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PII: S0149-7634(19)30711-0
DOI: https://doi.org/10.1016/j.neubiorev.2019.08.014
Reference: NBR 3514

To appear in:

Received Date: 8 August 2019
Revised Date: 16 August 2019
Accepted Date: 19 August 2019

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Dajie Zhang\textsuperscript{1,2,3}, Francesco Bedogni\textsuperscript{4}, Sofie Boterberg\textsuperscript{5}, Carol Camfield\textsuperscript{6}, Peter Camfield\textsuperscript{6}, Tony Charman\textsuperscript{7,8}, Leopold Curfs\textsuperscript{9}, Christa Einspieler\textsuperscript{2}, Gianluca Esposito\textsuperscript{10,11}, Bianca De Filippis\textsuperscript{12}, Robin P. Goin-Kochel\textsuperscript{13,14}, Günter U Höglinger\textsuperscript{15,16,17}, Daniel Holzinger\textsuperscript{18,19}, Ana-Maria Iosif\textsuperscript{20}, Giulio E. Lancioni\textsuperscript{21}, Nicoletta Landsberger\textsuperscript{4,22}, Giovanni Laviola\textsuperscript{12}, Eva M. Marco\textsuperscript{23}, Michael Müller\textsuperscript{24}, Jeffrey L. Neul\textsuperscript{25}, Karin Nielsen-Saines\textsuperscript{26}, Anders Nordahl-Hansen\textsuperscript{27}, Mark F. O’Reilly\textsuperscript{28}, Sally Ozonoff\textsuperscript{29}, Luise Poustka\textsuperscript{3,3}, Herbert Roeyers\textsuperscript{5}, Marija Rankovic\textsuperscript{30}, Jeff Sigafoos\textsuperscript{31}, Kristiina Tammimies\textsuperscript{32}, Gillian S Townend\textsuperscript{3}, Lonnie Zwagienbaum\textsuperscript{33}, Markus Zweckstetter\textsuperscript{30,34}, Sven Bölte\textsuperscript{32,35}, Peter B Marschik\textsuperscript{1,2,3,32}

