



Press release

The 13th *Colloque Médecine et Recherche* of the Fondation Ipsen in the Endocrinology series: “Brain Crosstalk in Puberty and Adolescence”

Paris (France), 3rd December 2013 - We all have experience of the turbulence of adolescence: the physical, psychological and social changes involved in the key transitional phase between childhood and adulthood. The human brain undergoes considerable structural and functional changes during adolescence, as a result of the hormonal changes driving reproductive maturation during puberty. The mechanisms linking these changes and their implications for well-being in adolescence have been discussed by thirteen internationally recognised experts at the 13th *Colloque Médecine et Recherche* in the Endocrinology series hosted by Fondation IPSEN, in Paris on Monday December 2nd. The organisers were Jean-Pierre Bourguignon (*University of Liège, Belgium*), Jean-Claude Carel (*Hôpital Robert Debré, Paris, France*), Jacques Young (*University Paris Sud and Assistance Publique Hôpitaux de Paris, Hôpital Bicêtre, Inserm U693, Paris, France*) and Yves Christen (*Fondation Ipsen, Paris, France*).

This has been a fascinating day for increasing our understanding the turbulence of adolescence and for furthering knowledge of how the complex and delicate changes that are triggered by puberty can be disturbed, resulting in serious behavioural and mental health problems. Not only should the work that has been reported here help us to be more tolerant but it will also illuminate practical ways of supporting the difficult transition from childhood to adulthood.

Puberty, the defining event of adolescence, is the biological process of establishing reproductive competence. As the production of hormones from the gonads increases, so the familiar physical, psychological and behavioural developments associated with adolescence appear. In the brain, the complex interaction between gonadal hormones and brain structures results in both structural and functional reorganisation, especially in the regions associated with social behaviour, processing emotions, pleasure and reward, and decision-making and action (**Cheryl Sisk**, *Michigan State University, East Lansing, USA*). Structural changes, detected using magnetic resonance imaging (MRI), are correlated with chronological age and pubertal status (**Anne-Lise Goddings**, *UCL Institute of Child Health, London, UK*). Functional MRI is showing that the rate of development differs between various structures, offering clues for understanding cognitive development during adolescence. As the adolescent brain develops, it not only gets larger but, more importantly, becomes more interconnected; the changes can be correlated with gender, health and illness, as well as cognition and behaviour (**Jay Giedd**, *National Institute of Mental Health, Bethesda, USA*). Drug use, a common aspect of adolescent experimentation and risk-taking, can affect brain development: mice given cocaine show abnormal development in the social brain structures and increased locomotor activity; the effects were greater when cocaine was given to adolescent mice than to young adults (**Paul Frankland**, *Hospital for Sick Children, Toronto, Canada*).

The age when puberty begins has a potent impact on psychological and behavioural development and ability to adjust and may influence the emergence of sex-based problems, such as eating disorders, self-harm and depression in girls and behavioural issues in boys (**Sisk**; **Pierre-André Michaud**, *University of Lausanne, Switzerland*; **Russell Viner**, *UCL Institute of Child Health, London, UK*). Work with rats and mice shows that the effects of gonadal hormones on the brain decline with time, so the age when puberty begins may contribute to the risk of developing such problems (**Sisk**). Both the early and late onset of puberty are associated with higher exploratory and risk behaviour than seen when puberty starts at the normal age but the impact is different in boys and girls (**Michaud**). The reason that onset of puberty varies may lie in childhood problems, such as poverty, neglect and



abuse, as well as poor self-image (**Michaud; Viner**). Population studies indicate that early puberty may well be an evolutionary response to adversity, mediated by stress (**Viner**).

Factors, such as the metabolic state of the body are also involved: because reproduction is energy intensive, especially in females, fertility is reduced when food is scarce; conversely, obesity may be a driver of increasingly early puberty (**Manuel Tena-Sempere**, *University of Córdoba, Spain*). In the hundred years from the mid-nineteenth century, the onset of puberty advanced by about four years before stabilizing. Since 2000, various aspects of reproductive development are changing at different rates, for example, girls are growing breasts at a younger age but the age when menstruation starts has remained the same (**Bourguignon**). Environmental endocrine disrupters may be partly responsible.

Signals of metabolic status are linked to GnRH production and other regulators of puberty through a pathway involving kisspeptins and other recently identified molecules that are thought to participate in the metabolic control of the onset of puberty (**Tena-Sempere; Nicolas de Roux**, *Inserm U676, Hôpital Robert Debré, Paris, France*). Hunger and satiety signals converge on nuclei in the hypothalamus where neuropeptides are released that regulate energy balance and feeding behaviour (**de Roux**). Components of this metabolic 'gate' are being identified at the cellular level (**Tena-Sempere**), as are synaptic proteins involved in integrating metabolic signals into the control of sex-hormone production (**de Roux**).

Periods, when the sexual differentiation of the brain is particularly susceptible to steroid sex hormones, occur before and after birth, as well as during puberty. Atypical hormone levels in the perinatal period may be a cause of gender dysphoria, the strong feelings experienced by some children that they have been born with the wrong sex (**Julie Bakker**, *University of Liège, Belgium*). The effects of sex hormones during puberty on gender identity as well as on cognition and social development are being explored in young people treated with gonadotropin releasing hormone (GnRH). This is the hormone that regulates the production of sex hormones by the gonads, and is used with some gender-dysphoric children to facilitate gender-reassignment surgery.

The onset of puberty, including the activation of GnRH production, involves complex epigenetic regulation: a network of genes controls both the transcription of particular genes and the production of proteins (**Sergio Ojeda**, *Oregon Health Sciences University, Beaverton, USA*; **Vincent Prévot**, *Inserm U837, University of Lille 2, France*). Key developmental processes are initiated and maintained by activators but reigned in by repressors and repressors of repressors: some of these regulatory genes are being identified and their actions described (**Ojeda**). The production of GnRH by the neurons of the hypothalamus is tailored to different stages of puberty in mice by specific sets of micro-RNAs – a special type of regulatory molecule – found in these neurons (**Prévot**). Other details of cellular mechanisms underlying pubertal changes in the brain are also emerging. In mice, GnRH seems to regulate the prenatal migration and connectivity of the GnRH neurons in the hypothalamus (**Prévot**), while in pubertal rats, GnRH modifies the production of new neurons and supporting glial cells in certain brain nuclei involved in reproduction (**Sisk**).

In young men with rare genetic diseases in which the GnRH pathway is insufficient and sex hormones are not produced (congenital hypogonadotropic hypogonadism and Kallmann's syndrome), the testes fail to develop and puberty does not occur. A programme to treat patients with these conditions that takes into account its effects on personality and social interactions has been reported (**Carel and Young**).

About the Fondation Ipsen

Established in 1983 under the aegis of the Fondation de France, the mission of the Fondation Ipsen is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the Fondation Ipsen aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialization of these professions. The ambition of the Fondation Ipsen is to initiate a reflection about the major scientific issues of the forthcoming years. It



has developed an important international network of scientific experts who meet regularly at meetings known as *Colloques Médecine et Recherche*, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover the Fondation Ipsen has started since 2007 several meetings in partnership with the Salk Institute, the Karolinska Institutet, the Massachusetts General Hospital, the Days of Molecular Medicine Global Foundation as well as with the science journals Nature, Cell and Science. The Fondation Ipsen produced several hundred publications; more than 250 scientists and biomedical researchers have been awarded prizes and research grants.

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