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Deficits in voice and multisensory processing in patients with Prader-Willi syndrome

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ABSTRACT

Prader-Willi syndrome (PWS) is a rare neurodevelopmental and genetic disorder that is characterized by various expression of endocrine, cognitive and behavioral problems, among which a true obsession for food and a deficit of satiety that leads to hyperphagia and severe obesity. Neuropsychological studies have reported that PWS display altered social interactions with a specific weakness in interpreting social information and in responding to them, a symptom closed to that observed in autism spectrum disorders (ASD). Based on the hypothesis that atypical multisensory integration such as face and voice interactions would contribute in PWS to social impairment we investigate the abilities of PWS to process communication signals including the human voice. Patients with PWS recruited from the national reference center for PWS performed a simple detection task of stimuli presented in an uni-o or bimodal condition, as well as a voice discrimination task. Compared to control typically developing (TD) individuals, PWS present a specific deficit in discriminating human voices from environmental sounds. Further, PWS present a much lower multisensory benefits with an absence of violation of the race model indicating that multisensory information do not converge and interact prior to the initiation of the behavioral response. All the deficits observed in PWS were stronger for the subgroup of patients suffering from Uniparental Disomy, a population known to be more sensitive to ASD. Altogether, our study suggests that the deficits in social behavior observed in PWS derive at least partly from an impairment in deciphering the social information carried by voice signals, face signals, and the combination of both. In addition, our work is in agreement with the brain imaging studies revealing an alteration in PWS of the "social brain network" including the STS region involved in processing human voices.

1. Introduction

Prader-Willi syndrome (PWS) is a neurodevelopmental and multisystem genetic disorder caused by the absence or inactivation of paternal genes carried by the 15q11.2-q12 region of chromosome 15 (Cassidy and Driscoll, 2009; Nicholls and Knepper, 2001). The absence of gene expression is due to a deletion (DEL) in approximately 55% of the cases or to a maternal uniparental disomy (mUDP) in 40% of the cases. A few patients (5%) have either a chromosomal translocation or an imprinting deficit that may be due to a microdeletion or an epigenetic modification. Epidemiological studies of PWS have estimated its incidence at birth at around 1/20000 (Vogels et al., 2004; Whittington, et al., 2001).

Clinically, PWS is characterized by the expression of endocrine, cognitive and behavioral problems that occur after a very consistent postnatal phenotype of severe hypotonia and sucking deficit, which may result in failure to thrive and subsequent tube feeding to ensure normal weight gain (Holm et al., 1993). Other characteristics include typical dysmorphic features such as a narrow bi-frontal diameter, dolichocephaly, almond-shaped eyes, and a thin and down-turned upper lip, associated with small hands and feet. Starting at about two years, the nutritional phenotype shifts from failure to thrive to excessive weight gain and, ultimately, a true obsession with food and a deficit of satiety that lead to hyperphagia and severe obesity. For these reasons, we consider PWS to be a disease that starts with anorexia and progresses to

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obesity (Tauber et al., 2014). The pathological fixation on food is partially linked to hypothalamic dysfunctions that also cause impaired growth hormone secretion (Lee et al., 1995), as well as other pituitary hormone deficits such as hypogonadism, hypothyroidism and occasionally corticotropin deficit (Burman et al., 2001; Goldstone et al., 2008).

In addition to these core phenotypic characteristics, neuropsychological studies have detailed several cognitive deficits in PWS, such as intellectual disability (Copet et al., 2010; Whittington et al., 2001). The neuropsychological dysfunctions also include attention deficits (Gross-Tsur et al., 2001; Jauregi et al., 2007) and short-term and long-term memory alterations, with the latter being more severely affected (Cassidy, 1997; Conners, 2000). Auditory processing is worse than visual processing, with high scores in Block Design and Coding or Mazes (Curfs et al., 1991), and deficits have been observed in executive tasks with a relative impairment in the phonological loop, perhaps related to the capacity of the phonological store, which is particularly salient for patients with a deletion. Compared with other genetic syndromes with mild levels of intellectual disability, high rates of behavioral problems have been reported in PWS, including temper outbursts, obsessive behaviors, skin picking, perseverative speech, rigid thinking and difficulties in coping with change (Clarke et al., 2002; Dykens et al., 1992). These behavioral problems are part of the neuropsychiatric abnormalities of an affective disorder, including mood instability, nonpsychotic depression, and psychosis (Soni et al., 2007).

The observation that some of the behavioral symptoms found in PWS are also commonly observed in autism spectrum disorders (ASD) was of interest for the present study. The abnormal behaviors that are similar include obsessive behavior that is often ritualistic, repetitiveness in actions and speech, lack of inhibition, stereotyped behaviors, rigid thinking, and difficulty in coping with change and temper outbursts. Comorbidity with psychiatric disorders has been related to obsessive-compulsive disorders (Dimitropoulos et al., 2006; Dykens et al., 1996), different forms of psychosis (Boer et al., 2002; Verhoeven and Tuinier, 2006) and ASD (Veltman et al., 2005). In addition the level of cognitive impairment in PWS is not associated with severity for most of the maladaptive behaviors (Curfs et al., 1991; Jauregi et al., 2013). In a meta-analysis of case reports, Veltman and colleagues (Veltman et al., 2005) present evidences that the rate of ASD found in PWS patients is of about 25–30%. Such ASD prevalence in PWS is probably underestimate, and is significantly higher in mUPD patients compared to patients with DEL, a result that reinforce the common susceptibility of chromosome 15 in both ASD and PWS.

In addition to this genetically common origin, PWS and ASD are also characterized by similar behavioral alterations. Patients with PWS display altered social interactions, with notable difficulty in interpreting and responding to social information (Dimitropoulos and Schultz, 2007). Both PWS and ASD patients find it hard to establish harmonious peer group relationships, demonstrating disinhibition, lack of empathy and social withdrawal (Holland et al., 2003a, 2003b; Koenig et al., 2004). Studies in autism have suggested a relationship between the social deficits and cognitive processing, like emotional perception (Ozonoff et al., 1990), difficulties in understanding the intentions of others theory of mind; (Baron-Cohen et al., 1999), executive functions (Rumsey and Hamburger, 1988) and central coherence (Frith, 1989).

The difficulties that ASD patients display with personal relationships and communication with others are probably related to abnormal processing of human face and voice information (Adolphs et al., 2001; Ujiie et al., 2015). In humans and animals, voice processing is important for social interactions since it carries speech information as well as non-speech identity information about gender, age, physical factors and emotions. From this perspective, the voice can be considered to be an “auditory face” (Belin et al., 2004). Neuropsychological (Van Lancker et al., 1989) and brain imaging studies (Belin et al., 2000; Von Kriegstein and Giraud, 2004) have revealed specific cortical regions, mostly in the temporal lobe, involved in processing voice information. In humans and monkeys, visual cues (facial displays) have a strong impact on the perception of communication sounds (Chandrasekaran et al., 2009; McGurk and MacDonald, 1976). As the visual and vocal information about a person's identity show strong complementarity, several models of face/voice interactions have been proposed as giving rise to an internal supra-modal representation of the person (Campanella and Belin, 2007).

