into AGRE for longitudinal study. Genotypic, biochemical and phenotypic characterisation will proceed faster when they are not conducted in isolation from each other: known genetic polymorphisms can guide searches for neuroanatomical correlates at the same time as neuroanatomical clustering can identify subgroups for genetic analyses, and both can be correlated with endophenotyping for mitochondrial abnormalities (*e.g.* lactate, pyruvate, carnitine), organic and amino acids, lipid profile, oxidative stress markers and inflammatory cytokines, all of which have shown abnormalities in autism (Johnston, 2000) and which may provide crucial links between the widely separated levels of genetics on the one hand and neuroanatomy, neurophysiology, and behaviour on the other. These correlative strategies can be applied not only within the patient population but also in 'unaffected' relatives and in the normal population: for example, exploratory genetic studies could be targeted at relatives or even normal controls

whose brain volumes or behavioural measures lie in the tails of the distribution. Focusing on these normal extremes may provide clues as to what to look for within the autism population.

A key question in combining imaging with a genetic database is whether one should aim to image probands only, or entire pedigrees, given financial and practical constraints on the total number of scans that can be collected within the scope of the initial study. Imaging probands only would of course be most efficient for identifying and characterising subtypes within the diagnosis, and for evaluating anatomical phenotypes across the lifespan. On the other hand, studying entire pedigrees is a more effective strategy for pursuing endophenotypes which extend within and beyond the diagnosis (Belmonte et al., 2004b), and well characterised genetic abnormalities within individual extended pedigrees may point the way to gene networks relevant to autism. Given these opposing goals for subphenotyping and longitudinal studies on the one hand and endophenotyping on the other, we suggest a compromise in which half of the available scans are devoted to AGRE or other pedigrees and half to singleton patients not necessarily associated with AGRE. Pedigree scans would include, at minimum, the proband, the most closely matched sib (if available), and the parents. In order to maximise enrolment and to minimise attrition, participating families must receive clear benefits, including interaction with a case worker, a summary of results, and payment for their time (typically $200 per study, recognising that control families may need more incentive to participate than do autism families) and for their travel expenses.

The full value of these imaging data cannot be realised without a standardised and comprehensive yet practical set of phenotypic measures. We have drafted such a standard,

presented in Table 1. In designing this phenotypic battery, we have considered all functional domains affected in autism spectrum conditions, including non-diagnostic domains such as motor and sensory function. We also hoped to include measures applicable to subclinical traits in family members, and to the milder traits in some non-retarded people with autism spectrum conditions. Thus we considered symptoms in degrees, rather than as the simple, binary distinction of diagnosis or not. Of especial interest were variables with potential significance for biological and genetic subtyping, such as regression onset, mode of language development, presence of seizures, psychiatric comorbidity, and head circumference. At the same time, since the spare time available to a family dealing with autism is even more limited than that of a normal family, this standard battery cannot practically include every test that may be of interest. The suggested test battery is minimal and targets verbal school age and adult subjects. The battery could be modified for younger and lower ability subjects or substantially expanded to address specific hypotheses.

[place Table 1 about here]

Governance by and for the affected researchers

Such is the zeitgeist for collaborative resources that extension of a genetic resource such as AGRE seems inevitable. The question, though, is whether this extension will be accomplished in a way that preserves and augments the innovative capacity of independent research groups, or whether it may create unnecessary strictures that suppress novel approaches. AGRE is contributing its Internet System for Assessing Autistic Children (ISAAC) (Hollander et al., 2004) and all its clinical assessment data to the National Database for Autism Research

(NDAR), an NIH-sponsored effort to facilitate and to promote sharing of all types of data in autism research. Though the spirit behind NDAR is laudable, the organisers of NDAR must beware of dictating too many of the specifics, and must be careful to solicit input from the researchers affected. Otherwise, the relationship between NDAR and the research groups best positioned to conduct innovative studies may develop into one of adversarial tension rather than cooperative support. In order to forestall such a development, NDAR must actively solicit ongoing input from the autism research community, perhaps by instituting a steering committee similar to that of AGRE, the majority of whose membership consists of investigators for whom autism is a primary and long-term focus of research. Where appropriate, input as to the goals and direction of NDAR ought also to be solicited from representatives of the patient community. Though its goal of data sharing enjoys broad support within the autism research community, *without such a participatory structure for its governance, NDAR itself may not gain acceptance from autism researchers.*