1 Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany
2 IDN - interdisiciplinary Developmental Neuroscience, Division of Phoniatrics, Medical University of Graz, Graz, Austria
3 Leibniz ScienceCampus Primate Cognition, Goettingen, Germany
4 Neuroscience Division, IRCCS San Raffaele Scientific Institute, Milan, Italy
5 Department of Experimental Clinical and Health Psychology, Faculty of Psychology and Educational Sciences, Ghent University, Ghent, Belgium
6 Department of Pediatrics, Dalhousie University and the IWK Health Centre, Canada
7 Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, London, UK
8 South London and Maudsley NHS Foundation Trust, London, UK
9 Rett Expertise Centre-GKC, Maastricht University Medical Centre, Maastricht, the Netherlands
10 Social & Affliiative Neuroscience Lab, Psychology Program, Nanyang Technological University, Singapore
11 Affiliative Behaviour & Physiology Lab, Department of Psychology and Cognitive Sciences, University of Trento, Trento, Italy
12 Center for Behavioral Sciences and Mental Health, Istituto Superiore di Sanità, Rome, Italy
13 Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA
14 Autism Center, Texas Children’s Hospital, Houston, TX, USA
15 German Center for Neurodegenerative Diseases (DZNE), Munich, Germany
16 Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Germany
17 Department of Neurology, Hannover Medical School, Hannover, Germany
18 Hospital of St. John of God, Institute for Neurology of Senses and Language, Linz, Austria
19 Research Institute for Developmental Medicine, Johannes Kepler University Linz, Linz, Austria
20 Department of Public Health Sciences, University of California – Davis, Davis CA, USA
21 Department of Neuroscience and Sense Organs, University of Bari, Bari, Italy
22 Neuroscience Division, IRCCS San Raffaele Scientific Institute, Milan, Italy
23 Department of Genetics, Physiology and Microbiology, Faculty of Biological Sciences, Universidad Complutense de Madrid, Madrid, Spain
24 Institute of Neuro- and Sensory Physiology, University Medical Center Goettingen, Georg-August-University Goettingen, Germany
25 Vanderbilt Kennedy Center, Nashville, TN, USA
26 Department of Pediatrics, David Geffen School of Medicine, University of California – Los Angeles, CA, USA
27 Faculty of Education, Ostfold University College, Halden, Norway
28 Department of Special Education, University of Texas at Austin, Austin TX, USA
29 Department of Psychiatry and Behavioral Sciences, MIND Institute, University of California – Davis, Sacramento CA, USA
30 Department for NMR-based Structural Biology, Max Planck Institute for Biophysical Chemistry, Goettingen, Germany
31 School of Education, Victoria University of Wellington, Wellington, New Zealand
32 Center of Neurodevelopmental Disorders (KIND), Division of Neuropsychiatry, Centre for Psychiatry Research, Department of Women’s and Children’s Health, Karolinska Institutet, Stockholm, Sweden
33 Department of Pediatrics, University of Alberta, Edmonton, Canada
34 German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany
35 Curtin Autism Research Group, School of Occupational Therapy, Social Work and Speech Pathology, Curtin University, Perth, Western Australia
Despite intensive research for many years, developmental regression remains a puzzling phenomenon. Scientific and clinical interest in this topic increases steadily and is likely to persist in the upcoming years. Among the reasons are novel evidence of higher than previously assumed occurrence of developmental regression in some disorders, particularly early regression during the first years of life in autism spectrum disorder (ASD), a change in view of the nature of regression in specific disorders such as Rett syndrome (RTT), the growing understanding of aetiological mechanisms, protective, and causal factors of regression, and the necessity to develop effective interventions dealing with the dramatic loss of skills (e.g., Boterberg et al., 2019; Ozonoff and Iosif, 2019; Thurm et al., 2018).

Developmental regression has been defined as loss of previously acquired skills not caused by brain injury or other traumatic events. As yet, there is no consensus on how this definition of ‘regression’ should be operationalized, nor do standard measurements to capture developmental regression and its antecedents exist. There is only a restricted body of knowledge about the onset of regression and even less is known about the divergent pathways of regression and the severity of affected developmental domains. In clinical practice and research, it is not always possible to precisely and thoroughly document the achievement of skills, the onset of their loss, and the developmental trajectory before and following the skill loss. An ideal approach to document regressive functions would involve applying closely meshed multidimensional prospective assessments over time starting prior to regression. This works for some disorders when studying high-risk cohorts (e.g., ASD sibling studies; e.g., Bölte et al., 2013; Varcin and Jeste, 2017), but is not applicable to (rare) disorders for which such cohorts are unfeasible to obtain (e.g., RTT, Landau Kleffner syndrome, Phelan McDermid syndrome). Retrospective assessments (e.g., anamnestic assessments, questionnaires or checklists, retrospective audio-video analysis), on the other hand, are inherently adulterated by well-known memory or sampling bias, leaving the assumption of attaining or losing skills equivocal (e.g., Boterberg et al., 2019; Marschik and Einspieler, 2011). When it comes to defining the severity of regression or its representation, i.e. the partial or complete loss of functions, we are entering even less understood and researched grounds. Although the use of this terminology is widespread, a precise definition, again, is still absent. After all, without being able to specify characteristics and pathways prior to regression in terms of quality, quantity, time and timing, definitions of partial loss are fated to be vague and heterogeneous. The same challenge holds true for the definition of the phenomenological onset, the differentiation between transient or persisting regressive trajectories, as well as our understanding of improvement or ‘recovery’.