Behavioral and brain imaging studies of ASD patients have revealed severely impaired processing of the communication cues embedded in face and voice stimuli. Hypoactivity has been observed in the frontal and temporal integration cortices in these individuals, and this suggests that they may recruit the parieto-frontal network as an alternate compensatory system, given the absence of engagement in integrative emotional networks during audiovisual emotion matching (Doyle-Thomas et al., 2013). Further, in addition to abnormally reduced activity in response to complex spectro-temporal speech stimuli, ASD patients show no activation in the temporal voice areas (TVAs), which are typically more sensitive to vocal stimuli (Gervais et al., 2004). Similar abnormalities have been found for face processing, indicating a general face discrimination deficit in these individuals (Critchley et al., 2000; Klin et al., 1999). Interestingly, in patient suffering of Prader-Willi syndrome, a recent brain imaging study of our group (Mantoulan et al., 2011) revealed a restricted set of hypo-perfused cortical areas at rest compared with that of normal subjects. The areas encompassed the anterior cingulum and cingulate cortex, known to be involved in theory of mind and empathy, as well as the auditory area of the superior temporal gyrus, specialized in processing vocal and speech information.

The present study aimed to determine how PWS patients process multisensory information, including visual and auditory communication cues. We hypothesized that atypical multisensory integration (MSI) would contribute to their social impairment, which manifests as the avoidance of over-stimulating environments and a focus on repetitive sensory attributes (Lovaas et al., 1979). Again, the hypothesis of a global deficit in multisensory integration in PWS emanates from previous studies showing evidences for such impairment in ASD (see Martinez-Sanchis (2014)). ASD patients present deficit in MSI that affect both low levels of multisensory processing as well as more complex mechanisms including speech (Charbonneau et al., 2013; Smith and Bennetto, 2007). Children with ASD present impaired responses to bimodal stimuli during a simple detection task, a deficit that probably reflects a neuronal alteration in integrating both modalities (Brandwein et al., 2015, 2013). However, in spite of some controversies suggesting that MSI deficits in ASD patients might reflect a general alteration of temporal sensitivity for synchrony (see de Boer-Schellekens et al. (2013)) and that such deficit is present specifically in children or young adults (Foxe et al., 2013), it has been reported that the deficit observed in binding sensory events is directly related to the severity of ASD symptom (Brandwein et al., 2015; Stevenson et al., 2014). In the light of these observations, it is highly probable that PWS will present similar MSI deficits, and that UPD patients, who present more ASD symptoms, will be more strongly affected. Major cognitive theories in autism support the hypothesis that ASD perception is mainly locally oriented (Brock et al., 2002; Frith and Happe, 1994), leading to deficient performance of tasks that require a more global or integrative approach (Behrmann et al., 2006; Dakin and Frith, 2005). Such a perceptual approach is consistent with impaired MSI (Iarocci and McDonald, 2006), which we assumed might well

characterize our PWS patients.

Lastly, we aimed in the present study at differentiating if and how patients with mUPD and DEL present different performance levels in the integration of social communication information. As mentioned previously, the prevalence of ASD in patients with mUPD is about 4 times higher that observed in patients with DEL (Veltman et al., 2005) a result that is also apparent when clinical differences are analyzed between the two populations especially concerning social cognition and psychosis. Using a genetically confirmed diagnosis of PWS subtypes combined to a standardized behavioral assessment in a large cohort of patients, a recent study showed that there were higher levels of behavioral disorders in patients with mUPD (Sinnema et al., 2011). It has also be mentioned that patients with mUPD showing a higher level of impairment than patients with DEL (Holland et al., 2003a, 2003b; Stauder et al., 2005). Considering those differences we decided to distinguish mUDP from DEL especially when evaluating social interaction and behavioral disorders.

To investigate our hypothesis of MSI impairment in PWS, we developed a series of tests in which participants were asked to respond to natural environmental visual and auditory stimuli, including human faces and voices. We assumed that the comparison of PWS and control group performances in detecting and discriminating these stimuli would reveal a strong and specific impairment in the integration of bimodal information in the PWS group.

2. Material and methods

2.1. Participants

Twenty-six native French patients with PWS were recruited from the dedicated center for PWS in the Hendaye Hospital, which is part of the national reference center (Hendaye, France) in collaboration with the University Hospital in Toulouse. The patients with PWS have been recruited and tested at the Hospital Marin d'Hendaye that is a structure of care and following devoted to PWS only. Patients are living in home life for adults across France and they are scheduled to stay regularly in the care unit of Hendaye for about one month in life conditions very similar to their everyday life.

First, 21 patients were recruited to participate in the study. In parallel, 21 typically developing (TD) individuals were also selected and recruited to be age- and gender-matched with the PWS cohort. In addition, a second set of five PWS patients was recruited to complete the genetic subgroup of patients presenting with UPD. Therefore, the total group of PWS patients was composed by 26 French native patients (see Table 1) included 10 men and 16 females with a mean age of 30.3 years (range: 27.6–33.5). All PWS participants met the criterion of IQ above 45 to ensure correct comprehension of the procedure. The mean Wechsler IQ score for the PWS group was 59.3 (range: 55.3–64.6).

The diagnosis of PWS was genetically confirmed using the standard DNA methylation test. The patients were divided into two subgroups based on their genotype alteration. Sixteen patients carried a DEL and 10 patients a UPD. The DEL and UPD subgroups had a similar mean age (respectively, 30.5 ± 5.3 and 30.9 ± 5.4 years, $p > 0.05$). The two subgroups also had a similar mean IQ: 60.8 ± 14.8 for DEL and 56.8 ± 9.8 for UPD ($p > 0.05$). Patients had normal or corrected-to-normal vision and normal audition as they all benefit of steady medical follow up.

A third group of 21 typically developing (TD) individuals were gender- (8 male) and age-matched (mean age: 30.7, range: 19.1–29.6) to the PWS group. The TD participants were native French speakers with self-reported normal or corrected-to-normal vision and normal audition, and were without known language or cognitive disorders. TD were recruited in Toulouse and tested in the Research Center CerCo by the same experimenter who was testing the PWS in Hendaye.

The study was approved by the ethic boards of the University Hospital Center of Toulouse (Toulouse Hospital CHU 13.6873.03; National EudraCT 2013-004437-33), and all participants gave written informed consent prior to their inclusion in the study.

