Factores determinantes del consumo infantil de verduras

Paloma Rohlfs Domínguez

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FACTORES DETERMINANTES DEL CONSUMO INFANTIL DE VERDURAS

DETERMINANT FACTORS OF CHILD VEGETABLE CONSUMPTION

Doctoranda (PhD student): Dña. Paloma Rohlfs Domínguez

Director de tesis (thesis director): Prof. Dr. Jaime Vila Castellar

Universidad de Granada

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RESUMEN

1. Antecedentes y objetivos centrales de la presente tesis doctoral

El consumo de verduras está considerado por la Organización Mundial de la Salud (OMS[1]) como esencial para el mantenimiento de un buen estado de salud y para la prevención de enfermedades, en general (OMS, 2002). De hecho, la OMS recomienda un consumo diario de ≥ 400 g para toda la población. Por otra parte, el consumo de verduras durante la infancia previene la aparición de enfermedades infantiles, tales como el sobrepeso infantil, uno de los problemas de salud pública más preocupantes en todo el mundo (OMS, 2009) y dificultades respiratorias (Antova et al. 2003). Además, el consumo de verduras en la infancia favorece el desarrollo cognitivo (Contento, Bronner, Lytle, Maloney, Olson y Swadener, 1995) y previene el desarrollo de enfermedades en la edad adulta, tales como trastornos coronarios, hipertensión y cáncer (Van Duyn y Pivonka, 2000).

Sin embargo, y a pesar de los beneficios derivados del consumo infantil de verduras que acabamos de comentar, lo cierto es que la tasa de consumo infantil de verduras no se corresponde con las recomendaciones de la OMS ni con las nacionales en Estados Unidos (Johnson y Kennedy, 2000) y Europa (Yngve et al. 2005).

Esta tesis se centra en el estudio de los factores determinantes del consumo de verduras en niños y niñas pequeños como su primer objetivo central. Dado que, debido a diversos factores, tales como el poco desarrollo cognitivo de los niños y niñas pequeños, lo que comen los niños y niñas pequeños se basa en sus preferencias por el sabor de los alimentos, es decir, en lo que les gusta o no les gusta comer, esta tesis

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[1] Las referencias en relación con las publicaciones de la OMS aparecen en la lista de referencias con el acrónico Inglés de la OMS, es decir, WHO.

intenta responder a la pregunta ¿por qué los niños y niñas pequeños tienen determinadas preferencias alimenticias? Esta pregunta equivale a la pregunta ¿por qué les gusta o no le gusta la verdura? Por otra parte, esta tesis se centra en el desarrollo y evaluación de la efectividad de una estrategia que favorezca el incremento del consumo infantil de verduras que se pueda aplicar en el ámbito escolar, en concreto, en los comedores, así como en la casa familiar, como un segundo objetivo central.

2. Metodología

Para el estudio de los factores determinantes del consumo de verduras en niños y niñas pequeños, hemos llevado a cabo una investigación basa en la revisión sistemática de la literatura científica publicada sobre los siguientes aspectos:

1. El impacto que la variación genética individual de los niños y niñas pequeños en relación a la sensibilidad hacia el sabor amargo de los glucosinolatos contenidos en las verduras, indicado por la sensibilidad hacia el componente químico 6-n-propylthiouracil (PROP), puede tener en el consumo de verduras de niños y niñas pequeños así como en índice de masa corporal de niños y niñas pequeños (ver capítulo dos).
2. Identificación de períodos sensibles de desarrollo de preferencias por los sabores mediante técnicas de neuroimagen (ver capítulo tres).
3. Identificación de las representaciones cerebrales del valor hedónico en respuesta a sabores, olores y comidas en población en desarrollo (ver capítulo tres) para comprobar la correspondencia entre estas representaciones cerebrales específicas y las representaciones cerebrales de las emociones.

4. El impacto que la experiencia con sabores, olores y comidas, especialmente durante períodos sensibles, puede tener en el desarrollo y aprendizaje de las preferencias por sabores y alimentos en niños y niñas (ver capítulo cuatro).

Para el desarrollo y evaluación de la efectividad de una estrategia que favorezca el incremento del consumo infantil de verduras que se pueda aplicar en el ámbito escolar, en concreto, en los comedores, así como en la casa familiar, hemos llevado a cabo, en colaboración con el grupo de investigación de la Dra. Milagros Gallo de la Universidad de Granada y con el Dr. Kees De Graaf de la Universidad de Wageningen de los Países Bajos, un estudio experimental en los comedores escolares de cuatro colegios de Granada (España), basado en la provisión a los niños y niñas pequeños de la oportunidad de que puedan elegir la verdura que quieren comer durante la comida, es decir, en la provisión de elección (capítulo cinco).

3. Resultados

1. Nuestra revisión sistemática del conjunto de los resultados aportados por los estudios que han examinado *ad hoc* la relación entre la variación genética individual en relación a la sensibilidad hacia el sabor amargo de los niños y niñas pequeños y su aceptación de verduras (capítulo dos) indica que cuanto más sensible es un niño o una niña al sabor amargo de los glucosinolatos contenidos en las verduras, menor será su aceptación de verduras. Existen indicaciones de que el calcio de las verduras pueda ser otra de las fuentes de su sabor amargo. En el futuro, habría que investigar la posible relación causal entre el nivel de calcio contenido en las verduras y el nivel de aceptación y rechazo por las

mismas en niños y niñas pequeños. Por otra parte, nuestra revisión sistemática del conjunto de los datos aportados por los estudios que han examinado *ad hoc* la relación entre la variación genética individual en relación a la sensibilidad hacia el sabor amargo de los niños y niñas pequeños y su índice de masa corporal (capítulo dos) indica que dicha relación aún no está clara, y que habría que investigar en el futuro si el estatus socioeconómico de los niños y niñas pequeños puede modular dicha relación.

2. Existen indicaciones de que los períodos sensibles de desarrollo de preferencias por los sabores, olores y comidas se pueden identificar mediante la aplicación de las técnicas de neuroimagen (capítulo tres). Por ejemplo, Poncelet et al. (2010) encontraron patrones de activación cerebral en respuesta a un olor (té de menta) diferenciados en una muestra de adultos jóvenes, en función de si habían experimentado este olor en fases tempranas de la vida o no. Concretamente, los participantes provenientes de una cultura argelino-francesa, que tuvieron una experiencia temprana con este olor mostraron latencias P2 más largas que los participantes europeo-franceses, los cuales no habían tenido tal experiencia temprana con dicho olor. Si existe un período sensible durante el que la exposición al olor de menta induciría tal patrón de activación cerebral debe ser investigado en el futuro. También debe ser investigado en el futuro si la exposición a sabores y comidas durante períodos sensibles induce patrones de activación cerebral específicos de dicha exposición.
3. El capítulo tres muestra que el procesamiento cerebral del valor hedónico (placentero vs. no placentero) de los sabores y olores en población de desarrollo es lateralizado. Concretamente, los sabores y olores placenteros se procesan en el hemisferio izquierdo, mientras que los sabores y olores no placenteros se

procesan en el hemisferio derecho. Esta lateralización cerebral del valor hedónico de los sabores y olores se corresponde con la teoría del procesamiento cerebral de las emociones expuesta por Gray (1987), que es igualmente lateralizado, en tanto que las emociones positivas se procesan en el hemisferio izquierdo y las emociones negativas en el hemisferio derecho. Los sabores y olores son estímulos que elicitan emociones (Rolls, 2005). Esta correspondencia neuronal evidencia que las emociones juegan un papel relevante en el consumo de verduras de los niños y niñas. Concretamente, y en términos de la teoría de regulación cerebral de la conducta de Gray (1987), si las verduras provocan una emoción negativa en el niño porque su sabor es malo, esto provocará la activación del sistema conductual y neuronal inhibitorio en el niño, impidiendo su aproximación a las verduras.

4. El capítulo cuatro revela que la gran variedad de experiencias con sabores y olores que tienen lugar durante el desarrollo pueden producir modificaciones en las preferencias por los sabores y por las comidas de los niños y niñas. Estas experiencias tienen lugar en diferentes fases vitales, tales como en la etapa prenatal del desarrollo y el período lactante y en diferentes contextos, tales como el colegio o la casa familiar. Investigación futura deberá revelar si estas experiencias inducen una invariabilidad en las preferencias por los sabores y por las comidas observable durante la adultez madura.
5. El capítulo cinco muestra por primera vez que la provisión de elección, como única estrategia, en el contexto de una intervención escolar centrada en la comida servida en el comedor escolar, produce un incremento en el consumo de verduras en niños y niñas de entre 2 y 6 años de edad. Esta estrategia es de fácil aplicación para los padres y demás figuras cuidadoras de los niños y niñas

pequeños en la casa familiar. Investigación futura deberá examinar los efectos a largo plazo de esta estrategia en relación con el consumo infantil de verduras.

4. Conclusiones

Diversos factores determinan el consumo de verduras en niños y niñas pequeños. Los más destacables son:

1. El grado con el que el niño está genéticamente predispuesto a sentir el sabor amargo de las verduras y, por tanto, a rechazar su consumo.
2. La maduración del sistema nervioso, de la que depende, entre otras cosas, el desarrollo cognitivo del niño o niña.
3. La gran variedad de experiencias con sabores, olores y comidas que el niño o niña ha tenido a lo largo de su desarrollo en diferentes contextos. En este sentido, destaca el papel de las personas adultas, tales como padres, cuidadores de comedores escolares, etc. como principal responsables de tales experiencias, en el sentido de que tales personas adultas suelen decidir los sabores, olores y comidas con las que los niños y niñas van a tener tales experiencias.
4. Las emociones de agrado o desagrado que se generan en el niño o niña al consumir verduras.

Estos factores operan en paralelo, unos a otros, por lo que sus fuerzas se pueden compensar entre sí. Por ejemplo, un niño o niña puede estar altamente predispuesta genéticamente a ser sensible al sabor amargo de las verduras, lo que le puede producir un gran rechazo a la hora de comer verduras, ya que está predispuesto o predispuesta a sentir una emoción negativa al probar las verduras. Sin embargo, la repetida exposición de este niño o niña a las verduras en la casa familiar o en el comedor escolar de los colegios puede modificar la expresión fenotípica de dicha predisposición genética, es decir, que puede favorecer un incremento en la aceptación de las verduras de este niño o niña.

Por otro lado, la provisión de elección a niños y niñas pequeños, como única estrategia, en el contexto de una intervención escolar centrada en la comida servida en el comedor escolar es eficaz para incrementar el consumo de verduras en niños y niñas pequeños, al menos en la región de Granada (España).

SUMMARY

1. Background and main objectives of this thesis

The consumption of vegetables is considered by the World Health Organization (WHO) as essential for maintaining a good health and prevention of disease in general (WHO, 2002). In fact, consumption of vegetables in childhood promotes cognitive development (Contento, Bronner, Lytle, Maloney, Olson & Swadener, 1995) and prevents the development of diseases in adulthood such as coronary disorders, hypertension and cancer (Van Duyn & Pivonka, 2000). However, despite the benefits of children's consumption of vegetables just discussed, the fact is that children's consumption rate of vegetables does not correspond with the recommendations of the WHO or the national recommendations in U.S. (Johnson & Kennedy, 2000) and Europe (Yngve et al. 2005). This thesis focuses on the study of the determinants of vegetable consumption in young children as the first main objective of this thesis. Specifically, this thesis attempts to answer the question why children like or do not like vegetables? As a second central objective, this thesis focuses on the development and evaluation of the effectiveness of a strategy to encourage an increase in the vegetable consumption of young children.

2. Methodology

To study the determinants of vegetable consumption in young children, we have conducted an investigation based on a systematic review of the published scientific literature regarding the following aspects:

1. The impact that young children’s individual genetic variation in their bitter taste sensitivity may have on their vegetable consumption and body mass index (BMI).
2. Identification of sensitive periods of development of preferences for flavors through neuroimaging techniques.
3. Identification of brain representations of the hedonic value in response to tastes, smells and foods in developing populations, in order to check the correspondence between these specific brain representations and the brain representations of emotions.
4. The impact that experience with flavors, smells and foods, especially during sensitive periods may have on development and learning of taste and food preferences in children.

For the development and evaluation of the effectiveness of a strategy to encourage increases of vegetable consumption in young children, we have conducted, in collaboration with the research group of Dr. Milagros Gallo of the University of Granada and Dr. Kees De Graaf of the University of Wageningen in the Netherlands, an experimental study in the school canteens of four Grenadian schools based on the provision to young children of the opportunity to choose the kind of vegetables, they wanted to eat at lunch, that is, on the provision of a vegetable choice.

3. Results

1. The more sensitive is a child to the bitterness of the glucosinolate content of vegetables, the lower is its acceptance of vegetables (chapter two). Furthermore, there are indications that calcium from vegetables can be another source of

bitterness. In the future, the possible causal relationship between the level of calcium in vegetables and the level of children's acceptance of vegetables should be investigated. In addition, the relationship between individual genetic variation in relation to sensitivity to the bitter taste of children and their body mass index (chapter two) remains still unclear and it should be investigated in the future if the socioeconomic status of young children may modulate that relationship.

2. There are indications that the sensitive periods of development of preferences for flavors, smells and foods can be identified by means of neuroimaging techniques (chapter three), in view of the results obtained by Poncelet et al. (2010). Indeed, these authors found differentiated brain activation patterns in response to an odor (mint tea) in young adults as a function of whether they had experienced the smell in early stages of life or not. However, we still need confirmatory evidence regarding usefulness of neuroimaging techniques for identifying sensitive periods of development of those preferences.
3. Chapter three shows that pleasant tastes and odors are processed in the left hemisphere, while unpleasant tastes and odors are processed in the right hemisphere. This brain lateralization of the hedonic value of tastes and odors corresponds to Gray's theory of emotional brain processing (Gray, 1987). This theory states that positive emotions are processed in the left hemisphere and negative emotions in the right hemisphere. Tastes and smells elicit emotions (Rolls, 2005). This correspondence indicates that emotions play an important role in children's vegetable consumption. Specifically, and in terms of Gray's theory, if the "bad" taste of vegetables causes a negative emotion in children,

then, children's behavioral and neuronal inhibitory system will be activated, so that children will not approach vegetables.

4. Chapter four shows that the variety of experiences with tastes, smells and flavors that may occur during development may induce modifications in children's preferences for flavors and foods. Future research should reveal whether these experiences may induce an invariance in the preferences for flavors and food that is observable in middle adulthood.

4. Conclusions

Results of the research developed in the context of elaboration of this thesis led us to present the following conclusions:

On the one hand, several factors determine the consumption of vegetables in young children. The most noteworthy are:

1. The degree to which a child is genetically predisposed to feel the bitter taste of vegetables and, therefore, to reject this kind of food.
2. Maturation of the nervous system, on which depends, among other things, the cognitive development of the child.
3. The variety of experiences with flavors, smells and foods that the child has got over its development in different contexts. In this regard, it should highlight the role of adults such as parents and other caregivers as the main determining factor of such experiences, as those adults tend to decide the flavors, smells and foods with which children have any experience.
4. The emotions of pleasure or displeasure generated in the child when eating vegetables.

These factors operate in parallel to each other, so that their forces can offset each other. For example, may be genetically predisposed to be highly sensitive to the bitter taste of vegetables, which can produce high rejection at the time of eating vegetables. However, repeated exposure of the child to the vegetables in the family home or in the school dining halls may modify the phenotypic expression of that genetic predisposition, which may encourage an increase in the acceptance of vegetables of this child.

On the other hand, the provision of choice to young children as the only strategy in the context of a school intervention focused on the food served in school meals is effective in increasing vegetable consumption in young children, at least in the region of Granada (Spain). This strategy can be also easily applied by parents at home.

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CHAPTER 1

GENERAL INTRODUCTION

1. Introduction

This Ph.D. thesis studies the primary determinants of vegetable consumption in young children and develops a flexible school- or home-based strategy to increase vegetable consumption in a sample of children living in Granada, Spain.