According to recent studies (Ozonoff et al., 2018; Pearson et al., 2018), when applying dimensional (in contrast to categorical) methods to measure regression, most children diagnosed with autism experience a regression in social functions from 6 months onwards with a decreasing rate of expected social behaviours. Before 6 months of age, children later diagnosed with autism did not seem
to differ from their typically developing peers in overt social behaviours (Elsabbagh et al., 2014; Landa and Garrett-Mayer, 2006; Ozonoff et al., 2010; Rozga et al., 2011; Young et al., 2009; Zwaigenbaum et al., 2005), giving the impression that the initial development of these infants might be intact. However, recent research suggests an array of atypical signs related to, and, beyond the social domain detectable by 6 months in infants who later develop autism (e.g., oculo-motor functions, motor behaviour, visual perception, vocalizations, and their underlying neural structure and functions; Bhat et al., 2012; Bosl et al., 2018; Brisson et al., 2014; Einspieler et al., 2014; Estes et al., 2015; Iverson et al., 2019; Jones and Klin, 2013; Paul et al., 2011; Wolff et al., 2012). Notably, observable social behaviours (e.g., orienting toward or scanning of socially relevant audio and visual information) that appear similar between young infants with and without ASD may rely on disparate neural mechanisms (e.g., Blasi et al., 2015; Braukmann et al., 2018; Elsabbagh et al., 2012; Lloyd-Fox et al., 2018). Learning from studies with RTT, the ostensible normal pre-regression development is marked by genuine atypicalities from the first months of life (Einspieler and Marschik, 2019, for a review). That said, even if we reach consensus on an operational definition based on gold standard assessments for regression for specific disorders, we are compelled to decrypt the nature of this puzzle – whether it is a slant-down from typical development, or it is a manifestation of actual deviation in origin which emerges subtly and divulges itself only when the individual capacity could no longer meet the age-appropriate behavioural demands or expectations? The solution but also the challenge remains to better understand and characterize the enigmatic pre-regression period.

To date, the precise origins of regression are still largely unknown but probably linked to a complex interaction between biological and environmental factors. Future research will benefit from a constructivist approach to encompass knowledge on structural and functional development of single disorders, and tackle similarities and dissimilarities across-syndromes. On the one hand, we need to search for disorder causing mechanisms, disorder promoting and protective factors, and the structural underpinnings of various functional representations. On the other hand, we need to try to rigorously define and characterize the acquisition and loss of behavioural representations of altered neurobiological causes. The increasingly sophisticated understanding of pathogenic liabilities of regression (e.g., Thurm et al., 2018) will help us to decipher deteriorating development, the pathways to it, and the ways beyond.

**Conclusion**

Developmental regression is a complex phenomenon seen in several developmental disorders and needs to be defined by objective and dimensional parameters that specify its measurement, prevalence, age of onsets, key profiles, and pathways for each single disorder. To resolve the puzzle of regression, long-term cross-disciplinary efforts are necessary to define the loss of acquired skills,
functions, and capacities before and after its onset. Only concerted research efforts and a synthesis of knowledge from different scientific disciplines and approaches will allow to essentially move this field forward. More specifically, we need to determine what are the possible impacts of some very early acquired or absent skills on the development of other functions within and across early neurodevelopmental domains during the infancy period that is characterised by rapid brain and behavioural development. A consensus operational definition of developmental regression and recommendations for measurement will set the start to decipher its neurological underpinnings, unfolding trajectories, and cross-domain impact. This might in return refine our initial understanding of regression and hence enable more targeted early interventions.

Acknowledgements

We would like to sincerely thank all contributors to the special issue on developmental regression in this Journal, all reviewers and colleagues who discussed this important topic with us and who will further develop the better understanding of regression. PBM was supported by FWF (P25241, TCS24), OeNB (P16430) and the Bill and Melinda Gates Foundation Grand Challenges Exploration Grant (OPP 1128871). Initiating discussions were supported by a “Think Tank Symposium” through the Leibniz ScienceCampus Primate Cognition.

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