Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: Improving the validity of autism spectrum disorder assessment nationally

1. Summary of the impact

Our research has had substantial impact on the mental health and welfare of children with suspected autistic disorders, on their education, on the well-being of their families, and on the activities of healthcare professionals and their services for children in both paediatric and psychiatric practice. We developed a new diagnostic test for autistic spectrum disorders, which allows for better, more reliable diagnosis of these conditions. The test has been included in healthcare guidelines and professional standards in the UK and many other countries around the world, including influencing the revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5).

2. Underpinning research

Since the mid-1990s, the UCL Institute of Child Health has, with international grant funding, supported a research programme into the diagnosis of autism spectrum disorders (ASD), combining both clinical and epidemiological research. This has been led by Professor David Skuse, in his role both as head of the Behavioural and Brain Sciences Unit at the Institute, and also as head of the clinical Social and Communication Disorders Clinic (National Centre for High Functioning Autism) at Great Ormond Street Hospital. In this work he has collaborated with Dr William Mandy (Division of Psychology and Language Sciences) over the past decade.

In the context of an innovative programme of research, which was at its inception the only such programme world-wide dedicated to studying high-functioning ASD, we developed the first computerised interview-based procedure for the assessment of autistic disorders. Our design conceptualised autistic traits as comprising sets of related symptoms that were continuous with typical development, and thus dimensional in character. We recognised the value of computerisation as a way of summarising complex data through clinical enquiry that could efficiently combine unprecedented phenotypic detail with unprecedented reliability **[1]**.

Our work led to the establishment of the largest and most detailed phenotypic database of autistic children (~2000) outside North America. This database was compiled, and has been managed by Mandy. Based upon the systematic collection of DNA from families attending clinical services at Great Ormond Street, combined with phenotypic fidelity, we became the largest contributor to the autism component of the UK10k Exome-Sequencing project. With colleagues at Cold Spring Harbor we contributed to the first evidence, published in *Science*, which described copy number variations as an important risk factor in autism **[2]**.

As well as clinical studies, we have also engaged in genetic epidemiological research, based on screening instruments we developed to measure autistic traits in the general population **[3]**. In collaboration with the Avon Longitudinal Study of Parents and Children we have shown that gene variants, formerly thought to be exclusively related to ASD, influence sub-clinical autistic traits in typical children too **[4]**. These findings have contributed to the current view that ASD is a dimensional disorder, with no clear boundary between normality and abnormality **[5]**.

Joint research led by Mandy and Skuse, based on the uniquely dense phenotyping they had compiled for cases/controls on their database, led to the discovery that autism-related social and communication impairments are closely correlated, both in clinically-identified and in typical populations. This finding contributed to the current revision in the guidelines for ASD diagnosis recently published by the American Psychiatric Association (DSM-5) and influenced the decision to simplify the diagnostic rubric for ASD **[6]**. The revision allowed the incorporation into the autism

spectrum of atypical cases where functional impairment was nevertheless severe **[7]**.

3. References to the research

[1] Skuse D, Warrington R, Bishop D, Chowdhury U, Lau J, Mandy W, Place M. The developmental, dimensional and diagnostic interview (3di): a novel computerized assessment for autism spectrum disorders. J Am Acad Child Adolesc Psychiatry. 2004 May;43(5):548-58. http://dx.doi.org/10.1097/00004583-200405000-00008

[2] Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M. Strong association of de novo copy number mutations with autism. Science. 2007 Apr 20;316(5823):445-9. http://dx.doi.org/10.1126/science.1138659

[3] St Pourcain B, Wang K, Glessner JT, Golding J, Steer C, Ring SM, Skuse DH, Grant SF, Hakonarson H, Davey Smith G. Association between a high-risk autism locus on 5p14 and social communication spectrum phenotypes in the general population. Am J Psychiatry. 2010 Nov;167(11):1364-72.

[4] Skuse DH, Mandy WP, Scourfield J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. Br J Psychiatry. 2005 Dec;187:568-72. http://dx.doi.org/10.1176/appi.ajp.2010.09121789

[5] Skuse DH. DSM-5's conceptualization of autistic disorders. J Am Acad Child Adolesc Psychiatry. 2012 Apr;51(4):344-6. http://dx.doi.org/10.1016/j.jaac.2012.02.009.