Data showing that children do not meet World Health Organization (WHO) or national recommendations for vegetable intake motivated this thesis. The WHO (2003) recommends a daily intake of at least 400 g of vegetables. Spanish recommendations for daily vegetable intake in children less than 6 years old, children between 6 and 8 years old, children between 9 and 11 years old, and children 12 years and older are 150 g, 200 g, 220 g, and 250 g, respectively (Aranceta Bartrina et al., 2008). Dutch recommendations for daily vegetable intake in children between 4 and 8 years old and children between 8 and 12 years old are 100-150 g and 150-200 g, respectively (The Netherlands's Nutrition Center, 2008). However, the actual average vegetable consumption of Spanish children between 2 and 13 years old is estimated to be 66.1 g/day (Serra Majem & Aranceta Bartrina, 2002). Furthermore, a study carried out in Granada revealed that children between 6 and 11 years old had a daily vegetable intake of 116 g and that vegetable intake varied as a function of location (the school cafeteria vs. home; López-Frías, Nestares, Iañez, De la Higuera, Mataix & Llopis, 2005). Children consumed 126 g/day of vegetables at school but only 109 g/day at home. Actual vegetable consumption in Dutch children between 4 and 6 years old is as low as

44 g/day (Ocke et al., 2008). Several reports have also informed of low vegetable consumption rates in young children in the United States (Johnson & Kennedy, 2000; Lorson, Melgar-Quinonez & Taylor, 2009) and Europe (Yngve et al., 2005). Therefore, research on the factors that determine low vegetable consumption in children and the strategies that might improve consumption has scientific and social relevance.

Our research focuses on human food consumption; however, data derived from animal research have also been included when they elucidate human behavior. Indeed, a finding in animal research may or may not be replicated in research using human subjects (personal communication with Dr. Seiquer, 21th July 2010). Our thesis also examines brain representations related to food intake. The brain detects sensory stimuli such as tastes and smells, facilitates the perception of relevant food-related information, and controls behaviors such as feeding (Longstaff, 2005).

Our research targeted young children. Based on Goldstein, Daum & Tepper (2007), we considered children young if they were 6 years old or younger. The rationale for selecting this age range as our target population is based on the following facts. First, young children's vegetable consumption counteracts childhood obesity (Lakkakula, Zanovec, Silverman, Murphy, & Tuuri, 2008), one of the most serious public health problems in the world (WHO, 2009), and it prevents illnesses such as cancer and vascular disease in adults (Maynard, Gunnell, Emmett, Frankel, & Davey Smith, 2003; Mikkilä, Räsänen, Raitakari, Pietinen, & Viikari, 2004; Ness et al., 2005). Secondly, preferences for foods—including vegetables—and eating habits are usually established in early childhood, determining positive or negative eating behavior until at least young adulthood (Nicklaus, Boggio, Chabanet, & Issanchou, 2005; Pearson, Biddle, & Gorely, 2009). Nevertheless, we include data from older children and adults whenever they facilitate the understanding of the determining factors of young children's vegetable consumption.

The present thesis tries to answer a basic question: Why do young children have flavor (i.e., taste and odor) preferences? The foods children consume directly match their taste and olfactory preferences (Nasser, 2001; Sorensen, Möller, Flint, Martens & Rabens, 2003; Zeinstra, Koelen, Kok & De Graaf, 2007; Mennella & Beauchamp, 2010). The flavor of a food is its most salient feature (Beauchamp & Mennella, 2009). The term *preference* refers to the choice of one item over another item and differs from liking, which refers to a positive affective reaction (Rozin & Vollmecke, 1986). Young children eat what they like; they prefer—and thus eat—foods that taste and smell "good" rather than "bad" (Birch, 1979; Birch, 1998; Burguess-Champoux, Marquart, Vickers & Reicks, 2006). Therefore, the terms *preference* and *liking* are equivalent for young children.

2. Thesis structure

This thesis is divided into six chapters. The first three chapters, after this introduction , review the published literature on three topics: (1) the genetic determinants of bitter taste sensitivity (the typical taste of vegetables), (2) sensitive periods in development for flavor preferences based on neuroimaging techniques, and (3) the effects of experience on the development and acquisition of flavor preferences in children. Chapter 5 presents an experimental study on the effectiveness of a school-based intervention to increase vegetable consumption through provisions of child vegetable choice. The final chapter discusses the general results and conclusions of this study. Here, we summarize the central topics of each chapter and detail the aims and objectives of our thesis.

The second chapter reviews the literature examining the impact of genetic variation in bitter taste sensitivity on vegetable acceptance (either preference for or consumption of vegetables). Specifically, there is a generalized innate predisposition for children to like sweet foods and reject bitter ones (Mennella, Pepino & Reed, 2005). For example, cruciferous (green) vegetables such as broccoli and spinach tend to be rejected by young children due to their bitter taste (Anliker, Bartoshuk, Ferris & Hooks, 1991; Aranceta & Pérez Rodrigo, 1996; Cooke & Wardle, 2005). However, vegetable rejection may vary due to (among other factors) children's genetic level of sensitivity to 6-n-propylthiouracil (PROP), which accounts for the bitterness of some green vegetables (Wardle, Sanderson, Gibson, & Rapoport, 2001). This chapter also reviews literature on the genetic variation in bitter taste sensitivity and body mass index (BMI) in young children. In fact, young children prefer to eat foods high in sugar and fat instead of vegetables (Knai, Pormerleau, Lock, & McKee, 2006).

The third chapter presents and discusses applications of neuroimaging techniques to identification of sensitive developmental periods for flavor preferences. Sensitive periods of development, although often reflected in behaviors such as expressions of flavor/food preferences, are properties of neural circuits (Knudsen, 2004). Therefore, we review studies published in the last 10 years on brain activation patterns of taste and olfactory systems in developing populations. We describe the biological basis of human taste and olfactory perception in this chapter as well as the neuroimaging techniques utilized. We devote several sections of this chapter to the hedonic processing of gustatory and olfactory stimuli in developing populations. The subjective sensation of pleasantness or repellence in response to a taste, odor, flavor or food is commonly designated as the item's hedonic value (Bahn, 1989; Stoeckel, Cox, Cook, & Weller, 2007; Robert & Lundy, 2008). Moreover, because hedonic value is an emotion-related dimension, it is also referred to as “emotional valence”, which refers to the feeling it elicits (e.g., pleasantness vs. unpleasantness; Koestler, 1999; Bachorowski & Owren, 2003). Gustatory and olfactory stimuli, such as flavors and foods, can elicit emotions (Bahn, 1989; Rolls, 2002; Rolls, 2005) that play important roles in young children’s food preferences (Bahn, 1989) and food intake (Stoeckel et al., 2007).

The fourth chapter discusses learning flavor preferences through experience. We describe several experience-related mechanisms, including parental and scholastic influences, which may alter flavor preference during development. Experience refers to contact with foods or flavors in any context (e.g., at home or school, watching TV, etc.). Some flavor- or food-linked experience-related mechanisms may operate prenatally (Budge, Gnanalingham, Gradner, Mostyn, Stephenson, & Symonds, 2005; Mennella & Beauchamp, 2002; Skinner, Carruth, Wendy, & Ziegler, 2002) or during breastfeeding (Mennella, 2001). These early experiences with flavors or foods contribute to the establishment of stable food preference patterns that may last until young adulthood or beyond (Haller, Rummel, Henneberg, Pollmer, & Köster, 1999; Nicklaus, Boggio, Chabanet, & Issanchou, 2004). Furthermore, early positive or negative experiences may have health-related effects in adults (Gidding, Dennison, Brich, Daniels, Gilman, Lichtenstein, et al., 2005). Thus, this chapter describes and discusses flavor- or food-linked experience-related mechanisms in early life.

The fifth chapter examines the effectiveness of an intervention to increase vegetable consumption in young children. Teaching young children healthier eating habits, such as those related to vegetable intake, would benefit children’s health (Warren, Parry, Lynch & Murphy, 2008). This experimental study was conducted in collaboration with Professor Milagros Gallo and her research team at Granada University (Spain) and Professor Kees De Graaf at Wageningen University (The

Netherlands). Our intervention was school-based but could also be applied at home. The intervention focused on school lunch and manipulating the degree of choice provided to young children (range: 2 to 6 years old). This chapter, which is currently in the process of being published, summarizes the intervention's scientific antecedents, hypotheses, methodology, results, and discussion.

The last chapter provides a general discussion of the overall findings and tries to integrate the different factors that contribute to food preferences and vegetable consumption in young children. The chapter ends with a discussion of future research perspectives, which are followed by a list of the most relevant conclusions.

3. Specific aims and objectives

The preset thesis has the following aims and objectives:

1. To perform a critical analysis of the role of genetic variation in bitter taste sensitivity in young children's vegetable acceptance and body mass index (BMI). As mentioned before, dislike for bitter-tasting foods—including green vegetables—seems to be related to genetic variation in bitter taste sensitivity (Tanaka, Reed & Ordovas, 2006). In addition, current child eating patterns of foods high in sugar and fat typically lead to childhood obesity (García-Bailo, Toguri, Eny & El-Sohemy, 2009). Thus, variation in bitter taste sensitivity might be one of the major determinants of child vegetable consumption.

2. To perform a critical analysis of the literature that identifies sensitive periods of postnatal taste and smell by analyzing brain activation patterns in developing populations. Gustatory and olfactory neural systems perceive tastes and smells. This knowledge may help predict the course of different sensitive periods for the gustatory

and olfactory systems, leading to the design of more effective interventions to increase children’s vegetable consumption. Thus, the existence of sensitive periods in the gustatory and olfactory systems might help determine vegetable consumption in young children.

3. To perform a critical analysis of the literature that identifies brain structures that process the hedonic value (pleasant vs. unpleasant, like vs. dislike) of tastes and smells using neuroimaging techniques to examine the correspondence between these specific brain structures and emotions. Gustatory and olfactory cues elicit emotions (Rolls, 2005), and young children base their food preferences and intake on liking or disliking (Burguess-Champoux, Marquart, Vickers & Reicks, 2006). Thus, the existence of such neural correspondence would support the notion that emotions also play a role in the consumption of vegetables in young children.

4. To perform a critical analysis of the literature on the impact of experience, including parental influence and school-based initiatives, on the development of food and drink preferences. Young children tend to eat foods they prefer (Burguess-Champoux et al., 2006), and such experiences impact food preferences as a function of development (Liem & De Graaf, 2004). Thus, changes in flavor and food preferences in children based on exposure will provide evidence in support of early experience as a determining factor in child vegetable consumption. This evidence will also provide the basis for the experimental study conducted in the present thesis.

5. To perform an intervention that provides young children with choices between different green vegetables in school meals in an effort to increase vegetable intake. Current data indicate that most children do not eat the recommended amount of vegetables (López-Frías, Nestares, Iañez, De la Higuera, Mataix & Llopis, 2005). School-based interventions, however, may increase vegetable consumption (Hendy,

Williams & Camise, 2005). Indeed, school dining halls are susceptible to initiatives aimed at educating children about healthy eating habits (Aranceta Bartrina et al. 2008).

6. To integrate the preceding information into a coherent theoretical model that explains the relationships between the determining factors of vegetable consumption in young children.

CHAPTER 2

INSIGHTS INTO THE IMPACT OF GENETIC VARIATION IN BITTER TASTE SENSITIVITY ON YOUNG CHILDREN'S ACCEPTANCE OF VEGETABLES AND BODY MASS INDEX: AN UPDATE

Abstract

Vegetable consumption by young children does not meet national recommendations in either the United States or in Europe due in part to the bitter taste of vegetables. Cruciferous vegetables contain natural bitter-tasting substances (glucosinolates) that share the same chemical structure as phenylthiocarbamide (PTC) and its chemical derivative 6-n-propylthiouracil (PROP). The degree to which the bitter taste from PTC/PROP is perceived is genetically determined and individual food likes are associated with this genetic trait, especially in children. Therefore, a critical analysis of the impact of young children's PTC/PROP taster status on their vegetable acceptance is required. Human adults' ratings regarding bitterness of vegetables correlates with their calcium (Ca) content. The ability to taste Ca influences the ability to taste the bitterness of vegetables, and therefore vegetable acceptance in rats but this has not yet been studied in young children. On the other hand, evidence that young children typically develop obesity because of their high consumption of high calorie content foods instead of vegetables requires critical analysis of the same impact on young children's body mass index (BMI). This two-fold analysis found conflicting results in studies that have examined *ad hoc* the relationship between PTC/PROP taste sensitivity and young children's vegetable acceptance and BMI. Genetic variation in the ability of young children to taste Ca might modulate the relationship between PTC/PROP taste sensitivity and vegetable acceptance in young children while socioeconomic status (SES) might modulate the relationship between PTC/PROP taste sensitivity and BMI. Thus further research on these possible modulations is recommended.

Keywords: young children, vegetable consumption, PTC/PROP taste sensitivity, genetics and obesity.

1. Introduction

The taste of a food is the main determinant of food likes and dislikes in humans and, especially in children, of food choices and food consumption (Nasser, 2001; Sorensen, Möller, Flint, Martens, & Raben, 2003; Zeinstra, Koelen, Kok, & De Graaf, 2007; El-Sohemy et al. 2007; Brug, Tak, Te Velde, Bere, & De Bourdeaudhuij, 2008). This principle is based on the strong correlations between alimentary preferences and consumption that have been found in research on human nutrition (Baxter, Thompson, & Davis, 2000) and is of particular importance when dealing with vegetable intake (Resnicow et al. 1997; Blanchette & Brug, 2005; Rasmussen et al. 2006). Indeed, it has been established that humans are universally predisposed at birth to like sweet tastes and reject bitter ones (Rozin & Vollmecke, 1986; Looy & Weingarten, 1995; Beauchamp & Mennella, 2009). For newborns, sweetness is synonymous with a “good” taste of food, while bitterness signifies a “bad” taste of food. The differentiated pattern of intense facial expressions, already found in preterm and full term newborns, in response to those different flavors confirms this natural human characteristic (Steiner, 1979; Rosenstein & Oster, 1988; Mennella & Beauchamp, 1998a; Ganchrow & Mennella, 2003). Furthermore, several authors have suggested that this natural liking for sweetness and rejection for bitterness is a response that provides an evolutionary advantage by favoring the satisfaction of two needs: an adequate intake of calories from nutrient foods and a protection against food poisoning derived from the ingestion of toxic substances which typically taste bitter, such as some xenobiotica-related substances (Drewnowski & Rock, 1995; Glendinning, 1994; Hladik, Pasquet, & Simmen, 2002, Behrens & Meyerhof, 2006). This bipolar taste-based food classification constitutes an instinctively programmed criterion for food acceptance, which enhances satisfaction of both of the mentioned needs (De Belloy, 2007) and thus promotes survival.

It has also been established that the extent to which a taste is perceived as sweet or bitter depends, among other factors, on the individually programmed genetic sensitivity to tastes, which influences whether a food is liked or rejected (Reed, Tanaka, & McDaniel, 2006). That means that taste sensitivity is a hereditary trait and that different individuals perceive tastes according to their differentiated inherited ability to taste gustatory stimuli (Rao & Morton, 1977). Since there is genetic variation in taste sensitivity, the natural human attraction to sweet, and withdrawal from bitter tastes is an issue of the differentiated degree to which a person is genetically predisposed to perceive a sweet or a bitter taste as “good” or “bad”, compared to other persons, rather than a question of universal tendencies that characterize human taste affecting all humans equally. Thus, individuals live together in separate taste-related sensory worlds.

The most studied case of genetic variation in taste sensitivity concerns the bitter taste of phenylthiocarbamide (PTC) and its derivate 6-n-propylthiouracil

(PROP) (Guo & Reed, 2001). Knowledge in this issue has been gained through *in vitro* studies and through the Human Genome Project, which aimed to identify human structural genes (United States' Department of Energy, 2009). Indeed, both approaches have provided valuable information regarding the possible genes that underlie individual variability in bitter gustatory perception and have led to the discovery of the TAS2R38 gene (and its high polymorphism degree) as the responsible gene for that individual variability (Kim & Drayna, 2004; Drayna, 2005). Meanwhile, genetic variation in sensitivity to Ca has been found with the taste receptor gene TAS1R3 explaining 7-13% of the phenotypic variation in the preference for Ca and magnesium in rats (Tordoff, 2008; Tordoff et al. 2008; Tordoff & Sandell, 2009). A strong correlation has been observed between Ca content in vegetables and ratings of perceived bitterness in adult humans (Tordoff & Sandell, 2009). Furthermore, there is genetic variation in human sweet and umami taste receptors, which is associated with the taste receptor gene families TAS1R and TAS2R (Bachmanov & Beauchamp, 2007), while PKD1L3 and PKD2L1 have been proposed as candidate sour taste receptors (Ishii et al. 2009), CD36 as a candidate fat taste receptor (Laugerette, Gaillard, Pasilly-Degrace, Niot, & Besnard, 2007), and the amiloride-sensitive epithelial sodium channel (EnaC) as a candidate salt taste receptor (Kim, Breslin, Reed, & Drayna, 2004).

