

# Behavioural phenotypes: from models to intervention

Heussler, HS; Oliver, Christopher

DOI:

[10.1111/j.1365-2788.2011.01473.x](https://doi.org/10.1111/j.1365-2788.2011.01473.x)

## Document Version

Early version, also known as pre-print

## Citation for published version (Harvard):

Heussler, HS & Oliver, C 2011, 'Behavioural phenotypes: from models to intervention', *Journal of Intellectual Disability Research*, vol. 55, no. 10, pp. 945-947. <https://doi.org/10.1111/j.1365-2788.2011.01473.x>

[Link to publication on Research at Birmingham portal](#)

## Publisher Rights Statement:

The definitive version is available at [www3.interscience.wiley.com](http://www3.interscience.wiley.com)

## General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

## Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



UNIVERSITY OF  
BIRMINGHAM

Behavioural phenotypes: From models to intervention.

Heussler, H.S. and Oliver, C.

*Cerebra Centre for Neurodevelopmental Disorders,*

*School of Psychology,*

*University of Birmingham*

Please use this reference when citing this work:

Heussler H. S.& Oliver C. (2011). Behavioural phenotypes: From models to intervention. *Journal of Intellectual Disability Research*, 55, 945-947. (doi: 10.1111/j.1365-2788.2011.01473.x)

The Cerebra Centre for Neurodevelopmental Disorders,

School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT

**Website:** [www.cndd.bham.ac.uk](http://www.cndd.bham.ac.uk)

**E-mail:** [cndd-enquiries@contacts.bham.ac.uk](mailto:cndd-enquiries@contacts.bham.ac.uk)

A notable trend in the Society for the Study of Behavioural Phenotypes Scientific Symposium abstracts that are published annually in this special edition, is the increase in the number of papers that refer explicitly to intervention for intellectual disability at a level other than behaviour change. This trend reflects and is driven by the greater clarity of understanding of the pathways from genetic disorder to central nervous system development, to cognitive endophenotype, to behaviour and the interaction between behaviour and the immediate and remote environment. The study of pathways to behavioural phenotypes associated with genetic disorders has influenced the conceptualisation of intellectual disability by attempting to account for behavioural variability by demonstrating the effects of individual cognitive difference and developmental trajectories alongside environmental influences. This redresses the balance within biopsychosocial models of behavioural outcome in intellectual disability and emphasises the need for models that: 1) have empirical support, 2) identify the pathways from biological disorder to behaviour, 3) have multiple levels of explanation and 4) are set in a developmental context.

The invited review in this edition by Moore and George (2011) provides a way of describing these models that helps demonstrate complexity and indicates different points of intervention. By using the methods suggested by Moore and George, it is possible to make specific predictions about the immediate and longer term effects of intervention. The concepts and levels of explanation made explicit by this approach are to some extent evident in many of the studies described in the published abstracts. Cornish and Hocking (2011) suggest an influence on inhibition and working memory of the number of CGG repeats in males with the Fragile X premutation. Similarly, Wong et al. (2011) suggest that TSC1 and TSC2 mutations lead to different cognitive outcomes in Tuberous Sclerosis Complex. Studies like these are providing the evidence needed to complete the models that Moore and George are promoting.

As these multilevel models evolve and become more refined so we see evidence of targeted intervention with clinical trials currently being run in many centres for disorders such as Tuberous Sclerosis Complex, Fragile X, Angelman and Rett syndrome. Some of these trials are promising and are in a variety of stages of development from Phase 1-3 trials. Tuberous Sclerosis, for example, is now understood to involve the TSC complex with resultant decreased

activation of mTOR signaling, part of the growth factor signaling. Thus, mutations in TSC1 and TSC2 involve loss of control of cell growth and cell division. Targeted therapies including rapamycin and everolimus have shown interesting effects. Rapamycin has been shown to rescue learning and memory deficits in mouse models (Ehninger and Silva, 2011) and Everolimus has been approved in some countries for use in Subependymal Giant Cell Astrocytoma (SEGA) after an open label study of 28 patients (children and adults) with SEGAs (Krueger et al., 2010). Positive effects were seen in size of the SEGA, facial angiofibromas and in seizures. However, no changes were observed in neuropsychological outcome. The changes seen in animal models may be directly related to learning and memory and also to commonly observed autistic like behaviours in this group. Common links to mTor pathways in animal models are present in Fragile X and neurofibromatosis, both of which are disorders with common presentations of autistic phenotypes and epilepsy. This suggests that this pathway may be implicated in developmental aspects of these phenotypes.