[6] Mandy WP, Charman T, Skuse DH. Testing the construct validity of proposed criteria for DSM-5 autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2012 Jan;51(1):41-50. http://dx.doi.org/10.1016/j.jaac.2011.10.013

[7] Mandy W, Charman T, Gilmour J, Skuse D. Toward specifying pervasive developmental disorder-not otherwise specified. Autism Res. 2011 Apr;4(2):121-31. http://dx.doi.org/10.1002/aur.178

4. Details of the impact

Improved diagnosis of autism spectrum disorders

Through the underpinning research described above, we developed a new diagnostic test for ASD, the computerised **Developmental**, **Dimensional and Diagnostic Interview (3Di) [a]**. We also established a company (IXDX Ltd) to oversee the training of clinicians in how to use this product **[b]**. In the period 2008-13, over 1,000 clinicians from the UK and around the world were trained to use the interview. The majority of these have been psychiatrists, paediatricians and clinical psychologists working in the NHS. Courses have been held throughout the UK, including some specifically commissioned by NHS Education Scotland and by the Welsh Assembly, who have funded courses across Wales over the last five years, as part of the ASD Strategic Action Plan **[c]**. Courses have also been run in South-East Asia, Europe and South America **[d]**.

The 3Di is now in regular use in the UK and around the world. For example, a survey of clinicians in Wales in 2011 revealed that the 3Di was the most popular history-taking instrument in the diagnosis of autism spectrum disorders **[e]**. At our own specialised clinic for High Functioning Autistic Disorders – the first such national dedicated multidisciplinary clinic for this patient group in the UK – we see over 300 patients per year for assessment and treatment, and the 3Di is used in all clinical assessment procedures. Our research directly informs the way we provide services **[f]**. The National Autistic Society recommends our clinical services for parents of children in mainstream school, who are suspected of having an autistic spectrum disorder.

Use of the 3Di has led to an improvement in the standard of clinical assessment of autism spectrum disorders. One NHS Consultant Child and Adolescent Psychiatrist reports the following: "*Feedback from patients and their families has been excellent… Other agencies (e.g. Children's Services and Education) have commented favourably upon the value of such a thorough assessment, in the context of observations of the child. I have been using the 3Di for several years and each one of my patients has derived benefit from a greater understanding of their difficulties*" **[g]**.

Guidelines

The 3Di is recommended in NICE Clinical Guideline 128, *Autism in Children and Young People*. **[h]**. Similarly, the Scottish Intercollegiate Guidelines Network recommend use of the 3Di in Clinical Guideline 98, *Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders* **[i]**.

Our work has influenced the revision of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-5), published in May 2013. This included major changes to the content and structure of autistic symptoms. The committee identified studies conducted with the 3Di as offering the best test of the proposed revised symptom model. The DSM-5 workgroup also acknowledged that the 3Di offers a unique opportunity to study phenotypic features not captured by other instruments. Studies by our team, which focused on children who failed to meet all diagnostic criteria for 'classical autism' as conventionally defined, influenced the introduction of a new diagnostic term 'Social Communication Disorder' in DSM-5 **[j]**.

International use of the test

Several 3Di translations including Thai, Flemish, Dutch and Spanish **[k]** have been made available. Other countries in which translations are in regular usage range from Scandinavia (Norway, Sweden, Finland) through the United Arab Emirates and India, to Hong Kong. A Swahili version is currently underway, our first in Sub-Saharan Africa. We have been invited to train practitioners in the standardised diagnostic process of autistic disorder evaluation, using our procedures, in over 20 countries worldwide. In 2011-12, for example, we trained over 230 practitioners across Argentina in a Spanish translation of our procedures **[l]**. The President of the Argentine Program for Children, Adolescents and Adults with Autism Spectrum Conditions (Panaacea) reports that: "*In Argentina, the 3Di is currently the most used diagnostic interview in the ASD field. The general feedback has been that the 3Di is a very valuable instrument in clinical settings, reliable and easy to use.*"

Informing and stimulating public debate

Our work on raising awareness of the dimensional characteristics of autistic disorders has had national and international coverage. For example, 3Di work on sex differences was featured on Radio 4's Woman's Hour, and our research has featured on blogs such as John Brock's *Cracking the Enigma*, where a post on our research entitled 'What is PDD-NOS?' has received over 300,000 hits **[m]**. In particular, our work has informed public and media debate about how ASD should be defined and who should qualify for the diagnosis. Mandy was quoted in a recent Scientific American piece about whether the new DSM-5 ASD diagnostic criteria will unfairly exclude some children **[n]**. A number of articles in newsletters of the Simons Foundation Autism Research Initiative (SFARI) have highlighted our research in this area, and these articles have garnered many comments from interested members of the public **[o]**.