Based on the genetic variation in bitter taste sensitivity, individuals who are sensitive to PTC/PROP can be classified as being *tasters, medium tasters* or even *supertasters*, while those not sensitive to these substances can be classified as *non-tasters* (Bartoshuk, Duffy, & Miller, 1994). Furthermore, a heightened sensitivity to the chemical compounds PTC and PROP has been associated with a reduced liking for bitter-tasting foods, such as cruciferous, green and high glucosinolate content vegetables, high fat content foods, green tea, soy products, alcohol and foods with a general strong taste, such as sharp cheeses (Gayathri, Henderson, & Drewnowski, 1997; Drewnowski, Henderson, Levine, & Hann, 1999; Drewnowski, Henderson, & Barratt-Fornell, 2001a; Tanaka, Reed, & Ordovas, 2008; Tepper et al. 2009). In the specific case of vegetables, it is assumed that their associated glucosinolate compounds have a thiourea moiety, this being one of the sources of their bitter taste (Tordoff & Sandell, 2009). Examples of glucosinolate-content vegetables are: broccoli, Brussels sprouts, cabbage, cauliflower, bok choy, radish, rutabaga and turnip (Troyer, Stephenson & Fahey, 2001). Another source of their bitter taste is Ca (Tordoff & Sandell, 2009). The contrary pattern of liking is observed in individuals with PTC and PROP insensitivity, as non-tasters are more likely to prefer edibles with these sensory properties (Goldstein, Dun, & Tepper, 2007). As a consequence, food intake and food choices may be influenced by this inherited trait (Duffy & Bartoshuk, 2000; Drewnowski et al. 2001a; García-Bailo, Togury, Eny, & El-Sohemy, 2009).

Taste ability decreases as individuals advance in age (Mojet, Christ-Hazelhof, & Heidema, 2001; Segovia, Hutchinson, Laing, & Jinks, 2002). In the specific case of the ability to taste PTC or PROP, changes throughout the life span have been reported as a function of age. While it is high in young children, it progressively diminishes as individuals become mature and age (Whissel-Buechy, 1990; Schiffman et al. 1994a; Navarro-Allende, Khataan, & El-Sohemy, 2008). Similarly, the association between PTC/PROP sensitivity and food preferences has been shown to be more pronounced in children than in adults (Mennella, Pepino, & Reed, 2005a; Navarro-Allende et al. 2008), although experience may modify children’s eating behavior patterns (Gibson & Bruston, 2007).

Children typically reject vegetables (Baxter & Schroder, 1997; Drewnowski, Henderson, & Shore, 1997a; Rasmussen et al. 2006) and vegetables are their least preferred kind of food (Lamb & Ling, 1946; Harper, 1963). This rejection has been mainly attributed to the bitter taste from green and cruciferous vegetables, such as spinach, broccoli and Brussels sprouts (Drewnowski & Rock, 1995; Gibson, Wardle, & Watts, 1998; Visser, Kroeze, Kamps, & Bijleveld, 2000; Wardle, Sanderson, Gibson, & Rapoport, 2001). Indeed, natural bitter substances from many cruciferous vegetables, which are usually glucosinolates, isothiocyanates and goitrin, share the same chemical group as PTC and PROP, namely N–C=S (Kalmus, 1971; Jerza-Latta, Krondl, & Coleman, 1990; Engel, Martin, & Issanchou, 2006), and therefore taste bitter. Furthermore, high correlations between low liking rates for vegetables and low vegetable intake in young children have been observed (Aranceta et al. 2008; Lorson, Melgar-Quinonez, & Taylor, 2009). It is not surprising then that vegetable consumption in young children does not meet national recommendations in the United States (Krebs-Smith et al. 1996; Johnson & Kennedy, 2000; Lorson et al. 2009) or in Europe (Yngve et al. 2005). This is especially worrying since vegetable consumption in young children counteracts childhood obesity (Lakakkula, Zanovec, Silverman, Murphy, & Tuuri, 2008), one of the most serious public health problems throughout the world (Weker, 2006; WHO, 2009) and prevents development of cancer and vascular disease in adulthood (Maynard, Gunnell, Emmett, Frankel, & Davey Smith, 2003; Mikkilä, Räsänen, Raitakari, Pietinen, & Viikari, 2004; Ness et al. 2005). Furthermore, young childhood is the life phase in which preferences for foods, including vegetables, and eating habits are most likely to be established, and thus determines positive or negative eating behavior at least until young adulthood (Nicklaus, Boggio, Chabanet, & Issanchou 2005a; Pearson, Biddle, & Gorely, 2009).

Young children typically prefer, and tend to consume, sweet and snack foods, instead of vegetables (Douglas, 1998; Knai, Pomerleau, Lock, & McKee, 2006; Warren, Parry, Lynch, & Murphy, 2008). These eating habits have been observed to produce childhood obesity (Skinner, Bounds, Carruth, Morris, & Ziegler 2004). Children who prefer fruits and vegetables are, in turn, less likely to become overweight (Lakkakula, Zanovec, Silverman, Murphy, & Tuuri 2008).

Since perception of the bitter taste of foods is genetically determined and since food preferences and eating habits are established in young childhood and maintained in adulthood (Nicklaus et al. 2005a; Pearson et al. 2009), a systematic review of studies in which the impact of young children's PTC/PROP taste sensitivity on their liking for vegetables has been examined *ad hoc* (Anliker, Bartoshuk, Ferris, & Hooks, 1991) is warranted. On the other hand, since current young children's eating behavior, among other factors, typically leads to obesity (García-Bailo et al. 2009), a systematic review of studies investigating the same impact on BMI (weight/height^2) in young children is also warranted. Therefore, the present review is mainly concerned with a critical discussion of the involvement of genetic variation in PTC/PROP taster status in both young children's acceptance of vegetables and their BMI. Based on Goldstein et al. (2007), young children will be here considered as being 6 years-old or younger. Firstly however, a review of the history of research on genetic variation in PTC/PROP sensitivity and its association with human food likes and dislikes will be presented as well.

2. The discovery of genetic variation in PTC taste sensitivity and the consequent research on genetic determinants of taste sensitivity

Bitter taste constitutes the original focus of the study of the genetic variation in taste sensitivity and goes back to Fox's discovery in 1931 that there is a universal bipolar distribution of individuals based on their sensitivity to the bitter taste of the chemical compound phenylthiocarbamide (PTC). Specifically, he found that some persons perceived PTC as bitter, while some others perceived it as tasteless (Fox, 1932). This discovery was serendipitous in nature in that Fox was preparing PTC in his laboratory when the crystals spread through the air and were unavoidably tasted by him and his colleague (Dr. C.R. Noller). Interestingly, the crystals tasted bitter to Dr. Noller, while they had no taste for Dr. Fox. They knew that PTC contained the chemical group N-C=S that had been previously described by Berlinerblau (1884) as being quite bitter. Dr. Fox then began to explore this gustatory difference across different populations and concluded that, regardless of any demographical variable, there was a universal bimodal distribution of individuals in relation to their perception of the bitter taste of the mentioned substances –tasters and non-tasters or taste blinds-, and therefore concluded the genetic origin of that distribution (Fox, 1932; Blakeslee & Fox, 1932).

Numerous subsequent efforts aimed to ascertain the specific genetic contribution to this variability in the perception of the bitter taste. By means of family studies, it was soon proposed that taste sensitivity or insensitivity to PTC was inherited as a two-allele trait within a simple Mendelian model of inheritance, with these two alleles being recessive in the case of the inherited insensitivity to PTC (Snyder, 1931; Blakeslee, 1931). However, the responsible gene and its chromosomal location were then unknown. The Mendelian model of taste sensitivity inheritance proposes that PTC sensitivity relies on the dominant allele T, so that tasters inherit their taste efficiency as one (tT/Tt) or two-dominant-allele trait (TT), while non tasters inherit their taste deficiency as a recessive insensitive allele trait (tt) (Bartoshuk, Duffy, Reed, & Williams, 1996; Kim et al. 2004). Subsequent family studies observed robust correlations between the sensitivity degree to PTC of parents and that of their children (Blakeslee, 1932; Merton, 1958; Rao & Morton, 1977), thus reinforcing Snyder's and Blakeslee's hypothesis of a Mendelian model of inheritance of bitter taste sensitivity.

However, the original simple Mendelian model of PTC-related sensitivity inheritance could not explain the results of several other studies. For example, other genetic issues and non-genetic factors were also demonstrated to have an impact on the inherited taste sensitivity to PTC (Morton, Cantor, Corey & Nance, 1981; Bartoshuk, et al. 1996; Drayna, 2005). Furthermore, it was found that children of non-taster parents were taster, which contradicts an explanation based in a one-locus model (Das, 1958) and is better explained by alternative models, such as two-locus and multiple loci models (Olson, Boehnke, Neiswanger, Roche, & Siervogel, 1989). In view of these conflicting results, the search for the gene responsible for the variation in PTC taste ability became the priority objective of the first linkage studies on this trait, although these efforts added more conflicting results to the debate (Kim & Drayna, 2004; Drayna, 2005). For example, some of these studies demonstrated linkage to the chromosome 7q (Chautard-Freire-Maia, 1974; Conneally, Dumont-Driscoll, Huntzinger, Nance, & Jackson, 1976), while a subsequent study didn't replicate this finding (Spence et al. 1984) and a third showed linkage to the chromosome 5q (Reed et al. 1999).

The controversy derived from those conflicting results stimulated further research on the topic through linkage studies and resulted in the publication of two significant discoveries. The Utah family linkage study (Drayna et al. 2003) found involvement of a single major locus in chromosome 7q, as the main candidate gene for the variation in PTC-related bitter taste perception, although a second gene located on chromosome 16p appeared to be responsible for that variation in some of the studied families (n=26). Meanwhile, Kim et al. (2003) reported the existence of a gene within chromosome 7q, designated as TAS2R38, as being responsible for individual variation in gustatory sensitivity to PTC (Kim et al. 2003). Moreover, Kim et al. (2003) found the implication of three functional alleles of TAS2R38 in the variation of PTC perception as a result of the linkage analysis of the participating human families. These three alleles configure two main different haplotypes (PAV and AVI), also called genotypes. A haplotype consists of a group of alleles that tend to be inherited together (Reed, 2004). These haplotypes are different from each other because of the polymorphic nature of their corresponding constituent amino-acids, as these amino-acids vary at three positions: 49 (alanine or proline), 262 (valine or alanine) and 296 (isoleucine or valine) (Kim et al. 2003).

The corresponding phenotype of the PAV haplotype is described as the *major taster form* and the phenotype of the AVI haplotype is described as the *major non-taster form*. Thus, the major taster form corresponds to the haplotype that contains a proline, an alanine and a valine (PAV) at those 3 positions respectively, while the major non-taster form corresponds to the haplotype that contains an alanine, a valine and an isoleucine (AVI) (Kim et al. 2003). Individuals carrying twice the PAV haplotype (PAV/PAV) are the most sensitive to PTC, individuals who carry both kinds of haplotypes (PAV/AVI) have an intermediate sensitivity (Bufe et al. 2005;

Navarro-Allende et al. 2008), and those homozygous for AVI (AVI/AVI) are the least sensitive. Furthermore, different combinations of amino acids at those positions (haplotypes), such as AAI, AAV, and PVI yield a greater range of PTC taste sensitivities (Kim et al. 2003; Kim et al. 2004; Wooding et al. 2004) in addition to the two most frequent combinations. The bitter-taste receptor gene TAS2R38 and its genotypes have also been found to be responsible for individual variation in gustatory sensitivity to the bitter taste of glucosinolate-containing cruciferous vegetables –a natural kind of food-, such as turnip or broccoli (Sandell & Breslin, 2006), besides PTC, thus providing evidence to the hypothesized natural selection of the sensitivity to the bitter taste as a via to detect toxins within foods.

The TAS2R38 gene belongs to the TAS2Rs family, also referred as Ht2Rs, of human bitter taste receptor genes (Adler et al. 2000). “TAS” is associated with a taste receptor gene while “2” indicates a bitter taste gene (Tepper, 2008). The human TAS2Rs family consists of 25 bitter taste receptor genes, which are grouped within the chromosomes 5p, 7q and 12p, and with TAS2R38 located on chromosome 7q (Kim et al. 2003; Tepper, 2008).

It is assumed that each of the human TAS2Rs may be involved in the recognition of a vast range of similarly structured bitter substances, thus responding to a great diversity of potentially harmful compounds (Beauchamp & Mennella, 2009), although there is also at least one bitter taste receptor, namely hTAS2R14, which is activated in response to structurally diverse natural bitter compounds (Behrens et al. 2004; Behrens & Meyerhof, 2006).

While TAS2Rs genes produce bitter receptors, TAS1Rs produce sweet and umami receptors (Drayna, 2005). Salty and sour tastes are mediated by ion channels serving as receptors (Beauchamp & Mennella, 2009). In humans, TAS2Rs and

TAS1Rs constitute the two most known gene families for encoding gustatory receptors residing on the surface of taste cells within the taste buds of the tongue, called G-protein coupled receptors (GPCRs) (Adler et al. 2000; Matsunami, Montemayeur, & Buck, 2000). GPCRs mediate the sweet, bitter and umami tastes by means of their expression in taste cells within taste buds (Drayna, 2005). Once GPCRs come into contact with water-soluble taste molecules, taste cells are activated and taste transduction takes place, which is followed by neural taste processing and taste perception (Conte, Ebeling, Marcuz, Nef, & Andres-Barquin, 2002; Beauchamp & Mennella, 2009). There are multiple bitter taste receptors, through which humans can identify multiple bitter compounds, so that bitter taste transduction is dependent on the specific bitter compounds (Drewnowski, 2001).

The existence of the two main forms of phenotypic expression of the TAS2R38 gene, namely the major taster form and the major non-taster form, has been consistently observed throughout the world. Indeed, several studies have examined the ratio of tasters to non-tasters worldwide (see Guo & Reed, 2001 for a review) yielding the conclusion that 75% of the population perceive bitterness intensively, while the remainding percentage of the population is less sensitive to it (Kim & Drayna, 2004; García-Bailo et al. 2009). Furthermore, there are some differences in such proportions between regions. For example, while in the United States and Europe, 30% of the adult caucasian population is insensitive (Tepper, 1998; Keller & Tepper, 2004; Lumeng, Cardinal, Sitto, & Kannan, 2008; Yeomans, Prescott, & Gould, 2009), in West Africa only 3% of the population is insensitive (García-Bailo et al. 2009), and in Japan, China and Sub-Saharan Africa, 10-20% is insensitive (Guo & Reed, 2001). In India, 40% or more of the population is insensitive (Tepper, 1998; García-Bailo et al. 2009) although this proportion varies between Indian regions (see

Bhasin, 2006 for a review). Interestingly, there is an absence of bitter non-tasters in a small community of Brazilian Indians (Delwiche, Buletic, & Breslin, 2001).

Other TAS2Rs genes show a similar variation to that of TAS2R38, although variation is regional rather than worldwide (Drayna, 2005). This is the case, for example, of the human bitter taste receptor TAS2R16, which encodes GPCRs in response to amygdalin, salicin and many bitter β-glucopyranosides, which was the first bitter taste receptor gene to be identified as being responsible for sensitivity to natural bitter compounds (Bufe, Hofmann, Krautwurst, Raguse, & Meyerhof 2002; Soranzo et al. 2005; Sausenthaler, Kohlhammer, Schäffer, Koletzko, & Koletzko 2006). Specifically, while both its alleles, namely the less sensitive and the more sensitive, coexist with high frequency in African populations, only the more sensitive allele is observed in most other populations (Soranzo et al. 2005; Behrens & Meyerhof, 2006).