Table 1
Clinical and genetics characterization of PWS and TD. 26 PWS patients were tested for intelligence quotient (IQ) and Developmental Behavior Checklist (DBC). 26 PWS patients and 21 typically developing (TD) were matched by age and gender.

Patient ID	Age	Gender		Mutation		IQ	DBC
		M	F	DEL	UPD		
Mean PWS (SD)	30.3 (7.01)	10	16	16	10	59.3 (13.6)	0.27 (0.18)
Mean TD (SD)	30 (6.94)	8	13				

2.2. Procedure

The PWS patients and the TD participants performed a set of four psychophysical tests but the results of only two of them are presented in this study. The results of the others will be presented in a companion publication. The TD participants were tested at the CerCo Laboratory in a sound-attenuated room with volume adjusted to 65 dB SPL. PWS patients were tested in a quiet room using similar stimulation conditions as that done for the TD subjects. To take into account fatigability, which is frequent in PWS patients, the tests were administered in two sessions on two consecutive days with a random order of presentation.

2.2.1. Multisensory detection task

The first detection task was administered to both groups. A short auditory, visual or visuo-auditory stimulus was presented to the participants and the task was to respond as fast as possible to the stimulus by pressing a response key. The stimuli presentation and data collection were controlled by E-Prime software connected to a computer.

All the visual stimuli were in color and were normalized in both luminance and contrast. They were presented until the participant provided a response. The visual stimuli were presented either at low (30%) or high (70%) contrast. Pictures were extracted from the International Affective Picture System (IAPS, (Lang et al., 2008)) and divided into three categories according to their semantic representation. The first category included pictures of human faces with different emotional expressions. The second set of images was made up of everyday objects. We have also included a specific set of images of food. Our hypothesis is that patients who are suffering a lack of satiety (Tauber et al., 2014) would react differently to this high motivational category of stimuli especially as patients have a controlled diet during the stay at the hospital. The third category contained the previous pictures to which a Fourier transform had been applied to randomize their spectral content.

Sound stimuli from the International Affective Digital Sounds base (IADS) were calibrated using Pratt software to obtain two intensities at high (60 dB) and low (35 dB) levels. We selected three sound categories to be consistent with the visual categories: human voices, natural environmental sounds and vocoded sounds. For the last category, we used stimuli from the previous two sound sets and two-band vocoding alteration (see Rouger et al. (2007)) to make them barely recognizable. The sounds were presented binaurally via Sennheiser Eh 250 headphones in a pseudo-random order.

Last, the third series of stimuli was composed of the combination of the previous visual and auditory stimuli and presented with semantic visuo-auditory congruency.

Overall, the task included the presentation of 576 stimuli, with 192 in a visual-only condition (V), 192 in an auditory-only condition (A) and 192 in a bimodal condition (AV). In the A, V and AV conditions, half of the stimuli were of high saliency and half of low saliency. The A, V and AV stimuli were randomly presented and the interval between presentations was also randomized in a range that varied from 750 ms to 2000 ms. The stimuli presentations were divided in eight blocks of 72 stimuli to reduce fatigability and maintain the patients' sustained attention level during testing. All participants sat in a silent and dimly lit room and they instructed to press a button as fast as possible when they detected a stimulus. They first underwent a training session to ensure full comprehension of the test.

The performances were analyzed by computing the reaction times (RTs) with respect to the individual conditions of stimulus presentation (A, V or AV). To eliminate anticipatory responses of the subjects, especially TD subjects, RTs lower than 20 ms were excluded from the analysis. In addition, only trials with RTs included within 2 standards deviations of the average RTs were considered for further analysis (see Foxe et al. (2013)). The amount of outliers was quite low and similar in both subjects groups and did not differ statistically (PWS: 0,18% of Total RTs, TD, 0.19% of total). From these RTs, we computed the multisensory gain (MSG) for each participant as the normalized decrease in RTs observed in the AV condition compared with the shortest unisensory condition. Further, to test whether the MSG or redundant-signals effect: RSE; (Raab, 1962) exceeded the facilitation predicted by probability summation, we applied the "race model" inequality (Miller, 1982). According to the race model (Raab, 1962), information does not necessarily need to converge to obtain an MSG. Stimuli independently compete for response initiation and the faster of the two stimuli mediates the behavioral response. The probability summation can account for shortening of the RTs in the AV conditions because the likelihood of either of the two stimuli producing a fast RT on any given trial is higher than that from either stimulus alone. Conversely, in the co-activation model (e.g., (Miller, 1982)), the multisensory stimuli converge and interact prior to the initiation of the behavioral response, leading to a decrease in the threshold for initiating a response. The Miller inequality tests whether the probability of a

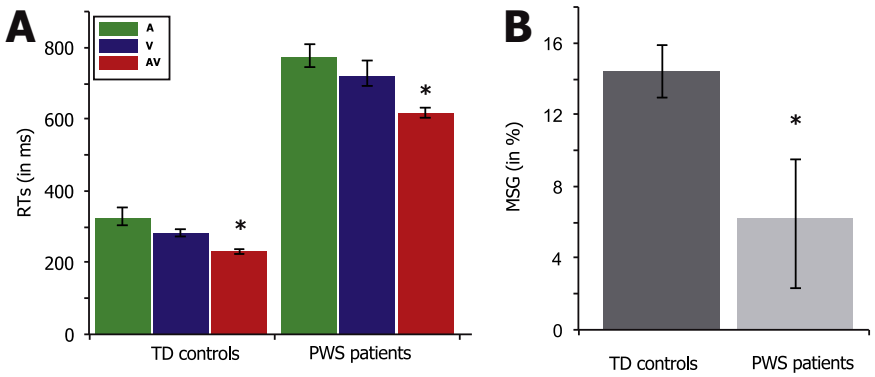

Fig. 1. A. Reaction time (RTs) values during the detection task in typically developing (TD) subjects and Prader-Willy syndrome(PWS) patients. Means RTs are presented with confidential intervals in the auditory (A), visual (V) and visuo-auditory (AV) conditions. In both groups, the mean RTs values are significantly lower in the bimodal condition compared to both unimodal presentations (bootstrap, indicated by a *). B. Normalized Multisensory gain (MSG) computed from the fastest unimodal condition. Increasing MSG values corresponds to a decrease in the RTs in the visuo-auditory presentation compared to the unimodal condition. Prader-Willy syndrome (PWS) patients present a significant lower MSG (bootstrap, indicated by a *) compared to typically developing (TD) subjects.

reaction time to a multisensory stimulus will be higher than the summed probabilities for an equally fast reaction time to either unisensory stimulus alone. This is based on the computation of a cumulative probability distribution for each condition. The RT distributions are divided into 5% bins and a model of the probability distribution for each multisensory combination is then calculated. For each 5% bin, the modeled value equals the sum of the probabilities for each component unisensory condition minus their joint probability (see Cappe et al. (2010), Corballis (1998)).

