Morphological integration in human skull and its possible role in etiogenesis of neuropsychiatric disorders: Deciphering the link between evolution, development and disease

*Ashutosh Kumar^{1, 5}, *Sada Nand Pandey^{2,5}, Muneeb A. Faiq^{3, 5}, Vikas Pareek^{4, 5}

1. Department of Anatomy, All India Institute of Medical Sciences, New Delhi-110029, India.
2. Department of Biophysics, All India Institute of Medical Sciences, New Delhi-110029, India.
3. Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi-110029, India.
4. Computational Neuroscience and Neuroimaging Division, National Brain Research Centre, Manesar, Haryana-122051, India.
5. Etiologically Elusive Disorders Research Network (EEDRN), New Delhi, India.

***Correspondence:**

Ashutosh Kumar

Email: aiims.ashu@gmail.com

Sada Nand Pandey

Email: snpandey2011@gmail.com

Abstract

Structure-function interdependence is a universal phenomenon in biological systems. Any alteration in structural features may result in change in functions—leading to natural selection of a particular trait, or dysfunctions thereof. Many such alterations arise during the course of evolution of a species and may meticulously be traced during embryonic development of an organism. Through, the theoretical construct of morphological integration, a set of phenotypic traits alter in a coordinated and integrated manner during evolution and embryonic development of an organism yielding efficient and environmentally adapted physiological functions pertinent to those structures. Such integration may go awry sometimes, setting the basis for genesis of diseases.

Morphological integration in human skull has been established through various methods. The brain-skull co-development is handcuffed through evolution and development, and the very basis of a neuropsychiatric disorder could be underlying in dysmorphogenesis of the skull, its consequent effect on structures, and thus functions of the pertinent brain components. Here we propose that morphological integration in human skull may be mechanistically implied in etiology of certain neuropsychiatric disorders and should be borne in mind during clinical diagnosis and therapeutic interventions.

Key words: Morphological integration, dysmorphogenesis, skull, etiology, neuropsychiatric disorders

Introduction

Morphological integration implies simultaneous alterations in a set of phenotypic traits of an organism in the course of evolution, and embryonic development, to acquire the most efficient and environmentally adapted physiological functions pertaining to those structures (1). (In *morphological integration* a set of phenotypic traits vary in common. *Modularity* bears a conceptual similitude, where simultaneously varying traits are compartmentalized as modules—showing stronger intra-modular than inter-modular co-variance (2).) Morphological integration in human skull has evoked curiosity of the neuropsychiatry investigators for long. It has now been established through various scientific methods (3–6) and its molecular and genetic basis (3,7) has also been established.

Morphological integration provides rationale to explore the very basis of few neuropsychiatric disorders, whose etiology remains still elusive. A structural basis has, however, been speculated; as in the case of epilepsy (8,9), schizophrenia (10,11), bipolar disorder (12), and certain types of migraines (8,9). This also presents a missing link connecting evolution, embryonic development and multi-factorial etiology of such disorders. Evidences have been documented for the ontogenetic integration of skull landmark variations in modern and archaic humans (13,14). An ontogenetic evolutionarily linking integration, of phenotypic variations across generations in hominid skulls, has also been marked in literature (13,15). The narratives derived from available studies suggest that accumulating effects of erroneous cranio-cerebral development, which have been registered in the genomic structure of a population following the evolutionary trail, may emerge as a neuropsychiatric disorder (3,16–18).

Evolutionary aspect

The three dimensional architecture of the human skull passes through continuous and well orchestrated re-modeling in response to evolutionary changes in its each part (4,19). Even a small change in the dimensionality of a single landmark, in the course of evolution, has capacity to redirect the dimensionality of all the skull landmarks, and hence to create a different data set of measurements for inter-landmark distances (3). Although, such a re-modeling of the human skull may not always result in a functional gain and may predispose individuals to certain neuropsychiatric disorders (8,20,21), as a cost to the evolutionary benefits of the survival (22–24).

The human skull shows tremendous inter-individual variations (25,26) in its anatomy and dimensionality of the landmarks, which may be pronounced in a population representing admixture of different ethnic groups (27), as for example, Indian (28–31) and American populations (32). Plausibly, these variations accumulated in the long course of evolution (33–35), through assimilation of co-variances (34,35) and epigenetic changes (36) in the gross and genetic structure of a population respectively, implied morphological integration (34,37). The inclusion of variations in the skull components in the course of evolution might have subjected a population to acquire and propagate multiple errors at molecular level (3) and to express these as aberrant genotypes and phenotypes (38), setting basis for etiogenesis of certain neuropsychiatric disorders (10,12,18,7).

