Research in Developmental Disabilities 85 (2019) 229–242

Contents lists available at ScienceDirect

Research in Developmental Disabilities

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

Investigation of the relationship between electrodermal and behavioural responses to executive tasks in Prader-Willi syndrome: An event-related experiment

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ARTICLE INFO

Keywords:
Prader-Willi syndrome
Executive functions
Electrodermal activity

ABSTRACT

Background: Recent work suggests that maladaptive behaviors in genetic developmental disorders may emerge from autonomic dysfunctions impacting higher order executive functions. In Prader-Willi syndrome (PWS), executive functions are not well understood and investigations of possible underlying causes at the autonomic level are lacking.
Aims: This study aimed at clarifying the status of inhibition and working memory updating functions in PWS and searched for sympathetic signatures as well as to examine their links with executive performance.
Methods and Procedures: The performance of thirty adults with PWS was compared to that of thirty healthy adults on two tasks assessing inhibition and working memory updating while electrodermal activity (EDA) was recorded.
Outcomes and Results: PWS adults underperformed healthy adults in the inhibition and the working memory updating tasks and showed abnormal skin conductance responses. Distinct EDA have been found in PWS and healthy adults. Furthermore, while EDA reflected distinct cognitive processes, correlations between electrodermal and behavioural data were absent when examining the two groups separately.
Conclusions and Implications: PWS is associated with a slight impairment of inhibition and a severe impairment of working memory updating. Furthermore, there are specific sympathetic autonomic signatures in PWS that do not present straightforward links with executive dysfunctions.

1. Introduction

Prader-Willi syndrome (PWS) is a rare genetic neurodevelopmental disorder associated with intellectual disability and emotional disturbances leading to severe adaptation problems to everyday life activities (Laurier et al., 2015). In cognitive psychology research, the mechanisms responsible for adaptation are traditionally referred to as executive functions (EF). EF is an umbrella term covering higher-order mental functions that govern goal-directed actions and adaptive responses to non-routine situations, when automatized

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https://doi.org/10.1016/j.ridd.2018.11.013
Received 28 April 2018; Received in revised form 12 November 2018; Accepted 30 November 2018
Available online 24 December 2018

patterns of action are not sufficient (Hughes & Ensor, 2005; Norman & Shallice, 1986; Pribram & Broadbent, 1970; Stuss & Benson, 1984). In psychophysiology research, adaptation often refers to the activity of the autonomic nervous system (ANS) regulating homeostasis and allowing flexible behaviour repertoires (Wehrwein, Orer, & Barman, 2016). The ANS comprises a sympathetic division, which mobilizes the organism to act in face of unknown/potentially dangerous/threatening situations (i.e., the “fight or flight system”), and a parasympathetic division, in charge of the organism’s recovery (i.e., the “rest and digest system”). Although adaptation echoes different definitions depending on scientific domains, recent work has demonstrated that the cognitive system and the ANS are intrinsically and dynamically coupled (Critchley, Eccles, & Garfinkel, 2013; Park & Thayer, 2014; Thayer & Lane, 2009). This interplay is an emergent research topic in genetic neurodevelopmental disorders, such as PWS (Schwartz et al., 2016). Because different genetic aetiologies produce differentiable syndromes, a way to characterize them is to identify endophenotypes, that is, syndrome-specific signatures at different levels (e.g., biological and cognitive), and possible pathways through these levels (Hendren, 2013; Jauregi et al., 2007; Woodcock, Oliver, & Humphreys, 2009a, 2009b). To that end, clarifying the efficiency of key mechanisms at autonomic and cognitive levels is essential. To date, cognitive impairments in PWS are unclear, especially concerning executive functions. In addition, although medical staff are aware of physiological problems in PWS (Laurier et al., 2015), studies investigating the ANS are rare (Haqq et al., 2012). The two objectives of the present study are 1) to clarify the status of two executive functions in PWS in comparison to the normal population, - inhibition and working memory updating - which have received little attention in previous work, and 2) to search for psychobiological signatures that express simultaneously through cognitive impairments and abnormal autonomic responses.

1.1. Cognitive impairments in Prader-Willi syndrome

Prader-Willi syndrome (PWS) is a rare neurodevelopmental disorder caused by the loss of gene expression in the 15.q11-2.q13 region of the 15th paternal chromosome (Butler, Manzardo, & Forster, 2016). The loss of expression is due in 70% of cases to deletion of a part or the whole paternal region, in 25–30% of cases to duplication of the entire 15th maternal chromosome, maternal uniparental disomy (m-UPD), and in 1–2% of cases to an imprinting defect (Cassidy, Schwartz, Miller, & Driscoll, 2012). The genetic features of PWS produce a large symptomatology that severely affects endocrinal, neurological, physiological, cognitive and behavioural levels (Gunay-Aygun, Schwartz, Heeger, O’Riordan, & Cassidy, 2001). Individuals with PWS show emotional lability, intolerance to frustration and unpredictability, rigid thinking, routines of action and perseverations (Dimitropoulos, Feurer, Butler, & Thompson, 2001; Dykens & Roof, 2008). Daily adaptation is limited, notably in the social domain, due to temper outbursts, compulsions, impulsivity, difficulties in interpreting facial emotions and developmental delay in the theory of mind (Einfeld et al., 2014; Glattard, 2012; Key, Jones, & Dykens, 2013; Whittington & Holland, 2017). The cognitive profile is characterized by general delayed acquisition and realization (Diene, Postel-Vinay, Pinto, Polak, & Tauber, 2007), learning difficulties, especially in observational learning (Foti, Menghini, Petrosini et al., 2015; Whittington et al., 2004), poor abstract thinking, reading and arithmetic disabilities, and delayed language development (Whittington & Holland, 2017). An important feature of PWS is the presence of mild-to-moderate intellectual disability (Copet et al., 2010; Dykens, Hodapp, Walsh, & Nash, 1992). Deficits in short-term memory and spatial cognition contrast with relative preservation of long-term memory, intact visual capacity and skills with jigsaw puzzles (Conners, Rosenquist, Atwell, & Klinger, 2000; Foti, Menghini, Petrosini et al., 2015; Fox, Sinatra, Mooney, Feurer, & Butler, 1999; Verdine, Troseth, Hodapp, & Dykens, 2008).