This regional diversification of bitterness sensitivity and insensitive might be the product of Darwinian adaptation to the regionally differentiated existing vegetation (Shi, Zhang, Yang, & Zhang, 2003). That means that genes would have evolved that favor adaptation to regional conditions that are specifically related to the presence of toxins in vegetables (Reed et al. 2006). Moreover, balancing natural selection of the two previously mentioned main forms of genetic variation of bitter taste sensitivity (PAV for tasters and AVI for non-tasters) appears to be the most convincing mechanism through which that genetic variation can be explained (Kim et al. 2004; Wooding et al. 2004; Drayna, 2005; Lalueza-Fox, Gigli, de la Rasilla, Fortea, & Rosas, 2009). The main evidence supporting this mechanism refers to the demonstrated fact that the non-taster allele doesn't derive from mutation of the normal taster allele (Drayna, 2005). At the same time, this fact has yielded the hypothesis that the AVI allele might encode a functional receptor for other, as yet to be identified toxic bitter substances (Kim et al. 2004) that may be present in the surrounding environment. Alternatively, the other two proposed explanatory mechanisms for the high frequency of the non-taster allele are genetic drift, on the one hand, and population subdivision, on the other hand (Drayna, 2005). While genetic drift refers to hypothesized random fluctuations as a cause of variation in gene frequencies, population subdivision refers to the hypothesis that the high frequency of the non-taster allele is limited to one population. However, both of these proposals have been scientifically ruled out because the two major bitter taste haplotypes are too common in all populations (Drayna, 2005).

The identification of TAS2R38 as the single gene responsible for the phenotypic variation in PTC sensitivity confirmed the Mendelian model of inheritance for most of the bimodal phenotypic expression of PTC-related bitter perception, although not as a simple recessive model for the PTC-related insensitivity (Drayna, 2005). Nevertheless, the finding from Drayna et al. (2003) that chromosome 16p is implicated in variation in bitter taste sensitivity, in addition to chromosome 7q, has led several authors to suggest that PTC's genetics can be explained by a mixed model, based on a Mendelian and a complex trait (Kim & Drayna, 2004; Drayna, 2005). However, recent research has found a robust correlation between the Ca content of certain vegetables and the perception of their bitter taste in humans ($r = 0.93$). This has been supported through animal research with rats of different genetically determined sensitivity to Ca and choice tests between vegetables with a high Ca content and vegetables with low Ca content (Tordoff & Sandell, 2009). Furthermore, it has been shown that the taste receptor TAS1R3 explains a 7-13% of the phenotypic variation in the preference for Ca and magnesium (Tordoff, 2008; Tordoff et al.

2008). Thus, individual variation in bitter taste perception might be due to a combination of genes, rather than one gene, although more research is needed to establish the role of genetic variation in Ca sensitivity on bitter perception.

Apart from PTC, its derivative 6-n-propylthiouracil (PROP) has also been described as showing a differentiated distribution within and across populations (Barnicot, Harris, & Kalmus, 1951). PROP, like PTC, contains the typical chemical structure of "thioureas" –N-C=S-, which tastes bitter (Barnicot et al. 1951; Tepper, 1998). Furthermore, PROP taster status was found to be significantly correlated with PTC taster status (Barnicot et al. 1951; Harris & Kalmus, 1949). The question that then emerged was whether PROP and other substances with the same chemical structure and with bimodal distribution were also perceived through the operation of the same taste receptor (Kim et al. 2004). In this sense, it was confirmed via *in vivo* and *in vitro* studies that the taste receptor TAS2R38 also mediates responses to PROP, although it has been found that PTC matches with it better (Drayna, 2005; Tepper, 2008). Thus, the TAS2R38 receptor responds to all bitter substances if they belong to the thioureas.

Genetic studies on taste then began to use PROP frequently as a substitute for the potentially toxic effects and the sulfur odorous PTC (Fischer & Griffin, 1964; Lawless, 1980), and therefore most of the worldwide observations regarding genetic variation in bitter taste sensitivity have been derived from studies in which PROP has been used, instead of PTC. However, humans do not perceive both compounds identically and they are not interchangeable. For example, bitterness perception thresholds for PTC are lower than for PROP and the PTC's perceptive spectrum is more extensive than is PROP's (Tepper, 2008). Additionally, the distribution of the phenotypic expression of bitterness sensitivity to PROP within the population is "trimodal” rather than bimodal, as cases of PROP supertasters have been found (Reedy, Bartoshuk, Miller, Duffy, & Yanagisawa, 1993; Bartoshuk et al. 1994; Reed, Bartoshuk, Duffy, Marino, & Price, 1995). Furthermore, it has been shown that the density of taste receptors in the tongue –taste buds contained within fungiform *papillae*- correlates significantly with the perceived bitterness intensity of PROP (Bufe et al. 2005; Drayna, 2005; Tepper, 2008) with PROP supertasters showing the highest rates of fungiform *papillae* and thus perceiving the most extreme degree of bitterness (Prutkin et al. 2000; Bartoshuk, 2000a). Supertasters also perceive the most intense thermal and tactile sensations derived from foods, such as food creaminess, viscosity or burn within the oral cavity because pain and touch neurons also innervate fungiform *papillae* (Bartoshuk, 2000b). Interestingly, a gender effect on the density of taste buds has been observed with women having higher number of these *papillae* and taste buds than men (Reedy et al. 1993; Bartoshuk et al. 1994; Reed et al. 1995). Consequently, most adult tasters and supertasters are women (Bartoshuk, 1980). This gender-related distribution of tasters and non-tasters is not observed in young children (Keller, Steinmann, Nurse, & Tepper, 2002; Mennella et al. 2005a; Tepper, 2008) but from the beginning of puberty onwards (Whissel-Buechy & Wills, 1989; Goldstein et al. 2007). Thus, based on Drayna (2005), phenotypic distribution of taste sensitivity to PROP, especially the supertaster phenotype, is influenced by other factors in addition to genetic control.

3. Methodology for the evaluation of PTC/PROP taster status

There is no standardized protocol for the evaluation of PTC/PROP sensitivity status. On the contrary, a variety of methods have been used across research work on the topic to obtain reliable measures of individuals' taste sensitivity to PTC/PROP compounds. A profound analysis of the psychophysical methods is beyond the scope of this text, and readers are recommended to review comprehensive publications on this topic (Bartoshuk, 2000b; Tepper, Christensen, & Cao, 2001; Bartoshuk et al. 2004; Snyder, Prescott, & Bartoshuk, 2006). Furthermore, the work of Lawless (1980) shows an in-depth comparison of the effectiveness of different methods in making that evaluation. Rather, a short description of the main methods for the evaluation of PTC and PROP taster status will be here presented.

Research protocols examining differences in bitter taste perception and its genetic nature, prior to the discovery of the TAS2R38 gene, have included twins as subject samples or have used PTC/PROP screening tests (Navarro-Allende et al. 2008). The importance of twin designs relies on the *a priori* assumption that twin pairs, either monozygotic or dizygotic, live together under the same stimuli exposure conditions, so that any difference in taste perception is potentially attributed to differences of genetic nature (Reed et al. 2006). Screening tests, on the other hand, can be classified into two global categories: threshold and supra threshold methods (Tepper, 2008). Both are aimed to establish individualized PTC/PROP detection thresholds by exposing participants to these substances using PTC-soaked filter papers placed on the tip of the tongue (Drewnowski, Kristal, & Cohen, 2001b) or by them swallowing PTC content liquid forms. Threshold methods measure individuals' bimodal variation in PTC/PROP sensitivity based on their responses to single concentrations of these substances. Thus, subjects have only to affirm whether they perceive the taste solution or not, and thus they can be classified as either tasters or non-tasters (Boughter & Bachmanov, 2007). Supra-threshold methods or Supra-threshold scaling techniques, introduced by Stevens (1969), are based on the serial presentation of different PTC concentration samples and "forced choice blind tests" (Kim & Drayna, 2004), so that further subdivisions of the degree to which subjects perceive PTC or PROP can be addressed and medium tasters and supertasters can be classified (Bartoshuk et al. 1996; Prutkin et al. 2000).

The discovery of the TAS2R38 gene has led to the possibility of measuring genetic variability in PTC/PROP sensitivity directly through genomic DNA extraction and allele genotypification of the TAS2R38 gene (Mennella et al. 2005a; Navarro-Allende et al. 2008). All these PTC/PROP taster status-related measurement techniques have been used with adults as well as with children as young as 3 years old (Turnbull & Matisoo-Smith, 2002).

4. Genetic variation in PTC/PROP taster status and its association with perception of different substances, other tastes and other oral sensations

The main characteristic of PTC/PROP tasters is their ability to perceive low concentrations (i.e. 0.001M) of any bitter compound as aversively bitter, as opposed to non-tasters, who either cannot taste the bitterness of that substance or would need high concentrations of it to be able to recognize the bitter taste (Maier, 2007). Medium tasters perceive the bitterness of PTC/PROP with a lesser degree of aversion, than do tasters (Prescott, Ripandelli, & Wakeling, 2001a) and super tasters perceive an extreme bitter taste from PTC/PROP (Precott et al. 2001; Tepper, 2008).

Examples of typically bitter-tasting substances, to which humans may respond differently as a function of their sensitivity to PTC/PROP, are: caffeine, urea and quinine (Drewnowski & Rock, 1995; Hall, Bartoshuk, Cain, & Stevens, 1975; Leach & Noble, 1986; Mela, 1989), although Yokomukai, Cowart, & Beauchamp (1993) found no correlation between PROP sensitivity and urea or quinine. Furthermore, some authors have found that the intensity of the bitter taste of potassium chloride, sodium benzoate and potassium benzoate is also related to PROP taster status (Bartoshuk, 1979; Bartoshuk, Rifkin, Marks, & Hooper, 1988; Yackinous & Guinard, 2002; Pronin et al. 2007).

On the other hand, PTC/PROP sensitivity has been shown to be associated with sensitivity to other tastes. For example, PTC/PROP tasters typically perceive the sweetness of low concentrations of sucrose and saccharin as intensively sweeter than non-tasters (Blakeslee & Salmon, 1935; Bartoshuk, 1979; Gent & Bartoshuk, 1983; Looy & Weingarten, 1992; Drewnowski & Rock, 1995). However, genetic sensitivity to PROP did not predict sweetness intensity ratings or hedonic response to sweetness for sucrose solutions in a subject sample of young females of different ethnic origin (Drewnowski, Ahltrom, & Barrat-Fornell, 1997b). Citric acid has also been shown to be perceived as sourer by tasters than non-tasters (Prutkin, Fast, Lucchina, Snyder, & Bartoshuk, 1999) and sodium chloride as more salty (Bartoshuk, Duffy, Luchina, Prutkin, & Fast, 1998; Duffy & Bartoshuk, 2000). Although PTC and PROP are not natural bitter chemical compounds of foods, genetic variability in perception of their tastes has been shown to be strongly correlated with taste sensitivity to other natural bitter and sweet compounds that are present in foods (Blakeslee & Salmon, 1935; Hall et al. 1975; Bartoshuk, 1980; García-Bailo et al. 2009). Furthermore, sensitivity to fat and creaminess of foods has also been observed to be correlated with PROP taster status (Tepper & Nurse, 1997; Kirkmeyer & Tepper, 2005).

Several gustatory sensations, other than pure taste, have also been shown to be correlated with PTC/PROP status. For example, oral pain (Anliker et al. 1991), oral irritation produced by citric acid (Prescott, Soo, Campbell & Roberts, 2004) and the burning sensation caused by the capsaicin in chili peppers have been also shown to be perceived more intense by tasters than non-tasters (Karrer & Bartoshuk, 1991; Drewnowski & Rock, 1995; Tepper & Nurse, 1998). Similarly, PROP tasters have been found to perceive the intensity of ethyl alcohol more strongly than non-tasters (Bartoshuk et al. 1993). The vast variety of oral sensitivities which correlate with PTC/PROP taster status have led several authors to attribute a role of general oral marker to the PTC/PROP taster status (Ly & Drewnowski, 2001; Tepper, 2008).

5. Genetic variation of PTC/PROP taster status and its association with food likes and dislikes: evidence of age effects

The importance of this genetically determined gustatory variability relies on the manifest effects it has on individuals' eating habits. The main effect is the predisposition to establish individualized patterns of nutritional behavior, including food choices, preferences and intake patterns, because individuals' hedonic value of foods, and therefore food likes and dislikes, vary as a function of PTC/PROP taster status (Bartoshuk, 2000b; Drewnowski, 2001). Some of the products that have been shown to be more disliked and less preferred by tasters than non-tasters are dairy products, such as milk or cheese, cruciferous vegetables, such as spinach, broccoli, and Brussels sprouts (Anliker et al. 1991; Drewnowski & rock, 1995), alcohol (Duffy et al. 2006), and high-fat-content foods, sweets and meats (Tepper, 1998; Duffy & Bartoshuk, 2000). Moreover, it has been shown that PTC/PROP tasters tend to dislike strong tasting foods in general and exhibit more food dislikes, while PTC/PROP non-tasters display higher acceptance of a greater variety of foods in adults (Fischer, Griffin, England, & Garn, 1961; Glanville & Kaplan, 1965) as well as in children

(Korslund & Eppright, 1963; Anliker et al. 19991; Looy & Weingarten, 1992; Tepper, 1999; Keller et al. 2002).

Interestingly, the ability to taste PTC/PROP is heightened in young children and progressively decreases as people become older (Whissel-Buechy, 1990; Schiffman et al. 1994) and the association between PTC/PROP taster status and food likes and dislikes appears to be stronger in children than in adults (Mennella et al. 2005a). Specifically, Mennella et al. (2005a) reported that children with high sensitivity to PROP, that is, with PAV/PAV genotypes, or with moderate sensitivity to PROP, that is, with PAV/AVI genotypes, prefer sweet beverages and foods more than children with less sensitivity to PROP, while no correspondence between TAS2R38 genotypes and sweet preferences was observed in adults. In agreement with these findings, it has also been reported that use of bitter-tasting foods increases with increasing age (Lindgren, 1962; Pao, Fleming, Guenther, & Mickle, 1982; Navarro-Allende et al. 2008).

Taste ability, in general, has been shown to diminish as an individual ages (Mojet et al. 2001; Segovia et al. 2002) and as consequence, taste perception of foods is compromised in older subjects when compared to young adults (Rolls, 1999). Causes of the decrease in ability to taste have been attributed to use of pharmaceuticals as well as to an age-related progressive lost of taste receptors (Navarro-Allende et al. 2008). These findings, along with the lack of an association between TAS2R38 genotypes and sweet preference in adults (Mennella et al. 2005a), have led some authors to suggest that, as individuals mature, cultural influences and physiological factors, such as the loss of taste receptors as people age, exert a more important influence on food preferences and intake than taste sensitivity-related genetic influences (Mennella et al. 2005a; Navarro-Allende et al. 2008). The strong genetic impact of PTC/PROP sensitivity on young children's food preferences can be overcome if enough repeated exposure –at least 8 days- to any food, including vegetables, is applied (Birch & Marlin, 1982; Birch, 1999; Wardle, Herrera, Cook. & Gibson, 2003; Forestell & Mennella, 2007) and may last until, at least, young adulthood (Nicklaus et al. 2005a).

Based on these findings, we can conclude that the younger an individual is, the higher the impact of PTC/PROP taster status on that individual's food likes and dislikes will be. Furthermore, the more sensitive to the bitter taste a person is, the higher the proportion of foods that are disliked will be, while those less sensitive will prefer a wider spectrum of foods, and especially high-sugar- and high-fat-content foods. However, see Drewnowski, Henderson, & Cockroft (2007) for a contrary point of view.