Trials of medication targeted at modifying anxiety, cognitive impairments and autistic like features for those with Fragile X syndrome are currently underway. The study by Winarni et al., (2011) in this edition, suggests Sertraline may influence language beneficially in young children with Fragile X syndrome, although the study warrants replication using a more robust design. A better understanding of the molecular pathways in Fragile X syndrome has resulted in the development of a number of therapeutic strategies. Reduced expression of the Fragile X Mental Retardation Protein (FMRP), an RNA binding protein that negatively regulates protein synthesis, has a downstream effect increasing activity of mGluR5. Fenobam, STX 107, AFQ56, RO4917523 (mGluR5 antagonists) are currently being trialed in phase 2 and 3 studies internationally. Other trials are aimed at treating upstream or downstream of the mGluR5 complex with STX209 (Arbaclofen) being trialed as a stimulator of the GABA(B) receptors with evidence of decreased anxiety and hyperactivity (Krueger and Bear, 2011). Minocycline has also been used resulting in better dendritic spine growth in animal studies. Lithium which targets multiple intracellular pathways related to mGluR5 and Fragile X has also been trialed in pilot studies with some positive effects. Results of larger scale randomised blinded trials are eagerly anticipated. Importantly it may be that these findings may extend to wider populations of children with dysregulation of mGluR5.

Models of the neural development in Rett syndrome emphasise mutations in the gene coding for MECP2 which is critical for the growth of neural spines. Mutations in the CDLK5 gene have also been found in girls with a phenotype overlapping that of classical Rett syndrome. In particular an early seizure onset phenotype is associated with mutations in the CDLK5 gene. These pathways overlap and present with a similar phenotype (Mari et al., 2005, Weaving et al 2004). L Carnitine has been studied and shown positive effects in hand apraxia and increased heart rate variability. Animal models have suggested that IGF-1 can ameliorate this effect and current trials are underway testing this hypothesis in girls with Rett syndrome. Interest has been in read-through effects on the nonsense mutations seen in MECP2 by aminoglycosides, however the side effects have been problematic. Newer agents however are being evaluated and may be more clinically tolerable (Brendel et al., 2011). Other studies evaluating Dextromethorphan (NMDA/Glutamate receptor blocker) are also underway. The studies evaluating the role of methylation in this group have not shown a significant effect in objective clinical measures but are small (Glaze, Percy and Motil 2009). Finally, in this edition, the results of the study by Rawas et al., (2011) suggest a 5-HT1-A agonist might ameliorate some of the severe breathing dysrhythmias seen in Rett syndrome.

All of these disorders are rare and funding at national and international levels is often directed at more common disorders with a stronger lobby. It is not uncommon for Research Councils in the UK to reject funding applications on the basis of the rarity of a disorder. However, it could be argued that common behavioural phenotypes are likely to share common pathways and thus there is much to learn from specific syndromes. It is also likely that a multidisciplinary approach with clinicians and basic scientists working together will lead to translation of complex molecular information into understanding and therapies that are likely to benefit not only those with specific syndromes but also those with similar phenotypes. In this edition Holland (2011) notes the importance of behavioural phenotype research to the Foresight review conducted in the UK that was designed to map out the future research landscape and it is evident that the study of individual genetic disorders could play a critical strategic role in improving the understanding of mental health and behavioural difference and disorder in people with intellectual disability. Clear understanding of the behavioural attributes and differences between different groups are the basis to the model building that will make explicit similarities and differences in pathways that then

## Behavioural phenotypes

suggest shared or different points of intervention across groups. It is these shared and different pathways that will be discussed and debated at this year's SSBP meeting in Brisbane.

