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Developing an understanding of skin picking in people with Prader-Willi syndrome: A structured literature review and re-analysis of existing data

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ABSTRACT

A search of the PubMed and Web of Science databases for articles on skin picking in PWS was undertaken identifying case studies; trials of specific treatments; and descriptions of when skin picking occurs, what sites are chosen, and what initiates and sustains this behaviour. Published papers have also considered how skin picking might link to the PWS genotype and whether it is best considered to be part of the repetitive and ritualistic behaviours characteristic of the syndrome. To answer specific questions raised as a result of the review additional analysis was undertaken using data from our earlier population-based study of PWS. We consider this behaviour of skin picking using the framework of the Research Domains Criteria that is cross diagnostic and focuses on the identification of specific neurobiological, psychological and cognitive processes. PWS illustrates the likely interplay between different processes that first initiate and then maintain such behaviour. Treatment development depends on better understanding these mechanisms and their relative contribution to the behaviour.

1. Introduction

Skin picking, as a form of self-injurious behaviour, is highly prevalent in people with Prader Willi Syndrome (PWS) with reported rates ranging from 55 % to nearly 100 % depending on how the sample was chosen (at a conference, via the internet, in a clinic survey, etc), what criteria were used (frequency, severity), and who was providing the data (self, informant). This prevalence rate is in contrast with rates of self-injurious behaviour in people with intellectual disabilities in general of 4.9 % (Cooper et al., 2009). The behaviour of skin picking in people with PWS has been observed in all age groups above two years of age (see Appendix B for age data from the UK population study). The aim of this review is to address two broad questions: first, what is known about the characteristics, course and treatment of this specific form of self-injurious behaviour and, secondly, what is understood about the mechanisms that may initiate and maintain this behaviour and how might these be best conceptualized so as to inform future research and treatment developments. The databases PubMed and Web of Science were searched for articles relating to skin picking in Prader-Willi syndrome (PWS) using the search terms (Prader-Willi OR 15q11-13) AND (skin-picking OR self-injury) in title or as topic. This resulted in 74 and 116 articles respectively, but with significant overlap. Articles on PWS that mentioned skin picking in passing, reports of conference proceedings, articles not in English, and articles on skin picking that did not include studies on PWS, with the exception of reviews of treatments, were excluded. This left 40 articles for inclusion in this review. Of these, 9 were case reports (Table 1), five were reports of trials of pharmacological treatments of skin picking (Table 2), five were reviews and three were book chapters on self-injurious behaviour (Table 3). The remainder were investigations of various aspects of skin picking in PWS (Table 4).

In this review we first give a brief description of PWS (abstracts are included in Appendix C) and then go on to discuss the findings of the articles included. To address the questions set out at the beginning we have summarised the research findings in terms of the following: what sites are chosen, what initiates it, when and under what circumstances does skin picking occur, and what sustains it. We explore what is known of links between the genetics of PWS and the brain and consider treatments that have been tried and the extent to which the outcomes of these treatments provide insights to underlying psychological and neurobiological mechanisms. We consider skin picking in PWS in terms of self-injurious behaviour as it affects people with genetically determined neurodevelopmental syndromes generally and also in the context of what is known about the mechanisms that may underpin other behaviours reported to be of high prevalence in people with PWS examining the conjecture that skin picking is part of the repetitive and ritualistic behaviour of the PWS phenotype. To better understand mechanisms we go beyond a diagnostic approach and use the framework

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Table 1
Case Studies.

Study	Brief description
Warnock and Kestenbaum (1992)	Two people with PWS treated with fluoxetine showed decrease in skin-picking.
Benjamin and Buot-Smith (1993)	A nine year-old boy treated with fluoxetine and naltrexone showed marked improvement in skin-picking, weight control and behaviour.
Hellings and Warnock (1994)	Report of three people with PWS treated with serotonin reuptake inhibitors (SSRIs). Two showed decrease in skin-picking: one showed decrease in hoarding and temper outbursts.
Bhargava et al. (1996)	Describes three people with PWS whose skin picking included rectal picking resulting in lower gastrointestinal bleeding and anorectal disease.
Schepis et al. (1998)	Reports of 21 year old male and 18 year old female treated with fluoxetine with no change in skin picking
Banga and Connor (2012)	Naltrexone used to treat an adolescent PWS patient and wasreported to be an effective treatment in this person.
Hall et al (2013)	The heart rate of a boy with PWS was monitored over a period in which skin-picking episodes sporadically occurred. Heart rate rose during skin-picking episodes.
Salehi et al (2018)	Report of four cases of rectal picking in individuals with PWS
Wilson et al. (2012)	Compared photographs of wound surface area with direct observation before and after treatment in a woman with PWS. Concluded that the methods were equivalent.

Table 2
Pharmacological treatments.

Study	Brief description
Selikowitz et al (1990)	A double blind, placebo controlled trial of fenfluramine in 15 people with PWS who received the placebo and the drug for 6 weeks each. Skin-picking was unchanged by the drug.
Shapira et al (2002)	An 8 week open label trial of topiramate in 3 adults with PWS reported an attenuation of skin-picking with resultant lesion healing.
Shapira et al (2004)	An 8 week open-label study of topiramate in 8 adults with PWS. Found a clinically significant improvement in skin-picking.
Miller and Angulo (2014)	Describes an open label pilot study of N-acetylcysteine for skin-picking in 35 people with PWS. Symptoms and open lesions were assessed before and 12 weeks after the treatment. All 35 showed an improvement in skin-picking behaviour.
Singh et al. (2019)	Eleven of the twenty people with PWS treated with Guanfacine Extended Release (GXR) skin-pi cked. Nine showed an improvement in skin-picking.

Table 3
Reviews, book chapters and self-injurious behaviour.

Study	Topics
Reviews	
Petty and Oliver (2005)	Reviewed literature published in 2004 on self-injurious behaviour associated with intellectual disabilities. Concluded that pharmacological treatments are largely ineffective.
Lang et al. (2010)	A systematic review of skin-picking in people with developmental disorders.
Oliver et al. (2015)	A systematic review of N-acetyl cysteine (NAC).in the treatmentof O-C and related disorders. Regards skin-picking as an O-C disorder.
Selles et al. (2016)	Systematic review and meta-analysis of treatments for skin-picking in general populations. No specific treatment was found to be particularly beneficial.
Bonnot et al. (2016)	Reviewed all psychotropic treatments in PWS. Treated skin-picking and obsessive-compulsive (O-C) symptoms similarly. Found possible specific benefit for skin-picking treated with N-acetyl cysteine (NAC).
Book chapters and self-injurious behaviour	
Mikhail and King (2001)	Discusses self-injurious behaviour in the context of mental retardation and as part of the behavioural phenotypein genetic syndromes.
Devine and Symons (2013)	A review of different forms of self-injury, including skin-picking, in people with developmental disabilities, including PWS.
Oliver et al. (2013)	Questions operand conditioning as the causal model for self-injury in four genetic syndromes. Discusses prevalence of specific forms of self-injury in these syndromes.
Huisman et al. (2018)	Review of self-injurious behaviour (SIB) in people with intellectual disabilities and genetic syndromes, including PWS. Discusses prevalence of specific SIB in specific genetic syndromes.

of the Research Domain Criteria (Sanislow et al., 2010) to consider the potential role of neurobiological mechanisms previously explored in the context of non-suicidal self-injury (Westlund Schreiner et al., 2015).

1.1. Prader-Willi syndrome

PWS is a genetically determined neurodevelopmental condition associated with a particular phenotype that is partly apparent at birth and changes early in development. The core characteristics include severe muscle hypotonia and failure to thrive at birth and the subsequent development in early childhood of a marked interest in food that leads, if access to food is not controlled, to over-eating and severe obesity (Whittington and Holland, 2004). Other characteristics include developmental delay and a relative lack of growth and sex hormones leading to short stature, sexual immaturity, small hands and feet and a particular facial appearance (Holm et al., 1993). In addition to the hyperphagia, the main features of what is considered the 'behavioural phenotype' of PWS include, as well as skin picking, an increased propensity to temper outbursts; an insistence on routines; hoarding; repetitive questioning (the need to ask or tell); and to affective disorders and psychotic illness (Holland et al., 2003). Of potential relevance to understanding self-injurious behaviour in people with PWS has been the observation of a high pain threshold of probable central origin (Priano et al., 2009: Angulo et al., 2015) and, more recently, evidence from intervention studies of a possible abnormal autonomic nervous system response to threat (Manning et al; 2016; Manning et al., 2019 in press). The syndrome results from the absence of expression of specific maternally imprinted gene(s) at the chromosomal locus 15q11-13 for one of two main reasons: a 15q11-13 deletion of paternal origin or the presence of a chromosome 15 maternal uniparental disomy (mUPD). The maternally imprinted genes thought to be of most significance are Snord116, IPW and Magel2. Other imprinted and non-imprinted genes at that locus may contribute to the broader PWS phenotype (Hoybye, 2013 Chapter 2).

Table 4
Investigations of skin-picking.