Data sharing requires not only agreement on standards for data comparability but also agreements as to when or under what conditions the data from each individual laboratory would be released for general use. Our experience suggests that such agreements are attainable by individual investigators on a case-by-case basis. However, individual data sets and research objectives may vary widely as to the resources invested in data collection and the amount of time necessary to attain milestones in innovative or labour-intensive data analyses. For example, young children and infants who must be imaged during sleep, and people with low-functioning autism who may find it difficult to tolerate the scanner environment,

consume many more resources (and many more late-night hours on the part of investigators) than do adults or high-functioning cases. Furthermore, detailed, hand-traced morphometric measurements demand a great deal more time for exclusive analysis within the investigators' own laboratory than do automated methods such as voxel-based morphometry. Specific plans and timetables for data sharing must, therefore, be set by the individual investigators as appropriate for their specific methodologies. *Top-down efforts to impose a uniform time limit on release of data are unlikely to succeed, and risk destroying the incentive to collect data sets on the most difficult and valuable patient populations and age groups.*

Standards for comparability of derived data

Collaborative imaging efforts within the CPEA/STAART research community stand in contrast to NDAR in that they are led by the researchers themselves. Such efforts are sometimes slow to overcome initial obstacles, but in the end may achieve greater staying power. One of the first collaborations to emerge from this community is the Pooled MRI Data Project, an effort to combine data at the derived level of morphometric measures with an accounting for site-specific variance in these measures. The Pooled MRI Data Project comprises data from 18 projects at 15 sites, with an expected total of approximately 1200 cases, half autism-spectrum and half normal controls. Combined data will be analyzed for 18 specific brain regions, with particular attention to differences in developmental changes between the two groups. Methods for performing measurements are being evaluated to determine whether data from each site have been collected in such a way that they are reasonably comparable to data from other sites. Analyses will include site as a covariate to

adjust for minor differences in measurement technique. In addition, demographic, clinical, and neuropsychological data are being collected so that homogeneity of samples across sites can be assessed and analyses can be based on subgrouping.

Though the Pooled MRI Data Project is only a beginning, it exemplifies the perspective amongst autism researchers that a data sharing project can usefully focus on establishing comparability of derived measures even when characteristics of the raw data vary. Such comparability can be established by quality control procedures applied both within sets of raw images and across sets of derived quantities. Raw quality control should include measures general enough to make sense in application to all sets of scan parameters, such as signal-to-noise and contrast-to-noise. Derived measures can include segmented tissue volumes, landmarking and parcellation, structure volumes, and fibre maps in a set of standard subjects ('living phantoms') scanned at multiple sites. Validity of automated landmarking and parcellation could be established with reference to 'gold standard' measures, many of which already exist as by-products of studies of specific cortical and subcortical structures in autism (Carper et al., 2002; Aylward et al., 2002). These standards can be refined in collaboration with an independent expert in neuroanatomy. Such procedures can establish data comparability without corralling investigators into protocols that may be inappropriate to their specific scanning hardware or research foci. *Recognising the usefulness of standards for comparability at higher levels of data abstraction, funding agencies need not compel investigators to justify every deviation from recommended standards for raw data acquisition.*

Though it may be tempting to save scanning costs by assuming comparability of data

from existing normative studies, to rely on such an assumption may introduce serious methodological confounds. Strategies for establishing data comparability despite variations in acquisition and processing are not applicable in designs where the experimental factor of subject group is confounded with such variations. If each centre studies some autism subjects and some normal subjects, then cross-centre variation can be controlled and modelled, rendering the data comparable. If, though, the autism subjects are exclusive to one group of centres and the normal subjects to another, as is the case when prior normative studies are used as comparisons, then variation across centres is fundamentally confounded with variation between experimental groups. The results from such a study would be worthless since the effects of group and the effects of centre could not be disambiguated. In addition, for studies addressing autism in particular, prior normative studies may not have supplemented their imaging data with appropriate phenotypic and genotypic measures and therefore would be less useful comparisons in any case. Therefore, at the same time as new images are acquired for autism subjects, similar data on normal comparison subjects must be acquired at the same centres using the same acquisition and processing strategies. Such a strategy retains the opportunity to leverage preexisting normative databases by demonstrating the comparability (reliability) of such data with new control data specifically acquired for studies of autism. *Nevertheless, retrospective comparison against a normative database is not a complete substitute for prospective acquisition of new control data.*