Developmental aspect

Morphological integration may be instrumental in the developmental causality of the neuropsychiatric diseases (a physiological form of developmental integration at multi-levels and across multiple structures is often called ‘developmental modularity’). An erroneous

developmental process can introduce disease at multiple structural levels, and in multiple organs, due to inter-relationship and connectedness of a developmental process (39).

Studies of morphological integration in the skulls of birds (6) and animals (40) including humans (3,41,42) suggest that individual components of the skull maintain tight interdependence with each other in terms of dimensionality, and a change in the dimensions of the any component may also be reflected in other cranial components (3). This concept may be better understood by observing the interdependence of dimensionality in a deformed human skull where dimensional changes in any of the components would be reflected in whole of the skull. Now as the skull contains brain in closed and filling proximity, certainly a deformed skull has to harbor a correspondingly deformed brain. The development of skull and brain go in tandem (16) and a cranial deformity may present as a craniofacial anomaly, the associated dysmorphogenesis of brain may result in compromised neural functions at birth or may manifest as a neuropsychiatric disorder later in life (8,10,12) depending upon the degree of disruption and consequent remodeling of molecular regulation in developing brain (39,21).

Genetic aspect

The evolutionary and developmental influence on the expression of phenotypic traits can be traced in the genomic structure of an organism. Integration of various phenotypic traits during the course of evolution, may be an outcome of selection pressure, but it gets strictly registered in genetic structure of the organism (43). In a population, the genomic assimilation of the naturally selected genotypic variants, or sequence reading errors; or fresh mutations, may leave its impact on functions of complete genome, thus, influencing further phenotypic expressions (3,43). Genetic integration has been confirmed in the human skulls (3), and the evidences indicate that a

particular skull dysmorphogenesis may be a phenotypic expression of such a faulty genetic integration (3,16) which may manifest as neurocognitive dysfunction (17,18).

Functional modularity: Integration of function

‘Functional modularity’ is a functional equivalent to morphological integration and often used interchangeably. Functional modules (1,15) are the sets of related functions which are coordinated together in a biological system (39,45).

Literary evidences linking etiology of neuropsychiatric disorders

Morphological integration enjoys good support from various studies in literature which associate developmental dysmorphogenesis of skull (and consequently of brain) with genesis of certain neuropsychiatric disorders, which include various craniofacial anomalies (ending in neurocognitive dysfunction) (8), syndromes featuring mental retardation (7,21), and distinct psychiatric diseases (17,18). Associated studies assert that it may be one of the etiomechanisms involved in causation of such diseases (8,17,18). A study established links between posterior cranial fossa dysmorphogenesis and major depression (20). Studies also linked skull dysmorphogenesis with schizophrenia (10,11,17), bipolar illness (12) and other psychoses (18). It has also been linked to non psychotic neurological problems like epilepsy (8,9), and migraines (8,9).

Conclusions

Association of various neuropsychiatric diseases to evolution and embryonic development of skull and brain can be speculated through morphological integration, which provides a conceptual basis for understanding links between evolution, development and disease

etiogenesis.

Competing interests

The authors declare that they have no competing interests.

Grant information

The authors declare that no grants were involved in supporting this work.

Author (s) contributions

AK wrote first draft. SN, MA, and VP reviewed and edited first draft. MA language edited final draft.

References:

1. Klingenberg CP. Morphological Integration and Developmental Modularity. *Annu Rev Ecol Evol Syst.* 2008;39(1):115–32.
2. Klingenberg CP. Studying morphological integration and modularity at multiple levels: concepts and analysis. *Philos Trans R Soc Lond B Biol Sci.* 2014;369(1649):20130249.
3. Martínez-Abadías N, Esparza M, Sjøvold T, González-José R, Santos M, Hernández M, et al. Pervasive Genetic Integration Directs the Evolution of Human Skull Shape. *Evolution (N Y).* 2012;66(4):1010–1023.
4. Singh N, Harvati K, Hublin J-J, Klingenberg CP. Morphological evolution through integration: a quantitative study of cranial integration in Homo, Pan, Gorilla and Pongo. *J Hum Evol.* 2012;62(1):155–64.
5. Bruner E, Ripani M. A quantitative and descriptive approach to morphological variation of