Study	Brief description
When does it occur	
Dykens (2014)	Parents of 123 people with PWS completed measures of their child's adaptive, recreation and problem behaviours. Watching TV was associated with high levels of skin picking.
Hall et al. (2014)	Functional analyses with 13 people with PWS aged 6–23 years showed that highest levels of skin picking occurred in alone and ignore conditions compared to attention, play and demand. The authors suggest that skin picking is maintained by automatic reinforcement in these individuals.
Dykens (2004)	Examined predictors of maladaptive behaviours in children and adults with PWS. Increasing BMI and male gender were associated with skin picking.
Sites chosen	
Symons et al. (1999)	Survey of families of 62 people with PWS. Most prevalent sites of skin picking were the front of the legs and head. Deletion subtypes were said to target more sites than disomy subtypes.
Didden et al. (2007)	Investigated skin picking behaviour in 119 people with PWS. Most common sites of lesions were arms, legs and head. Functional assessment suggested that skin picking primarily had non-social functions.
Hustyi et al. (2013)	Interviews with parents of 55 people with PWS aged 6–25 years found 75% of skin picking occurred on arms, legs, hands and feet. Automatic sensory stimulation (52.7%) and access to social attention or preferred items (36.4%) were said to be the main sources of reinforcement.
Morgan et al. (2010)	Internet based survey of parents of 67 youth aged 5–19 years found associations between skin picking severity and symptoms of anxiety, inattention,oppositionality,developmental functioning and quality of life. Main areas picked were the extremities and face. Occasions of skin picking endorsed by more than 40% of respondents were at school, waiting, watching TV, in the car, lying in bed and reading.
What initiates it	
Didden et al (2008)	Conducted interviews with 10 people with PWS.7 people said skin picking is caused by itchiness, which some said was worse after swimming. Psychological reasons included nervousness and boredom.
Brandt and Rosen (1998)	Studied somatosensory functions in 5 children with PWS and 10 healthy controls. Tactual perception in the hands appeared normal in 4 PWS. Myelinisation of sensory nerve fibres also appeared normal. Sensory nerve action potentials amplitudes were only 40–50 % normal size in PWS suggesting a reduced number of normal axons in the median nerve.
What sustains it	
Hall et al (2013)	The heart rate of a boy with PWS was monitored over a period in which skin-picking episodes sporadically occurred. Heart rate rose during skin-picking episodes.
Klabunde et al. (2015)	fMRI used while episodes of skin picking were recorded on an MRI safe video recorder in 17 people with PWS aged 6–25 years. The 10 informative records showed that regions involved in interoceptive, motor, attention and somatosensory processing were activated more during skin picking episodes.The authors conclude that itch and pain processes appear to underlie the behaviour.
Skin-picking as O-C behaviour	
Feurer et al. (1998)	Examined the latent variable structure of the Compulsive Behaviour Checklist in people with PWS. Found a single factor solution for all items except skin picking which had a substantial unique variance.
Holland et al. (2003)	A factor analysis of PWS behaviours reported by parents/carers found three factors; skin picking and O-C behaviours loaded on different factors. Skin picking loaded on the same factor as mood swings.
Wigren and Hansen (2003)	Parents of 58 people with PWS aged 5 − 18 years completed Childhood Routines Inventory and Connors' Parent Rating Scale. Skin picking appeared as a single comorbid symptom less associated with childlike compulsions and ADHD-related problems.
Pignatti et al. (2013)	The behaviour of 31 adults with PWS was investigated via the Symptom Checklist-90 Revised, the Yale-Brown Obsessive Compulsive Scale and the Prader-Willi Behavioral Checklist. Statistical clustering revealed two patterns of unwanted behaviours: the first contained excessive food intake and skin picking, the other cluster contained O-C behavioursand aggression.
Genetic and brain abnormality conjectures	
Muscatelli et al. (2000)	Examined the behaviour of NECDIN knock-out mice. Reported that these mice exhibited skin scraping behaviour reminiscent of skin picking in people with PWS.
Rice et al. (2016)	Investigated the role of GABA in emotional and behavioural problems in 15 people with PWS and 15 typically developing controls using single voxel proton magnetic resonance spectroscopy. GABA levels were negatively correlated with skin picking.
Pujol et al. (2016)	Aimed to assess functional connectivity in basal ganglia circuits and their relationship with O-C behaviour and skin picking. Reported abnormally heightened functional connectivity in primary sensory cortex-putamen loop was associated with skin picking.

1.2. What sites on the body are chosen and what is the severity?

Symons et al., 1999 (Table 4) surveyed the families of 62 people with PWS and found that those who skin picked preferred the front of legs and head as targets. Hustyi et al., 2013 (Table 4) investigated skin picking in 55 people with PWS reporting the most common sites to be the extremities: arms, legs, hands and feet. Didden et al., 2007 (Table 4) found the most common sites (> 40 %) to be arms, legs and face in a survey of 119 people with PWS. Morgan et al., 2010 (Table 4) conducted an internet survey of 67 parents/carers of youths with PWS and found similar common sites. We note that these are sites that are visible either directly or in a mirror; this may be relevant to initiation. One site not visible and not commonly reported, possibly due to misdiagnosis in some cases, is the rectum as discussed by Bhargava et al. (1996) and Salehi et al. (2018) (Table 1). Some of the articles divided skin picking into 'mild', 'moderate' and 'severe' but these terms are not defined (e.g. Didden et al., 2007; Table 4) Hustyi et al. (2013) do define severity but do not give frequency or prevalence of skin picking in the PWS population. Only one paper addressed measurement of lesions comparing photographic with visual measurement (Wilson et al., 2012; Table 1).

1.3. What initiates skin picking?

One of the first mentions of skin picking attributed it mainly to picking at insect bites, advocating prevention by the use of insect repellent and of concealing clothing (Holme et al. 1981, Chapter 20). In our own research, informants have frequently mentioned that skin picking occurred at the site of a lesion or irritation such as an insect bite or nettle sting. One person had had an abdominal operation seven years previously that had still not healed due to skin picking. (see Whittington and Holland (2004) for a description of the research findings and the questionnaires used) However, some people were said to have started picking at previously unblemished sites (also found by Morgan et al., 2010; Table 4). Didden et al., 2008 (Table 4) interviewed 10 people with PWS about skin picking and found that the most common reason given was itchiness, which some said increased after swimming; other reasons included nervousness and boredom.

1.4. What sustains skin picking?

Two interventional investigations that shed light on this issue have

been published. Hall et al., 2013 (Table 4) conducted a case study in which they monitored the heart rate of a boy with PWS during skin picking episodes. Skin picking was associated with increased heart rate suggesting positive automatic reinforcement. Klabunde et al., 2015 (Table 4) undertook fMRI neuroimaging of 17 people with PWS while monitoring their activity on an MRI-safe video camera. Three participants skin picked continuously, three did not skin pick and one had unreadable data. For the remaining 10 people, brain regions associated with the skin picking behaviour were involved in interoceptive, motor, attentional and somatosensory processing. Scores on the Self-injury Trauma Scale were significantly negatively correlated with mean activation in the right insula and left precentral gyrus, indicating that itch and pain processes appear to underlie skin picking in PWS and the interoceptive disturbance may contribute to its maintenance. Huang et al., 2018 reported that in mouse models somatostatin is required for itch behaviour and is involved in inhibiting pain behaviour. People with PWS tend to have high pain thresholds reducing any negative consequences of skin picking. We revisited the Cambridge PWS database (see Whittington and Holland, 2004 for details) to see how informant reports of skin picking and high pain threshold were related. Where informants were sure about pain threshold (58 cases) high pain threshold was associated with higher rates of skin picking (see Appendix A). Brandt and Rosen, 1998 (Table 4) studied somatosensory functions in five children aged 11–13 years with PWS. Tactual perception in the hands appeared normal in four of them. Sensory nerve conduction velocities in the median nerve and latencies for sensory evoked potentials were similar to those of 10 normal control children. However, sensory nerve action potential amplitudes were reduced to an average of 40–50 % of normal, suggesting a reduced number of normal axons in the median nerve, possibly linked to reduced pain sensitivity, and tolerance of otherwise painful lesions.

1.5. When does skin picking occur?

Skin picking does not occur when the hands are busy doing something else. This is the basis for one of the obvious strategies used to reduce skin picking - giving activities that involve use of the hands (e.g. Lang et al., 2010; Table 3). In a paper that looked at leisure activities and their correlates (Dykens, 2014; Table 4), physical activities were associated with less skin picking and both partaking in sedentary games or puzzles and watching TV correlated with more skin picking. In an internet survey, Morgan et al., 2010 (Table 4) found ‘at school’, ‘waiting’, ‘watching TV’, ‘in the car’ and ‘in bed’ to be times of skin picking reported by more than 50 % of informers. Hall et al., 2014 (Table 4), using a functional analytical approach, observed skin picking behaviour under different conditions including alone, attention, play, demand and ignore. The highest levels of skin picking occurred in the alone and ignore conditions.