2.2.2. Voice discrimination task

Subjects were asked to perform a second task that consisted of discriminating a human voice from natural environmental sounds. Sounds were presented binaurally via the Sennheiser Eh 250 headphones at a 65-dB intensity. All stimuli came from a database of the vocal and non-vocal sounds used in previous experiments (Belin et al., 2000; Massida et al., 2011). The first set of 500-ms stimuli contained 55 different human voice stimuli, including 29 speech stimuli (phonemes presented in a /h/-vowel-/d/ context, words in different languages, or non-semantic syllables) and 26 non-speech vocal stimuli (e.g., laughs, coughs). The second set was composed of 55 non-voice stimuli consisting of a wide variety of environmental sounds (cars, telephones, bells, streaming water, etc.). Neither set contained animal vocalizations. The task was a two-alternative forced choice (2AFC) categorization: voice vs. non-voice. Each participant (TD and PWS) sat in a quiet dimly lit room looking at a cross fixation. They were tested with a 1-s inter-trial delay and were instructed to respond as accurately as possible using the left or right control buttons of the E-prime response-box corresponding to their answer (voice or non-voice). The response keys were counterbalanced across participants and each participant benefited from a short training session to ensure that they understood the test. The test included the 110 stimuli presented in two blocks.

We used signal detection theory (SDT, (Green and Swets, 1966)) to separate decisional bias from perceptual mechanisms. We measured the d-prime value (d′, [dprime=sqrt(2/(1+b*b))*(z_HR−b*z_FAR)]), which is a criterion of perception sensitivity independent of decision bias which was obtained by computing beta-values ([Beta=b.*exp(−0.5*((z_HR.2)−(z_FAR.2))]). The hit rate (HR) and false alarm rate (FAR) were calculated, with the task being to detect voices as the target. RTs were also compared with respect to the individual categories (voice, non-voice stimuli).

In order to evaluate the different effect of RTs values on the performance level, we computed a Speed Accuracy composite Scores, (SAC) which has been proposed (Charbonneau et al., 2013) as a good alternative to the originally proposed Inverse Efficiency Score (Townsend and Ashby, 1983). Speed Accuracy composite Scores are computed as SACS=(Z(D prime)−Z(RT)).

2.2.3. Developmental Behavior Checklist score (DBC)

It is an assessment instrument completed by lay informants to assess behavioral and emotional disturbance in adults with intellectual disability. To a total score, six subscales based on factor analyses can be computed. The six subscales are: disruptive, self-absorbed, communication disturbance, anxiety/antisocial, social relating and depressive.

2.3. Statistical analysis

Taking into account the deviation from normality and the repeated measures in our experimental protocol, we chose the bootstrap method for the statistical analysis (Carpenter and Bithell, 2000). Bootstrap methods were applied for direct comparisons both within and between groups. The data (RTs, d-prime values, etc.) were resampled 10,000 times, and we thus obtained a distribution of 10,000 simulated observations in each condition, from which we obtained the sample means. We used bias-corrected and accelerated confidence intervals (Carpenter and Bithell, 2000) and the effect was considered to be significant if there was no overlapping.

3. Results

All the PWS patients were able to perform the two protocols successfully, with no difficulties in understanding the instructions.

We first compared the performances of the original group of PWS with the age- and gender-matched TD individuals (21 participants in each group) and then compared performances between the patients in the PWS group according to the genetic subtype (DEL, 16 patients vs. UPD, 10 patients).

Our results showed that the PWS patients presented a strong deficit in integrating visuo-auditory information, and a specific impairment in discriminating human voices. Patients with UPD appeared to be more deficient in integrating multisensory communication information.

3.1. Multisensory detection task

3.1.1. Inter-group comparison

Globally, the PWS patients were much slower to react to the appearance of the stimuli (see Fig. 1A). They presented a mean RT of 620 ms (± 376), which was much longer than that observed in the TD group (255 ms ± 111). The TD value was significantly higher (bootstrap analysis, $p < 0.05$) and this approximately 60% difference in RTs was observed for every stimulus category (A: 60%, V: 59% and AV: 60%, see Table 2, each category bootstrap analysis, $p < 0.05$). There was no within-group difference for any stimulus category in the visual or auditory condition: the patients and TD participants responded with the same speed to any kind of stimulus, whether food, objects, human faces or voices.

The TD participants presented the classically reported decline in RTs in the AV condition compared with the unimodal V-or A-only presentation (228.8 ms vs. 278.0 ms and 323.6 ms, respectively, Fig. 1A). These AV RTs were significantly shorter than the RTs in the visual modality, which was the faster unimodal condition (bootstrap analysis, $p < 0.05$), leading to a mean MSG of 14.4% ± 3.4 (Fig. 1B). The PWS patients presented a similar pattern of RT distributions according to modality, despite having much slower responses to the stimuli. Indeed, the visual modality was faster (mean RTs 720.2 ms vs. 772.8 ms in A-only, Fig. 1A see

Table 2
21 PWS patients and 21 typically developing (TD) were tested for detection task and voice discrimination. Two subgroups of 16 PWS patients with deletion (DEL) and 10 PWS patients with uniparental disomy (UPD) were compared for same tasks. Data were presented with means and confidence intervals (CI).

	NT (n=21)	CI	PWS (n=21)	CI	DEL (n=16)	CI	UPD (n=10)	CI
Detection task								
RTs A-only	323.6	304.1	772.8	745.2	720.1	591.0	675.2	603.0
		354.9		807.4		869.4		879.2
RTs V-only	278.0	270.5	720.2	692.3	696.8	543.8	616.9	526.9
		291.8		762.3		850.4		927.8
RTs AV	228.8	224.0	616.9	603.9	600.7	484.4	590.5	528.9
		235.9		632.9		719.3		870.6
MSG	14.39	12.95	6.22	2.29	7.82	4.28	0.1	−8.63
		15.86		9.47		11.26		6.98
Voice discrimination								
RTs	264.7	258.0	615.1	556.7	652.5	527.5	590.5	528.7
		362.1		755.8		786.9		863.2
D prime	4.18	3.75	3.05	2.53	3.14	2.93	2.24	1.56
		4.64		3.43		3.57		2.86

Table 2). Further, as in TD, the PWS patients presented a multisensory effect, as expressed by a reduction in AV RTs of 617 ms and an MSG of 6.22% ± 7.5 (Fig. 1B). However, this audiovisual gain was much lower than that of the TD participants (14.4% vs. 6.2%, bootstrap analysis, $p < 0.05$), revealing a specific deficit in multisensory performances in the PWS patients.