Sensitivity to other tastes, such as sweet, salty or sour tastes has not been found to be related to food likes or dislikes (Fischer & Griffin, 1961; Fischer, Griffin, & Kaplan, 1963; Drewnowski & Rock, 1995; Donaldson, Bennett, Baic, & Melichar, 2009). However, human genetic variation in sweet taste perception has recently been found, in addition to findings of strong correlations between the allelic polymorphism of TAS1R3 and sweet taste sensitivity to sucrose (Fushan, Simons, Slack, Manichaikul, & Drayna 2009). Further research is needed to ascertain if there is genetic variation in the perception status of other tastes, and therefore, its association with the hedonic value of foods, as well as possible age-related modulations.

6. Impact degree of young children’s PROP taste sensitivity on their vegetable acceptance (preference and/or intake)

Several studies have examined *ad hoc* the relationship between PROP taste sensitivity and acceptance of bitter vegetables, such as cruciferous and non-cruciferous vegetables, in young children. Anliker et al. (1991) conducted a study with children aged between five and seven and found that PROP tasters reported a lower preference for raw broccoli, cooked broccoli and raw spinach, which are bitter-tasting vegetable from the *chenopodiaceae* vegetable family (Jerza-Latta et al. 1990) than non-tasters in a food-preference questionnaire. Turnbull & Matisoo-Smith (2002) observed that sensitivity to PROP predicted low acceptance of raw spinach in children aged between three and six. Another subsequent study conducted in four and five year-old children (Keller et al. 2002) concluded that PROP taster children reported a lower acceptance of raw broccoli than did non-taster children. Tepper & Steinmann had previously observed this pattern of vegetable acceptance in children, in view of a set of unpublished data (Tepper, 1998 p. 1272). Similar findings were replicated in a study of consumption of raw broccoli in three to four year-old children (Bell & Tepper, 2006). Furthermore, non-tasters ate more vegetables, including more raw bitter vegetables (cucumber, broccoli and black olives) than did tasters and ate more bitter than non-bitter vegetables (carrots and red peppers). These findings, taken as a whole, suggest an inverse relationship between PROP taste sensitivity and acceptance of vegetables in young children, although there are some contradictions among some of those studies that need to be highlighted. For example, while Anliker et al. (1991); Keller et al. (2002) and Bell & Tepper (2006) found such a positive relationship regarding raw broccoli in young children, Turnbull & Matisoo-Smith (2002) did not.

Furthermore, Turnbull & Matisoo-Smith (2002) did not find that relationship for cooked broccoli, besides raw broccoli in young children.

We speculate that one of the causes of this lack of robustness might be that the amount of the glucosinolate content of vegetables used in the different mentioned studies varied from each other. Indeed, different vegetables and even different species of the same kind of vegetable differ from each other in their bio-chemical composition (Dole Food Company, Mayo Clinic and University of California, 2002). Moreover, a vast variety of factors, such as horticultural crops, environment, cultural practices, and agrichemicals might affect the plant development, and therefore the taste of the final vegetable (Mattheis & Fellman, 1999). For example, the raw broccoli used by Anliker et al. (1991) and Keller et al. (2002) might have been cultivated in differently than that used by Turnbull & Matisoo-Smith (2002), and thus the raw broccoli used by the two former research teams might have been enough bitter to elicited a differentiated degree of taste sensitivity as a function of PROP taster status, in comparison to the raw broccoli used but the last research group. The amount of the Ca might also have varied among the vegetables used in those different studies. Indeed, Ca is another source of vegetables-related bitterness (Tordoff & Sandell, 2009). Moreover, it has been found a strong correlation (r = 0.93) between the Ca content of a great variety of vegetables and the vegetable bitterness ratings reported by adult humans (Tordoff & Sandell, 2009). Furthermore, genetically predisposed rats to consume Ca «probably due to mutations in taste receptor genes [which lead rats to not perceive the bitterness of Ca] » (Tordoff & Sandell, 2009, p. 499) have been found to prefer significantly high-Ca-content-vegetables, in comparison to normal (mutation-free) rats (Tordoff & Sandell, 2009), which tend to avoid Ca because of its associated aversive bitterness (Tordoff et al. 2008), within a causative relationship. The taste receptor gene that appears to be responsible for individual variability in sensitivity to Ca in rats is TAS1R3 (Tordoff, 2008; Tordoff et al. 2008).

The data regarding the correlative relationship between the Ca content of vegetables and human adults' ratings of perceived bitterness and the causative relationship between genetic predisposition to perceive Ca and acceptance of vegetables in rats, together with the data regarding involvement of TAS1R3 as the taste receptor gene for individual variability in sensitivity to Ca in rats extracted by Tordoff and colleagues open the question whether genetic variation in the sensitivity to Ca might impact vegetable acceptance within a causative relationship in young children. This has not yet been studied, and therefore the genetic variability in sensitivity to Ca has not been taken into account in studies that have examined the association between bitter taste sensitivity and vegetable acceptance in young children. Thus, since previous research points to an association between sensitivity to Ca and vegetable acceptance in rats (Tordoff, 2008; Tordoff et al. 2008; Tordoff & Sandell, 2009), it would be interesting to examine the role of genetic variation in Ca taste sensitivity in bitter taste perception of vegetables and its connection to vegetable acceptance in young children, as a combination of both traits, the trait underlying sensitivity to the bitter taste of glucosinolates and the trait underlying sensitivity to the bitter taste of Ca, and therefore more than one gene (TAS2R38 + the human equivalent of TAS1R3) might underlie the individualized pattern of responsiveness to the bitter taste of vegetables, and therefore vegetable acceptance in young children. However, that evidence-based opened line of research is currently difficult to develop due to both, a current lack of suitable research methods adapted to that line of research and a lack of knowledge regarding the molecular basis of Ca perception (Tordoff & Sandell, 2009).

7. Impact degree of young children's PROP taste sensitivity on their BMI

Studies examining the suspected association between PROP and BMI in young children have yielded conflicting results. Keller & Tepper (2004) reported contradictory relationships between BMI and PROP status, according to gender, in four to five year-old children, as non-taster boys showed higher BMIs than taster boys, and taster girls showed higher BMIs than non-taster girls. Furthermore, in a sample of low-income three to six year-old children, a correlation between PROP taster status BMI z-scores was found and the prevalence of overweight children was higher in the taster group (Lumeng et al. 2008). On the other hand, other studies have found no difference in weight or BMI as a function of PTC/PROP sensitivity status in the same age range of four to five years (Keller et al. 2002; Bell & Tepper, 2006). Goldstein et al. (2007), in a study of pre-adolescent children (age = 7-11 years), examined the hypothesis that PROP sensitivity might influence the eating behavior of young children, but that that differences in body weight emerge later in development, and concluded that there was no association between PROP status and body weight in their subject sample. These conflicting findings suggest the existence of a confounding factor that might be exerting an influence on this relationship. Although Keller & Tepper (2004) found a gender effect, this has never been replicated and gender is unlike to be such a confounding factor. Socioeconomic status (SES) is however, a more likely candidate. The rationale for this claim is offered by Lumeng et al. (2008) who state that, with the exception of their own work in which subjects were of low SES, previous studies, such as those of Keller et al. (2002), Keller & Tepper (2004), and Bell & Tepper (2006) were conducted with children of above average

SES. Indeed, all children who participated in these studies were enrolled in the Rutgers University Nutritional Sciences Preschool, which is a very exclusive nutrition-related educational program of the State University of New Jersey that is focused on preschool children. Furthermore, Baranowski et al. (2009) found a significant PROP sensitivity by SES interaction term (P = 0.010) in children aged between nine and ten and adolescents aged between seventeen and eighteen, regardless any other demographical variable. Specifically, supertasters showed the largest BMI percentile and Z-score, but only among the children with highest SES. However, no study has yet considered SES as an independent variable in order to examine whether the relationship between PROP taster status and BMI could change as a function of an individual's SES in young children, that is, children aged 6-year-old or younger. Thus, future research examining this possible influence in young children is warranted.

8. Final conclusions and future research

This review has aimed to critically discuss the role of genetic variation in bitter taste sensitivity in young children's vegetable acceptance and BMI and to achieve this aim, it was necessary to review the history of the study of genetic variation in PTC/PROP sensitivity and its association with human food preferences. The scientific consensus in a broad sense is that genetic variation in PTC/PROP sensitivity determines human food likes and dislikes (Duffy et al. 2006), and that this genetic determination is modulated by age. Specifically, a stronger genetic determination of food likes has been observed in young children than in adults and older individuals (Mennella et al. 2005a; Navarro-Allende et al. 2008), which suggests that experience with foods modifies children's eating behavioral patterns (Gibson & Bruston, 2007). Cultural and physiological conditions, combined with a negative correlation between age and chemo-sensitivity and taste sensitivity in particular (Bartoshuk et al. 1996; Navarro-Allende et al. 2008), may explain the lower impact of taste genetics on food preferences in mature and older subjects than in younger subjects.

Regarding the specific case of vegetable acceptance in young children, the present review revealed that several reports conclude that young children's acceptance or rejection for vegetables depends on their genetically determined sensitivity to the bitter taste, which is indicated by the participants' PROP taster status. In these studies, young children characterized by a low PROP taste sensitivity accepted vegetables, especially raw broccoli and raw spinach, more readily than did children characterized by higher PROP taste sensitivity (Anliker et al. 1991; Turnbull & Matisoo-Smith, 2002; Bell & Tepper, 2006). However, there are some contradictions among some of these studies regarding that dependency relationship. Indeed, while Anliker et al. (1991); Keller et al. (2002) and Bell & Tepper (2006) found such a positive relationship regarding raw broccoli in young children, Turnbull & Matisoo-Smith (2002) did not. These conflicting results might be due to differences in the glucosinolate and/or Ca content of the vegetables used in those different studies, and we think that these differences regarding the bio-chemical content of vegetables are probably due to differences in the conditions in which the different vegetable-leading plants were cultivated identified by Troyer et al. (2001). Thus, this should be taken into account in future review research.

Apart from genetic variation in PROP taster status, genetic variation in Ca taster status has also been shown to exert an influence on the degree to which the bitterness from vegetables is perceived, and to explain individual differences in preference for vegetables in rats (Tordoff, 2008; Tordoff et al. 2008; Todoff & Sandell, 2009). Furthermore, a strong correlation between the Ca content of vegetables and the degree, to which vegetables tastes bitter has been found in human adults (Tordoff & Sandell, 2009). The association between sensitivity to Ca and vegetable acceptance has not been studied in young children. Therefore, it would be interesting to examine the association between young children's Ca taster status and their vegetable acceptance. To develop this new research line is an arduous task, as there are currently great methodological obstacles as well as lack of proper information about the molecular basis of Ca perception, which would guide selection of the proper method of research for that research line (Tordoff & Sandell, 2009). The confirmation of this association would also confirm the claim that a probable combination of at least both of these genetic traits, instead of one unique genetic trait, may underlie the individualized pattern of responsiveness –sensitive *vs*. insensitive- to the bitter taste of vegetables, and therefore of preference for vegetables, thus improving the current state of scientific knowledge about determining factors of child vegetable consumption.

Since the bitter taste is the main determinant for rejection of consumption of vegetables in young children (Visser et al. 2000; Wardle et al. 2001) and since the process of debittering vegetables through different mechanisms is possible (Heany & Fenwick, 1980; Heany, Fenwick, & Mullin, 1983), food science would be well advised to make vegetables less bitter if young children are to increase their vegetable consumption. This recommendation is independent of the influence of genetic variation in bitter taste sensitivity on young children's vegetable intake. However, natural bitter compounds occurring in vegetables, such as glucosinates are important cancer-preventive substances (Zhang, Thalalay, Cho & Posner, 1992; Troyer et al. 2001). Thus, according to Drewnowski & Gómez-Carneros (2000), a solution to this dilemma is needed. Another strategy that can be applied to improve young children's vegetable consumption is the experience-related strategy of repeated exposure – without any reinforcement- to vegetables. Indeed, it has been shown that repeated exposure of young children to particular foods induces long lasting preferences for them (Wardle et al. 2003; Nicklaus et al. 2005a; Forestell & Mennella, 2007).

Conflicting results have been observed when examining the relationship between PROP taster status and BMI in young children. While some studies have found positive correlations, others have found negative correlations, gender-related contradictions, or have found no relationships at all. It has been suggested that confounding variables, such as SES might exert an influence on the mentioned relationship in old children, that is, children aged nine-year-old or older and adolescents (Baranowski et al. 2009). However, SES has never been used as independent variable in studies examining the relationship between PROP and BMI in young children and all young children in which that relationship has been studied have been of high SES. The exception is the study of Lumeng et al. (2008), which examined the relationship between PROP taster status and BMI in a sample of low-income three to six year-old children. Thus, further research on SES as a possible factor modulating that in young children, is needed.

CHAPTER 3

POSTNATAL AND LATER DEVELOPMENT OF THE TASTE AND OLFACTORY SYSTEMS IN LIGHT OF THE HUMAN BRAIN MAPPING APPROACH: AN UPDATE[1]

Abstract

Gustatory and olfactory functions are already present at birth, although a full development of both systems takes place postnatally. Existence of early postnatal sensitive periods throughout the development course of sensory systems, including the taste and olfactory, has been well documented. The normal postnatal and later development of any sensory function parallels development of the central nervous system and the development of its basic units, specifically white matter and gray matter. This development is associated with development-related plastic changes, such as myelination and axonic pruning, which is the typical development-related plastic change that occurs during sensitive periods. These plastic changes ensure the increasing efficiency of neural communication that takes place throughout development and correlate with signal changes acquired by means of neuroimaging techniques. In this paper, we review papers published in the last ten years with two related aims. We aim to ascertain the way in which developmental plastic changes within the taste and olfactory systems have been reflected in signals obtained through neuroimaging techniques, in order to identify sensitive periods of gustatory and olfactory development by conducting

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a systematic review research on brain activation patterns of taste and olfactory systems of developing populations that have been measured through neuroimaging techniques. The main contribution of the present review is the revelation of three obstacles that have partially limited achievement of these objectives. In order to overcome these limitations, further research on developmental brain mapping of the taste and olfactory systems in newborns, children and adolescents, and on the association between developmental plastic changes and imaging signals, is needed. In addition, further developmental research based on longitudinal designs is required. Despite these limitations, this review has however, revealed relevant insights into young adults' gustatory and olfactory systems.

Keywords: neuroimaging techniques, development, sensitive periods, taste system, olfactory system, developing populations.

1. Introduction

Flavor is the property of foods and drinks that is mainly generated by the integrated processing of two kinds of sensory information –gustatory and olfactory-, once tastes and odorants are detected by both respective sensory systems (Beauchamp & Mennella, 1998; Simpson & Sweazey, 2006), besides other somatosensory information, such as temperature and texture (Small & Prescott, 2005; Beauchamp & Mennella, 2009). Specifically, orthonasal or retro nasal activation of the smell sense, depending on the input entry, relies on the detection of odorants by olfactory receptors cells (ORCs) that are located either on the nasal mucosa or the nasopharynx (Espinosa Díaz, 2004; Simpson & Sweazey, 2006). Similarly, the sense of taste is activated whenever taste receptor cells (TRCs), located in the tongue, are stimulated by contact with food or drink particles (Gottfried et al. 2006). After contact between receptor cells and these stimuli has occurred, neural activity takes place in response to that contact, thus allowing our taste and olfactory perception and therefore flavor perception (Smith & Vogt, 1997).

In addition to the gustatory and olfactory systems, three other sensory systems are also involved in flavor perception. The somatosensory system is responsible for the sensation of thermal and tactile cues associated with foods, such as food temperature and food texture (Simpson & Sweazey, 2006), the visual system processes food-related visual cues, such as color and shape (Delwiche, 2004; O'Doherty, 2002), and the auditory system deals with food-related auditory cues, such as sounds associated with the action of chewing (Verhagen & Engelen, 2006) and the sound of foods (Small et al. 2004). Furthermore, human tasting implies the processing of several cognitive aspects, such as mental images of foods (Kikuchi et al. 2005; Okamoto & Dan, 2007) and processing of the hedonic value of foods –pleasant vs. aversive- (O'Doherty, 2001). Human flavor perception is, therefore, a very complex natural phenomenon. The primitive phylogenetic and ontogenetic origin of the taste, and by extension, the olfactory systems, has been often misinterpreted as being simple (Gallo, 2008).