1.6. Skin picking as obsessive compulsive behaviour and associations with other co-morbidities

Skin picking in PWS has been seen as a compulsive behaviour and treatments have included medications directed at controlling such behaviour (e.g. Warnock and Kestenbaum, 1992; Benjamin and Buot-Smith, 1993; Hellings and Warnock, 1994; Table 1). However, most of these medications proved ineffective or temporary (see below), Also factor analyses of PWS behaviours have not found that skin picking is part of an obsessive-compulsive factor (Feurer et al., 1998; Holland et al., 2003; Table 4). Furthermore, skin picking emerged as a single comorbid symptom in an analysis of PWS behaviours using the Childhood Routines Inventory and Connors’ Parent Rating Scale (Wigren and Hansen, 2003; Table 4). Pignatti et al., 2013 (Table 4) explored patterns of maladaptive behaviours in PWS via statistical clustering: skin picking and eating behaviour were assigned to the ‘usual phenotypic manifestations of PWS cluster, while some obsessive compulsive symptoms and aggressive behaviours were assigned to the ‘psychopathology-related’ cluster; again skin picking did not aggregate with obsessive compulsive behaviours. In support of the absence of a link between skin picking and obsessive compulsive behaviours is the observation that the anticonvulsant topiramate, which has been reported to reduce skin picking behaviour in people with PWS (Shapira et al., 2002, 2004; Table 2), has no effect on compulsions. A recent study of N-acetylcysteine (NAC) has also been reported to be beneficial for skin picking. It is claimed that this is because of its efficacy in treating compulsive behaviours (Miller and Angulo, 2014). However, its beneficial effects on a range of other disorders, including irritability in autism, Alzheimer’s disease in mouse models, and symptoms of schizophrenia and bipolar disorder (Deepmala et al., 2015), make this claim of a direct link with obsessive-compulsive behaviours unproven. Given the possibility that skin picking is a form of fidgeting or hyperactivity restricted to the hands (especially in more sedentary individuals) or of self-stimulation in periods of relative inactivity (Morgan et al., 2010; Hall et al., 2013, 2014; Table 4) we revisited our data from the Cambridge PWS study and found that ‘skin picking in past month’ was positively related to BMI (also mentioned by Dykens, 2004; Table 4) but not significantly to severity of eating behaviour, not significantly to attention deficit disorder (ADD) but was related to attention deficit hyperactivity disorder (ADHD) symptoms (see Appendix A; note that some variables had missing data so numbers of cases varies). This relation to ADHD is in line with observations about self-injurious behaviour in the general population (Cooper et al., 2009). In the study of Cooper et al. (2009) there was also a reported association between self-injurious behaviour and the presence of an autistic spectrum condition Given that autistic traits are more prevalent in the mUPD subtype of PWS, we revisited our data from the Cambridge PWS study and found rates of skin picking in the mUPD and deletion subtypes did not differ significantly (see Appendix A). This is in line with the findins of Hustyi et al. (2013).

1.7. The role of genetic and brain abnormalities

The only maternally imprinted gene in the 15q11-13 region to be potentially linked to skin picking is NECDIN. A necdin knock-out mouse model was observed to exhibit skin scraping (Muscatelli et al., 2000; Table 4) that could be the mouse equivalent of skin picking. However, a girl, who did not have PWS but was lacking the NECDIN gene, did not skin pick (Kanber et al., 2009), whereas a boy with PWS and who did express the NECDIN gene did skin pick (Duker et al., 2010). From the perspective of the brain, people with PWS with significant behaviour problems have been reported, using Magnetic Resonance Spectroscopy (MRS), to have lower GABA levels in the parieto-occipital lobe and that GABA levels in PWS correlated negatively with skin picking (Rice et al., 2016; Table 4). However, GABA levels also correlated negatively with total behaviour problem scores, temper outbursts, depression, social relating difficulties and self-absorption, so interpretation of cerebral GABA levels as a direct cause is not at present justified. It is of interest that the factor analysis in Holland et al., 2003 found skin picking on the same factor as mood swings, indicating that this link with cerebral GABA levels requires further investigation. Skin picking was also associated with abnormal functional connectivity in basal ganglia circuits (Pujol et al., 2016: Table 4).

1.8. What treatments are available?

A wide range of treatments are described in the literature from some of the earliest reports on PWS to the present day. Skin picking was mentioned in the report of the first scientific workshop on PWS (Holm et al., 1981) where the authors advocated the use of insect repellent and concealing clothing (based on the observation that insect bites often initiated skin picking). As the extent of skin picking in PWS was realised, professionals began to classify it as an obsession and, as described above, medication to treat obsessive behaviour was often prescribed

with mixed results (Selikowitz et al., 1990; Warnock and Kestenbaum, 1992; Benjamin and Buot-Smith, 1993; Hellings and Warnock, 1994; Schepis et al., 1998; Shapira et al., 2002, 2004; Banga and Connor, 2012; Miller and Angulo, 2014; Singh et al., 2019). (Tables 1 and 2). Most studies reported improvement but were not controlled and therefore most results could be placebo effects; similar conclusions were reached in the reviews by Petty and Oliver, 2005; Selles et al., 2016; and Bonnot et al., 2016 (Table 3). The most promising medication seems to be N-acetylcysteine, reviewed by Oliver et al., 2015 (Table 3) and reported to be effective in all 35 participants by Miller and Angulo, 2014 (Table 2). This treatment was tried in the belief that skin picking was part of the obsessive compulsive behaviours and such behaviour is thought to be a consequence of disturbance in the excitatory glutamergic pathways in the brain. N-acetylcysteine may act by modulating NMDA glutamate receptors or by increasing glutathione (Miller and Angulo, 2014).

Other treatments have included distraction strategies, wearing gloves, and behaviour therapy (Hustyi et al., 2013) (Table 4). Sensory stimulation, in the form of vibration or massage sessions several times a day, has also been advocated (Gourash & Foster) In the general literature on skin picking not specific to PWS, Lang et al., 2010 (Table 3) reviewed 65 behavioural treatments in people with developmental disorders, Torales et al., 2017 describe alternative therapies, and Schumer et al., 2016 discuss effectiveness of various treatments in a meta-analysis. Torales et al. concluded that yoga, aerobic exercise, acupuncture, biofeedback, hypnosis, and inositol and N-acetylcysteine all show promise in the treatment of excoriation disorder and other body-focused repetitive behaviors, such as trichotillomania, especially yoga and aerobic exercise in combination with psychotherapy and pharmacotherapy. In a meta-analysis Schumer et al., 2016 concluded that all interventions (including inactive control conditions) demonstrated significant improvement over the course of short-term clinical trials in skin picking disorder but only behavioural treatments demonstrated significant benefits compared with inactive control conditions. There was no evidence from RCTs that pharmacotherapy with selective serotonin reuptake inhibitors or lamotrigine were more effective at treating skin picking than placebo.

1.9. Interpretation of skin picking in PWS

PWS is not the only neurodevelopmental disorder in which self-injurious behaviour occurs with high prevalence rates. However, in some of these other disorders, the self-injurious behaviour takes different forms. There is considerable evidence that specific types of self-injurious behaviours (e.g. skin picking, self-biting, head banging) are associated with particular neurodevelopmental syndromes (e.g. PWS, Lesch-Nyhan, Fragile-X, Smith-Magenis) (Huisman et al., 2018; Powis and Oliver, 2014; Oliver et al., 2013; Devine and Symons, 2013; Mikhail and King, 2001; Table 3). Such observations of the specificity of behaviour in people with neurodevelopmental syndromes has led to a move away from a purely operant model of understanding, in which self-injurious behaviour is seen largely as learnt and having a function that arises as a consequence of being inadvertently reinforced, to models that integrate a neurobiological and functional understanding (see Oliver and Richards, 2010 for review). However, in PWS, as in other neurodevelopmental syndromes, a major unanswered question is how the genetics of a particular syndrome leads directly or indirectly to the specific form of self-injurious behaviour. Only by knowing the relevant cellular pathways and pathophysiological and psychological mechanisms in each syndrome will it be possible to develop targeted and effective treatments.

One possible approach to understanding self-injurious behaviour across syndromes is trans-diagnostically as has been set out in the Research Domain Criteria Project (Sanislow et al., 2010). This approach uses five 'domains' to classify behaviour: negative valence, positive valence, cognitive, social processes, and arousal/regulatory systems. Each of these is briefly considered.

Negative valence: both the Didden et al.(2008) interviews of people with PWS and the Klabunde et al. (2015) neuroimaging study implicate itch as a precipitating factor of skin picking. This carries implications of threat (to comfort) and perhaps fear and anxiety as to the cause and possible consequences of the itch. Boredom and anxiety were also cited as precipitating factors in Didden et al. and these too carry negative valence.

Positive valence: this may result from the relief of the itch by skin picking (Didden et al., 2008) and relief from anxiety in that the action gives a sense of control. The action may result in arousal (Hall et al., 2013) that carries positive valence.

Cognition: initially a perception of the precipitating factor (eg itch) and a response (pick skin at site of itch) establishes this response to future itch because of difficulties in terminating the behaviour due to the PWS deficit in task-switching and insistence on routine (Woodcock et al., 2009, 2010; 2011).