To reveal the presence of integrative multisensory processing, we tested the distribution of the RTs using the Miller inequality for each group (Fig. 2). We observed a significant violation of the race model for the fastest 5th percentiles (corresponding to 181 ms, IC95: 0.07–0.54) in the distribution of the TD participants in agreement with previous results on multisensory integration. Conversely, we observed no violation of the race model in the PWS patients, at any percentile of the distribution. These results reinforce the previous finding of impairment in the integration of diverse sources of sensory modalities in PWS.

3.1.2. Intra-group analysis

Based on our relatively large cohort of patients, we were able to compare a subgroup of patients with a genetic deletion (n=16) with those having UPD (n=10). We observed no significant difference in the overall performances of speed of reaction to the stimuli, although the DEL subgroup was slightly slower than the UPD (mean RTs: 652.5 ms and 590.5 ms, respectively, bootstrap analysis $p > 0.05$, see Table 2 and Fig. 3A). This approximately 10% difference was observed for the RTs to the audio and visual stimuli. However, in the AV conditions, DEL and UPD patients had very similar RTs (600.7 ms and 590.5 ms, respectively). Consequently, the DEL patients had much greater multisensory benefits, with MSG values of 7.82% ± 7.2 (Fig. 3B), but these values remained much lower than those of the TD participants (bootstrap analysis, $p < 0.05$). Conversely, the PWS patients with UPD did not present any gain from the multisensory presentation, as their MSG was not different from zero (mean MSG: 0.1% ± 10.1, Fig. 3B).

As expected from the overall analysis, there was no violation of the race model when it was tested separately in the DEL and UPD subgroups (not shown).

3.2. Voice discrimination task

Inter-group and intra-group comparisons

In the voice/non-voice discrimination task, the speed of response was not the primary instruction given to the subjects and the RTs values are just indicative. However, similar to the observations for the detection task, the PWS patients presented higher RTs than the TD participants (831.1 ms and 593.4 ms,

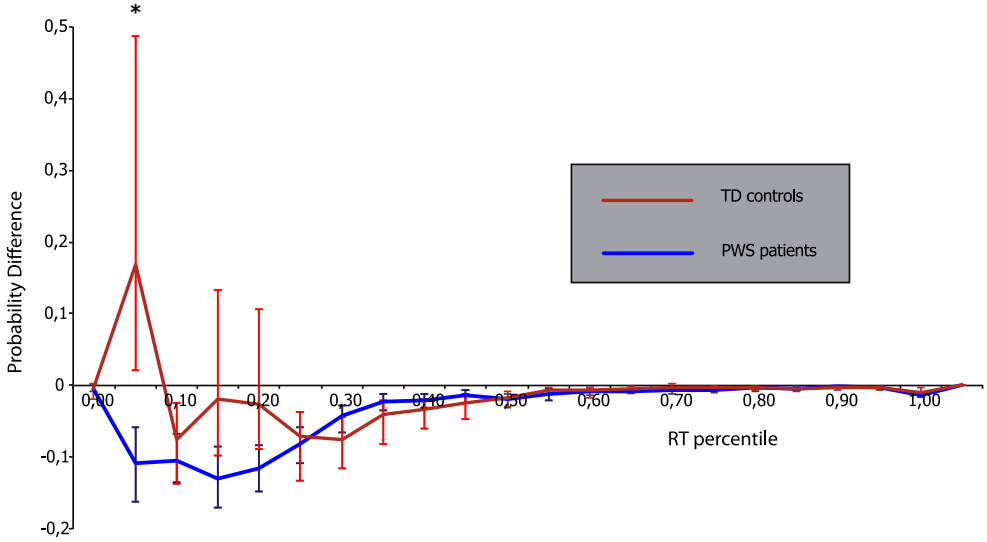

Fig. 2. Violation of the race model using the Miller's inequality methods. The positive values indicate that the probability of the RTs during the bimodal visuo-auditory condition exceeded the predictions of the race model suggesting a convergence and an integration of both modalities. In Prader-Willy syndrome (PWS) patients, we did not observed a violation of the race model, all probability differences between bi- and unimodal conditions are negative, while in typically developing (TD) subjects a violation of the Miller's inequality is present for the shortest RTs (indicated by a *).

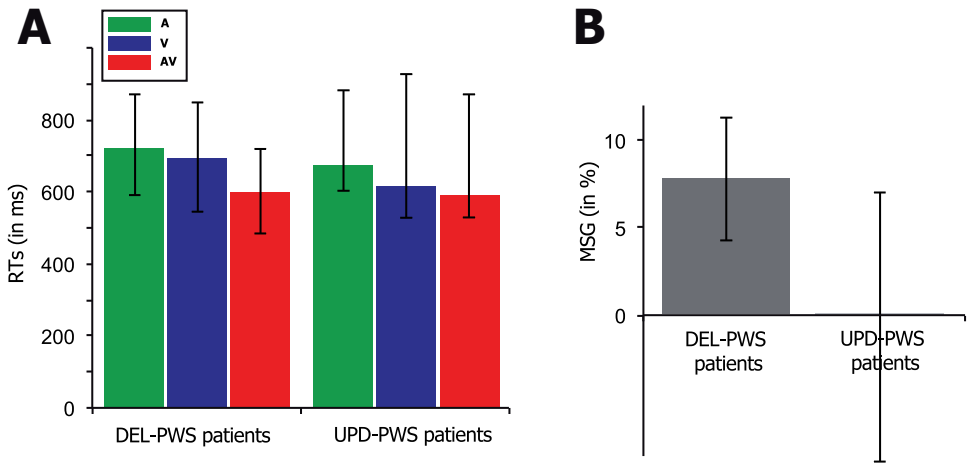

Fig. 3. Comparison of the performances of the two genetic groups of Prader-Willy syndrome (PWS) patients during the detection task. A. Mean RTs of patients with uniparental disomy (UPD-PWS) or a genetic deletion (DEL-PWS). B. Comparison of the normalized Multisensory gain (MSG). UPD-PWS patients do not present a decrease in RTs during the visuo-auditory detection tasks. Conventions as in Fig. 1.

respectively, bootstrap analysis, $p < 0.05$), a result observed for both the voice and non-voice stimuli (see Table 2).

Voice discrimination was assessed using a d-prime computation, in order to separate decisional bias from perceptual mechanisms. Globally, the perceptual sensitivity or d-prime values were lower for the PWS patients than the TD group (3.05 and 4.18, respectively, bootstrap analysis, $p < 0.05$, Fig. 4A), suggesting a clear impairment in discriminating human voices from natural environmental sounds. Further, when the two subgroups of patients were compared, the DEL subgroup appeared to be much more proficient than the UPD group (3.14 and 2.24, respectively, Fig. 4B) but their performances remained lower than those of the TD subjects (bootstrap analysis both comparisons, $p < 0.05$).