The scientific community has traditionally considered there to be five taste qualities which are able to be perceived by humans: sweet, salty, bitter, sour and umami –the taste of monosodium glutamate (MSG) - (Yoshida, et al. 2006), but see Erickson (2008) for a contrary point of view. In addition, there may be different transduction mechanisms for these five basic tastes (Medler, 2008; Roper, 2006). The number of odors that can be discriminated by humans has been estimated to be around half a million (Kringelbach, 2007), with multiple transduction mechanisms for these odorants.

According to Spector (2000), the taste sense serves three vital functions, namely: stimulus identification, ingestion motivation and digestive preparation. Stimulus identification refers to the association of specific flavors with other stimuli and/or consequences. For example, subjects who are allergic to fish may be helped to avoid ingestion by its distinctive taste. Ingestion motivation refers to the hedonic component of gustatory stimuli and the preference level of one food above others. Digestive preparation refers to preparation of the body for ingestion through the onset of several physiological processes, such as salivation. Olfaction, for its part, in addition to contributing to flavor perception, favours an individual’s survival by alerting them to damaging aerosolized particles and deteriorated foodstuffs (Jones & Rog, 1998). Additionally, odors allow the differentiation between gustatory and non-gustatory stimuli (Small et al. 2008).

Human behavioral research has consistently shown that the gustatory function, at least in terms of taste identification and merely liking or disliking, is already present in newborns (Mennella & Beauchamp, 2005). The differentiated pattern of intense facial expressions linked to the so-called gusto facial response, or reflex, found in newborns and preterm newborns, in response to different tastants, confirms this natural human characteristic (Ganchrow, Steiner & Daher, 1983; Rosenstein & Oster, 1988; Steiner, 1979). Furthermore, experiences with flavors take place prenatally through the mother’s amniotic fluid (Beauchamp & Mennella, 1998). Similar conclusions have been drawn with regard to the olfactory function, as it has been shown that neonates are able to identify and discriminate between odors (Faas, Spoltón, Moya & Molina, 2000) and prenatal experience with odors has also been deduced to take place (Beauchamp & Mennella, 1998). Although gustatory and olfactory functions are already present at birth, and even during prenatal stages (Beauchamp & Mennella, 1998; Mennella &

Beauchamp, 1998a), their development continues postnatally (Bartoshuk & Beauchamp, 1994; Mennella, Pepino & Reed, 2005a; Schaal, 1999; Schaal, 2005). Development of any sensory function implies the age-depending maturation of the corresponding sensory system and acquisition of new sensory information (learning) through experience with the environment.

Human behavioral research has also consistently shown the existence of early postnatal sensitive periods throughout the development course of sensory functions (Johnson, 2005; Knudsen, 2004). Sensitive periods can be defined as restricted periods of time across development, during which there is a biological display of an extreme neural sensitivity to the storage of experience-driven sensory –and probably conceptual- information, that is not present in other time periods, that promotes an individualized design, that is, a design specific of the individual’s idiosyncratic environment, of the shape and function of the brain, which is directed to individual’s survival, and thus, safeguards the normal development (disease-free) of sensory systems and probably cognitive systems (Hensch, 2004; Spolidoro, Sale, Berardi & Maffei, 2009; Thomas & Knowland, 2009), and that is reflected in behavior (Knudsen, 2004). Furthermore, effects of experience during postnatal sensitive periods are linked to facilitate the acquisition of essential abilities, which guarantee the individuals’ management of daily situations with an enough efficacy, these abilities providing individuals with appropriate behavioural responses, that is, according with individuals’ circumstances (Pascual-Leone, 2006). The main characteristic of a sensitive period regarding the effects of having experiences with stimuli during its time course –during a specific age- is the imprinting effect that these experiences induce in the individual for his whole following life, in the sense that these experiences induce irreversible changes in the individual’s behavior (Bruer, 2001) and in its underlying neural funciton. Imprinting effects can be displayed in the reported preferences for sensory stimuli as well as acquisition of complex abilities, such as a language, by a subject. Within the gustatory domain, for example, high correlations have been found between the acquired food preferences during early childhood –2-3 years of age- and the status of such preferences in late childhood (Skinner, Carruth, Bounds & Ziegler, 2002), adolescence (Nu, MacLeod & Barthelemy, 1996) and young adulthood (Nicklaus, Boggio, Chabanet & Issanchou, 2004). Furthermore, experience with the consumption of different formulas during the first 3-11 months of life has been found to induce differential flavor preferences at that age (Mennella & Beauchamp, 2005) with that learning subsequently affecting status of flavor preferences at the age of 4-5 years (Mennella & Beauchamp, 2002). In the case of olfactory preferences, the available evidence identifies perinatal time (4-37 min after birth) as a postnatal sensitive period for olfactory learning (Romantshik, Porter, Tillmann & Varendi, 2007). Prior experience, during the prenatal phase, with the odor of the mother's amniotic fluid causes full-term neonates to prefer that odor to other woman's amniotic fluid odor (Marlier, Schaal, Soussignan, 1998) and to milk formulas (Schaal & Marlier, 1998). Experience-related effects during sensitive periods of development are not always innocuous, however, as an aberrant environment may lead to an aberrant brain structure, brain function and pathological behavior (Pascual-Leone, 2006).

What is currently known about the ontogenetic development of the taste and olfactory systems is derived mostly from animal models (see Krimm & Barlow, 2008 and Gómez & Celii, 2008 for reviews of respective systems). However, the emergence of neuroimaging techniques allows the exploration of human functional organization of these and other sensory systems in mature (Alvarez et al. 2008) as well as immature brains (Sowell, 2003) with a *human brain mapping approach* (HBA). HBA refers to the research method in which the principal objective is «to visualize brain areas and their interconnection engaged in a certain function by using non-invasive [or neuroimaging] techniques» (Shibasaki, 2008, p.732). Thank this technology, we know for example, that normal human postnatal and later development of any sensory or even cognitive function parallels development of the central nervous system (CNS) in general and of its basic units, namely white matter (WM) and gray matter (GM), in particular. Furthermore, it has been shown that neuronal and axonal growth changes across the lifespan (Rivkin, 2000). Specifically, myelination –which causes the whiteness of WM (Ahrens, Blumenthal, Jacobs y Giedd, 2000)- begins at 12-13 post-conception weeks (PCW) in caudal brain regions and continues through childhood, adolescence and adulthood in more rostral regions (Girard et al. 2007), thus following a "back-to-front" maturation space course (Gogtay, 2008). This progressive *in crescendo* myelinitation process with increasing age occurs generally from inferior to superior regions of the brain and is assumed to be a linear developmental process due to its uninterrupted continuity until well into adulthood (Lebel, Walker, Leemans & Beaulieu, 2008; Lenroot & Giedd, 2006). GM, in turn, comprises the non-myeliniated parts of the neurons, i.e. somas and dendrites. While increases in GM volume during early development reflect neurogenesis, which also follows a lower-higher-order spatiotemporal developmental course (Rapoport & Gogtay, 2008), subsequent decreases in GM volume during development of adolescence, for example, may reflect, either synaptic pruning (Gogate, Giedd, Janson & Rapoport, 2001; Sowell, Thompson, Tessner & Toga, 2001), which is the typical neuronal event occurring during sensitive periods of development (Johnson, 2005) or changes in white-gray matter distribution, such as increased myelination (Casey, Galvan & Hare, 2005; Lu et al. 2007; Rapoport & Gogtay, 2008; Sowell et al. 2003) or, probably, a combination of both developmental processes. Thus, in contrast to WM, GM development is not assumed to be a linear process. All these development-related plastic changes in the CNS parallel the increasing efficiency of neural communication, due to two main processes that are inherent to the development of the CNS. These are the natural tuning of the neuronal afferent elements (GM) by spontaneously overproducing infinite synaptic contacts, which will be selectively pruned by experience-related stimulation, and to the increased speed of neural transmission due to progressive myelination (WM) of the non-previously pruned axonal elements. Both of these processes, in combination, lead to a similarly increased cognitive and behavioral expertise (Toga, 2006). Furthermore, these development-related plastic changes correlate with signal changes that have been acquired by means of neuroimaging techniques (Poldrack, 2000).

It is widely accepted that the postnatal development-related brain morphological and functional changes, such as myelination and the consequent increased speed of neural transmission, and those occurring during sensitive periods, such as axonic pruning and its linked establishment of useful synaptic connections (Greenough, Black & Wallace, 1987), are unlikely to occur in adults although immature –developing-populations may show these changes (Sowel et al. 2003; Toga, 2006), and this is the reason why the global mechanism that allows succession of the mentioned development-related on brain morphology and function is usually designated as developmental neural plasticity (Pigiucci, 2001), also designated by Greenough et al. (1987) as experience-expectant plasticity (EEP). Developmental neural plasticity can be defined as the brain’s ability to (change) reorganize its morphology and function based on experience with the stimuli of the surrounding environment during development and its associated behavioral plasticity can be defined as the organism’s ability to change behavior –such as expression of flavor preferences- based on experience with stimuli during development. Developmental neural plasticity is essential for behavioral adaptation to the changing environment and subject's survival within his cultural environment (Greenough et al. 1987). It is likewise essential for later learning (Koizumi, 2004). That means that a mature individual's current learning will be acquired through the patterns of learning acquisition that have been shaped during stages of development. Behavioral performance, such as musical training –i.e. playing the keyboard- during early childhood, on its part, may also lead to a reorganization of neural circuits –i.e. changes in the size of the motor cortex- during development (Trainor, 2005), besides experience with surrounding environment-derived stimuli, thus leading to a reciprocal relationship between brain and behavior, in that brain structures enable behavioral performance and behavior shapes brain structures.

Based on the existing evidence of the mentioned brain morphological and functional changes, we have considered the following four questions. How are these development-related brain, and consequent functional, changes within the taste and olfactory systems reflected in brain activation patterns measured through neuroimaging techniques? Do brain activation patterns in response to gustatory and olfactory stimuli change across postnatal and later development of taste and olfactory systems? How is the above-mentioned extreme neural sensitivity to experience, typically displayed within sensitive periods of development, reflected in brain activation patterns in response to taste and olfactory stimuli? Are we able to identify sensitive periods of taste/odor (flavor) learning and taste/odor (flavor) preferences by analyzing brain activation patterns and the development-related changes?

The present review is an attempt to answer these questions by presenting an updated state of the art of research on normal human postnatal and later development of the gustatory and olfactory systems by means of the HBA research method. The integration of gustatory and olfactory inputs is fundamental to the generation of flavor perception, so this analysis will specifically focus on the development of this integration as well as on the development of the human gustatory and olfactory systems. One way of ascertaining the way in which human gustatory and olfactory systems develop is by reviewing the relevant information published in the last ten years regarding this topic and in which data have been extracted by imaging those sensory systems in developmental populations through neuroimaging techniques. As the perypheral gustatory system has been imaged by means of scanning electron microscopy (Hersch & Granchow, 1980; Witt & Reutter, 1997), the extracted data of the corresponding images are here presented as well. Thus, we begin the present review with a brief description of the anatomical basis of the gustatory and olfactory systems and its integration. We continue with a short description of the main neuroimaging techniques applied to both chemical systems and their integration. Then, we present a body of published empirical data related to developing populations' brain activation patterns in response to gustatory and olfactory stimuli, individually and in combination, extracted by means of neuroimaging techniques. This allows us to describe the functional organization of these systems and their integration at the cortical level during postnatal and later development that finally may allow us to offer possible answers to the questions. Additional data extracted by means of imaging techniques regarding development of the peripheral gustatory system are here integrated as well, in order to stimulate readers' reflexion, besides that of own author's, about the possible impact that bottom-up interactions could exert on development of the gustatory system at the cortical level.

2. Human anatomy of the gustatory system

The anatomy of the gustatory system has been mainly studied in animals (rodents, such as rats and hamsters and non-human primates, principally monkeys). Animal models, based on monkeys, are considered to be the nearest approximation to humans (Pritchard & Norgren, 2004) and most of the information presented in this review section derives from animal studies. Human studies will be clearly indicated in the text.

The gustatory system consists of the peripheral gustatory system and the central gustatory system (Spector & Travers, 2005).

2.1. The peripheral gustatory system

The main structures of the peripheral taste system are the taste receptor cells (TRCs) situated in the tongue, soft palate, larynx, pharynx and the epiglottis (Breslin & Huang, 2006). These receptor cells are chemosensitive in nature and are grouped within the taste buds, which also contain basal cells and glial cells (Martin, 2000). Taste buds expose the gustatory pore, to which receptor cells extend their microvilli, in which signal transduction takes place. Microvilli are the only structures of the gustatory cells exposed to the oral cavity (Meng et al. 2006). Taste buds also contain the neural fibers of several cranial nerves (Breslin & Huang, 2006) (see figure 1). There are between 50 and 100 taste buds grouped within the gustatory *papillae* on the tongue (Breslin & Spector, 2008). All taste buds are epithelial in nature. Taste buds located outside the tongue are embedded in the surrounding epithelium without the emergence of the *papilla* (Martin, 2000).

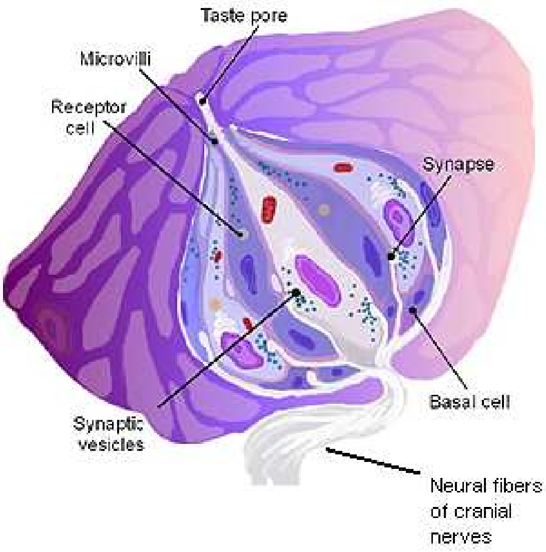

Figure 1. Anatomy of a taste bud.[2]

Studies on human cadavers show that there are three types of gustatory *papillae* on the tongue: fungi form, circumvallate and foliate (Breslin & Spector, 2008). Fungi form *papillae* are found in the tip and anterior edges of the tongue, whereas circumvallate and foliate *papillae* are found in the posterior part and latero-posterior regions of the tongue (Pritchard & Norgren, 2004) (see figure 2).

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[2] This figure has been adapted from Hutchins (2001) with permission. I am very grateful for this permission.

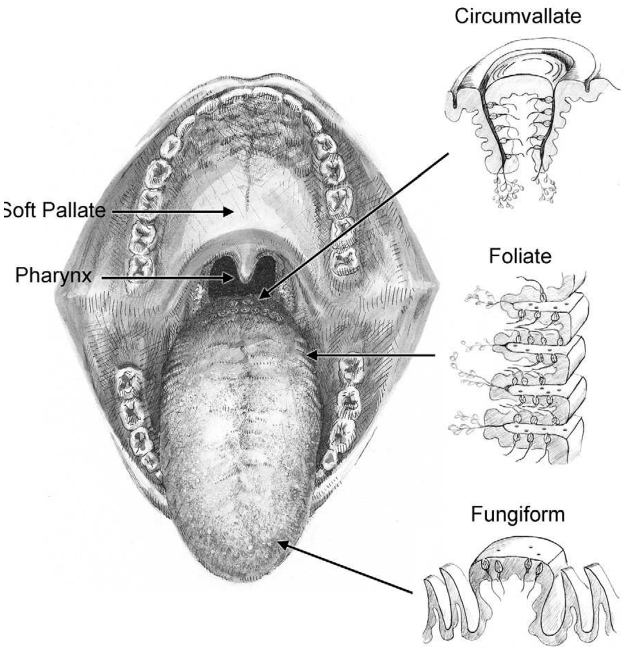

Figure 2. Human gustatory *papillae*.[3]

Interestingly, the density of human gustatory *papillae* of the fungi form type may be determined by age and gender in humans. Indeed, it has been shown that women have more fungi form *papillae*, and thus taste buds, than men (Bartoshuk, Duffy & Miller, 1994. Similarly, male children possess a higher number of *papillae* than adult males (Segovia, Hutchinson, Laing & Jinks, 2002). Other mammals have been found to present *papillae* on the upper esophagus as well (Laugerette, Gaillard, Pasilly-Degrace & Besnard, 2007).