Social processes: the evidence seems not to support attention-seeking as a driver of skin picking in PWS (Hall et al., 2014). The inability of people with PWS to interact normally with their peers may lead to boredom or anxiety, which is relieved by skin picking in the absence of such peer group relationships.

Arousal/regulatory systems: skin picking has been found to increase heart rate (Hall et al., 2013) and has been found to be associated with brain regions associated with itch (Klabunde et al., 2015). Associations with reduced nerve action potentials (Brandt and Rosen, 1998), GABA levels (Rice et al., 2016), somatostatin (Huang et al., 2018) and pain threshold, ADD, ADHD (Appendix A) have also been reported.

2. Conclusions

The review of the literature indicates that skin picking is by far the most prevalent form of self-injurious behaviour in people with PWS, and that other self-injurious behaviours, such as head banging, self-biting and self-mutilation, are not present in excess. The skin picking is not in itself obviously abnormal in that it is observed in the typically developing population. What appears different in PWS is its very high prevalence and its severity and persistence over time In the case of PWS we hypothesise that it is not that there are abnormal neural pathways or brain networks that underpin the increased propensity to skin picking, rather that the threshold for such behaviour is shifted downwards compared to the typically developing population, and it is this change in threshold that accounts for the increased prevalence and severity of this behaviour.

The behaviour has been observed to start as young as three years of age (Appendix B). Although not invariably the case, the picking usually starts where there is an initial lesion, such as an insect bite, which is often visible to the person (with the exception of rectal picking), and then persists over time leading to serious tissue damage. The behaviour occurs more commonly when the person is unoccupied. Surprisingly, we found only one study of direct interviews with people with PWS about skin picking behaviour, and this supports the conjecture that itchiness may initiate skin picking. Once picking starts then a local inflammatory response develops resulting in irritation through activation of the nocioceptive pathways (Symons, 2011). It is therefore likely that the bodily location and initiation of self-injury in PWS is primarily due to the visualization of a pre-existing lesion or, in the case of rectal picking, where some existing irritation is present. In addition, as Brandt and Rosen (1998) argued, people with PWS have a higher pain threshold and, whilst local inflammation may result in irritation, an increased pain threshold may make skin picking less aversive that it would otherwise have been Skin picking does not appear to be part of the obsessive-compulsive cluster of symptoms of the PWS phenotype although the likelihood of such behaviour occurring may change with mood state. Findings from animal studies and in humans also suggest that skin picking is unlikely to be a result of the absence of, or the lack

of expression of, the necdin gene. However, more research is needed on the possible causal roles of cerebral levels of the neuroinhibitory transmitter, GABA, and circulating somatostatin levels.

The review indicates that it is unlikely that there is a single major and direct mechanism that links the genotype of PWS with the behaviour of skin picking. There is clearly an increased propensity to such behaviour which may then emerge under specific conditions. The behaviour is initiated by a visual or tactile sensation and having been initiated, we propose it may continue in part as a behaviour aimed at ameliorating the effects of a local inflammatory response. Stopping the behaviour is problematic requiring a shift in attention, something that places an additional cognitive demand, particularly for a person with PWS. We propose that there is also likely to be a lowered threshold for such behaviour as a consequence of an atypical state of arousal potentially linked to the abnormal satiety response. Such an hypothesis can be tested as new treatments aimed at reducing hunger and hyperphagia are tested because, if effective, they may then reduce states of arousal and anxiety and in turn skin picking. Treatments need to focus on two aspects. Firstly, the peripheral and nocioceptive response when skin picking first starts and the development of strategies that facilitate a shift away from skin picking. Secondly, on the internal state of arousal, our hypothesis is that skin picking may bring some relief to this state which is therefore reinforced.

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Appendix A. Correlates of skin picking in the UK population based study of PWS Skin picking in past month

	Insignificant (0,1)	Noticeable (2,3,4)	
Average BMI	28.2 (n = 40) sd 9.47	33.1 (n = 51) sd 12.32	t = 6.97
ADD score(0,1)	9	6	Odds ratio 2.40
Add score (2–8)	20	32	95% CI 0.74–7.76 ns
ADHD score (0,1)	13	10	Odds ratio 2.28
ADHD score (2–6)	16	28	955 Ci 1.25–4.30
High pain threshold	19	29	Odds ratio 13.74
Low pain threshold	9	1	95% CI 4.37 to 320
Mild eating behaviour	16	11	Odds ratio 2.29
Severe eating b'h'r	26	41	95% CI 0.92–5.70 ns
Deletion	29	30	Odds ratio 1.22
Disomy	15	19	95% CI 0.52–2.86 ns

Appendix B. Skin picking by age among PWS and ID participants

Age	PWS pick	PWS not pick	ID pick	ID not pick
0	0	2	0	0
1	0	1	0	0
2	0	3	0	0
3	1	3	0	1
4	0	3	0	1
5	0	1	0	0
6	3	1	0	3
7	0	4	0	1
8	3	3	0	1
9	2	0	0	1
10	2	2	0	7
0–10	11	23	0	15
11–20	15	12	5	11
21–30	17	6	3	8
31–40	10	6	4	5
41–50	3	1	1	5
50+	0	0	0	2
N=	56	48	13	46
Mean age	22	16	26	20

Appendix C. Abstracts of studies by the data Table

Table 1

Warnock & Kestenbaum

Prader-Willi syndrome (PWS) is characterized by hypotonia at birth, hypogonadism, early childhood obesity, and mental deficiency. Other behavioral symptoms that become prominent during adolescence and adulthood include temper outbursts, stealing and hoarding food, and skin picking. The self-excoriating skin picking behavior observed in individuals with PWS is quite common and can lead to persistent sores and infections, even requiring hospitalization.

Two patients with PWS who displayed repetitive, self-mutilatory behavior of skin picking are described. They were both treated successfully with different doses of fluoxetine, a selective serotonin reuptake inhibitor. The skin-picking behavior in patients with PWS may be a variant of the spectrum of obsessive-compulsive disorders. Obsessive-compulsive disorders have been successfully treated with serotonin reuptake inhibitors such as fluoxetine. Thus, fluoxetine may be considered an option in the management of skin-picking behavior in patients with PWS.

Benjamin & Buot-Smith

The case discussed is of a 9-year-old boy with a diagnosis of Prader-Willi, compulsive eating, severe skin picking, mild mental retardation, and behavioral problems. Prehospital, hospital, and posthospital course is reviewed. An approach using fluoxetine and naltrexone shows a marked improvement in weight control, skin picking, and behavior. Obesity and self-mutilation are discussed with regard to the use of fluoxetine and naltrexone.

Hellings &Warnock

Low central nervous system (CNS) serotonin levels have been associated with impulsive, aggressive and self-injurious behavior (SIB). Persons with Prader-Willi Syndrome (PWS) often engage in self-injury by severe compulsive skin picking and gouging and often manifest compulsive eating, hoarding, and explosive outbursts. Some of the compulsive behaviors seen in patients with obsessive-compulsive disorder (OCD) bear similarity to behaviors associated with PWS: Skin picking, trichotillomania, and onychophagia (nail biting). There is abundant evidence that selective serotonin reuptake inhibitors (SSRIs) are effective in treating OCD. Three cases are described in which persons with PWS responded favorably to SSRI treatment. Two persons showed a significant decrease in skin picking. The third case showed a significant decrease in hoarding and explosive outbursts. Strategies are discussed for investigating the possibility of a shared neurochemical basis for the self-injurious, aggressive, and compulsive behaviors in persons with PWS. PWS may provide a relatively homogenous model for the study of skin picking and explosive outbursts among other populations.

Bhargava et al.

Individuals with Prader-Willi syndrome manifest severe skin picking behavior. We report three patients with this syndrome in whom an extension of this behavior to rectal picking resulted in significant lower gastrointestinal bleeding and anorectal disease. The recognition of this behavior is important to avoid misdiagnosing inflammatory bowel disease in this group of patients.

Hall et al.

Few studies have examined the relationship between heart rate and self-injurious behavior (SIB) shown by individuals with IDD (intellectual and developmental disabilities). In this single-case study, we simultaneously monitored heart rate and activity levels during a functional analysis of severe skin picking behavior exhibited by a young man with Prader-Willi syndrome (PWS). Results of the functional analysis indicated that the participant's skin picking was maintained by automatic reinforcement. A within-session analysis of the data indicated that skin picking bouts resulted in an increase in heart rate, suggesting a positive- automatic reinforcement function. These data indicate that inclusion of heart rate and activity-level monitoring during a functional analysis may provide important additional information concerning the determinants of SIB.

Salehi et al.

Prader-Willi syndrome (PWS) is a genetic syndrome in which individuals have multisystem medical challenges. Gastroenterological difficulties in the syndrome include decreased vomiting, constipation, delayed gastric emptying, delayed colonic transit, dysphagia, increased choking, and increased risk of gastric dilation and rupture. In addition, self-injurious behavior such as rectal picking may be present and severe enough to lead to rectal ulceration and bleeding. Many patients have extensive gastroenterological workup and treatment before their ultimate diagnosis of severe rectal picking. We describe 4 new cases of rectal picking in individuals with PWS leading to rectal bleeding and ulceration as well as a review of the literature of prior cases of severe rectal picking in PWS and potential treatment options. It is important to recognize these cases early in order to prevent unnecessary treatments and implement appropriate behavioral interventions.

