Neuroscience and Biobehavioral Reviews 72 (2017) 153–167

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

# Cognition in people with Prader-Willi syndrome: Insights into genetic influences on cognitive and social development

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ARTICLE INFO

*Article history:*
Received 16 July 2016
Received in revised form 1 September 2016
Accepted 15 September 2016
Available online 9 November 2016

*Keywords:*
Prader-Willi syndrome
Cognition
Ability
Attainment
Social cognition

ABSTRACT

We present a mini-review of cognition in Prader-Willi syndrome. Studies cited include findings on general ability (IQ), IQ correlates with family members, strengths and weaknesses in cognitive profiles in genetic subtypes, attainment in literacy and numeracy, language, comprehension, modality preferences, executive functions, and social cognition. The latter includes investigations of theory of mind, emotion recognition, face processing and knowledge of social norms. Results from research on mouse models and brain imaging studies relevant to cognition are briefly discussed.

The importance of these studies to understanding and managing education and behaviour in PWS and the limitations of the studies in terms of small numbers, non-representativeness, and lack of replication is also touched upon.



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## 1. Introduction

The dictionary defines cognition as 'knowledge in its widest sense'. As such it encompasses, not only intellectual abilities and attainments, but also social abilities and understanding. Human cognition has been studied largely for three main reasons: for scientific understanding, for insights into learning and education, and to inform our understanding of social behaviour. In the typically developing population there is an extensive literature on all such aspects of cognition and how cognitive profiles vary but additional unique insights into all aspects of cognition can be gained by examining how cognition is altered in groups whose development is atypical, such as those with specific genetic syndromes. While edu-

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http://dx.doi.org/10.1016/j.neubiorev.2016.09.013
0149-7634/

cational and social implications will be similar, in the sense of what particular educational or social profiles follow from given cognitive abilities, strengths or weaknesses, there will be an added dimension to scientific enquiry knowing the genetic origin (genotype) of that syndrome. The new questions then for psychology and neuroscience are 'How does the known genetic abnormality affect developmental brain processes and how do these, in turn, result in systematic changes in cognition that are characteristic of that particular group'? The first steps to progress is a characterization of the cognitive findings. We describe what progress has been made in the scientific understanding of the atypical cognition, and its educational and social consequences, in the genetically determined neurodevelopmental disorder, Prader-Willi Syndrome (PWS).

The references cited include preferentially those where PWS has been determined by genetic testing and not by clinical features only. Many early reports are unreliable because the diagnoses of PWS of those included in the studies were largely by clinical criteria only. In addition, because of the small sample sizes in many studies there is a need for replication of the findings. The focus of this article is inevitably on the cognitive deficits associated with PWS but it is also important to acknowledge that individuals with PWS have strengths as well as weaknesses – these are also commented on. We first give a broad overview of PWS and then consider the different components of the cognitive phenotype, including social cognition We go on to look at how the manipulation of key 'PWS genes' affect aspects of cognition in mouse models of the syndrome. Finally we review the evidence for brain abnormalities associated with cognition in PWS.

## 2. Overview of PWS

PWS has a birth incidence rate of 1:20,000 to 1:25,000, and a population prevalence of about 1:50,000. The syndrome results from the loss of expression of paternally expressed genes from the PWS imprinted cluster in the q11-13 region of the paternally inherited chromosome 15. The loss is due to a deletion of part, or all, of this region (deletion subtype) or to the inheritance of two maternally marked chromosome 15s and no paternally marked copy (uniparental disomy – UPD subtype). Coded in this 'critical region' of chromosome 15 are both imprinted and non-imprinted genes (see Fig. 1), SNORD 116, Magel 2 and IPW being the genes whose absence of expression at the locus 15q11-13, singularly or in combination, are considered central to PWS. Whilst the different genetic sub-types described have a common genotype, that is the absence of expression of the paternally related alleles of maternally imprinted genes at 15q11-13, there are genetic differences between the sub-types that might account for the phenotypic differences that are observed between the different genotypes (see Hoybye chapter 2 (2013) for full details of the genetics of PWS). Imprinted genes are known to be actively expressed in the foetus and the placenta (Keverne, 2015) and in PWS this is apparent in the fact that there is a recognizable phenotype at birth (see below). Whilst many of the major criteria of the phenotype described above, and some additional aspects (e.g. poor temperature control, sleep abnormalities), can be attributed to abnormalities in hypothalamic development and functioning, the reason for the cognitive impairments remains uncertain.