Taste stimulating molecules, usually derived from food particles, must be dissolved in the saliva to be bound by receptor cells, which are not neurons because they lack an axon (Breslin & Huang, 2006). Taste binding induces chemosensory transduction, which can be defined as the intracellular signal generated by the binding of taste stimuli by TRCs (Kinnamon, 1996). More specifically, the contact between a

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[3] Reprinted from Current Biology, 18/4, Breslin, P.A.S. & Spector, A.C. Mammalian taste perception, Pages No. 145-158, Copyright (2008), with permission from Elsevier. I am very grateful for this permission.

tastant and a TRC induces TRC depolarization followed by an increase in intracellular calcium, in turn causing transmitter release and therefore the activation of the gustatory nerve fibers (Damak & Margolskee, 2003; Kinnamon, 1988). Gustatory transduction mechanisms are taste-specific (see Kinnamon, 2008 for review). While receptor cells bind sweet, bitter and umami tastes through the G-protein coupled receptors (GPCRs) located on the surface of receptor cells (Matsunami, Montemayeur & Buck, 2000), salty and sour tastes are mediated by ion channels serving as receptors (Beauchamp & Mennella, 2009). Elucidating the way in which human gustatory transduction takes place by means of non-invasive techniques is prevented by technical problems (Nagai et al. 2002), which remain apparently unresolved up until now. These difficulties explain why most of the published information regarding gustatory-related transduction mechanisms is based on animal models.

The electrical information resulting from transduction enters the taste neural fibers located within taste buds and is transmitted to the corresponding cell bodies (Breslin & Huang, 2006). The cell bodies of these neural fibers are situated within the sensory ganglia of three cranial nerves, namely the VIIth, IXth and Xth (Araujo, 2003; Breslin& Huang, 2006). The intermedio-facial facial nerve (VIIth) innervates most taste receptor cells of the fungi form and foliate *papillae* in the anterior region of the tongue, while the nerve providing axonal innervation to the rest of the foliate and circumvallate *papillae* is the glossopharyngeal nerve (IXth) (Pritchard & Norgren, 2004). The vagus nerve (Xth) innervates taste buds from other regions of the mouth, such as the epiglottis (Craven, 2007). With the exception of the intermedio-facial nerve, these cranial nerves also provide touch, pain and temperature innervations, in addition to taste innervation, to the oral cavity (Harlow & Barlow, 2007). The gustatory information is then transmitted afferentely from these cranial nerves to neurons of the rostral nucleus of the dorsal medullar solitary tract (NST) (Longstaff, 2005), thus favouring the beginning of feeding behavior, and to the digestive tract, inducing digestive secretions (Laugerette et al. 2007).

2.2. The central gustatory system: the primary and secondary taste cortices

Once the gustatory information has reached the NST, it is next directly and afferentely sent to the thalamus, or more specifically to the parvicellular division of the ventral posterior medial (VPMpc) nucleus of the thalamus in primates (Scott, 2005; Small et al. 2007). In rats, but not primates, there are further synapses between the NST and the pontine parabrachial taste nuclei before continuing ventrally to the amygdala and the hypothalamus (Kringelbach, 2007; Rolls, 2006; Zatorre & Marilyn-Gotman, 2000). Subsequently, ascending transmission continues to the primary and secondary taste cortex.

Animal and human studies carried out through neurophysiological and neuroimaging techniques, respectively, have defined the anatomy of the primary taste cortex as consisting of the dorsal region of the anterior insula and the frontal operculum (Rolls, 2007; Small et al. 1999; Smits, 2007). The gustatory information is transmitted to these areas via the VMPpc, providing both separate and combined representations of the quality of different tastes (sweet, salt, bitter, sour and umami), the hedonic value of taste stimuli, the temperature and texture of food stimuli, and any other sensory information of the mouth (Kringelbach, 2007; Rolls, 2006; Rolls, 2009). Cerf-Ducastel et al. (2001) found a more specific involvement of the operculum in the discrimination of somatosensory information, and of the insula in discriminating pure tastes. The anterior primary somatosensory cortex also receives gustatory information from VMPpc

(Kringelbach, 2007). Similarly, the amygdala has been observed to be involved in human gustatory processing. It is thought that this central subcortical structure may be involved in the perception of the satiety feeling (Wang, 2007), the intensity of taste concentration (Small et al. 2003), the pleasure of a taste (O'Doherty et al. 2002; Small et al. 2003), aversion to a taste (Small et al. 2003) and anticipatory chemosensation (Small et al. 2008).

On the other hand, the secondary taste cortex consists of the orbitofrontal cortex (OFC), which is a region of the prefrontal cortex (Smits, 2007) that receives projections from the nucleus of the thalamus and is involved in gustatory processing. The OFC provides representations of the integration of food-related visual, gustatory and olfactory stimuli as neurons, which in primates, have been found to respond to combinations of these stimuli (Rolls, 1997; Rolls, 2004) and to unimodal stimuli (Rolls, 2009). This integrative function of the OFC has led several authors to propose that it is the anatomical location of flavor perception (Rolls, 2009; Zatorre & Jones-Gotman, 2000). Studies in humans have shown that the OFC is also involved in the processing of the hedonic value of foods (Small et al. 2007; Small et al. 2003) and that regions of the dorsolateral prefrontal cortex are implicated in human taste identification (Kringelbach, De Araujo & Rolls, 2004).

3. Human anatomy of the olfactory system

The classical olfactory system is linked to autopreservation and flavor perception (Scherer & Quast, 2004; Stockhorst & Pietrowsky, 2004). Non-human animal species are provided with an additional olfactory system linked to sexual reproduction, the vomeronasal system that consists mainly of the vomeronasal organ which is located at the base of the nasal septum and contains the receptor cells responding to pheromones (Möller, 2003). The vomeronasal system appears to be nonfunctional in humans, however, as it has been observed in fetuses as a vestigial organ, which does not develop further and does not appear clearly in adults (Stockhorst & Pietrowsky, 2004). The present review section will focus on the classical olfactory system. The information presented below has been extracted from published reviews and experimental work on humans.

3.1. The peripheral olfactory system

As in the case of the peripheral taste system, olfactory receptor cells (ORCs) are the basic structures of the peripheral olfactory system. The surface of these receptor cells is covered with olfactory receptors called 7-transmembrane GPCRs. Each receptor cell expresses a unique receptor, and each receptor recognizes a few odorants (Beauchamp & Mennella, 2009). The number of human olfactory receptors, and thus encoding genes, has been estimated to be more than one thousand (Beauchamp & Mennella, 2009; Kandel et al. 2001). However, two-thirds of these receptors are not functional (Beauchamp & Mennella, 2009).

ORCs, along with supporting and basal cells, are located on the olfactory *neuroepithelium* of the nasal mucosa of both nasal cavities (Kandel et al. 2001). While supporting cells produce the nasal mucosa, basal cells replace ORCs whenever these cells degenerate (Jackson, 2002). Odorants reach the *neuroepthelium* via nasal cavities during passive or active inhalation (orthonasal olfaction) or through the posterior region of the nasopharynx due to food or drink intake (retro nasal olfaction) (Negoias et al. 2008; Pierce & Halpern, 1996). This latter route is particularly involved in the emergence of flavor (Jackson, 2002). Another epithelium –the respiratory epithelium- has the function of filtering the air that is introduced through the nose, with the mucosa protecting the *neuroepithelium* from this air (Price, 2004).

ORCs are pure first-order neurons and are bipolar in nature (Shipley, Mclean, Zimmer & Ennis, 1996). They are the only neurons exposed directly to the external environment of the body, which makes them more vulnerable than other kinds of neurons**.** They have been shown to degenerate easily (Price, 2004). The periphery of each of these neurons is constituted of the chemosensible *cilia*, which are the olfactory structures that are extended into the mucosa layer (Martin, 2000). Indeed, the cilia are the anatomical parts in which olfactory receptors are located, and therefore those where odorant binding takes place (Shipley et al. 1996). Odorants must be dissolved in the mucosa to be bound by olfactory receptors (Stockhorst & Pietrowsky, 2004).

Odorant binding is followed by olfactory transduction, which elicits neuronal action potentials (Stockhorst & Pietrowsky, 2004). Binding of an olfactory stimulus to GPCRs induces an increase in cyclic nucleotides, leading to activation of CNG-gated channels, and to an accumulation of cyclic adenosine monophosphate (CAMP). This leads to activation of CAMP-gated channels, which in turn causes ORC depolarization and excitatory activation of the olfactory nerve (Kashiwayanagi, 2002).

The central part of such an olfactory neuron consists of an unmyelinizated axon projected to the central nervous system (Martin, 2000). Further, axons of olfactory neurons are grouped in bundles called olfactory *fila* and the collection of the olfactory fila constitutes the olfactory nerve, olfactory tract or cranial nerve (Ith), that transmits olfactory information to the central olfactory system (Simpson & Sweazey, 2006).

3.2. The central olfactory system: the primary and secondary olfactory cortices

The function of the central olfactory system is linked to the discrimination of different odors, generation of olfactory consciousness and the integration of information from different sensory stimuli, which leads to the generation of flavor (Price, 2004). As with the gustatory system, the olfactory is divided into the primary and the secondary olfactory cortices.

Olfactory *fila* of each nasal cavity transmit information ipsilaterally to second order neurons of the olfactory bulb, which are then ipsilaterally projected via the olfactory tract to the primary olfactory cortex. The primary olfactory cortex consists of the anterior olfactory nucleus, the cortical nucleus of the amygdala, olfactory tubercle, the prepiriform cortex, the periamygdaloid cortex and lateral entorhinal cortex, of which each participates differently in the processing of olfactory information (Jackson, 2002; Martin, 2000; Simpson & Sweazey, 2006). In contrast to gustatory afferent transmission, olfactory information is transmitted to the primary olfactory cortex directly, without synapses in the thalamus (Stockhorst & Pietrowsky, 2004).

The olfactory bulb has been proposed to be the first anatomical location responsible for odor discrimination because axons of a group of neurons expressing an olfactory receptor converge onto one or two glomeruli of the olfactory bulb (Price, 2004), which converge into mitral cells (Lefingwell & Associates, 2001) (see figure 3 and 4).

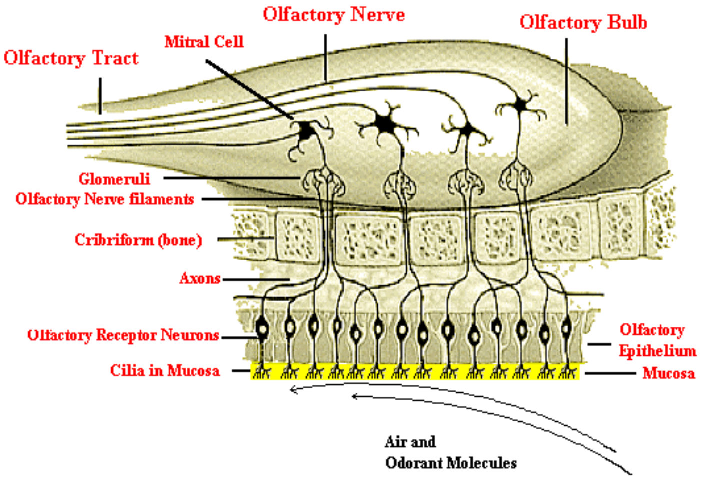

Figure 3. Peripheral and part of the central olfactory system (taken from Leffingwell & Associates, 2001, with permission).

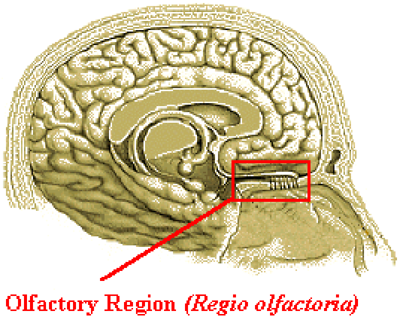

Figure 4. Sagittal plane of the anatomical localization of the olfactory region.[4]

The secondary olfactory cortex, for its part, projects olfactory information to the secondary olfactory cortex, which is mainly formed by the orbitofrontal and ventral granular insular cortices, either directly or via a relay in the dorsomedial nucleus of the thalamus (Simpson & Sweazey, 2006). The OFC may be involved in at least three different functions, namely in the subjective pleasantness of the stimuli, in the integration of smell and taste information to generate taste-smell associations, and thus flavor (see figure 5), and in the integration of somatosensory information coming from the oral and nasal cavities, such as temperature and irritation (Kringelbach, 2007). Other

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[4] Figures 3 and 4 are taken from Leffingwell & Associates (2001) with permission. I am very grateful for this permission.

areas to which the primary olfactory cortex further projects olfactory information may be the hypothalamus, the medial thalamus, the nucleus basalis Meynert, the hippocampus, the septal region, the subtantia innominata, and the mesencephalic reticular system (Stockhorst & Pietrowsky, 2004).

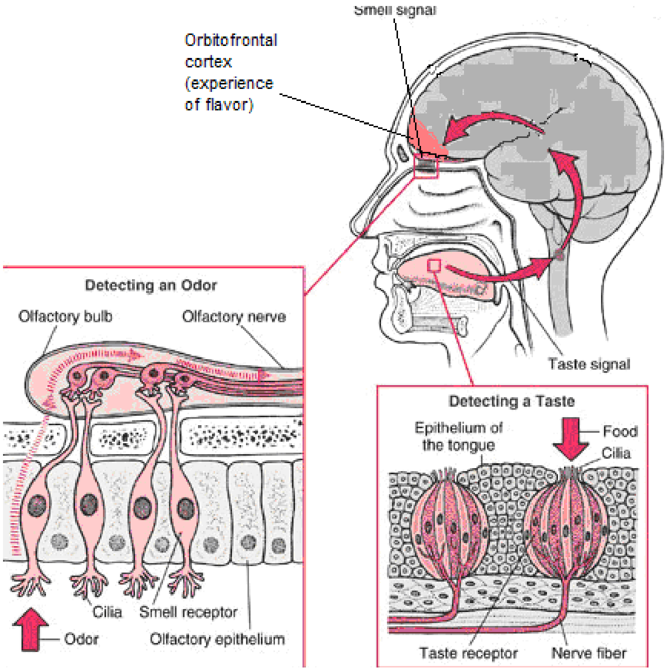

Figure 5. Integrated perception of tastes- and odors signals, both of these converging in the OFC and thus leading to the experience of flavour.[5]

4. Neuroimaging techniques commonly applied to the chemical senses

The use of neuroimaging techniques in general and of magnetic resonance in particular, has become indispensable in obtaining physiological, anatomical and functional information about the brain in the fields of basic and applied research. Advantages of these techniques are the high temporal and spatial resolution, which

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[5] Figure 5 has been adapted from Sensaslim (2009) with permission. I am very grateful for this permission.

overcomes spatial limitations of the electrophysiological techniques, their non-invasive quality, which permits measurement of neural activity without the necessity of placing electrodes surgically in the brain, and the possibility of conducting these measurements *in vivo*. Limitations, on the other hand, are the difficulty in accessing them due to the high costs and size of the necessary technology. We will briefly describe the underlying physics and physiology in the following section.

4.1. Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is one of the most commonly used neuroimaging techniques in the study of neural response to chemical stimuli. The MRI technique does not measure neural activity directly, but different aspects of the emerged hemodynamic response following activation of neurons, such as regional cerebral blood flow (rCBF), blood volume and blood oxygenation level (González & Romero, 2004; Kriegeskorte & Bandettini, 2006). Blood oxygenation level is the most commonly parameter within an fMRI paradigm-based experiment. Neural activity results in an increased blood oxygenation level, or oxyhemoglobin (OH), which results in decreased deoxyhemoglobin (DOH), known as the blood oxygenated level-dependent effect (BOLD), and thus an increase in the magnetic resonance signal (Song, Huettel & McCarthy, 2006). This signal is considered to be an indirect reflex of neural activity. fMRI makes use of the energy generated by the so called “spin” or precession movement of protons of living tissues. Protons are able to rotate around their own axis when they are found within a magnetic field, such as that of an MRI scanner (Krasuski et al. 1996). When the MRI scanner sends electromagnetic energy (excitatory pulses) to protons, they rotate in parallel to the magnetic field, thus absorbing this energy. This is known as the parallel magnetic moment. When the excitatory pulse ends, protons rotate or precess antiparallel to the magnetic field. This is the antiparallel magnetic moment or relaxation time (Alvarez et al. 2008; Krasuski et al. 1996). At this moment, protons emit the absorbed energy and this emission is detected and converted by the MRI machine as the MRI signal (Matthews, 2001). The duration of the relaxation time depends on the size of the tissue water molecules in which protons are located (Krasuski et al. 1996). The most important advantage provided by this technique is the possibility of examining individual neural activity as well as inter-individual differences (Faurion, Kobayakawa & Cerf-Ducastel, 2008).