Wilson et al.

We evaluated an inexpensive, efficient, and noninvasive technique for measuring tissue damage produced by self-injurious behavior (SIB). The technique involved computerized measurement of wound surface area (WSA) based on digital photographs. In Study 1, we compared photographic measurement to a more commonly used procedure, transparency measurement, in estimating WSA of 20 wound models. Results showed that both methods were reliable and that there was a high degree of correspondence between the 2 sets of measures. In Study 2, we compared photographic WSA measures to direct-observation measures in documenting changes over time in the SIB exhibited by a woman with Prader-Willi syndrome. Results showed that increases and decreases in observed SIB during baseline and treatment conditions corresponded with changes in WSA measures, indicating that the computer-assisted photographic technique may be useful as a corroborative measure or as a primary measure when direct observation of SIB is not feasible.

Table 2

Selkowitz et al

A double blind trial was conducted to determine the effect of fenfluramine on the weight and behaviour of patients with the Prader-Willi syndrome. Fifteen subjects, aged 5.5–27 years, received the placebo and the active drug, each for a period of six weeks. The dose of fenfluramine varied according to the age of the patient. Treatment with fenfluramine was associated with significant weight loss, improvement in food related behaviour, and a decrease in aggressive behaviour directed towards others. Skin picking and other self mutilation were unaffected by the drug. None of the subjects suffered from any side effects while taking the drug. These findings suggest that short term treatment with fenfluramine may have a role in the management of some patients with Prader-Willi syndrome. It could be used during periods when exposure to large amounts of food cannot be avoided and aggressive behaviour is particularly difficult to contain. It may also be useful in those whose lives are threatened by the complications of obesity.

Shapira et al., 2002

Self-injurious behaviour (SIB), most notably skin picking, has been described by various terms in the literature ranging from neurotic/psychogenic excoriations to compulsive/pathological skin picking. Prader–Willi Syndrome (PWS) is a neurogenetic multisystem disorder characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, dysmorphic features, and hyperphagia with a high risk of obesity. Psychiatric manifestations include SIBs in the form of skin picking, nail biting and rectal gouging. Topiramate is a novel anti-epileptic medication without significant liability of weight gain. There are no published reports of topiramate being utilized in PWS or SIB. We report attenuation of SIB with resultant lesion healing in three PWS adults treated with topiramate in an 8-wk open-label trial. Although our findings should be treated with caution, they suggest that double-blind or cross-over studies with topiramate are warranted to establish the possible role of topiramate in attenuating SIB in PWS and other disorders that involve SIB.

Schapira et al.2004

Prader-Willi syndrome is a multisystem neurogenetic obesity disorder with behavioral manifestations, including hyperphagia, compulsive behavior, self-injury, and mild to moderate mental retardation. In an 8-week open-label study, we evaluated adjunctive therapy with the anticonvulsant topiramate in 8 adults with Prader-Willi syndrome. Appetite was measured by a 1 -h access to food four times throughout the study and

quantified with a visual analogue scale. Topiramate did not significantly change calories consumed, Body Mass Index, or increase self-reported appetite. In addition, there were no significant changes in compulsions. Surprisingly, topiramate treatment resulted in a clinically significant improvement in the self-injury (i.e., skin-picking) that is characteristic of this syndrome. Potential benefits of topiramate for self-injury should be evaluated further in controlled trials.

Miller & Angulo

Prader-Willi syndrome (PWS) is a complex neurodevelopmental disorder caused by an abnormality on the long arm of chromosome 15 (q11-q13) that results in a host of behavioral characteristics including excessive interest in food, skin picking, difficulty with a change in routine, and obsessive and compulsive behaviors. Skin-picking can result in serious and potentially life-threatening infections. Recent evidence suggests that the excitatory neurotransmitter glutamate is dysregulated in obsessive-compulsive behaviors, and modulation of the glutaminergic pathway may decrease compulsive behaviors, such as recurrent hair pulling or skin-picking behaviors. N-acetylcysteine (NAC), a derivative of the amino acid cysteine, is thought to act either via modulation of NMDA glutamate receptors or by increasing glutathione in pilot studies. Thirty-five individuals with confirmed PWS (ages 5–39 years, 23 females/12 males) and skin-picking behavior for more than 1 year were treated with N-acetylcysteine (Pharma-NAC®) at a dose of 450-1,200 mg/day. Skin-picking symptoms and open lesions were assessed after 12 weeks of treatment by counting and measuring lesions before and after the medication. All 35 individuals had improvement in skin-picking behaviors. Ten (29 %) individuals (six males and four females) did not have complete resolution of skin-picking behavior, but had significant reduction in the number of active lesions. Longer-term, placebo-controlled trials are needed to further assess the potential benefit of this treatment.

Singh et al.

Twenty from a total of 27 individuals with genetically confirmed PWS, 6–26 years of age, with the following symptoms were identified: significant aggression/agitation, skin picking, and/or symptoms of attention-deficit/hyperactivity disorder (ADHD). Response to GXR for the above noted symptoms was categorized as improved, worsened, or unchanged, while assessing for side effects and tolerability.Eleven of the 20 individuals reported skin-picking, 17 reported aggression/agitation, and 16 reported symptoms of ADHD. Nine (81.8 %), 14 (82.3 %), and 15 (93.7 %) individuals showed an improvement in skin-picking, aggression/agitation, and ADHD, respectively, while on GXR treatment. Two patients with prior complaints of psychotic symptoms did not respond to GXR. Of note, no abnormal weight gain or significant adverse reaction was observed in this group, while on GXR. In this study, GXR demonstrated improvement in symptoms of skin picking, aggression/agitation, and ADHD in patients with PWS. GXR was not effective in reducing psychosis or agitation related to psychotic symptoms. Future studies are warranted to further establish the utility of GXR in PWS patients.

Table 3

Petty & Oliver

In this paper we review literature published in 2004 on self-injurious behaviour in individuals with intellectual disabilities. Reviewed studies examine phenomenology and comorbidity, pharmacological and other interventions, genetic syndromes, and behavioural assessment and treatment. Key findings include the possible association between self-injury and impulse control and stereotyped behaviours. Reports on the use of pharmacological interventions provide little evidence for the use such interventions, although the findings of studies on naltrexone seem stronger. In the behavioural phenotype literature the predictors of self-injury in Prader-Willi syndrome are becoming more refined. The behaviour analysis literature reports further development of assessment methodology to cater for idiosyncratic functions and low-rate behaviours. Developments in the fields of applied behaviour analysis and genetic syndromes highlight the importance of tailored assessments and interventions. Evidence from the pharmacological literature suggests that although significant numbers of individuals are prescribed such interventions, the research evidence for their efficacy is, at best, weak.

Lang et al.

Skin-picking is a type of self-injurious behavior involving the pulling, scratching, lancing, digging, or gouging of one's own body. It is associated with social impairment, and increased medical and mental health concerns. While there are several reports showing that skin-picking is common in individuals with developmental disabilities, knowledge about effective treatment approaches is sparse. We therefore reviewed studies involving the treatment of chronic skin-picking in individuals with developmental disabilities. Systematic searches of electronic databases, journals, and reference lists identified 16 studies meeting the inclusion criteria. These studies were evaluated in terms of: (a) participants, (b) functional assessment procedures and results, (c) intervention procedures, (d) results of the intervention, and (e) certainty of evidence. Across the 16 studies, intervention was provided to a total of 19 participants aged 6–42 years. Functional assessment procedures included direct observations, analog functional analyses, and functional assessment interviews. The most commonly identified function was automatic reinforcement. Treatment approaches included combinations of differential reinforcement, providing preferred items and activities stimuli (e.g., toys), wearing protective clothing (e.g., helmets or gloves), response interruption and redirection, punishment, and extinction. Improvements in behavior were reported in all of the reviewed studies. Suggestions for future intervention research are offered.

Oliver et al.

Obsessive compulsive and related disorders are a collection of debilitating psychiatric disorders in which the role of glutamate dysfunction in the underpinning neurobiology is becoming well established. N-acetyl cysteine (NAC) is a glutamate modulator with promising therapeutic effect. This paper presents a systematic review of clinical trials and case reports exploring the use of NAC for these disorders. A further objective was to detail the methodology of current clinical trials being conducted in the area.

PubMed, Web of Science and Cochrane Library Database were searched for human clinical trials or case reports investigating NAC in the treatment of obsessive compulsive disorder (OCD) or obsessive compulsive related disorders. Researchers with known involvement in NAC studies were contacted for any unpublished data.: Four clinical trials and five case reports/series were identified. Study durations were commonly 12-weeks, using 2,400-3,000 mg/day of NAC. Overall, NAC demonstrates activity in reducing the severity of symptoms, with a good tolerability profile and minimal adverse effects. Currently there are three ongoing randomized controlled trials using NAC for OCD (two adults and one pediatric), and one for excoriation.: Encouraging results have been demonstrated from the few pilot studies that have been conducted. These results are detailed, in addition to a discussion of future potential research.