As with other genetically determined neurodevelopmental syndromes, PWS is associated with a particular pattern of cognitive and social development and an increased risk for specific co-morbid behavioural and psychiatric problems (Hoybye, 2013 chapters 6–7). What is referred to as the 'behavioural phenotype' of PWS emerges with development. There is an initial extreme hypotonia and failure to thrive followed in early childhood by hyperphagia, developmental delay, evidence of relative growth and sex hormone deficiency (short stature and impaired sexual development); and a marked propensity to problem behaviours, such as temper outburst, repetitive and ritualistic behaviours and skin picking (Whittington and Holland, 2004). Whilst those with the genetic sub-types of PWS have the core features of PWS in common, there are differences depending on whether the person has PWS due to a deletion or a UPD, and within the deletion subgroup whether the deletion is larger (Type 1, between breakpoints 1 and 3) or smaller (Type 2, between breakpoints 2 and 3).

**Table 1**
Stability of IQ.

| N | Age at 1st test Mean (sd) Range | Age at 2nd test Mean (sd) | IQ at 1st test Mean (sd) | IQ at 2nd test Mean (sd) |
|---|---|---|---|---|
| 9 | 6.36 (0.40) 3–6 | 9.87 (3.01) | 60.22 (2.75) | 60.44 (3.13) |
| 9 | 8.78 (0.88) 7–9 | 12.01 (2.76) | 58.56 (12.65) | 56.11 (19.37) |
| 7 | 14.34 (2.75) 10–19 | 16.87 (2.84) | 51.29 (12.20) | 59.00 (10.85) |
| 6 | 23.58 (3.13) | 27.45 (2.42) | 61.33 (10.56) | 60.17 (8.93) |
| Total 31 | 12.25 (6.64) 5–29 | 15.50 (7.02) 6–30 | 57.94 | 58.81 |

## 3. Intellectual Cognition in PWS

Cognitive impairments in people with PWS include low IQ for family background and, in particular, difficulties with abstract ideas and comprehension. In addition, social cognition is usually impaired and peer group relationships may be poor or absent, presenting in a similar manner to some of the features associated with autism spectrum conditions. As discussed in detail below, compared to the general population, performance on tasks of executive function are also affected with specific deficits, for example, in task switching that may also be associated with repetitive symptoms, such as repetitive questioning, and aversion to changes in routine. Caution is needed in looking at specific individuals with PWS. Whilst, in many studies, the cognitive impairments and associated behavioural problems have been reported to be characteristic of people with PWS, they vary in severity from person to person. As in the general population, such differences may reflect differences in familial genetic background and/or environment. These observations from systematic research studies are important indicators of common consequences of PWS but their salience needs to be determined for each individual and not assumed. These different aspects are now considered in greater detail.

### 3.1. General ability (IQ)

Several studies, not primarily concerned with general ability, have reported FSIQ scores in small samples of people with PWS. Here we describe studies whose primary aims were either to investigate cognitive ability in PWS or to investigate differences between genetic subtypes including ability differences. We found only one study (Dykens et al., 1992) that looked at the stability of IQ, and which showed stability over periods ranging from 1 year to over 9 years, (mean 3.25 + 2.30) but not all participants were genetically confirmed to have PWS. The 31 study participants included 15 tested twice with the age-appropriate Wechsler scales and 16 tested twice with the Stanford-Binet scale (see Table 1).

Table 2 documents other studies of IQ in people with PWS. The first was a population study with genetic confirmation of PWS and comprised all ages from 4 years. The distribution of IQ was found to be roughly normal. The second was an early study of children