Based on the speed-accuracy trade-off, it has been proposed that when subjects present speeded responses, it is at the cost of the accuracy of response. While, the PWS are presenting an opposite behavior (i.e. being slower to respond and less performing) we applied a Speed-accuracy composite score (SACS,(Charbonneau et al., 2013)) to take into account the differences in reaction time between patients and controls. We did not find a statistical difference in SAC between the two populations (1.6e-14 and 0.01 respectively, bootstrap analysis, $p < 0.05$). This suggests that both populations are behaving similarly in term of behavioral strategy (speed vs. precision) and that the difference in RTs values does not influence the performance level of the patients in discriminating human voices.

Lastly, decision criteria (beta-values) were compared and did not reveal a difference between both groups (0.88 [0.74, 1.14] and 1.31 [1.11, 1.55] respectively, bootstrap analysis, $p < 0.05$), adding further evidences that the difference in voice discrimination is not linked to criterion response.

3.3. Impact of patient characteristics on task performances

We selected PWS patients with an IQ above 45. Nevertheless, IQ scores varied across patients from 45 to 90. In order to evaluate the impact of IQ on the execution of the task, we searched for any correlation between IQ and performance in both the detection and discrimination tasks. Using a Spearman test, we found no correlations between IQ scores and the overall RT value ($Rho = -0.39$, $p = 0.06$) or the MSG ($Rho = 0.085$, $p = 0.88$). Similarly, the D-prime values were also not correlated with IQ ($Rho = 0.038$, $p = 0.85$). Lastly, while all our statistical comparisons were performed with bootstrap methods, we search any effect of IQ on patient's deficits. When comparing UPD and DEL groups, an Ancova analysis using IQ as a covariate did not reveal any statistical effect of IQ on MSG

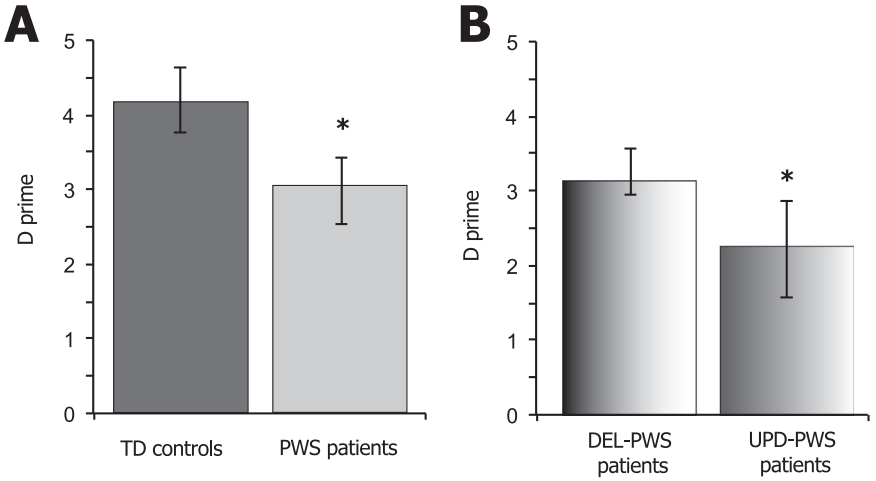

Fig. 4. Mean D prime values (± confidential intervals) for the voice discrimination test in typically developing (TD) subjects and Prader-Willy syndrome (PWS) patients. A. PWS patients present significant lower mean values compared to TD. B. Comparison of the D primes values of the two genetic groups of Prader-Willy syndrome (PWS) patients during the voice discrimination detection task. UPD-PWS patients present a stronger deficit compared to DEL patients. Conventions as in Fig. 3.

and D primes values (respectively $F=3.60$; $p=0.07$ and $F=0.076$; $p=0.78$). Altogether, this suggests that the impairment of the PWS patients in the two perceptual tasks was not directly influenced by their intellectual deficiency.

Last, we were able to retrieve the DBC for 14 of the 21 PWS patients (7 with deletion). First we used the global DBC score that assesses a broad range of behavioral and emotional disturbances in young people with intellectual or developmental disability. In this case, no correlation was observed between global DBC scores and RTs or d-prime values (both cases, Spearman correlation, $p > 0.05$) However, when the correlation analysis were performed using the subdivision of the DBC that question specifically social disturbances, we observed a negative relation between the DBC subscore and the d-prime values in the voice discrimination test ($p=0.034$ $r=-0.610$). These results suggest that the deficit in processing social information such as voice stimuli is linked to the severity of clinical and social disturbance in PWS. No correlation was obtained with the multisensory benefits in the detection task ($p=0.69$ $r=-0.114$).

4. Discussion

In the present study, we were able to reveal specific deficits in patients with PWS using simple tasks and natural stimuli having high ecological value, such as human voices and faces. The deficits express impairments in discriminating human voices from environmental sounds and an abnormal lack of facilitated sensory processing during bimodal visuo-auditory presentation. Further, the results clearly showed that patients with UPD have more severe deficits than patients with a deletion, adding further evidence of the difference in impact on cognitive processing of these two genetic subtypes.

4.1. Altered multisensory processing in PWS

This study is the first to explore the processing of multisensory information in PWS. We used a simple detection task in which reaction time reflects basic sensory processing with limited involvement of cognitive skills beyond the global attention level required to perform the task. First, the patients with PWS performed the detection task much more slowly, with RTs more than two times longer than those of the TD participants. The longer RTs were probably not related to a perceptual deficit per se, as they were observed in the same value range in all modalities (A, V and AV). In addition, although the RTs were longer, they were similar to those of the normal participants in that they progressively declined from the auditory and visual to the audiovisual conditions. Last, compared to TD controls, we observed similarly longer RTs during the voice discrimination task, in agreement with previous studies in which patients with PWS were engaged in more complex protocols such as visual discrimination (Woodcock et al., 2009) or Go-No-Go tasks (Stauder et al., 2005). Lastly, it is know that PWS are suffering of hypotonia and present difficulties in motor coordination (Reus et al., 2011). However, hypotonia has been shown to be severe during the neonatal and childhood period, between the age of two to six years and then it does regress over time and adults remain only mildly hypotonic (Driscoll et al., 1993). During the present testing, we help the patients to be correctly installed to insure that they can press the button without any difficulty and in our set of patients; their fine motor skills are even higher than in the general population. Indeed when using a visuo-motor test such as the jigsaw puzzle task, it has been shown that patients with PWS outperformed the typically-developing group (Dykens, 2002). Moreover in child development fine motor skills are also than better fine motor ability than gross motor ability (Chen et al., 2010). Further, when we have excluded the outliers, especially when considering the long RTs (over 2 SD) it appears that they occur in a similar proportion than that observed in TD subjects, suggesting no specific motor difficulties in doing the task. Altogether, it is highly probable that the slower reactions times observed in our study resulted from the early developmental deficits that cause global alterations in visual-motor integration skills in PWS (Lo et al., 2015).