Selles et al.

While individual trials suggest benefit of interventions for excoriation (skin-picking) disorder (ExD),limited systematic evaluation of treatments, or their collective benefit, exists.

The present study examined the current state of treatments for ExD in a systematic review and metaanalysis and explored potential treatment moderators. Twelve trials were identified for review, including five with a control condition. Of these, nine were eligible to be included in the meta-

analysis (three with a control).: A fixed-effects meta-analysis found a large overall treatment effect size (g = 1.13), comprised of large effects for behavioral treatments (g = 1.19), lamotrigine (g = 0.98) and selective serotonin reuptake inhibitors (g = 1.09). Clinician-rated measures did not significantly differ fromself-rated measures; however, larger effects were observed on self-rated measures of severity, as compared to impairment [Q (1) = 4.63, P = .03]. Treatment type, trial length and trial methodological quality were not significant moderators. For controlledtrials, the comparative efficacy of treatments for ExD was in the moderate range (g = 0.47).: Findings suggest that treatment for ExD has benefit; however, the meta-analysis did not provide strong evidence to support any specific treatment or to suggest its unique clinical benefit over control conditions. Overall, there is a lack of study on treatments for ExD and additional randomized controlled trialswith inclusion of multiple informants in assessment is needed.

Bonnot et al.

Prader-Willi syndrome (PWS) is a rare genetic syndrome. The phenotype includes moderate to intellectual disability, dysmorphia, obesity, and behavioral disturbances (e.g., hetero and self-injurious behaviors, hyperphagia, psychosis). Psychotropic medications are widely prescribed in PWS for symptomatic control. We conducted a systematic review of published literature to examine psychotropic medications used in PWS. MEDLINE was searched to identify articles published between January 1967 and December 2014 using key words related to pharmacological treatments and PWS. Articles with original data were included based on a standardized four-step selection process. The identification of studies led to 241 records. All selected articles were evaluated for case descriptions (PWS and behavioral signs) and treatment (type, titration, efficiency, and side effects). Overall, 102 patients were included in these studies. Treatment involved risperidone (three reports, n = 11 patients), fluoxetine (five/n = 6), naltrexone (two/n = 2), topiramate (two/n = 16), fluvoxamine (one/n = 1), mazindol (one/n = 2), N-acetyl cysteine (one/n = 35), rimonabant (one/n = 15), and fenfluramine (one/n = 15).

We identified promising treatment effects with topiramate for self-injury and impulsive/aggressive behaviors, risperidone for psychotic symptoms associated with uniparental disomy (UPD), and N-acetyl cysteine for skin picking. The pharmacological approach of behavioral impairment in PWS has been poorly investigated to date. Further randomized controlled studies are warranted.

Behavioral disturbances in Prader-Willi syndrome including aggressive reactions, skin picking, and hyperphagia might be very difficult to manage. Antipsychotic drugs are widely prescribed, but weight gain and increased appetite are their major side effects.

Topiramate might be efficient for self-injury and impulsive/aggressive behaviors, N-acetyl cysteine is apromising treatment for skin picking and Antidepressants are indicated for OCD symptoms. Risperidone is indicated in case of psychotic symptoms mainly associated with uniparental disomy.

Mikhail & King

Self- self-injury as part of their behavioral phenotype. Advances in the understanding of developmental influences injurious behavior occurs in the context of mental retardation. Some genetic syndromes are particularly likely to include on the expression of self-injury in persons with syndromal mental retardation, as well as knowledge gained from animal models of self-biting behavior will continue to inform the treatment of this significant clinical problem.

Devine & Symons

A broad spectrum of individuals with intellectual and developmental disabilities (I/DD) exhibit self-directed behavior that has the capacity to produce tissue injury. Different forms of self-injury (e.g. self-biting, self-hitting, head-banging) may partially segregate in specific neurodevelopmental disorders, although there is also significant overlap. For example, individuals with Prader–Willi syndrome typically pick at their skin, whereas those with Lesch–Nyhan syndrome bite themselves, while individuals with autism exhibit an array of self-injurious behaviors (self-hitting, self-biting, head-banging). Many individuals have “preferred” forms and target locations, and their self-injurious acts can be highly repetitive and stereotyped. Such structural characteristics can differ substantially between individuals even when they have the same genetic syndrome or type of neurodevelopmental disorder. Furthermore, self-injurious behavior (SIB) emerges in a variety of environmental contexts, and may be closely associated with impoverished institutional environments and/or emotional distress, suggesting that these may be common establishing conditions. It is worth noting that SIB is also seen in animals under a variety of circumstances, including laboratory models, domestic pets, and animals kept in zoos or farms. Thus, the etiology and expression of SIB is not unique to humans. Overall, these observations raise a variety of questions about the etiology and expression of self-injury. Do the various forms of self-injury represent the same or different phenomena across the different groups? Are there common underlying mechanisms, or does each pattern of SIB represent a distinct form of predisposing neuropathology? Because self-injury is prevalent across disparate diagnostic groups, is there reason to believe that perturbation of common biological mechanisms make it more likely that SIB will emerge? This question could be restated to ask whether risk factors (which seem to vary widely at the phenomenological level) are mediated through some common pathophysiological mechanism(s) such that biological vulnerabilities – regardless of diagnostic differences – can be identified to estimate developmental risk for SIB. The ultimate goal of a developmental account is to promote prevention in the form of risk reduction. Our specific purpose in writing this chapter is to selectively review the research evidence for “risk factors” that promote vulnerability for SIB specific to I/DD, and then suggest that our current approach to understanding SIB risk has been limited by relying for too long on conventional prevalence ratio study designs. We argue that adopting approaches informed from bench studies of risk factors may help move us forward faster in understanding which individuals with I/DD are likely to develop SIB and the circumstances under which it will most likely occur.

Oliver et al., 2013

The operant learning theory account of behaviors of clinical significance in people with intellectual disability (ID) has dominated the field for nearly 50 years. However, in the last two decades, there has been a substantial increase in published research that describes the behavioral phenotypes of genetic disorders and shows that behaviors such as self-injury and aggression are more common in some syndromes than might be expected given group characteristics. These cross-syndrome differences in prevalence warrant explanation, not least because this observation challenges an exclusively operant learning theory account. To explore this possible conflict between theoretical account and empirical observation, we describe the genetic cause and physical, social, cognitive and behavioral phenotypes of four disorders associated with ID (Angleman, Cornelia de Lange, Prader–Willi and Smith–Magenis syndromes) and focus on the behaviors of clinical significance in each syndrome. For each syndrome we then describe a model of the interactions between physical characteristics, cognitive and motivational endophenotypes and environmental factors (including operant reinforcement) to account for the resultant behavioral phenotype. In each syndrome it is possible to identify pathways from gene to physical phenotype to cognitive or motivational endophenotype to behavior to environment and back to behavior. We identify the implications of these models for responsive and early intervention and the challenges for research in this area. We identify a pressing need for meaningful dialog between different disciplines to construct better informed models that can incorporate all relevant and robust empirical evidence.

Huisman et al.

Self-injurious behavior (SIB) is a relatively common behavior in individuals with intellectual disabilities (ID).Severe SIB can be devastating and

potentially life-threatening. There is increasing attention for somatic substrates of behavior in genetic syndromes, and growing evidenceof an association between pain and discomfort with SIB in people with ID and genetic syndromes. In this review on SIB phenomenology in people with ID in general and in twelve genetic syndromes, wesummarize different SIB characteristics across these etiologically distinct entities and identify influencing factors. We demonstrate that the prevalence of SIB in several well-known genetic intellectual disability syndromes is noticeably higher than in individuals with ID in general, and that characteristics such as age of onset and topographies differ widely across syndromes. Each syndrome is caused by a mutation in a different gene, and this allows detection of several pathways that lead to SIB. Studying these with the behavioral consequences as specific aim will be an important step toward targeted early interventions and prevention.

Table 4

Dykens, 2014

Although hyperphagia and compulsivity in Prader-Willi syndrome (PWS) are well described, recreation and adaptive skills are relatively unexplored. Parents of 123 participants with PWS (4–48 years) completed measures of their child's adaptive, recreation, and problem behaviors. Offspring received cognitive testing. Watching TV was the most frequent recreational activity, and was associated with compulsivity and skin picking. BMIs were negatively correlated with physical play, and highest in those who watched TV and played computer games. Computer games and physical activities were associated with higher IQ and adaptive scores. People with PWS and other disabilities need to watch less TV and be more engaged in physical activities, games, and leisure pursuits that are fun, and may bring cognitive or adaptive advantages.