- the endocranial base in modern humans. *Am J Phys Anthropol.* 2008;137(1):30–40.
6. Kulemeyer C, Asbahr K, Gunz P, Frahnert S, Bairlein F. Functional morphology and integration of corvid skulls - a 3D geometric morphometric approach. *Front Zool.* 2009;6:2.
 7. Martínez-Abadías N, Heuzé Y, Wang Y, Jabs EW, Aldridge K, Richtsmeier JT. FGF/FGFR Signaling Coordinates Skull Development by Modulating Magnitude of Morphological Integration: Evidence from Apert Syndrome Mouse Models. Stein G, editor. *PLoS One.* 2011;6(10):e26425
 8. Richtsmeier JT, DeLeon VB. Morphological integration of the skull in craniofacial anomalies. *Orthod Craniofac Res.* 2009;12(3):149–58.
 9. Aldridge K, Kane AA, Marsh JL, Yan P, Govier D, Richtsmeier JT. Relationship of brain and skull in pre- and postoperative sagittal synostosis. *J Anat.* 2005;206(4):373–85.
 10. Mishra V, Sharma S, Kulsreshtha V, Kumar V, Gurunani KC. Anthropometrical association of the craniofacial dysmorphology with schizophrenia. *J Clin diagnostic Res JCDDR.* 2012;6(10):1620–3.
 11. Waddington JL, Lane A, Larkin C, O’Callaghan E. The neurodevelopmental basis of schizophrenia: clinical clues from cerebro-craniofacial dysmorphogenesis, and the roots of a lifetime trajectory of disease. *Biol Psychiatry.* 1999;46(1):31–9.
 12. Hennessy RJ, Baldwin PA, Browne DJ, Kinsella A, Waddington JL. Frontonasal dysmorphology in bipolar disorder by 3D laser surface imaging and geometric morphometrics: Comparisons with schizophrenia. *Schizophr Res.* 2010;122(1–3):63–71.
 13. Bookstein FL, Gunz P, Mitteroecker P, Prossinger H, Schaefer K, Seidler H. Cranial integration in Homo: singular warps analysis of the midsagittal plane in ontogeny and

- evolution. *J Hum Evol.* 2003;44(2):167–87.
14. Ponce de León MS, Zollikofer CPE. Neanderthal cranial ontogeny and its implications for late hominid diversity. *Nature.* 2001;412(6846):534–8.
 15. Bastir M. A systems-model for the morphological analysis of integration and modularity in human craniofacial evolution. *J Anthropol Sci.* 2008;86:37–58.
 16. Richtsmeier JT, Flaherty K. Hand in glove: brain and skull in development and dysmorphogenesis. *Acta Neuropathol.* 2013;125(4):469–89.
 17. Waddington JL, Lane A, Scully P, Meagher D, Quinn J, Larkin C, et al. Early cerebro-craniofacial dysmorphogenesis in schizophrenia: a lifetime trajectory model from neurodevelopmental basis to “neuroprogressive” process. *J Psychiatr Res.* 1999;33(6):477–89.
 18. McGrath J, Grim V, Cardy S, Chapple B, Mowry B. Dysmorphogenesis in psychosis: Quantitative and qualitative measures involving the head and face. *Schizophr Res.* 2000;41(1):84.
 19. Goswami A. Cranial modularity shifts during mammalian evolution. *Am Nat.* 2006;168(2):270–80.
 20. Shah SA, Doraiswamy PM, Husain MM, Escalona PR, Na C, Figiel GS, et al. Posterior fossa abnormalities in major depression: a controlled magnetic resonance imaging study. *Acta Psychiatr Scand.* 1992;85(6):474–479.
 21. Starbuck J, Reeves RH, Richtsmeier J. Morphological Integration of Soft-Tissue Facial Morphology in Down Syndrome and Siblings. *Am J Phys Anthropol.* 2011;146(4):560–8.
 22. Lawler RR. Morphological integration and natural selection in the postcranium of wild verreaux’s sifaka (*Propithecus verreauxi verreauxi*). *Am J Phys Anthropol.*

2008;136(2):204–13.