A core protocol with optional extensions

Given differences in scanners, the varying technical demands of site-specific research

aims, and ongoing developments in MR protocols, it would be impractical to require an inflexible imaging protocol for use by all studies within an imaging consortium. Fortunately, such an absolute standard for comparability of raw data, though helpful, is not essential to comparability of derived measures. Whereas prospective collaborations can and should recommend protocols that yield the highest degree of comparability in the raw data, they need require comparability only at the level of derived data. Such comparability must be demonstrated by pilot data evaluated on raw and derived measures – at a minimum, signal-to-noise, contrast-to-noise, and automated tissue segmentation results, and maintained by ongoing quality control procedures on physical phantoms, living subjects, and incoming data sets. A core protocol ought to include recommendations for high-resolution anatomical imaging and diffusion-tensor imaging, whose specific implementations at each site would yield comparable derived data and largely compatible raw data. This core protocol ought to consume at most one hour of imaging time, bearing in mind that each individual group of investigators will have their own, site-specific adjuncts to their implementation of the core protocol. In addition, optional protocols may be specified for magnetic resonance spectroscopy, magnetisation transfer imaging, arterial spin labelling, PET, fMRI, and EEG/ERP studies. Support for these core and optional protocols should be provided by a collaborative technical group which would meet regularly. Given the difficulties of inferring developmental courses and endophenotypes from cross-sectional observations (Kraemer et al., 2000), subjects should receive longitudinal follow-up if resources allow.

Diffusion tensor imaging (DTI), though still an evolving technique, is included in the core

protocol because of its strong relevance to autism's neuroanatomical abnormalities of white matter growth and neurophysiological abnormalities of functional connectivity. DTI exploits the observation that water molecules diffuse more freely along axons than across axonal membranes and myelin sheaths. The direction of diffusion can be determined by collecting a set of MR images sensitive to diffusion in different directions. The direction of diffusion, expressed as a tensor, is calculated using least squares minimisation (Basser & Pierpaoli, 1996), and visualised as colour-coded displays of fibre orientation (Pajevic & Pierpaoli, 1999). Initial DTI results on autism have indicated reductions in diffusion anisotropy in white matter communicating with brain regions implicated in social and complex processing (Barnea-Goraly et al., 2004).

Proton magnetic resonance spectroscopy (^{1}H MRS) has been used to detect cellular abnormalities in brain regions that appear normal in MRI, as well as to elucidate cellular pathology underlying MRI-visible abnormalities. Using standard clinical MRI scanners, ^{1}H MRS can measure brain tissue concentration and mobility of neurochemicals such as choline (Cho), creatine, (Cre), N-acetylaspartate (NAA), myo-inositol (mI), glutamate+glutamine (Glx) and lactate, providing information on membrane turnover, tissue energetic status and neuronal and glial cell viability. Some – though not all – MRS studies of autism have yielded evidence of differences in tissue maturation or neuronal integrity, either generalised or specific to distinct developmental age points or brain regions. In this context, and because common ^{1}H MRS tools are available on most clinical scanners, single-voxel MRS is specifically proposed as an optional extension to the core imaging protocol. A recommended protocol

for single-voxel proton MRS at short echo time (on the order of 20 to 30 ms), using a widely available pulse sequence (such as PRESS), would entail standardised voxel placement in regions of interest such as right medial temporal lobe, right parieto-occipital white matter region, right frontal lobe, and cerebellum. To ensure comparability across sites, each voxel acquisition would require a similar water scan (same echo time) for metabolite quantification. Each combined metabolite/water voxel acquisition would take on the order of ten minutes including placement, set-up and acquisition. Total time requirements would depend on the number of regions sampled but are clinically feasible for a cooperative (or sedated) subject.

Instantiating the protocol in future studies

In Table 2 we outline in very general terms a possibity for a future study based on the protocol that we have described. The aforementioned objectives of endophenotypes within autism families and subphenotypes across the autism population are balanced by selecting half the study population from probands and their first-degree relatives (at a minimum, the parents and the most closely matched sib) in AGRE, and the other half from autism probands at participating centres. The study would include patients from birth to 40 years of age, across the full spectrum of autism symptoms and IQ levels. In light of results on abnormal brain growth and white matter enlargement (Courchesne et al., 2004), the core imaging protocol attempts to define further autism's structural phenotype, both in whole brain and specifically in white matter with a focus on DTI and magnetisation transfer. We aim also to include measures of brain function, without over-specifying the particular functional protocols (a topic perhaps best left for a separate consensus statement). Functional assays

could include complementary fMRI and EEG measures in an agreed set of behavioural tasks spanning social domains (e.g. face and emotion recognition) and non-social domains (e.g. attention and perception), and also PET applied for selected ligands, the receptor systems to be determined only at the time when studies actually commence and insights as to the best choices would be enhanced. To enable meta-analyses across diagnoses but within symptom complexes, clinical and imaging protocols should include features of overlap with patients with Rett syndrome, Fragile X syndrome, Tourette syndrome and possibly others. Although the scope of data collection is limited by subject tolerance, costs, and in some cases radiation exposure, if resources allow then subjects would receive longitudinal follow-up. A small number (two to three) imaging sites should be selected for proximity to the AGRE population and, most importantly, imaging expertise.