In the last decade, studies on cognitive aspects of PWS have argued that impairment in executive functions may account for the associations between some behavioural and cognitive symptoms (Gross-Tsur, Landau, Benarroch, Wertman-Elad, & Shalev, 2001; Jauregi et al., 2007). The most compelling evidence concerns the association of impaired mental switching with repetitive behaviour and preference for routine (Woodcock et al., 2009a, 2009b; Woodcock, Oliver, & Humphreys, 2011; Whittington & Holland, 2017). Mental switching refers to the capacity needed to shift attention from different mental sets (Rogers & Monsell, 1995). This EF represents one of three important functions (Miyake et al., 2000), which are highly predictive of IQ in normal functioning (Arffa, 2007; Duggan & Garcia-Barrera, 2015; Friedman et al., 2006) as well as in PWS (Chevalère et al., 2015, 2013). Given the strong predictive power of EFs for a range of cognitive domains, the study of EFs is a promising avenue for understanding psychological problems in the syndrome. While a notable progress has been made in understanding the mental switching capacity in PWS, few studies investigated the other functions, namely behavioural inhibition (i.e., the ability to withhold pre-potent responses) and working memory updating (i.e., the ability to refresh the content of working memory). Bringing light on the status of these functions may help to better identify their role on behavioural problems. Indeed, impaired behavioural inhibition is widely accepted as a marker of impulsivity and compulsive behaviour (Dalley, Everitt, & Robbins, 2011; Verbruggen & Logan, 2008). Since these symptoms are common in PWS, one can expect that PWS individuals will underperform healthy adults on tasks typically requiring response inhibition. In an event-related potentials study, Stauder et al. (2005) compared the performance of PWS adults (m-UPD and deletion sub-groups) to that of healthy adults on an AX-CPT paradigm. This is a sustained attention task where participants continuously respond to certain stimuli (i.e., to press a key each time a capital letter appears on screen) but on some trials, are required to withhold their responses (i.e., when an “A” follows an “X” on screen). While the m-UPD sub-group showed impaired behavioural performance relative to the deletion sub-group and a control group of healthy adults, both PWS sub-groups showed an absence of typical N200 amplitude reflecting inhibitory process in comparison to healthy adults. More recently, a study by Chevalère et al. (2015) assessed behavioural inhibition in PWS adults and healthy adults matched on chronological age using a Stop Signal Paradigm. This task requires participants to press different keys when an “O” or an “X” appears on screen, and to withhold their responses when an auditory tone is presented randomly. In comparison to healthy adults, PWS adults showed increased stop signal reaction times, suggesting impaired inhibition.

Also unclear is how PWS individuals actively maintain information in WM. One of the components of WM is updating, which taps into attentional control (Ecker, Lewandowsky, Oberauer, & Chee, 2010) and refers to the ability to change actively the content of WM with incoming events, by substituting no longer relevant information with relevant new information (Morris & Jones, 1990). WM updating is commonly assessed using N-Back tasks, in which participants are asked to maintain only the last items of lists varying in length, without being aware of the lists lengths. In Miyake's tripartite model of EF, WM updating was found to best predict intelligence (Friedman et al., 2006), therefore it is a crucial mechanism in human cognition. Previous work has found that the ability to update WM content predicts performance in arithmetic, reading comprehension, reasoning and problem solving (Pelegrina, Capodieci, Carretti, & Cornoldi, 2015). In addition, Carretti, Belacchi, and Cornoldi, (2010) found WM updating to play an important role in distinguishing intellectual disability from typically developing (TD) children. To our knowledge, only one study by Chevalère et al. (2015) compared the WM updating performance in PWS adults to that of healthy adults. They used a Letter Memory paradigm, a verbal N-Back task involving to-be-remembered letters and varying in the number of updating. Results showed a main effect of group, with PWS adults recalling fewer letters relative to controls, suggesting impaired WM in PWS. More importantly, the lack of Group x Number of Updating suggested no specific impairment of attentional control in PWS, but rather a WM storage deficit. Because executive functions are linked with regions of the frontal lobe that also govern autonomic functions, (Beissner, Meissner, Bär, & Napadow, 2013; Thayer, 2007), the following section will emphasize on potential associations of executive impairments and autonomic dysfunctions which may further our understanding of the endophenotype of PWS.

1.2. Psychobiological approaches in genetic neurodevelopmental disorders

According to diagnostic criteria in genetic neurodevelopmental disorders, psychological conditions are often concomitant with biological dysfunctions resulting from genetic abnormalities (Jauregi et al., 2007). Researchers are just beginning to examine these associations. Crucially, the identification of pathways from genotype to phenotype may provide justification of pharmacological treatments acting on autonomic regulation (Heilman, Harden, Zageris, Berry-Kravis, & Porges, 2011), as well as give important insights on how symptoms at a certain level (e.g., autonomic dysfunctions) may contribute to our understanding of symptoms at higher levels (e.g., cognitive impairments and behavioural problems).

The Neurovisceral Integration Model (NIM, Laborde, Mosley, & Thayer, 2017; Park & Thayer, 2014; Thayer & Lane, 2000; 2009) has brought important insights into the understanding of psychobiological interactions. The model describes complex anatomo-functional networks of autonomic control, from prefrontal-circuits to cardiac regulation through the brainstem and the vagus nerve, which underpins the balance between the parasympathetic and sympathetic innervations of the heart. Thayer et al. have focused on individual differences in resting state heat rate variability, accounting for differences in cognitive performance in normal participants (Hansen, Johnsen, & Thayer, 2003; Thayer & Lane, 2009). More precisely, the model establishes a connexion between psychological states (emotional regulation and cognitive performance) and parasympathetic vagal inhibitory influences regulating sympathetic arousal. Consequently, it is a powerful avenue for understanding cognitive endophenotypes in genetic neurodevelopmental disorders because it allows making predictions based on the imbalance of activation of the ANS divisions and their consequences on cognitive functions. The current dominant hypothesis is that several neurodevelopmental disorders present with parasympathetic underactivity associated with sympathetic overarousal (Bujnakova et al., 2016), which may account for behavioural problems such as temper outbursts (Heilman et al., 2011; Manning et al., 2016; Schwartz et al., 2016). Consequently, researches focus largely on the role of vagal control (Porges et al., 2013). For instance, Autism Spectrum Disorder (ASD) and Fragile X syndrome have been associated with atypical parasympathetic regulation (Bujnakova et al., 2016. Heilman et al., 2011). In PWS, Haqq et al. (2012) reviewed four prior studies on the autonomic nervous system. They have found several autonomic dysfunctions: abnormal temperature regulation, abnormal circadian rhythm and altered perception of pain. The authors found higher resting state heart rate and general diminished parasympathetic activity of interest in PWS.

Although studies acknowledge that inhibition of sympatho-excitatory response is parasympathetic in nature (Thayer & Lane, 2009), it is also true that both branches rely on non-dependent mechanisms (Ellis & Thayer, 2010; Giuliano, Gatzke-Kopp, Roos, & Skowron, 2017). Therefore, sympathetic activity may have unique contribution to cognitive performance. Accordingly, a meta-analysis of thirty-two fMRI and twelve PET scan studies in healthy adults by Beissner et al. (2013) found that sympathetic associated brain regions are predominantly active during cognitive tasks relative to parasympathetic associated brain regions. Furthermore, electrodermal activity (EDA), which is a relatively pure measure of sympathetic arousal (Boucsein et al., 2012; Christie, 1981; Dawson, Schell, & Filion, 2007; Sequeira, Hot, Silvert, & Delplanque, 2009), reflects executive inhibition in the Stop Signal paradigm: the amplitude of skin conductance responses increases from go trials to inhibition trials (Zhang et al., 2012). In addition, previous work showed that EDA is sensitive to working memory and attentional demands during cognitive tasks (Garcia, Uribe, Tavares, & Tomaz, 2011; Munro, Dawson, Schell, & Sakai, 1987; Yuille & Hare, 1980). In genetic neurodevelopmental disorders, investigation of sympathetic reactivity has received little attention, studies are not consensual, and cognitive functions are rarely assessed simultaneously. Contrary to predictions of sympathetic overarousal in ASD, a resting state study by Bujnakova et al. (2016) found that EDA magnitude was lower in ASD relative to healthy adults. These results were in line with those of Kushki et al. (2013) who found lower resting state EDA and fewer skin conductance responses (SCRs) in children with ASD relative to TD children. However, the authors concluded in favour of the sympathetic overarousal hypothesis as they have found ASD children to show a greater elevation of SCRs than TD children during a Stroop task. In females with Fragile X syndrome, Roberts, Mazzocco, Murphy, and Hoehn-Saric, (2008) have found decreased skin conductance responses associated with poor arithmetic performance relative to healthy females. In PWS, Priano et al. (2009) assessed EDA, but not during cognitive tasks. They have found sympathetic responses to be within normal ranges.