23. Melo D, Marroig G. Directional selection can drive the evolution of modularity in complex traits. *Proc Natl Acad Sci*. 2015;112(2):470–5.
24. Klingenberg CP. Evolution and development of shape: integrating quantitative approaches. *Nat Rev Genet*. 2010;11(9):623–35.
25. Maina R, Ducati A, Lanzino G. The Middle Cranial Fossa: Morphometric Study and Surgical Considerations. *Skull Base*. 2007;17(6):395–403.
26. Djalilian HR, Thakkar KH, Hamidi S, Benson AG, Mafee MF. A study of middle cranial fossa anatomy and anatomic variations. *Ear Nose Throat J*. 2007;86(8):474, 476–81.
27. Martínez-Abadías N, González-José R, González-Martín A, Van der Molen S, Talavera A, Hernández P, et al. Phenotypic evolution of human craniofacial morphology after admixture: a geometric morphometrics approach. *Am J Phys Anthropol*. 2006;129(3):387–98.
28. Reich D, Thangaraj K, Patterson N, Price AL, Singh L. Reconstructing Indian population history. *Nature*. 2009;461(7263):489–494.
29. Moorjani P, Thangaraj K, Patterson N, Lipson M, Loh PR, Govindaraj P, Berger B, Reich D, Singh L. Genetic evidence for recent population mixture in India. *The American Journal of Human Genetics*. 2013; 93(3):422-38.
30. Sahoo S, Singh A, Himabindu G, Banerjee J, Sitalaximi T, Gaikwad S, et al. A prehistory of Indian Y chromosomes: evaluating demic diffusion scenarios. *Proc Natl Acad Sci U S A*. 2006;103(4):843–848.
31. Kivisild T, Rootsi S, Metspalu M, Mastana S, Kaldma K, Parik J, et al. The genetic heritage of the earliest settlers persists both in Indian tribal and caste populations. *Am J*

- Hum Genet. 2003;72(2):313.
32. Perez AD, Hirschman C. The Changing Racial and Ethnic Composition of the US Population: Emerging American Identities. *Popul Dev Rev.* 2009;35(1):1–51.
 33. Bastir M, Rosas A, Lieberman DE, O’Higgins P. Middle Cranial Fossa Anatomy and the Origin of Modern Humans. *Anat Rec Adv Integr Anat Evol Biol.* 2008;291(2):130–140.
 34. Hallgrímsson B, Lieberman DE, Young NM, Parsons T, Wat S. Evolution of covariance in the mammalian skull. *Novartis Found Symp.* 2007;284:164.
 35. Hallgrímsson B, Jamniczky H, Young NM, Rolian C, Parsons TE, Boughner JC, et al. Deciphering the Palimpsest: Studying the Relationship Between Morphological Integration and Phenotypic Covariation. *Evol Biol.* 2009;36(4):355–76.
 36. Hallgrímsson B, Lieberman DE, Liu W, Ford-Hutchinson AF, Jirik FR. Epigenetic interactions and the structure of phenotypic variation in the cranium. *Evol Dev.* 2007;9(1):76–91.
 37. Goswami A, Binder WJ, Meachen J, O’Keefe FR. The fossil record of phenotypic integration and modularity: A deep-time perspective on developmental and evolutionary dynamics. *Proc Natl Acad Sci.* 2015;112(16):4891–6.
 38. Hlusko LJ. Integrating the genotype and phenotype in hominid paleontology. *Proc Natl Acad Sci U S A.* 2004;101(9):2653–7.
 39. Klingenberg CP. Morphological Integration and Developmental Modularity. *Annu Rev Ecol Evol & Syst.* 2008;39:115–32.
 40. Goswami A. Morphological integration in the carnivoran skull. *Evolution.* 2006;60:169–83.
 41. Singh N, Harvati K, Hublin J-J, Klingenberg CP. Morphological evolution through

- integration: a quantitative study of cranial integration in Homo, Pan, Gorilla and Pongo. *J Hum Evol.* 2000;62(1):155–64.
42. Bruner E, Ripani M. A quantitative and descriptive approach to morphological variation of the endocranial base in modern humans. *Am J Phys Anthropol.* 2008;137(1):30–40.
 43. Cheverud JM. Phenotypic, genetic, and environmental morphological integration in the cranium. *Evolution.* 1982;36(3):499-516.
 44. Bastir M, Rosas A. Hierarchical nature of morphological integration and modularity in the human posterior face. *Am J Phys Anthropol.* 2005;128(1):26–34.
 45. Klingenberg CP. Studying morphological integration and modularity at multiple levels: concepts and analysis. *Philos Trans R Soc B Biol Sci.* 2014;369(1649).