## References

- Brendel C, Belakhov V, Werner H, Wegener E, Gärtner J, Nudelman I, Baasov T, Huppke P. Readthrough of nonsense mutations in Rett syndrome: evaluation of novel aminoglycosides and generation of a new mouse model. *J Mol Med (Berl)*. 2011 Apr;89(4):389-98.
- Cornish, K. and Hocking, D.R. (2011). Carriers of the FMR1 gene: Does size matter? *Journal of Intellectual Disability Research*, 55, XX –XX.
- Dykens EM, Roof E, Bittel D, Butler MG. TPH2 G/T polymorphism is associated with hyperphagia, IQ, and internalizing problems in Prader-Willi syndrome. *J Child Psychol Psychiatry*. 2011 May;52(5):580-7.
- Ehninger D, Silva AJ. Rapamycin for treating Tuberous sclerosis and Autism spectrum disorders. *Trends Mol Med*. 2011 Feb;17(2):78-87. Epub 2010 Nov 4.
- Glaze DG, Percy AK, Motil KJ et al A Study of the Treatment of Rett Syndrome With Folate and Betaine *J Child Neurol*. 2009 May; 24(5): 551–556.
- Holland, A.J. (2011). The evolving nature of research into intellectual disabilities: Priorities and possibilities. *Journal of Intellectual Disability Research*, 55, XX –XX.
- Lossie AC, Whitney MM, Amidon D, Dong HJ, Chen P, Theriaque D, Hutson A, Nicholls RD, Zori RT, Williams CA, Driscoll DJ. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. *J Med Genet*. 2001 Dec;38(12):834-45.
- Kates WR, Antshel KM, Faraone SV, Fremont WP, Higgins AM, Shprintzen RJ, Botti JA, Kelchner L, McCarthy C. Neuroanatomic predictors to prodromal psychosis in velocardiofacial syndrome (22q11.2 deletion syndrome): a longitudinal study. *Biol Psychiatry*. 2011 May 15;69(10):945-52.
- Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T, Franz DN. Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis. *N Engl J Med* 2010; 363:1801-1811

Krueger DD, Bear MF. Toward fulfilling the promise of molecular medicine in fragile X syndrome. *Annu Rev Med.* 2011 Feb 18;62:411-29.

Mari F, Azimonti S, Bertani I, Bolognese F, Colombo E, Caselli R, Scala E, Longo I, Grosso S, Pescucci C, Ariani F, Hayek G, Balestri P, Bergo A, Badaracco G, Zappella M, Broccoli V, Renieri A, Kilstrup-Nielsen C, Landsberger N. CDKL5 belongs to the same molecular pathway of MeCP2 and it is responsible for the early-onset seizure variant of Rett syndrome. *Hum Mol Genet.* 2005 Jul 15;14(14):1935-46.

Moore, D. and George, R. (2011). A tool for the visualisation and modelling of typical and atypical development: ACORNS an Accessible Cause-Outcome Representation and Notation System. *Journal of Intellectual Disability Research*, 55, XX –XX.

Peters SU, Bird LM, Kimonis V, Glaze DG, Shinawi LM, Bichell TJ, Barbieri-Welge R, Nespeca M, Anselm I, Waisbren S, Sanborn E, Sun Q, O'Brien WE, Beaudet AL, Bacino CA. Double-blind therapeutic trial in Angelman syndrome using betaine and folic acid. *Am J Med Genet A.* 2010 Aug;152A(8)

Raux G, Bumsel E, Hecketsweiler B, van Amelsvoort T, Zinkstok J, Manouvrier-Hanu S, Fantini C, Brévière GM, Di Rosa G, PHum Mol Genet. ustorino G, Vogels A, Swillen A, Legallic S, Bou J, Opolczynski G, Drouin-Garraud V, Lemarchand M, Philip N, Gérard-Desplanches A, Carlier M, Philippe A, Nolen MC, Heron D, Sarda P, Lacombe D, Coizet C, Alembik Y, Layet V, Afenjar A, Hannequin D, Demily C, Petit M, Thibaut F, Frebourg T, Champion D. Involvement of hyperprolinemia in cognitive and psychiatric features of the 22q11 deletion syndrome. 2007 Jan 1;16(1):83-91.

Rawas, S. A., Delamont, R. S., Engerström, I. W., Hansen, S., Apartopoulos, F., Smeets, E.E.J., Curfs, L.M.G., Pini, G. and Julu, P.O.O. (2011). The modification of apneustic breathing in Rett Syndrome with a 5-HT1-A agonist. *Journal of Intellectual Disability Research*, 55, XX –XX.

Weaving LS, Christodoulou J, Williamson SL, Friend KL, McKenzie OL, Archer H, Evans J, Clarke A, Pelka GJ, Tam PP, Watson C, Lahooti H, Ellaway CJ, Bennetts B, Leonard H, Gécz J.

Mutations of CDKL5 cause a severe neurodevelopmental disorder with infantile spasms and mental retardation. *Am J Hum Genet.* 2004 Dec;75(6):1079-93.

Winarni, T.I., Chanchaiya, W., Au, J., Adams, E., Mu, Y., Nguyen, D.V. and Hagerman R.J. (2011). Sertraline improves the developmental trajectory for language in young children with Fragile X syndrome. *Journal of Intellectual Disability Research*, 55, XX –XX.

Wong, H.T., McCartney, D.L., Lewis, J., Sampson, J.R., Howe, C.J. and de Vries, P.J. (2011). Individuals with TSC1 and TSC2 mutations show distinct patterns of intellectual abilities. *Journal of Intellectual Disability Research*, 55, XX –XX.