1.3. The present study

Even though previous studies reported evidence for impaired EF and autonomic dysfunctions in PWS, several issues are still unclear. Regarding executive functions in PWS, previous work has focused largely on mental switching (Woodcock et al., 2009a, 2009b; 2011) in comparison to inhibition and WM updating. Therefore, the present study emphasizes on these latter functions. In addition, a few studies assessing inhibition and WM updating yielded inconsistent results that need clarification. Concerning inhibition, inconsistent results on behavioural measures (Chevalère et al., 2015; Stauder et al., 2005) may be due to the use of different paradigms, which possibly differ in WM demands due to instruction's complexity and varying number of stimuli. To examine inhibition without undesirable effects of WM load, the present study uses a simple version of the Go-nogo task, with straightforward instructions and only two stimuli. Concerning WM updating, we aim at further investigating this EF in PWS, given its importance in normal and pathological cognitive functioning (Carretti et al., 2010; Friedman et al., 2006; Pelegrina et al., 2015). Because the only one study reported so far used a verbal WM updating task (Chevalère et al., 2015), we choose to investigate spatial WM updating in PWS to improve the generalizability of results. N-back tasks usually assess both attentional and storage components of WM and previous work failed to find a deficit of "pure" attentional component of WM possibly due to confounding factors. To cope with that issue, we minimized storage demands in the present task by restricting the memory load to two items (i.e., N-2-Back task). To examine whether a putative deficit of spatial WM updating could be perceptual in nature, we are also interested in examining whether PWS adults could show the same performance while updating either a change in spatial location or updating an absence of change in spatial location. For that purpose, we distinguished between "match" trials, corresponding to a stimulus appearing in the same spatial location as two trials before, and "no-match trials", where the current stimulus appears at a different spatial location as two trials before. If there is a specific perceptual deficit of spatial WM updating in PWS, we should observe specific differences between match and no match trials in PWS adults relative to healthy adults.

Because studies on autonomic functions are scarce in PWS, we examine EDA as an index of sympathetic arousal. One reason is that the sympathetic division in under investigated in genetic neurodevelopmental disorders relative to the parasympathetic division (Giuliano et al., 2017; Heilman et al., 2011). Another reason is that previous work predicted sympathetic overarousal in a range of genetic neurodevelopmental disorders (Bujnakova et al., 2016; Kushki et al., 2013), but inconsistent results challenge this hypothesis. A source of confusion may come from the use of different EDA variables leading to opposite conclusions. In the present study, we differentiated the tonic component (i.e., the skin conductance level) from the phasic component of EDA (i.e., the skin conductance responses). Only the phasic component of EDA is thought to mirror cognitive phenomenon (Dawson et al., 2007). Adopting a straightforward view of the sympathetic overarousal hypothesis, we expect PWS adults to show higher tonic and phasic components of EDA than healthy adults across trials and tasks. In contrast, regarding the link between cognitive functions and sympathetic activity, only skin conductance responses (SCRs) are expected to vary depending on the type of trial.

2. Method

2.1. Participants

Thirty adults with PWS (19 females, 11 males) with an age ranging from 20 years old to 52 years old (mean = 30.4 ± 7.9 years old) took two executive tasks assessing inhibition and working memory updating and were compared to a control group of healthy adults. The PWS group included participants with an IQ ≥ 52, who were able to understand tasks instructions. All of them were recruited at the Marin Hendaye Hospital, a French dedicated center for PWS patients. Intellectual Quotient (IQ) levels were obtained from each patient's medical record. IQ assessments were conducted by the staff psychologist of the Rare Disease Pole at Marin Hendaye Hospital using the Wechsler Adult Intelligence Scale 3rd Edition (WAIS III, Wechsler, 1997). IQ level ranged from 52 to 90 (mean = 66.2, ± 8.8). IQ was not available for two participants. It should be noted that all PWS participants were treated pharmacologically. A group of thirty healthy adults (16 females, 14 males) of approximately similar chronological age acted as controls (age from 17 to 35 years old, mean = 22.6, ± 4.9 years). In addition to the executive tasks, all participants completed the MoCa, (Montréal Cognitive Assessment, Nasreddine et al., 2005). It is a neuropsychological screening tool of rapid administration, similar to the Mini Mental State Examination, that has been proved to show high reliability among many clinical populations (Edge, Oyefeso, Evans, & Evans, 2016; Julayanont, Phillips, Chertkow, & Nasreddine, 2013). Recently, Edge et al. (2016) proved the reliability of the MoCA in a population with learning disabilities (LD). The authors reported excellent reliability (Cronbach α = .78) on the current version of the MoCa, based on the performance of twenty five people with LD (19 with mild LD, 6 with borderline LD). In the present study, twenty-two PWS adults scored under a threshold of 26/30, delimitating normal cognitive efficiency from mild cognitive impairment (mean = 23.7, ± 2.9). In contrast, all healthy adults (N = 30) scored above this threshold (mean = 28.2, ± 1.4). Therefore, none of them were excluded from the study. None of the healthy adults were treated pharmacologically.

2.2. Procedure

On admission at the Marin Hendaye Hospital, a patient with PWS and his/her legal guardian were informed that he/she would be asked whether they wanted to participate on ongoing research studies during their stay. With respect to the principles of the Declaration of Helsinki and the World Medical Association, thirty PWS patients took part of this study on a voluntary basis after they completed an informed consent, which they signed, in agreement with the medical staff of the Rare Disease Pole. Each PWS participant separately took the tasks in a quiet room of the Marin Hendaye Hospital.

All participants read and completed an informed consent form before completing the MoCa. Then, electrodes were placed for the purpose of EDA measurement. Participants were instructed to relax for a short period before the experiment started. The order of the two executive tasks was randomized for all participants. Adults with PWS were administered the session in a quiet room at the Marin Hendaye Hospital. Healthy adults were administered the session in an experimental box at the University of Bordeaux.