However, the simple detection task revealed a specific impairment when the patients with PWS had to respond to a bimodal AV stimulus. The deficit was twofold. First, the lower audiovisual gain for the PWS group compared with the TD group suggested that patients with PWS benefit less from the contribution of a second modality. Second and more important, the TD group showed a violation of the race model that reflected the integration of visual and auditory information. This effect was not found in the PWS group, suggesting that the observed gain was induced by the faster modality and did not reflect a convergence of the two sensory modalities. There is now strong evidence in all species, from rodents to primates (see Cappe et al. (2010)), that behavior in multisensory conditions is much faster and more accurate than it is in their unisensory components (Stein and Meredith, 1993; Welch and Warren, 1986). This behavioral facilitation exceeds the predictions based on probability summation (Miller, 1982), revealing the occurrence of an interaction between the visual and auditory signals before the production of the motor response. The lack of violation of Miller's race model inequality in PWS demonstrates that the neuronal mechanisms of merging sensory modalities are impaired, leading to independent processing of the sensory signals during bimodal stimulation. It should be noted that this dysfunction was present during a task that engaged only low-level sensory processing (a detection task), suggesting that the more complex multisensory interaction mechanisms that are needed in real life might also be altered in PWS.

In both humans and monkeys, several brain regions in the temporal, frontal and parietal lobes have been associated with multisensory integration, whereas interactions between sensory modalities can occur at low levels of sensory processing down to the primary unisensory cortices (Giard and Peronnet, 1999; Martuzzi et al., 2006; Wang et al., 2008). To date, no brain imaging study in PWS patients has yet searched for a specific dysfunction in the cortical network implicated in merging sensory signals. A few studies have explored brain activity in PWS patients, and most of them have used passive protocols, examining brain activity only during resting state conditions. Moreover, these studies confirm that high-order areas present abnormal activity levels at rest (Kim et al., 2006; Mantoulan et al., 2011), including the prefrontal, parietal and frontals lobes, areas known to house multisensory interactions in both humans and monkeys (see Cappe et al. (2009)), for review).

To our knowledge, our study is the first to report a specific deficit in multisensory processing in PWS patients. However, similar results have been described in ASD, a neurodevelopmental disorder that shares numerous psychological deficits with PWS (Dykens et al., 2011). In different aspects, multisensory interactions have been shown to be deficient in ASD patients, including cognitive processes like the integration of emotional expressions (Charbonneau et al., 2013) and the audiovisual integration of speech (de Gelder et al., 1991; Foxe et al., 2013; Irwin et al., 2011), but these also concern low-level multisensory interactions (Collignon et al., 2013; Foss-Feig et al., 2010). Globally, ASD patients seem to benefit less from multimodality than TD subjects, and the diversity of multisensory mechanisms that are impaired in ASD suggests that this dysfunction in multisensory integration may be the origin of the social communication inabilities that characterize these patients. Because of the similarities in the symptoms of ASD

and PWS, it is quite likely that PWS patients also present alterations of some of the aspects of multisensory interactions, including the speech and face-voice integration that is at the heart of social communication (Campanella and Belin, 2007).

Multisensory interactions depend on the ability to bind sensory information from different modalities, a process consistent with the model of weak central coherence described in both ASD and PWS. Binding multiple sensory inputs requires interactions between distant cerebral areas through long-range connections, which agrees with the models suggesting impairment in areal communication through anatomical alteration and functional dysfunction in ASD (Cherkassky et al., 2006; Magnee et al., 2008; Thomas et al., 2011; Weinstein et al., 2011). Specifically, ASD patients present altered connectivity at both the anatomical (Courchesne and Pierce, 2005) and functional levels concerning the frontal cortex (Martinez-Sanchis, 2014), which contributes to multisensory processing through a top-down modulation of activity in the posterior temporal and parietal lobes (Engel et al., 2012). Of interest in young PWS patients, both the temporal gyrus and the parietal lobes present significant abnormal hypo-perfusion (Mantoulan et al., 2011), in addition to the altered functional connectivity of the frontal cortex with the posterior areas (Zhang et al., 2013). Altogether, in PWS there is converging evidence of changes in the long-range communication between distant areas, which is crucial for binding sensory modalities and which would account for the present observation of altered multisensory integration. Further work will be required to assess how this alteration in functional connectivity contributes to the cognitive deficits, including the lack of normal merging of modalities, observed in these patients.

4.2. Altered processing of human voices and social information in PWS

Several studies have associated PWS with severe alterations in social functioning, with behavioral characteristics that approach those observed in patients with ASD (Dimitropoulos et al., 2013) or patients presenting frontal dysfunctions after focal lesion (Jauregi et al., 2007). It has been proposed that such a social impairment results principally from a deficit in interpreting and using information related to social communication rather than as the consequence of maladaptive behaviors. This hypothesis guided the present study in which we examined how PWS patients react to natural visual and auditory information that presents important emotional or communication content. First, in the simple RT task, we observed no specific impact on the RTs with respect to the semantic category of the stimuli in the visual (face, image of food) or auditory (voice, environmental sounds) domains. In particular, when presented with images of food, the PWS patients reacted at the same speed as for the other stimuli. Because the valence of a stimulus is known to affect categorization processing (Calvo and Avero, 2009), we expected that the pathological food obsession that characterizes PWS (Cataletto et al., 2011) would be reflected by the RTs to food-related stimuli. The absence of such an effect was somewhat surprising, given the known alteration in the eating-related neuronal network (Zhang et al., 2015). This lack of a specific response was probably due to the short duration of stimulus presentation and the overall decrease in RTs, which may have masked specific reactions to food-related images. Similarly, the stimuli with strong social content, human faces and voices, were equally processed in term of RTs.

However, when the patients were engaged in an active discrimination task, a specific impairment in voice processing became apparent. This deficit, which was expressed by a strong decrease in d-prime values, was present in the PWS group and closer analysis revealed that the UPD subgroup was much more deficient than the DEL subgroup. It is important to mention that while being much slower, PWS are not presenting a higher performance level, in contradiction with the well established rule of “speed-accuracy trade-off” which states that a decrease in RTs is frequently associated to a decrease in response accuracy. When we normalized the data with respect to the RTs and d-prime values, no difference emerged suggesting that both TD and PWS are using a similar behavioral strategy to perform the task, the patients being globally slower. The lack of difference in processing strategy is also reinforced by a lack of statistical difference in beta-values. All together, we are confident that the difference in performance level for voice discrimination is not related to the difference in the time to effectively integrate the information, in agreement with previous reports in developing TD and ASD children (Brandwein et al., 2015).