Hall et al., 2014

Skin picking is an extremely distressing and treatment resistant behavior commonly shown by individuals with Prader-Willi syndrome (PWS). However, with the exception of a limited number of published single-case and survey studies, little is known about the environmental determinants of skin picking in this population. In this study, functional analyses were conducted with thirteen individuals with PWS, aged 6–23 years, who engaged in severe skin-picking behavior. In addition to the conditions typically employed in a functional analysis (i.e., alone, attention, play, demand), we included an ignore condition to examine potential effects of stimulus control by the presence of an adult. Twelve participants engaged in skin picking during the functional analysis, with the highest levels occurring in the alone and ignore conditions for eight participants, suggesting that skin picking in these participants was maintained by automatic reinforcement. For the remaining four participants, an undifferentiated pattern of low-rate skin picking was observed across conditions. These data confirm previous studies indicating that skin picking in PWS may be maintained most often by automatically produced sensory consequences. There were no associations between demographic characteristics of the participants (e.g., sex, age, IQ or BMI) and levels of skin picking observed in the functional analysis. Additional investigations are needed to identify the nature of the sensory consequences produced during episodes of skin picking in PWS. Behavioral interventions designed to extinguish or compete with the potential sensory consequences arising from skin picking in PWS are also warranted.

Dykens, 2004

Although maladaptive and compulsive behaviors are increasingly well-described in young persons with Prader-Willi syndrome, it is unclear how these problems manifest in older adults with this syndrome. In Part I, I compared maladaptive and compulsive behaviors in 45 older adults with Prader-Willi syndrome (ages 30–50 years) to 195 children, adolescents, and young adults. Young adults were at highest risk for problems. In contrast, maladaptive and compulsive symptoms diminished significantly in older adults with Prader-Willi syndrome. In Part II, I examined predictors of problems other than age: IQ, gender, BMI, and-for adults-living status. Gender and BMI were significant predictors of skin-picking and other symptoms. Possible reasons are discussed for sweeping declines in problems among older adults.

Symons et al.

With few exceptions (e.g., Lesch-Nyhan syndrome), the specific nature of self-injury in relation to identified genetic syndromes associated with mental retardation is poorly understood. In the present study we surveyed the families of 62 persons with Prader-Willi syndrome to determine the prevalence, topographies, and specific body locations of self-injurious behavior. Self-injury was reported for 81 % of the participants. Skin-picking was the most prevalent form, with the front of the legs and head being disproportionately targeted as preferred self-injury body sites. Individuals with the 15q11-q13 deletion injured significantly more body sites than did individuals with maternal disomy 15. Results are discussed in relation to previous self-injury body site findings and implications for the relevance of syndrome-specific behavioral phenotypes.

Didden 2007

Individuals with Prader-Willi syndrome (PWS) are at increased risk for mental health and behaviour problems, such as skin-picking and compulsive behaviours. Prevalence and functional assessment of skin-picking, and its association with compulsive behaviour and self-injury, were investigated in a large group of individuals with PWS (n = 119).

Data on demographic characteristics, skin-picking and compulsive and self-injurious behaviours were collected by questionnaires. Behavioural function of skin-picking was assessed by administering the *Questions About Behavioral Function* scale.

Skin-picking was found in 86 % of the sample, and correlated positively with compulsive behaviours. No associations were found between skin-picking and other variables. Functional assessment suggest that in most cases (i.e. 70 %) skin-picking primarily had non-social functions. Skin-picking and compulsive behaviours are common in PWS. In most cases, skin-picking may be maintained by contingent arousal reduction. Controlled studies on behavioural treatment are lacking. Implications for treatment selection are discussed.

Husyi et al.

We examined the topography, severity, potential sources of reinforcement, and treatments utilized for skin-picking behavior shown by individuals with Prader-Willi syndrome (PWS). The parents of 55 individuals with PWS, aged 6–25 years, were interviewed about their child's skin-picking behavior using the Self-Injury Trauma Scale (SIT; Iwata, Pace, Kissel, Nau, & Farber, 1990) and the Functional Analysis Screening Tool (FAST; Iwata, DeLeon, & Roscoe, 2013). Results showed that skin picking in PWS occurred on the extremities (i.e., arms, legs, hands, and feet) for 75 % of cases and resulted in bodily injury for 83.7 % cases. Skin picking posed a high risk to the individual concerned in 41.8 % of cases. Automatic sensory stimulation was identified as a potential source of reinforcement in the majority of cases (52.7 %) followed by access to social attention or preferred items (36.4 %). Treatments utilized by parents were primarily behavioral strategies (56.3 %) followed by basic first aid (54.5 %). There were no differences in the topography, severity or potential source of reinforcement between those with the deletion (DEL) subtype and those with the uniparental disomy (UPD) subtype. Taken together, these data indicate that skin picking shown by individuals with PWS is a particularly severe and intractable behavioral issue that may be maintained by (as yet unknown) sensory consequences. Further studies to identify the determinants of skin picking in PWS are therefore needed. The implications for interventions are discussed.

Morgan et al.

To examine the nature and psychosocial correlates of skin-picking behavior in youth with Prader-Willi Syndrome (PWS). Parents of 67 youth

(aged 5–19 years) with PWS were recruited to complete an internet-based survey that included measures of: skin-picking behaviors, the automatic and/or focused nature of skin-picking, severity of skin-picking symptoms, anxiety symptoms, developmental functioning, symptoms of inattention, impulsivity, and oppositionality, and quality of life. Results indicated that skin-picking was endorsed in 95.5 % of youth. Direct associations of moderate strength were found between skin-picking severity and symptoms of anxiety, inattention, oppositionality, developmental functioning, and quality of life. Other descriptive data, such as areas picked, cutaneous factors, antecedents, and consequences related to skin-picking are reported. The prevalence and consequences associated with skin-picking in PWS indicate a greater need for clinician awareness of the behavior and interventions tailored to meet the needs of this population.

Brandt & Rosen

The Prader-Willi syndrome (PWS) is associated with a tendency to self-injury and a reduced sensitivity to painful stimuli. Somatosensory functions were studied in 5 children aged 11–13 years with PWS. Tactual perception in the hands (stereognosis) was apparently normal in 4 of them. Sensory nerve conduction velocities in the median nerve and latencies for sensory evoked potentials were similar in the PWS subjects and in 10 healthy controls indicating a preserved myelinisation of sensory nerve fibers in PWS. Sensory nerve action potential amplitudes in the PWS group were on an average only 40–50 % of normal size ($p = 0.03$), suggesting a reduced number of normal axons in the median nerve. The results may be relevant for the impaired pain sensitivity in PWS because similar neurographic findings and a low density of peripheral nerve fibers have been reported in patients with hereditary or congenital insensitivity to pain.

Hall et al., 2013

Few studies have examined the relationship between heart rate and self-injurious behavior (SIB) shown by individuals with IDD (intellectual and developmental disabilities). In this single-case study, we simultaneously monitored heart rate and activity levels during a functional analysis of severe skin picking behavior exhibited by a young man with Prader-Willi syndrome (PWS). Results of the functional analysis indicated that the participant's skin picking was maintained by automatic reinforcement. A within-session analysis of the data indicated that skin picking bouts resulted in an increase in heart rate, suggesting a positive- automatic reinforcement function. These data indicate that inclusion of heart rate and activity-level monitoring during a functional analysis may provide important additional information concerning the determinants of SIB.

Klabunde et al.

Individuals with Prader-Willi syndrome (PWS), a genetic disorder caused by mutations to the q11–13 region on chromosome 15, commonly show severe skin-picking behaviors that can cause open wounds and sores on the body. To our knowledge, however, no studies have examined the potential neural mechanisms underlying these behaviors. Seventeen individuals with PWS, aged 6–25 years, who showed severe skin-picking behaviors, were recruited and scanned on a 3 T scanner. We used functional magnetic resonance imaging (fMRI) while episodes of skin picking were recorded on an MRI-safe video camera. Three participants displayed skin picking continuously throughout the scan, three participants did not display skin picking, and the data for one participant evidenced significant B0 inhomogeneity that could not be corrected. The data for the remaining 10 participants (six male, four female) who displayed a sufficient number of picking and nonpicking episodes were subjected to fMRI analysis. Results showed that regions involved in interoceptive, motor, attention, and somatosensory processing were activated during episodes of skin-picking behavior compared with nonpicking episodes. Scores obtained on the Self-Injury Trauma scale were significantly negatively correlated with mean activation within the right insula and left precentral gyrus. These data indicate that itch and pain processes appear to underlie skin-picking behaviors in PWS, suggesting that interoceptive disturbance may contribute to the severity and maintenance of abnormal skin-picking behaviors in PWS. Implications for treatments are discussed.

Feurer et al.