2.3. Material

2.3.1. Executive tasks

Two executive tasks assessing behavioural inhibition and working memory updating were administered to the PWS and healthy adults. The inhibition measure was a Go-no go task. It is a computerized programmed task with Eprime 2.0 software made of 192 trials divided into 4 blocks of 48 trials with a familiarization block and three experimental blocks (144 trials). Each trial corresponds to a total duration of 1500 ms where the participant has to press a key when a go stimulus is presented in the centre of the screen (i.e. a letter "M", approximately 100*80 pixels) or does not respond when a no go stimulus appears (the letter "W"). The 1500 ms are split up in 3 successive phases. The first phase is a blank screen superimposed with a fixation cross for 500 ms. Then, a letter M or W then appears for 200 ms and the third phase corresponds to the remaining time for the participant's response (800 ms) with a blank screen. The letter M occurs within 75% of the trials while the letter W occurs only in 25% of the cases. This manipulation is performed to develop an overlearned pattern of response (a majority of go trials), which would contrast with the unexpected need to suppress the same pattern during the no go trials. The order of the go and no go trials was randomized, thereby preventing the development of response strategies. Dependent variables were reaction times to the go trials and percentage of errors on the no go trials (i.e., pressing the key erroneously, commission errors). Commission errors are thought to be an indicator of impulsivity (Logan, Schachar, & Tannock, 1997; Reynolds, Ortengren, Richards, & de Wit, 2006). Because no go trials require an absence of behavioural response, it was helpful to rely on EDA as an indicator of cognitive inhibition. Moreover, the EDA responses to no go trials (SCL in microsiemens, the number of SCRs, the latency of SCRs in seconds and the amplitude of SCRs in microsiemens) enabled a direct comparison with go trials that was not made possible with behavioural data alone.

Working memory updating was assessed with an N-2-Back task. This is a computerized task with 128 trials divided into 4 blocks of 32 trials with one familiarization block and 3 experimental blocks. For each trial, the participant has to remember the position N-2 of the letter M in a 4 × 4 grid. The N-2 position means the position of the letter two trials before the current trial. Participants have to judge whether the current letter M at N0 is actually in the same cell as in the trial before last N-2 by pressing either "enter" for yes or "0" for no. This manipulation ensures that a putative deficit of spatial WM updating is not restricted to perceiving a change or perceiving an absence of change in spatial location. A block begins with the presentation of two successive and random M positions in the grid, for 500 ms each, to allow the first two M positions to be retained, followed by the display of the blank 4 × 4 grid for 1000 ms and ends with the presentation of only one M position (i.e., the trial N0) in the grid for unlimited response time. The sequence of the trials was determined a priori to ensure equal matching and no matching N-2 trials ($n = 16$ in each condition), and was generated randomly using a random number generator program.

2.3.2. Event-related design and data acquisition

To locate specific electrodermal responses related to distinct cognitive processes during the executive tasks, we used an event-related design in which different EDA markers were assigned to specific trials. EDA markers distinguished between activation and inhibition trials in the Go-no go task and between updating-a-change trials (no match trials) and updating-an-absence-of-change trials (match trials) in the N-2-Back task. Electrodermal responses were acquired with the BIOPAC module MP150 (BIOPAC Systems, Inc). This represents micro-variations in the electrical conductance of skin submitted to a constant voltage of 0.5 V using the EDA100C module. Acquisition parameters were set with AcqKnowledge 4.1 for an event-related analysis. Sampling rate was 1000/s, which is suitable for this design (Braithwaite, Watson, Jones, & Rowe, 2013). Event-related markers were sent from the Eprime software to the BIOPAC STP100C module to ensure acquisition of electrodermal responses to specific events. Confidence interval for collecting EDA peaks was set at 1–5 seconds (i.e., the time interval for isolating EDA peaks locked to experimental events). Raw data were high pass-filtered (0.05 Hz) to separate the tonic and phasic components of EDA. For the phasic component, the SCR detection threshold was set at 0.01 μs.

2.3.3. EDA recording

Traditionally, electrodes are placed on the palmar part of the hand. As participants used both hands during the executive tasks, the electrodes were placed on the medial plantar part of the feet, which provides enough concentration of eccrine glands (Boucsein et al., 2012). The signal was amplified with the EDA100c module. Electrodes were placed on the left foot of all the participants. Dependent variables were the tonic component of EDA – as measured with the skin conductance level (SCL) – and the phasic component – as measured with the number of skin conductance responses (SCRs), the latency of SCRs in seconds, and the amplitude in microsiemens (μs). It should be noted that height and weight influence EDA (Bach, Flandin, Friston, & Dolan, 2010; Peterson et al., 1988). Therefore, Body Mass Index (BMI) was measured in all participants (see in Table 1). The experiment started with a habituation period of approximately 3 min.

2.3.4. Statistical analyses

To determine whether PWS presents with impaired inhibition and WM updating relative to the healthy population, our analysis approach consisted in comparing the performance of a sample of 30 adults with PWS to that of 30 healthy adults on the two executive

Table 1
Participant's characteristics.

	PWS adults (*N* = 30)	Healthy adults (*N* = 30)
N (females)	19	16
Mean Age in years (*SD*)	30.4 (7.9)	22.6 (4.9)
Age Range (years)	20-52	17-35
Mean Full Scale IQ (*SD*)	66.2 (8.8)	–
Montréal Cognitive Assessment (*SD*)	23.7 (2.9)	28.2 (1.4)
Body Mass Index	45.7 (12.3)	21.6 (2.9)

tasks. The same comparison strategy was used to assess whether PWS adults show abnormal EDA relative to the healthy population. In experiment 1 (inhibition), we sought to determine whether distinct cognitive processes (i.e., inhibition and activation) may lead to differentiable EDA responses and whether this effect may vary in PWS relative to the normal population. The analysis of behavioural performance was made by running a series of one-way analysis of variance to determine the effects of group (PWS adults; healthy adults) on reaction time and percentage of errors separately. We also conducted mixed-designs analysis of covariance to determine the main effects of groups and type of trials (inhibition vs. activation) on EDA measures and to examine whether the type of trials effects were the same in the two groups (Group x Type of Trial interactions). The mixed design ANOVAs were conducted separately for each EDA dependent variable (SCL, number of SCRs, latency of SCRs and amplitude of SCRs). Analyses of covariance allowed us to control potential undesirable effects that age, gender and body mass index may have on executive performance and EDA measures. In experiment 2 (WM updating), a series of mixed design ANOVA were conducted to assess the main effects of groups on WM updating performance. Here, the Group x Type of Trial (match; no match) interaction effects allowed to test whether a potential WM updating deficit in PWS could be perceptual in nature. The undesirable effects of age, gender and body max index were determined prior to analysis of executive performance and EDA, using Chi^2 independence test for gender comparisons and one-way analyses of variance for age and BMI comparisons. Finally, we examined the relation between cognition and sympathetic arousal using a cautious correlational approach. It consisted of conducting correlations in separate groups as well as in the whole cohort to ensure the detection of systematic psychobiological associations only. The *p* value was divided by the number of correlations.