5. Sources to corroborate the impact

[a] UK Patents GB2382290A&B, GB2412832A&B.
http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=26&ND=3&adjacent=true&locale=en_EP&FT=D&date=20051005&CC=GB&NR=2412832A&KC=A

[b] http://www.ixdx.org/3di-index.html

[c] Statement from the ASD National Strategic Coordinator, Welsh Local Government Association. Copy available on request.

[d] Report on training courses, including locations and numbers of participants, provided by the Technical Director, IXDX. Contact details provided.

[e] http://psych.cf.ac.uk/home2/warc/conf_posters/2011/How%20Are%20Standardised%20Developmental%20Assessments%20Used%20in%20Clinical%20Practice.%20Qualitative%20and%20Quantitative%20Findings%20on%20the%20Diagnosis%20of%20Autism.pdf

[f] http://www.gosh.nhs.uk/medical-conditions/clinical-specialties/child-and-adolescent-mental-health-services-camhs-information-for-parents-and-visitors/services/national-centre-for-high-functioning-autism And see sub-page on Research.

[g] Supporting statement from Consultant Child & Adolescent Psychiatrist, Norfolk & Suffolk NHS Foundation Trust. Copy available on request.

[h] CG 128 Autism in children and young people: full guideline http://guidance.nice.org.uk/CG128/Guidance

[i] Scottish Intercollegiate Guidelines network 98 (pages 11, 15): www.sign.ac.uk/pdf/sign98.pdf

[j] Papers showing our influence on DSM-5:
1. Swedo SE, Baird G, Cook EH Jr, et al. Commentary from the DSM-5 Workgroup on Neurodevelopmental Disorders. J Am Acad Child Adolesc Psychiatry. 2012 Apr;51(4):347-9. http://dx.doi.org/10.1016/j.jaac.2012.02.013 *The committee identified studies conducted with the 3Di as offering the best test of the proposed revised symptom model*.
2. Lord C, Jones RM. Annual research review: re-thinking the classification of autism spectrum disorders. J Child Psychol Psychiatry. 2012 May;53(5):490-509. http://doi.org/p2j *The DSM-5 workgroup also acknowledged that the 3Di offers a unique opportunity to study phenotypic features not captured by other instruments*.
3. Happé F. Criteria, categories, and continua: autism and related disorders in DSM-5. J Am Acad Child Adolesc Psychiatry. 2011 Jun;50(6):540-2. http://doi.org/c45qp4 *Shows how studies by our team focused on children who failed to meet all diagnostic criteria for 'classical autism' as conventionally defined, influenced the introduction of a new diagnostic term 'Social Communication Disorder' in DSM-5*.

[k] This article discusses the difficulties of translating autism diagnostic tests into other languages and cultures, and highlights some of the work being done by our team: http://sfari.org/news-and-opinion/news/2012/autism-in-translation-garners-more-research-interest

[l] Training in Argentina was provided on behalf of the Argentine Program for Children, Adolescents and Adults with Autism Spectrum Conditions (Panaacea): http://www.panaacea.org/panaacea-novedades-detalle.php?id=1f0e3dad99908345f7439f8ffabdffc4.
Supporting statement provided by the President of Panaacea. Copy available on request.

[m] Blog: Cracking the Enigma. The post: http://crackingtheenigma.blogspot.co.uk/2011/05/what-is-pdd-nos.html

[n] http://www/sicentificamerican.com/artiocle.cfm?id=autism-math-problem.

[o] Simons Foundation Autism Research Initiative website articles:
Jan 2012 'Studies shore up proposed guidelines for autism diagnosis': http://bit.ly/HNyLUB
April 2012 'Analysis of new diagnostic criteria for autism sparks debate': http://bit.ly/HOlYwG
Oct 2012 'Proposed guidelines won't miss autism cases, study says': http://bit.ly/QKm7qX