The presence and severity of compulsive behaviours may be evaluated via the Compulsive Behaviour Checklist (CBC) and this instrument has been successfully employed in people with intellectual disability. However, the applicability of the overall CBC scoring system, which entails tallying the number of behavioural categories represented (i.e. five) as well as the number of individual behaviours endorsed (i.e. 25), is not known in the population with Prader-Willi syndrome (PWS). The present investigation examined the latent variable structure of the CBC in people with PWS in order to identify possible population-specific scoring and interpretation considerations. The 25 behaviour-specific items of the CBC were analysed for 75 people with PWS (44 females and 31 males) aged between 4 and 41 years (mean +/- SD = 11.4+/-9.4) via factor analysis with principal component extraction and equamax rotation. The most suitable solution was determined on the basis of multiple empirical criteria: (1) the scree test; (2) eigenvalues > 1.00; (3) salient loadings > 0.30; (4) the clarity of item assignment to a single latent dimension; (5) the internal consistency of the latent dimension(s) (coefficient alpha > or = 0.70); and (6) item-total correlations between 0.20 and 0.79. In addition, solutions were examined with respect to psychological theory and previous research. A 'general factor' (i.e. single latent dimension) solution which adhered to all a priori criteria was indicated. Twenty-four out of 25 items achieved salient loadings ranging from 0.46 to 0.80 on the general factor. The single item which failed to achieve salience, 'deviant grooming-skin picking', exhibited both substantial unique variance (0.997) and moderate reliability ($r = 0.59$, $P < 0.001$). The internal consistency of the general factor was strong (alpha = 0.93) and all salient items were suitably correlated with the unit-weighted total score (r(item-total) = 0.41-0.77). The traditional CBC scoring system, which includes tallying the number of categories represented, would not be relevant in this PWS sample. In addition, the recommended tallying of the number of individual behaviours endorsed does not reflect the empirically indicated notion of compulsive behaviour in this special population. These findings indicate that the 24 salient items should be scored as a unit-weighted composite and that the score on the substantially unique item (skin picking) should be considered a separate measure when evaluating compulsive behaviours via the CBC in people with PWS.

Holland et al.

Prader-Willi syndrome (PWS) is a genetic disorder resulting in obesity, short stature, cryptorchidism, learning disabilities (mental retardation) and severe neonatal hypotonia. Associated with the syndrome are a number of behaviours that are sufficiently distinctive that the syndrome is considered to have a specific 'behavioural phenotype'. Through multiple sources we attempted to identify all people with PWS living in one region in the U K. This cohort was augmented by people with PWS from other regions, and a contrast group of people with learning disabilities of varied aetiologies. The main carers were interviewed, using structured and semi-structured interview schedules, to establish the presence and severity of specific behaviours, and PWS diagnostic criteria. The intellectual functioning and attainments of all were determined. Blood samples were obtained for genetic diagnosis from all consenting participants. Although excessive eating was recognized as a potentially severe problem in those with PWS, it was almost universally controlled by food restriction, and therefore not seen as a 'problem behaviour'. Those with PWS differed from a learning disabled group of other aetiologies in the prevalence rates of skin picking, temper tantrums, compulsive behaviours and mood fluctuations, and also in the profile of their adaptive behaviours. The study confirms the distinct behavioural phenotype of PWS. Specific behaviours occurred significantly more frequently in PWS, compared with an age and BMI matched learning disabled comparison group. A factor analysis of the behaviours involved

resulted in three factors that we hypothesized to be independent, and to arise from different mechanisms.

Wigren & Hansen

Prader-Willi syndrome (PWS) is characterized by an increased risk for obsessive-compulsive disorder. This study investigated the nature of compulsive-like behaviours in the PWS. Parents of 50 individuals with PWS (aged 5 − 18 years) and 50 typically developing 4-year-old children completed the Childhood Routines Inventory. This instrument measures compulsive-like behaviours in normative childhood.Many childhood compulsive behaviours are prevalent among older children and adolescents with PWS. Group differences were observed in that the PWS group, independent of age, gender and cognitive dysfunctions, exhibited more intense compulsive behaviours related to insistence on sameness in many daily activities and social contexts. Findings also revealed an age-independent low-prevalent pattern of PWS compulsivity, probably related to other features in the PWS symptomatology.Compulsions of childhood do not subside with age in adolescents with PWS. The findings indicate that the differentiation between delayed childhood rituals and pathological manifestations of compulsive features is complex in PWS populations.

Pignatti et al.

Obsessive-compulsive (O-C) traits, and excessive food intake are well known behavioural manifestations among individuals with Prader-Willi Syndrome (PWS). Other unwanted behaviours are also frequently observed, but they need a more specific investigation, especially in the adult population.

The behaviour of 31 PWS adults was investigated via the Symptom Checklist-90-Revised (SCL-90-R), the Yale-Brown Obsessive Compulsive Scale Symptom Checklist (Y-BOCS-SC), and the Prader-Willi Behavioural Checklist (PBC). The PBC is a quick screening questionnaire prompted specifically for the investigation on adults with PWS.

Statistical clustering revealed two patterns of unwanted behaviours from the PBC. Behaviours belonging to the first cluster (e.g., Excessive food intake, Skin picking) appear to be linked to the usual phenotypic manifestation of PWS. By contrast, many other behaviours (e.g., some O-C symptoms and aggressive actions) could show a relationship also to individual psychopathologies.

Both internal (Anxiety and Depression) and external (Hostility) difficulties in managing impulses should account for individually distinct behaviours in adults with PWS.

Muscatelli et al.

Prader-Willi syndrome (PWS) is a complex neurogenetic disorder with considerable clinical variability that is thought in large part to be the result of a hypothalamic defect. PWS results from the absence of paternal expression of imprinted genes localized in the 15q11-q13 region; however, none of the characterized genes has so far been shown to be involved in the etiology of PWS. Here, we provide a detailed investigation of a mouse model deficient for NECDIN: Linked to the mutation, a neonatal lethality of variable penetrance is observed. Viable NECDIN: mutants show a reduction in both oxytocin-producing and luteinizing hormone-releasing hormone (LHRH)-producing neurons in hypothalamus. This represents the first evidence of a hypothalamic deficiency in a mouse model of PWS. NECDIN:-deficient mice also display increased skin scraping activity in the open field test and improved spatial learning and memory in the Morris water maze. The latter features are reminiscent of the skin picking and improved spatial memory that are characteristics of the PWS phenotype. These striking parallels in hypothalamic structure, emotional and cognitive-related behaviors strongly suggest that NECDIN is responsible for at least a subset of the multiple clinical manifestations of PWS.

Rice et al.

Prader-Willi syndrome (PWS) is characterized by infantile hypotonia, hypogonadism, small hands and feet, distinct facial features and usually intellectual impairment. The disorder is associated with severe behavioral disturbances which include hyperphagia leading to morbid obesity, temper outbursts, skin-picking, and compulsive behaviors. While the brain mechanisms that underpin these disturbances are unknown these behaviors suggest a lack of inhibition and thus gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter may be implicated. In the present study, we investigated in vivo brain GABA and its relationship with emotion and behavior in individuals with PWS. Single voxel proton magnetic resonance spectroscopy (1H-MRS) was performed on 15 individuals with PWS and 15 age- and gender-matched typically developing controls. GABA levels were measured in the parieto-occipital lobe. All other metabolite levels (N-acetyl aspartate, myo-Inositol, glutathione, glutamate, and glutamine + glutamate) were measured in the anterior cingulate cortex (ACC). GABA levels were significantly lower in the participants with PWS who had clinically significant emotional and behavioral problems relative to typically developing control participants and participants with PWS who did not have emotional and behavioral problems within the clinically significant range. GABA levels were negatively correlated with total behavioral problem scores as well as temper outbursts, skin-picking, depression, social relating difficulties, and a tendency to be self-absorbed. Our data suggests that alterations of the GABAergic system may play an important role in aspects of the pathophysiology of PWS. Pathological mechanism found in PWS may be relevant to understanding the control of similar behaviors in the general population.

Pujol et al.

Prader Willi syndrome is a genetic disorder with a behavioural expression characterized by the presence of obsessive-compulsive phenomena ranging from elaborate obsessive eating behaviour to repetitive skin picking. Obsessive-compulsive disorder (OCD) has been recently associated with abnormal functional coupling between the frontal cortex and basal ganglia. We have tested the potential association of functional connectivity anomalies in basal ganglia circuits with obsessive-compulsive behaviour in patients with Prader Willi syndrome.

We analyzed resting-state functional MRI in adult patients and healthy controls. Whole-brain functional connectivity maps were generated for the dorsal and ventral aspects of the caudate nucleus and putamen. A selected obsessive-compulsive behaviour assessment included typical OCD compulsions, self picking and obsessive eating behaviour.

We included 24 adults with Prader Willi syndrome and 29 controls in our study. Patients with Prader Willi syndrome showed abnormal functional connectivity between the prefrontal cortex and basal ganglia and within subcortical structures that correlated with the presence and severity of obsessive-compulsive behaviours. In addition, abnormally heightened functional connectivity was identified in the primary sensorimotor cortex-putamen loop, which was strongly associated with self picking. Finally, obsessive eating behaviour correlated with abnormal functional connectivity both within the basal ganglia loops and between the striatum and the hypothalamus and the amygdala.

Limitations of the study include the difficulty in evaluating the nature of content of obsessions in patients with Prader Willi Syndrome and the risk of excessive head motion artifact on brain imaging.

Patients with Prader Willi syndrome showed broad functional connectivity anomalies combining prefrontal loop alterations characteristic of OCD with 1) enhanced coupling in the primary sensorimotor loop that correlated with the most impulsive aspects of the behaviour and 2) reduced coupling of the ventral striatum with limbic structures for basic internal homeostasis that correlated with the obsession to eat.

Appendix D. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.01.029.

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