3. Results

3.1. Age, gender and body mass index

A one-way analysis of variance (ANOVA) with group as between-participants factor revealed that PWS adults were older (30.4 years) than healthy adults (22.6 years), $F(1, 58) = 20.5$, $MSe = 43.5$, $p < .001$, $\eta^{2p} = .26$. A Chi^2 test revealed that the proportion of females was homogeneous in PWS (63.3%) and healthy adults (53.3%), $X^2 < 1$, *ns*. A one-way ANOVA with group as between-participants factor revealed that PWS adults had a higher BMI (45.7) than healthy adults (21.6), $F(1, 58) = 108.24$, $MSe = 80.57$, $p < .001$, $\eta^{2p} = .65$. All the following analysis were corrected for age and BMI.

3.2. Experiment 1 inhibition

To examine behavioural data, a series of one-way analyses of covariance (ANCOVAs) with group as between-participants factor and age and BMI as covariates were conducted separately on reaction time (go trials) and percentage of errors (no go trials). As shown in Fig. 1, PWS adults (448 ms) were slower than healthy adults (363 ms) during go trials, $F(3, 56) = 10.35$, $MSe = 2410.94$, $p < 0.01$, $\eta^{2P} = 0.15$. During no go trials, PWS adults (3.5%) made more errors than healthy adults (2.2%), $F(3, 56) = 9.47$, $MSe = 4.08$, $p < 0.01$, $\eta^{2P} = 0.14$.

Electrodermal data were analysed with a series of 2(groups) x 2(type of trials: go vs. no go) mixed design ANCOVAs with age and

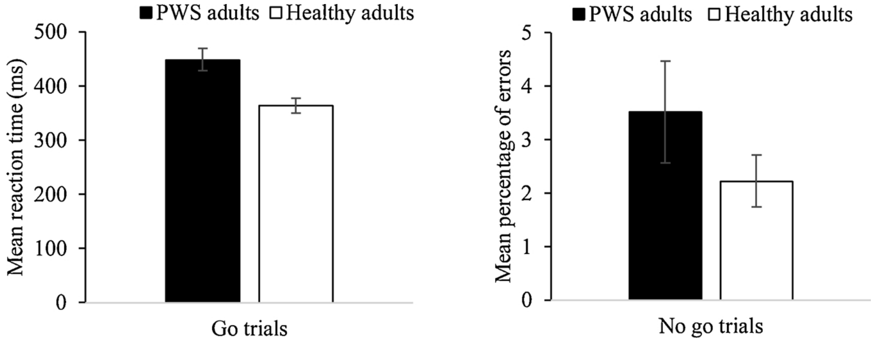

Fig. 1. Mean Go-nogo performance in PWS and healthy adults (CI:95%).

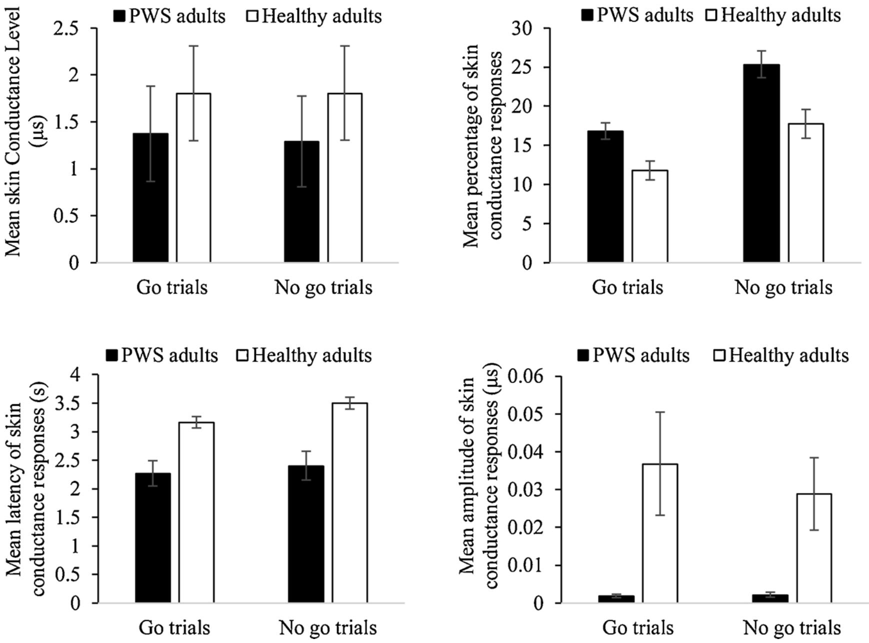

Fig. 2. Mean electrodermal activity in PWS and healthy adults for go and no go trials during the Go-nogo task (CI:95%).

BMI as covariates and group as the only between-participants factor.

3.2.1. Skin conductance level

As shown in Fig. 2, PWS adults (1.32 µs) and healthy adults (1.80 µs) showed equal SCL, $F < 1$. SCL was higher on go (1.58 µs) relative to no go trials (1.54 µs), $F(3, 56) = 9.65$, $MSe = 0.045$, $p < 0.01$, $\eta^{2P} = 0.14$. The Group x Type of Trial interaction was non-significant ($F < 1$).

3.2.2. Percentage of skin conductance responses

As there were three times more go trials than no go trials, we transformed the number of SCRs into a percentage of skin conductance responses across blocks and used it as dependent variable. The percentage of SCRs was calculated as follows: $\frac{number\ of\ SCRs}{number\ of\ trials}\ x\ 100$. PWS adults (21.2%) showed more SCRs than healthy adults (14.8%), $F(3, 56) = 9.48$, $MSe = 34.59$, $p < 0.01$, $\eta^{2P} = 0.14$. Participants showed less SCRs on go (14.3%) relative to no go trials (21.53%), $F(3, 56) = 10.68$, $MSe = 5.48$, $p < 0.01$, $\eta^{2P} = .16$. The Group x Type of Trial was non-significant, $F(3, 56) = 2.15$, $MSe = 5.48$, *ns*.

3.2.3. Latency of skin conductance responses

PWS adults (2.33 s) showed faster SCRs than healthy adults (3.33 s), $F(3, 56) = 15.04$, $MSe = 0.49$, $p < 0.001$, $\eta^{2P} = 0.21$. For all participants, latency was equal on go (2.71 s) and no go trials (2.95 s), $F < 1$. The Group x Type of Trial interaction was non-significant, $F(3, 56) = 3.61$, $MSe = 0.04$, *ns*.

3.2.4. Amplitude of skin conductance responses

PWS adults (0.002 µs) showed smaller SCRs than healthy adults (0.03 µs), $F(3, 56) = 16.30$, $MSe = 0.001$, $p < 0.001$, $\eta^{2P} = .22$. No other effect was significant ($Fs < 1$).

3.3. Correlational analyses

To examine the relation between behavioural measures themselves, EDA measures themselves and behavioural and EDA measures, we conducted Pearson partial correlational analyses controlling for age and BMI. As twelve comparisons were led between dependent variables, only correlations surviving a value of $p = .05/12 = p = .004$ were considered relevant. As shown in Table 2, results on the whole group revealed significant correlations between EDA measures, and between behavioural and EDA measures but an absence of correlation between behavioural measures themselves at $p = .004$. EDA measures correlated strongly with each other. Only latency and SCL and latency and amplitude were not correlated at $p = .004$. On correlations between behavioural and EDA measures, reaction time was positively correlated with number of SCRs at .44***.