These results are important in understanding the social behavior deficit reported in PWS. The voice signal is critical in social interactions for several reasons. First, the voice provides all the speech and linguistic-related information at the heart of human communication. However, individual voices also provide unique information about the speaker's identity: age, gender, familiarity or affective mood (see Belin et al. (2011)), for a review). Clearly, the inability to detect all the socially relevant information embedded in other voices will strongly disrupt normal communication interactions. Further, voice sensitivity appears very early in the developmental stage, about six months after birth (Grossmann et al., 2010), and thus well before speech comprehension (Friederici, 2006). It is therefore highly probable that the neurological developmental dysfunction that occurs early in life in PWS patients disturbs the early function of voice processing and later contributes to their growing social impairment.

As mentioned, although PWS patients have some quite specific symptoms, they share certain neuropsychological disorders with ASD patients. Several studies have looked at how well ASD patients discriminate the attributes contained in a voice signal (gender, emotion, familiarity), but the results have been somewhat contradictory, probably because of the broad spectrum that characterizes ASD. Some studies reported no deficits in gender discrimination (Groen et al., 2008; Lin et al., 2015), whereas the ability to extract emotional content or vocal identity was variable across the ASD population (see Boucher et al. (1998), Boucher et al. (2000), Lin et al. (2015)). In spite of these discrepancies in behavioral performances, there is evidence that in ASD the STS region devoted to voice processing (see Belin et al. (2000), Von Kriegstein and Giraud (2004)) shows abnormal activity (Gervais et al., 2004), which is coupled with anatomical abnormalities in the gray matter content (Boddaert et al., 2004). Brain imaging data suggest that STS abnormalities might be the first step in a cascade of cerebral abnormalities that cause social impairment (Zilbovicius et al., 2006). As noted, only a few studies have analyzed brain activity in PWS, with STS hypo-perfusion revealed during a PET scan study of our team (Mantoulan et al., 2011). The STS region is involved in several stages of social interaction, especially regarding social visual and auditory perceptions (eye gaze, voice perception), and in complex social cognition (Allison et al., 2000). Such results, in addition to the presently observed deficit in voice discrimination, seem to suggest that STS dysfunction contributes to the social impairment observed in PWS as it is thought to contribute in ASD patients.

The voice signal, considered as the auditory face, is important for social communication and complements face processing in social interactions. Numerous studies have revealed the abnormal processing of human faces in ASD, in both behavior ((Guillon, Hadjikhani, Baduel, and Roge, 2014), for a review) and on brain imaging findings (Bird et al., 2006; Bookheimer et al., 2008; Hadjikhani et al., 2007). In contrast, few studies have closely

investigated how patients with PWS integrate face information, and the findings have been mixed. On a behavioral task (Benton Face Recognition Task, BFRT), patients with PWS presented near-normal performances, and the UPD and DEL subgroups displayed similar skills (Halit et al., 2008). A recent study that also used the BFRT reported abnormal face recognition scores in PWS (Feldman and Dimitropoulos, 2014), in agreement with previous studies revealing the impaired ability of these patients to attribute emotional or mental states from human facial expressions (Tager-Flusberg et al., 1998; Whittington and Holland, 2011). Last, in a pilot study (Barone and Tauber, unpublished), we explored how PWS are processing human faces in simple discrimination tests. We showed that PWS present a weak recognition performance (about 20% lower that observed in TD) of both identity and emotional features contained in faces. This deficit was in addition linked to an abnormal oculomotor strategies when exploring the different faces to recognize. PWS were characterized by longer periods of exploration of the different faces with an abnormal avoidance of the eyes and a stronger focus on the mouth. Taken together, these studies suggest face processing is impaired in PWS but the deficits might be dependent on the genetic subtype of PWS (Halit, et al., 2008; Key et al., 2013) and the facial feature to discriminate.

Essentially, both voice and face processing are impaired in PWS patients. We also have clear evidence that multisensory processing is severely deficient in PWS, and that this deficit probably affects the multisensory integration of voices and faces. Yet face and voice interactions are crucial for social interactions (Campanella and Belin, 2007): first, because speech is multisensory by nature (see Vatakis et al. (2008)) but also because paralinguistic (Foxton et al., 2010; Munhall et al., 2004) and affective information are also based on cross-modal face/voice interactions (de Gelder and Vroomen, 2000). Consequently, there is a strong possibility that the deficit in social behavior observed in PWS derives at least partly from an impairment in deciphering the social information carried by face signals, voice signals, and the combination of both.

4.3. Specificity of deficit in PWS

Several studies have compared the cognitive deficits in PWS to those observed in other neurodevelopmental disorders, such as ASD or William syndrome. Although it depends on the task, PWS patients present specific impairments that cannot be solely explained by intellectual disability. In the present study, the patients with PWS were compared with the age-matched TD participants, but correlations were also sought between the patients' performances and the individual IQ values. For audiovisual gain and d-prime, we found no correlation with IQ. In addition, when the IQ was introduced as a covariate, we did not observe an effect of the IQ on d-prime or multisensory gain. Further, when DEL and UPD patients were compared, the performance levels were worse in UPD, although the mean IQ scores of the two groups were comparable. These results thus tend to be in favor of a defect characteristic of PWS rather than deficits due to intellectual disabilities.

The specificity of deficit link to the PWS is apparent when we made a correlation between the performances in voice processing and the social subscore of the DBC. This constitutes a strong argument that link the severity of the syndrome with the severity of the deficit regarding behavior. We also observed differences according to the genotype within the PWS group, with UPD patients displaying lower performances for voice discrimination compared with deletion patients. Clinical differences have already been noted between these two populations, especially concerning social cognition and psychosis, with patients with UPD showing greater impairment than patients with deletion (Holland et al., 2003a, 2003b; Stauder et al., 2005). In addition, patients with UPD showed greater mental rigidity than patients with deletion in infancy (Artigas-Pallares, Gabau-Vila, and Guitart-Feliubadalo, 2005; Veltman, et al., 2005). Of interest, part of the difference could be explained by a more severe impairment in voice processing in the UPD population.

5. Conclusions

Voice is an essential support to communication and comprehension, and our study is the first to evaluate voice processing and multisensory integration in patients with PWS. Our results suggest a specific neuropsychological deficit in PWS to process communication signal including the human voice. Based on our study, we hypothesize that the deficits in social behavior observed in PWS derive at least partly from an impairment in deciphering the social information carried by voice signals, face signals, and the combination of both. In addition, our work is in agreement with the brain imaging studies revealing an alteration in PWS of the "social brain network" including the STS region involved in processing human voices. A better understanding of these deficits would be valuable in clinical practice, as psychosocial rehabilitation and pharmacological treatment could be better adapted. PWS is a rare disease, and caregivers can also benefit from the large knowledge base on ASD to improve the social communication deficits.

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