[place Table 2 about here]

Sharing of analytical methods, tools, and processing

The informatic and neuroscientific work of data analysis represents a significant portion of experimental effort, over and above the clinical work of subject assessment and data acquisition. Though the research community strives for automation for reasons both of throughput and of reproducibility, the fact remains that MR image analysis never is as simple as pushing a button. Implementing and tuning data analysis strategies requires a considerable amount of algorithmic design, computer programming, and technical documentation – efforts that often are designed around specific, single experiments or research questions and cannot be generalised to other applications, and whose full potential therefore goes

unrealised. Rather analogously to the problem of underpowered imaging studies with small samples and incompatible protocols, the lack of cooperation and standardisation in analytical methods has produced a slew of software that is ungeneralisable, and often incomprehensible except to its authors and their own laboratory groups. This problem of duplication and insufficient generalisability can be addressed if schemes for sharing encompass not only the data but also the methods and tools applied to the data. One success story in this regard is the Insight Toolkit (Yoo & Metaxas, 2005), an applications programming interface for high-dimensional image processing which arose from a collaborative workshop on the Visible Human Project.

One way to implement shared analytical tools is to develop, test, and disseminate a standardised "core" data analysis pipeline, much as the ICBM have done, drawing on competitive input from all interested participants. However, by the same rationale we have developed in previous sections of this paper, innovative methods for image analysis that go beyond this pipeline also should be strongly encouraged. This bottom-up approach to innovation will enhance the generation of novel, important findings from new studies and investigators. Depending on processing demands and local computational resources, elements of the pipeline can be made available via downloads of software for processing at local sites, or via uploads of data for processing in a grid computing environment. Of course, uploading one's data to the grid for processing need not imply immediately releasing one's exclusive interest in those data; schedules and conditions for release of data can be defined in individual cases, as noted above, and sharing of analytical resources and methods need

not be simultaneous with sharing of data.

The technical, scientific, and social obstacles make data sharing a difficult problem, but the complexity and heterogeneity of autism make data sharing an imperative if researchers are to make headway. Fundamentally, therefore, data sharing will be a benefit both for the field as a whole and for the individuals involved in building it. A successful scheme will combine imaging with other phenotypic and genetic data to exploit correlations across these levels of analysis and to build endophenotypes, will extend to sharing of analytical tools, and will encourage cooperation without discouraging the creative efforts and strategies of individuals.

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Author Note

Offering to Share:

How to Put Heads Together in Autism Neuroimaging

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TEST OR MEASURE	SOURCE	TIME
DEMOGRAPHICS		
birth date, sex, race, ethnicity, SES, years of education, intervention history		5
DIAGNOSTICS		
Autism Diagnostic Interview – Revised (Lord et al., 1994)	WPS	120-180*
Autism Diagnostic Observation Schedule – Generic (Lord et al., 2000)	WPS	45-60
Mode of onset: delays, regression, both, or unknown		
Language and speech: clearly precocious or undelayed, clearly delayed, or not known		
ABILITY LEVEL		
Choose one or more according to ability level, testing time, investigator preference:		
Raven's Coloured Progressive Matrices	Harcourt	20
Differential Abilities Scale *(ages 2:6 - 17)*	Harcourt	45-65
Mullen Scales of Early Learning *(ages 0 - 5:8)*	AGS	40-60
WISC-IV *(ages 6 - 16)*	Harcourt	90
WAIS-III *(ages 16 - 89)*	Harcourt	90
WASI *(ages 6 - 89)*	Harcourt	50-60
Stanford-Binet Intelligence Scales *(ages 2 - 85+)*	Riverside	75-90
Vineland Adaptive Behaviour Scales II (Survey Interview)	AGS	20-30*
CURRENT LEVELS OF LANGUAGE AND SPEECH		
Clinical Evaluation of Language Fundamentals (CELF-4)	Harcourt	30-60
Peabody Picture Vocabulary Test (PPVT-4)	AGS	10-25
Expressive Vocabulary Test (EVT)	AGS	20
Oral and Written Language Scales (OWLS)	AGS / WPS	10-30
Test of Language Competence (TLC-E)	Harcourt	60
Comprehensive Test of Phonological Processing (CTOPP) – Nonword Repetition Test	Harcourt / WPS	5
ATTENTION		
Continuous Performance Test II	Harcourt	14
EXECUTIVE FUNCTION		
Wisconsin Card Sorting Test	PAR	20
Delis-Kaplan Tower Test	Harcourt	10
Behavioral Assessment of the Dysexecutive Syndrome (BADS)	Harcourt	40
WORKING MEMORY: SPATIAL AND VERBAL		
Wide Range Assessment of Memory and Learning (2nd ed.) Finger Windows	PAR	10
Detroit Tests of Learning Aptitude, Oral Directions subtest	Harcourt	5
ASSOCIATIVE MEMORY		
Wechsler Memory Scale subtests	Harcourt	
Paired Associate Learning (Verbal or Visual)		10
Story Recall, immediate and delayed recall		20
Porteus Maze	Harcourt	15-20
SOCIAL COGNITION		
Social Responsiveness Scale (SRS) (Constantino et al., 2003)	WPS	10-15*
Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001)	Cambridge Autism Research Centre	10
Benton Facial Recognition Test	PAR	10-15
SENSORIMOTOR FUNCTION		
Edinburgh Handedness Inventory *or* Oldfield Handedness Interview		5
Reitan-Klove Sensory Perceptual Examination (Reitan & Wolfson, 1985)		5
Halstead-Reitan Finger Tapping Test (Reitan & Wolfson, 1985)		10
Purdue Grooved Pegboard Test		3-5
Grip Strength Test		5
Sensory Sensitivity and Distortions Questionnaire (Minshew & Meyer, 2007)	Pittsburgh Autism Research Project	10-15*
Repetitive Behaviour Scale – Revised (RBS-R) (Bodfish et al., 2000)	UNC Department of Psychiatry	10*
PHYSICAL AND NEUROLOGICAL EXAMINATION		
CPEA/STAART Medical and Psychiatric History Form	CPEA/STAART Common Measures and Data Sharing Committee	30*
Height, weight, head circumference		5
Screening for tuberous sclerosis, dysmorphic features, strabismus		10
Pubertal Development Scale (Carskadon & Acebo, 1993)	Utah Autism Research Project	5*
GENETICS		
Fragile-X screening (FISH)		
Giemsa banding cytogenetics		
Telomerase cytogenetics		
Zygosity testing (for twins)		
Pedigree construction		
COMORBIDITY		
Autism Co-morbidity Interview – Present & Lifetime Version (Tadevosyan-Leyfer et al., in press)	Utah-Boston CPEA	60-120*
Choose any appropriate for reported symptoms:		
Family Self-Report Questionnaire for Tics, Obsessive-Compulsiveness, Attentional Difficulties, Impulsivity, and Motor Hyperactivity	Tourette Syndrome Association	30*
Developmental Behaviour Checklist – Primary Carer Version (DBC-P)	WPS	10-15*
Child (or Adult) Symptom Inventory 4 – Parent Checklist (CSI-4)	Checkmate Plus	10-15*
Pediatric Sleep Questionnaire	U. Michigan Sleep Disorders Center	10
FAMILY HISTORY		
Medical history, including affective, anxiety, seizure, gastrointestinal, immune or other disorders		30-45*
Broader Phenotype Autism Symptom Scale (BPASS) (Dawson, in press)	UW Autism Center	60-90
Social Responsiveness Scale (SRS)	WPS	10-15*

Table 1: Autism imaging phenotype battery for probands and relatives. The battery is designed with older verbal children and adults in mind. It can be adapted for younger or less testable individuals (for instance, in choices between verbal and visual tests), and/or expanded to focus on specific issues or hypotheses. Testing times are in minutes. Items marked with an asterisk are parent or caregiver interviews. As many tests are optional or alternative, testing times in this table are not additive.

STUDY POPULATION
birth – 40 years
500 from AGRE families (probands and relatives),
500 singleton probands,
1000 normal controls
ALL SUBJECTS
Multi-spectral structural MRI (T1, T2, proton density)
Diffusion Tensor Imaging
SELECTED SUBJECTS AT SPECIFIC SITES
^{1}H MRS (PRESS)
PET
fMRI (BOLD or arterial spin labelling)
EEG
Magnetisation Transfer MRI

Table 2: Outline of a strategy for autism brain imaging, conforming to the core protocol described in the text and balancing endophenotyping with subphenotyping.