Analysis of the PWS group showed some important changes. At the behavioural level, the negative correlation between reaction times and percentage of errors became significant (−0.53****) indicating a speed accuracy trade-off in PWS adults. The negative correlation between the number of SCRs and latency was reinforced (−.88**) while other correlations between EDA measures

Table 2
Pearson's partial correlations controlling for age and body mass index of behavioural and EDA measures, behavioural intra-correlations and EDA intra-correlations for the whole group, PWS adults, and healthy adults during the Go-nogo task.

		Behavioural		Electrodermal Activity			
PWS + Healthy adults		Reaction time (Go)	Percentage of errors (No go)	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time (Go trials)	–	−.28*	−0.15	.44***	.26*	−.36**
	Percentage of errors (No go)		–	−0.06	0.18	−.30*	−0.05
EDA	Skin Conductance Level			–	−.63***	.26*	.59***
	Number SCRs				–	−.71***	−.70***
	Latency SCRs					–	.36**
	Amplitude SCRs						–
		Behavioural		**Electrodermal Activity**			
PWS adults		Reaction time (Go)	Percentage of errors (No go)	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time (Go)	–	−.53***	−.21	.24	−.20	.12
	Percentage of errors (No go)		–	−.26	.08	−.19	.11
EDA	Skin Conductance Level			–	−.59**	.44*	.41*
	Number SCRs				–	−.88***	−.37
	Latency SCRs					–	.28
	Amplitude SCRs						–
		Behavioural		**Electrodermal Activity**			
Healthy adults		Reaction time (Go)	Percentage of errors (No go)	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time (Go)	–	−.27	−.20	.38*	.21	−.52**
	Percentage of errors (No go)		–	−.11	.30	.00	−.11
EDA	Skin Conductance Level			–	−.59***	−.19	.62***
	Number SCRs				–	−.11	−.90***
	Latency SCRs					–	.03
	Amplitude SCRs						–

Note. * = $p < .05$; ** = $p < .01$; *** = $p \leq .004$ (i.e., the only relevant significance level, controlling for number of comparisons).

themselves were no longer significant at $p = .004$. No other correlations were significant.

Analysis of the control group revealed no significant correlation between behavioural measures themselves suggesting no speed-accuracy trade-off in healthy adults. At the physiological level, EDA measures correlated strongly with each other except for latency that was not correlated with other EDA measures. There were no significant correlations at $p = 0.004$ between behavioural and EDA measures.

3.4. Experiment 2 working memory updating

To examine behavioural data, a series of 2(groups) × 2(type of trials: match vs. no match) mixed design analyses of covariance (ANCOVAs) with age and BMI as covariates and group as the only between-participants factor were conducted separately on reaction times and percentage of errors.

3.4.1. Reaction time

As shown in Fig. 3, PWS adults (1307 ms) were slower than healthy adults (946 ms), $F(3, 56) = 10.97$, $MSe = 112{,}837.76$, $p < 0.01$, $\eta^{2P} = .16$. Participants were equally fast on match (1026 ms) and no match trials (1227 ms), $F(3, 56) = 2.87$, $MSe = 14{,}988.25$, *ns*. The Group x Type of Trial interaction was non-significant ($F < 1$).

3.4.2. Percentage of errors

PWS adults (29.61%) made more errors than healthy adults (8.39%), $F(3, 56) = 34.47$, $MSe = 172.53$, $p < 0.001$, $\eta^{2P} = .38$. No other effect was significant, ($Fs < 1$).

Electrodermal data were analysed with a series of 2(groups) × 2(type of trials: match vs. no match) mixed design analyses of covariance (ANCOVAs) with age and BMI as covariates and group as the only between-participants factor.

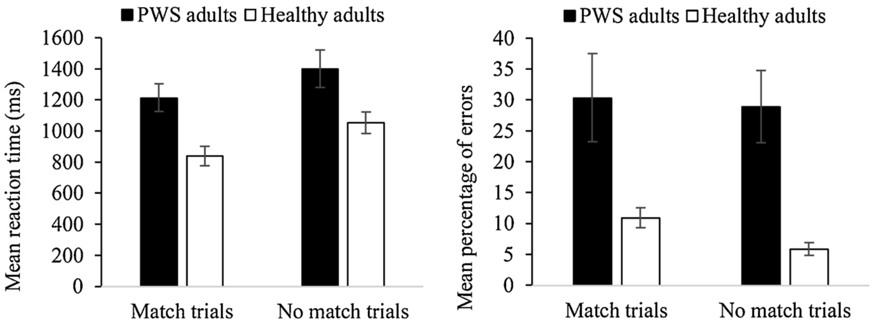

Fig. 3. Mean performance in PWS and healthy adults for match and no match trials during the N-2-Back task (CI:95%).

3.4.3. Skin conductance level

As shown in Fig. 4, PWS adults (1.32 μs) and healthy adults (1.74 μs) showed equal SCL, $F < 1$. No other effect was significant ($F < 1$).

3.4.4. Number of skin conductance responses

Because there were as many match trials and no match trial, the number of SCRs was used as dependent variable. PWS adults (23.15) showed more SCRs than healthy adults (12.3), $F(3, 56) = 14.92$, $MSe = 63.56$, $p < 0.001$, $\eta^{2P} = 0.21$. Participants showed as many SCR on match (17.5) and no match trials (17.9), $F < 1$. The Group x Type of Trial interaction was non-significant, $F(3, 56) = 3.52$, $MSe = 1.47$, *ns*.

3.4.5. Latency of skin conductance responses

PWS adults (2.39 s) showed faster SCRs than healthy adults (3.72 s), $F(3, 56) = 17.93$, $MSe = 0.7$, $p < 0.001$, $\eta^{2P} = 0.24$. For all participants, SCRs were equally fast on match (3.03 s) and no match trials (3.08 s), $F < 1$. The Group x Type of Trial interaction was non-significant, $F < 1$.

3.4.6. Amplitude of skin conductance responses

PWS adults (0.003 μs) showed smaller SCRs than healthy adults (0.023 μs), $F(3, 56) = 12.87$, $MSe = 0.001$, $p < 0.001$, $\eta^{2P} = .18$. No other effect was significant.

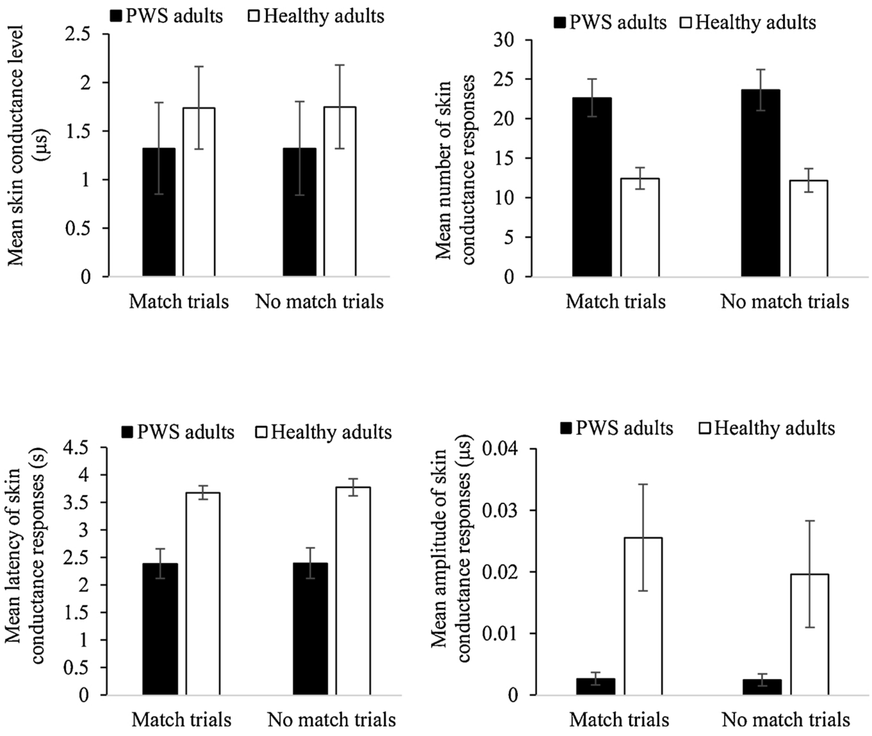

Fig. 4. Mean electrodermal activity in PWS and healthy adults for match and no match trials during the N-2-Back task (CI:95%).

Table 3
Pearson's partial correlations controlling for age and body mass index of behavioural and EDA measures, behavioural intra-correlations and EDA intra-correlations for the whole group, PWS adults, and healthy adults during the N-2-Back task.

		Behavioural		Electrodermal Activity			
PWS + Healthy adults		Reaction time	Percentage of errors	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time	–	.07	−.24	.15	−.22	−.27*
	Percentage of errors		–	.02	.33*	.34**	−.22
EDA	Skin Conductance Level			–	−.32*	.10	.43***
	Number SCRs				–	−.80***	−.49***
	Latency SCRs					–	.32*
	Amplitude SCRs						–
PWS adults		Reaction time	Percentage of errors	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time	–	−.12	−.07	.03	−.16	−.17
	Percentage of errors		–	.10	.09	.06	.01
EDA	Skin Conductance Level			–	−.27	.14	.32
	Number SCRs				–	−87***	−.42*
	Latency SCRs					–	.38*
	Amplitude SCRs						–
Healthy adults		Reaction time	Percentage of errors	Skin Conductance Level	Number SCRs	Latency SCRs	Amplitude SCRs
Behavioural	Reaction time	–	.19	.44*	.14	−.16	−.15
	Percentage of errors		–	−.07	−.07	.03	.09
EDA	Skin Conductance Level			–	−.53***	.12	.53***
	Number SCRs				–	−.29	−.54***
	Latency SCRs					–	.13
	Amplitude SCRs						–

Note. * = $p < .05$; ** = $p < .01$; *** = $p \leq .004$ (i.e., the only relevant significance level, controlling for number of comparisons).

3.5. Correlational analyses

Table 3 shows Pearson partial correlational analyses controlling for age and BMI. Analysis of the whole group revealed an absence of correlation between behavioural measures themselves. On the links between EDA measures themselves, amplitude was positively and moderately correlated with SCL (.43***). Amplitude was negatively correlated with the number of SCRs (−.49**). The number of SCRs was negatively and strongly correlated with latency (−.80***). There were no significant correlations between behavioural and EDA measures at $p = .004$.

Analysis of the PWS group showed important loss of correlations. The only significant correlation was between the number of SCRs and latency (−87***).

Analysis of the control group revealed some changes relative to the whole group analysis. Loss of correlations concerned the links between latency and the number of SCRs (−.29, *ns*) suggesting that these links were only present in PWS individuals. Inversely, the links between SCL and the number of SCRs became significant at $p = .004$ (−.53***).

4. Discussion

The aim of this study was twofold. A first objective was to clarify the status of inhibition and working memory updating capacities in PWS relative to the healthy population. A second objective was to search for sympathetic autonomic signatures during executive tasks and to examine their relationship with executive performance. We asked PWS and healthy adults to perform a task assessing inhibition and a task assessing working memory updating while electrodermal responses were recorded in an event-related design. PWS adults underperformed healthy adults on the inhibition task and on the WM updating task. PWS adults showed normal tonic skin conductance level but abnormal phasic skin conductance responses as indexed by a higher number of SCRs, shorter latency and smaller amplitude of SCRs. In addition, results support the existence of distinct sympathetic autonomic signatures depending on certain task conditions and groups. In the inhibition task, the SCL and the number of SCRs were distinct depending on activation (go) or inhibition (no go) trials. Across tasks, PWS adults showed less numerous and weaker correlation between EDA measures, but also different type of correlations relative to healthy adults. We have not found any consistent association between behavioural measures and EDA measures either in PWS or in healthy adults. The findings have implications for understanding executive dysfunctions and autonomic regulation in PWS. These issues are discussed in the following.

4.1. Executive dysfunctions in PWS

In recent years, knowledge on PWS cognitive profile has improved substantially, notably with the identification of impaired mental switching relative to the healthy population (Chevalère et al., 2015; Whittington & Holland, 2017; Woodcock et al., 2009a). While the presence of mental switching deficit in PWS is quite consensual, the status of other executive functions is unclear. Concerning inhibition, Stauder et al. (2005) observed no behavioural differences with the healthy population whereas Chevalère et al. (2015) did observe a lower performance in PWS. One reason for that inconsistency may have arisen from the use of different paradigms possibly varying in WM demands. In line with Chevalère et al. the present findings revealed impaired inhibition in PWS on behavioural measures, in a simpler version of the Go-nogo task than in Stauder et al. study, minimizing the impact of WM demands. It is worth noting that the group effect size observed here was small (0.09), suggesting a slight deficit in PWS which might have not been detected in Stauder's behavioural measures, possibly due to type II error related to small sample size (PWS n = 11). The slight impairment of inhibition capacities in PWS found here is consistent with reports of impulsivity (Puri, Sahl, Ogden, & Malik, 2016; Sinnema et al., 2011) even though the present study, in which impulsivity was not measured, was not able to establish this relationship. A way to further address this issue would be to consider the existence of different psychopathological profiles in PWS, as suggested by Thuilleaux et al. (2018). Based on clinical observation, the authors proposed a four-profile model to better characterize psychopathological features in PWS including basic, impulsive, compulsive, and psychotic profiles. A possibility is that the inhibition deficit, and its putative association with measures of impulsivity may be stronger in patients presenting with impulsive and perhaps compulsive profiles, relative to basic and psychotic profiles. Therefore, impaired inhibition may not be common to all PWS individuals. This would also be consistent with the Stauder et al. study reporting differences in inhibition capacity between disomy and deletion sub-groups.

The status of WM updating is also unclear. A study by Chevalère et al. (2015) assessing verbal WM updating failed to find a deficit of pure attentional WM updating. In the present study however, where WM storage demands were minimized using an N-2 Back procedure, the task was still very difficult to perform for PWS adults. Indeed, we found large group effect sizes on reaction times and percentage of errors (.38 and .57 respectively). The absence of Group x Type of Trial interactions suggests that the WM updating deficit is not perceptual. The present findings showing severe impairment of spatial WM updating in PWS can be linked to the recent literature on spatial competences in PWS (Foti, Menghini, Pestroni et al., 2011; Foti, Menghini, Petrosini et al., 2015,b). In ecological settings, Foti and colleagues investigated spatial functions in PWS, along with neuropsychological assessment of short-term memory. In the Foti, Menghini, Petrosini et al. (2015) experiment, participants had to search for hidden buckets in three different configurations of a real-size maze. The findings suggest that impairment of spatial abilities in PWS concern visuo-motor integration but are not mnesic in nature. In addition, PWS individuals showed normal performance on short-term memory tests, but interestingly, a lower spatial span relative to TD children in one setting of the experiment (the cross configuration). As pointed out by the authors, the cross configuration is particularly challenging and requires a strategy change during the search. Consequently, this setting possibly taps more into working memory updating (i.e., attentional control). Besides, short-term memory tests are known to minimize attentional demands relative to working memory tests (Cowan, 2008). A possible interpretation that would reconcile both the present findings and those of Foti and colleagues is that attentional control may be a crucial mechanism needed for succeeding in the cross-configuration maze and spatial WM updating tasks. Therefore, attentional control may be particularly impaired in PWS in the spatial domain. In the following section, we discuss whether the cognitive impairments may be linked to autonomic dysfunctions.

4.2. Autonomic activity in PWS during executive tasks

The contribution of ANS to cognition is becoming an increasingly hot research topic in genetic neurodevelopmental disorders, as recent work suggested that a range of maladaptive behaviours may emerge from parasympathetic underactivity associated with sympathetic overarousal (Bujnakova et al., 2016; Heilman et al., 2011; Porges et al., 2013; Schwartz et al., 2016). Focusing on the possibility that PWS adults may show sympathetic overarousal, and according to previous work showing a predominance of sympathetic brain regions during cognitive tasks, we expected PWS adults to show higher tonic and phasic EDA than healthy adults during executive tasks (Beissner et al., 2013; Bujnakova et al., 2016). Depending on which EDA dependent variable was examined, group comparisons revealed equal tonic EDA (SCL), in line with Priano et al. (2009), and a higher phasic EDA as evidenced by a higher number of SCRs in PWS, in favour of the sympathetic overarousal hypothesis, and consistent with results of Kushki et al., 2013 in ASD children. Moreover, one of the most fascinating and original finding here was the observation of unique sympathetic autonomic signatures in the two groups and across tasks as evidenced by different type of associations between EDA measures in the two groups. In healthy adults, SCL, the number of SCRs and the amplitude of SCRs were consistently correlated, while in PWS adults, latency of SCRs correlated with the number of SCRs. Interestingly, latency was shorter in PWS. As an explanation, Bach et al. (2010) suggested that some variance of latency of SCR might be linked to processing time in the central nervous system and Petrone, Carbone, and Champagne-Lavau, (2016) suggested that shorter latencies of SCRs may reflect higher sympathetic arousal that support rapid action preparation. In line with a cognitive perspective of EDA, where SCRs are particularly highly sensitive to cognitive performance (Dawson et al., 2007), our results suggest that overactivation of the sympathetic division in PWS may be related to difficulties during cognitive effort underpinned by less cognitive resource available for task performance. The presence of lower amplitude of SCRs in PWS relative to healthy adults is also in line with this possibility since amplitude is a good indicator of processing demands in cognitive tasks (Botvinick & Rosen, 2009; Critchley, 2002). A way to clarify the complex association of sympathetic activity with task performance would be to provide with incremental validity of sympathetic measurements by using other pure indicators as well, like the cardiac preejection period (Giuliano et al., 2017) and eventually merge them into a latent variable in order to grasp a common source of variance. The links between cognitive performance and autonomic responses are further confirmed with findings concerning specific sympathetic autonomic signature following distinct processes involved in EF tasks. EDA was reactive to different types of trials in the Go-nogo task, which is consistent with previous studies (Munro et al., 1987; Yuille & Hare, 1980; Zhang et al., 2012). Inhibitory process (i.e., no go trials) decreased SCL and increased the proportion of SCRs in all participants relative to activation of behaviour (i.e., go trials). These results suggest that sympathetic activity plays a role in cognitive performance, in line with the Neurovisceral Integration Model (Thayer & Lane, 2009).

Examining Group x Type of Trial interactions across tasks was of particular interest because it would shed light on straightforward links of specific cognitive impairments and sympathetic overarousal in PWS. However, we have not succeeded in this. None of the effects of interest were significant on any of the EDA measures, suggesting that sympathetic dysfunctions and executive impairments are more independent than expected, at least in PWS. Nevertheless, these results are to be confirmed. As PWS is a neurodevelopmental disorder, it would also be interesting to determine whether similar findings can be obtained among children with PWS. Because important systems are differentiating at both physiological level and cognitive levels during growth, there might be a closer interplay of autonomic and cognitive functions in children, possibly allowing for more effective therapeutic interventions.

4.3. Limitations of the study

The present study has a number of limitations. Even though the IQ level of the PWS sample was representative of the PWS population (Copet et al., 2010), the present results are not generalizable to all PWS adults, especially those with an IQ > 52. A second limitation concerns the potential effects of genotypes on executive performance or on sympathetic activity. Indeed, the present study did not compare PWS adults with different aetiologies. As we failed to find relevant associations between executive performance and sympathetic arousal in the PWS sample, it cannot be ruled out that a large disproportion of deletion and m-UPD participants might have masked the presence of specific psychobiological interactions in m-UPD. Future studies should examine psychobiological interactions by comparing the two main aetiologies in PWS: deletion and m-UPD. A third limitation concerns the lack of a control group matched on IQ level or mental age. In particular, such a control group would have brought important insights about the specificity of PWS endophenotype relative to other genetic developmental disorders in terms of executive performance, sympathetic arousal and their interplay.

In conclusion, the present study documented inhibition and working memory updating capacities in PWS. The findings suggest that PWS adults are associated with slightly impaired inhibition and severely impaired working memory updating functions. The psychobiological approach adopted here furthers our understanding of the cognitive endophenotype of PWS as evidenced by specific sympathetic autonomic signatures in PWS relative to healthy adults during executive tasks. Following up on this work may shed important light on the interplay of cognitive impairments and autonomic dysfunctions in PWS.

Conflict of interest

The authors have no conflict of interest to declare

Acknowledgements

We thank all the participants of this study and the medical staff at Hôpital Marin d'Hendaye for their enthusiasm.

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