4.2. Positron emission tomography (PET)

PET allows examination of the electromagnetic radiation resulting from the intravenous administration of a radioactive tracer to the subject’s organ, a brain region, for example, which is under study (Tordesillas-Gutiérrez, Rodríguez-Sánchez & Crespo-Facorro, 2008). Certain radioactive nuclei of the tracer emit a positron when they decay, this decay resulting in the simultaneous emission of a pair of photons that move around in opposite directions (Correia, 1992). These photons can then be detected by special photon detectors. This allows the computation of the concentration of radioisotope regionally in an organ and may therefore yield quantitative physiological information that can be presented in image form (Correia, 1992).

PET does neither measure neural activity directly, but rCBF, oxygen extraction fractions, total blood volume, glucose consumption rates and glucose metabolism in certain areas of the brain in health and disease (Rajagopalan, Krishnani, Passei & Macfall, 1995), depending on the used tracer. The most widely applied tracer in the study of brain metabolism is *[^{18}F]Fluoro-2-deoxy-2-D-glucose [[^{18}F]FDG]* as indicator of regional brain glucose consumption (National Institute of Health, 2005). It is quite used in the study of the taste and olfactory systems with young and older adults (Zald & Pardo, 2000a; Wang et al. 2004), although not as much as fMRI. Due to ist radioactive nature, use of this technique is not suitable for children (Goswami, 2004).

4.3. Functional near-infrared spectroscopy (fNIRS)

Another neuroimaging technique commonly used in the study of chemical senses is functional near-infrared spectroscopy (fNIRS). It has also been increasingly used in the study of relevant issues of brain development, such as the development of cognitive functions (Minagawa-Kawai, Mori, Hebben & Dupoux, 2008). On the basis of the same hemodynamic response as with fMRI, changes in the concentrations of OH and DOH in response to stimulation are also detected through fNIRS (Shibasaki, 2008). Participants wear several probes made of optical fiber on their heads, through which the near-infrared light is emitted to the brain at multiple wavelengths, passing through the cerebral cortex, skull and scalp, and being absorbed by hemoglobin, depending on its oxygen concentration level (Soul & Plesasis, 1999). This light emission leads to a luminous signal that is detected by fNIRS detectors (Minagawa-Kawai et al. 2008). Advantages of this technique are the possibility of measuring OH continuously because radiation can be continuously emitted and the fact that it does not require the head of the subject to be securely fixed, which is particularly appropriate for studies of children (Shibasaki, 2008). In contrast to other techniques, fNIRS allows subjects to taste gustatory stimuli in an upright position, rather than being required to adopt a supine position (Okamoto et al. 2006). The use of fNIRS is especially suitable for measuring activations in lateral cortical surfaces (Okamoto et al, 2009). The optical tomography (OT) system is a version of the classical NIRS which does not require the use of optic fibers, allowing it to be moved to the locality of the subject. It covers the whole brain through its more than 100 channels and allows three-dimensional image reconstruction of deep brain tissues (Atsumori et al. 2007; Gibson, Hebden & Arridge, 2005).

4.4. Diffusion-tensor magnetic resonance imaging (DTI) technique

The diffusion-tensor magnetic resonance imaging (DTI) technique allows tracking of the fiber pathways (white matter tracts) *in vivo*, with its basic physical principle being the anisotropic water diffusion within neural tissues (Beaulieu, 2002). Anisotropic water diffusion refers to the natural restricted movement of water molecules within neural tissues (García Segura & Viaño López, 2008). This restriction emanates from microscopic biological barriers, such as neuronal elements, for example axons, and constitutes a DTI parameter of which the symbol is $A\sigma$. Fractional anisotropy (FA) is the measure of anisotropic diffusion (Wozniak & Lim, 2006). During brain development the myelinization process has been observed to increase progressively with increasing age. In this process, the fat layer covering axons represents a barrier and favours anisotropy or the restriction of the movement of water molecules within neurons along certain directions. Thus, a consequence of the myelinization process is the generated directionality of axons, which means that water diffusion occurs along the direction of axonal fibers within the white matter tracts (Doron & Gazzaniga, 2008; Hess & Mukherjee, 2007). Isotropic water diffusion (D), in turn, refers to the random movement of those molecules with mean diffusivity (MD), alternatively symbolized with (D_{av}), as its statistical parameter. D decreases with increasing age through development due to either an age-related decrease in water content or an increase in myelinization (Hüppi & Dubois, 2006). In addition to the natural random movement of water molecules, other factors, such as the blood microcirculation of capillary vessels, may possibly affect their movement so that neuroimaging studies typically include that possibility and use the term of *apparent diffusion coefficient* (ADC) instead of D (Hess & Mukherjee, 2007). The advantage of this technique is that it allows the generation and interpretation of information about smaller structures than does the spatial resolution of the image (Hess & Mukherjee, 2007).

4.5. Electrophysiological techniques: the electroencephalography (EEG) and magnetoencephalography (MEG)

EEG allows the registration of the extracellular electrical activity generated as a consequence of activation of a group of neurons (evoked potentials, EPs or event-related potentials, ERPs) of which most of them are pyramidal in nature in response to external or internal stimulation by means of a series of electrodes located in the scalp and a special signal amplifier that captures potential differences between two electrodes (Nowak, Escera-Micó; Corral-López & Barceló-Galindo, 2008). The resulted EPs are measured based on the basis of its associated latencies, the time interval measured in milliseconds after the stimulus presentation and amplitudes, the time interval measured in milliseconds from the stimulus presentation until the point of maximal or minimum expression within a certain latency (Nowak et al. 2008). EEG facilitates acquisition of specific brain maps that correspond with the spatial localization of the source of the electrical activity, that is, specific brain regions that are activated in response to the target stimulation by means of a biophysical models and mathematic algorithms that solve the called inverse problem that constitutes the localization of the sources of the generated electrical activity (Escera-Micó et al. 2008).

MEG allows the registration of the intracellular magnetic fields resulted from activation of pyramidal neurons by means of electrodes and a special signal amplifier (Maestú-Unturbe, Maestú-Unturbe & Pozo-Guerrero, 2008).

In contrast to the non electrophysiological techniques, EEG and MEG measure neural activity in a direct way, as they capture the direct extracellular and intracellular currents associated with neural membrane conductivity changes occurring when neurons are stimulated (Otten & Rugg, 2005).

5. Imaging of chemical senses in developing populations

The aim of this section is to elucidate age-related consistencies and changes in brain activation patterns in response to gustatory and olfactory stimuli by presenting a review of the findings from a relatively large portion of the neuroimaging studies in which such brain activations have been investigated in developing populations. Specifically, data from newborns, children and adolescents are included, as these life phases are considered to be those with the most development-related changes (Shaw et al. 2008). In addition, we will also review data from human young adults (adults between 18 and 35 years old), since increases in WM have been shown to last at least until 30 years of age (see Lebel, et al. 2008 for a review), which leads us to consider young adulthood as a developmental life phase. Furthermore, the prefrontal cortex, a brain region consistently shown to be involved in gustatory processing (Kringelbach, De Araujo & Rolls, 2004; Okamoto & Dan, 2007; Rolls, 2004) has also been shown to dramatically lose GM across the this age range and beyond (Sowell, et al. 1999; Sowell et al. 2001), thus indicating a long and slow development course, through which development-related changes might also occur. In addition, data derived from animal research in the visual system (Sale et al. 2007) have clearly shown that certain changes that were considered that could only occur during development, such as cure of amblyopia, may also occur during young adulthood –in rats aged = 70 postnatal days-.

5.1. Reviewing imaging and neuroimaging studies on gustatory function in developing age ranges

5.1.1. The peripheral gustatory system

Development of human gustatory *papillae* at prenatal age – from the 8th to the 26th gestational week- has been carried out using scanning electron microscopy (Hersch & Ganchrow, 1980). Results of this study are summarized in the table 1.

Table 1. Progressive development of gustatory *papillae* at embryologic stages. On the basis of the study of Hersch & Ganchrow (1980).

Gestional week	**Emerged *papillae***
8-9	No signs of *papillae* in the anterior two-thirds of the tongue. Initial signs of circumvallate *papillae* –rounded elevations- in the just anterior region of the sulcus terminalis. An early taste pore is present on the dorsal surface of one such elevation.
10-13	Beginning of fungi form *papillae* on the anterior two-thirds of the tongue, tip and lateral edges. First signs of foliate *papillae* at 10th week.
15-18	Fungi form and filiform *papillae* are recognized.
23-26	Adult form of all *papillae* at 23 weeks. Some fungi forms contain a definitive pore.

Information about the development of human gustatory *papillae* of embryos and fetuses during the postovulatory weeks 6-15 has been derived from scanning electron microscopy (Witt &Reutter (1997). The main morphological changes of human *papillae* observed are summarized in the table 2.

Table 2. Development of gustatory *papillae* during peri-fecundation stages. On the basis of the study of Witt & Reutter (1997).

Postovulatory week number	**Main events**
6-7	Flat epithelium already covers the surface of the tongue. The first circumvallate papilla –already with its central pores- develops in the dorsal midline. Early fungi form *papillae* appear in the midline and in the anterior region of the tongue.
8-9	There are fungi form *papillae* at the anterior part of the tongue. Pores of circumvallate papillae contain microvilli of what are presumed to be underlying taste bud cells.
10-11	Numerous fungi form *papillae* appear predominantly on the lateral margins and the tip of the tongue. Fungi form *papillae* often show slight depressions on their apical epithelia, but no mature taste pores. The diameter of the *papillae* at this stage ranges from ~50 to 80 µm.
12-13	The fungi form *papillae* continue to grow especially on the tip and the margins of the tongue. Their pores occur only rarely and their shapes are still irregular.
14-5	Fungi form *papillae* are rare in the middle part of the tongue, but relatively numerous on the lateral margins and they are considerably larger in diameter than those of previous stages. Furthermore, they have up to two taste pores. If present, taste pores are larger than in earlier stages. Circumvallate *papillae* have increased in size. Filiform *papillae* have not yet developed.

Postnatal development of the peripheral gustatory system has been studied using the videomicroscopy procedure (Segovia et al. 2002). In this study, the authors found higher densities of fungi form *papillae* and taste buds in children aged 8-9 years, than in adults. The progressive growth of the tongue (width and length) with increasing age has also been measured, showing that the fungi form *papillae*-rich anterior region of the tongue reaches an adult size by 8-10 years, while the posterior region grows until 15-16 years of age (Temple et al. 2002).

5.1.2. The central gustatory system

5.1.2.1. Age-related brain activations in response to food images

Brain activations in response to visually presented food stimuli (high calorie and low calorie food images) have been examined by means of fMRI in several studies. Killgore & Yurgelun-Todd (2005) found an age-related differentiated brain activation pattern in a sample of 9-15-years-old female subjects. Specifically, increases and decreases in the BOLD signal, in response to high calorie food images (i.e. ice cream), were found to correlate with increasing age in several brain regions in this sample. In addition, comparison with a young adult female sample (age range = 21-28-years- old) yielded significant differences between the two samples in relation to the intensity of the neural activity, as young adults showed greater activation than adolescents in several brain regions (see table 3).

Table 3. Differentiated brain activations in response to high calorie food images as a function of age in the child/adolescent sample and comparison with young adults. On the basis of the study of Killgore & Yurgelun-Todd (2005).

BOLD increases as a function of age in the child/adolescent group	**BOLD decreases as a function of age in the child/adolescent group**	**Young Adults' greater activations in comparison to the child/adolescent group**
OFC	Bilateral anterior cingulate gyrus	Prefrontal cortex
Middle precuneus	Bilateral thalamus	Anterior cingulate gyrus
Right angular temporal gyri	Bilateral cerebellum	Precuneus
Right middle temporal gyri	Left superior frontal gyrus	Posterior cingulate gyrus

Changes in brain activations with increasing age were also found in the same child/adolescent subject sample in response to low calorie food images (vegetables). Specifically, BOLD signal increases were found in the left superior temporal gyrus, right middle temporal gyri, right angular gyri, anterior cingulate gyrus and right amygdala. BOLD decreases, in turn, were found in the right supplementary motor area, right superior parietal lobe and right cerebellum. Young adults also showed greater activation in several brain structures including the left inferior temporal gyrus, Left inferior parietal lobe and left precentral gyrus.

Regardless of the calorie content of foods, activations were found in the left inferior orbitofrontal gyrus, bilateral parahippocampal gyrus/hippocampus and bilateral fusiform gyri in response to food images (vegetables) in Killgore & Yurgelun-Todd's (2005) sample. Activations in the left OFC, bilateral insular and opercular cortex, with more pronounced activity in the left side, were seen in response to vegetable images in the subject sample of young adults (aged = 27.17±5.36) from the study of Porubská et al. (2006).

On the other hand, food-related utensils induced an increased activation with increasing age in the child/adolescent subject sample in several regions, including the left inferior frontal gyrus, left superior frontal gyrus, left anterior, and middle cingulate gyri, right thalamus, and bilateral medial frontal gyri, insula, and cerebellum. Age-related decreases in the BOLD signal were found in the precuneus and cerebellum. Young adults showed greater activation than adolescents within the angular gyrus, right thalamus, middle temporal and occipital gyri, and the right superior frontal gyrus. The 9-15-years-old subject sample, in turn, showed greater activity than young adults, mainly within the right hippocampus.

Rothemund et al. (2007) however, found a significant activation in the right inferior temporal gyrus in response to presentation of pictures of high calorie foods and no significant activations with low calorie food pictures in a sample of young adult women (29-years-old) were found. These results contrast with those of the study from Killgore & Yurgelun-Todd (2005), regarding young female subjects. Thus, brain activations in response to food images in female young adults need to be clarified.

5.1.2.2. Brain activations in response to tasting gustatory stimuli irrespective of the motivational state in young adults

Brain activations in response to water solutions flavored with basic tastes have been studied in young adults using various neuroimaging techniques. The major goal of this research work has been to identify the topographic representation of taste identification at the cortical level. The same primary taste cortex-related brain regions have been observed, using fMRI, to be activated by these different basic tastes. For example, activations in response to water solutions flavored with glucose, monosodium glutamate (MSG) and inosine 5-monophosphate (IMP) were found in the insula, the opercular region, the OFC and a part of the rostral anterior cingulate cortex in a sample of 20-year-old subjects. Furthermore, the addition of IMP to MSG yielded a BOLD signal increase of the kind of a supralinear additive effect in the OFC (De Araujo, Kringelbach, Rolls & Hobden, 2003). This supralinear additivity may be the reflex of the subjective enhancement of umami taste that has been previously described when IMP is added to MSG (De Araujo et al. 2003a). Subsequently, Schoenfeld et al. (2004) also found that water solutions flavored with the five basic tastes, including umami (MSG) elicited activation in the insula and opercular region in a sample of 20-35-year-old subjects. Activation in the insula, the frontal operculum and the rolandic operculum, in response to a salted taste, has also been observed in subjects aged 21-31 (Ogawa et al. 2005). Furthermore, Kringelbach, Araujo & Rolls (2004) found bilateral activation in the dorsolateral prefrontal cortex, the anterior insula, the frontal operculum and the caudal OFC in response to a salted and a sweetened water solution in a sample of 20-year-old participants. The amygdala, has also been observed through PET to be activated in response to a bitter and sweet solutions in 18-34-years-old subjects, in addition to the right posterior OFC (Zald et al. 2002).

There are fMRI data to suggest that sucrose, a natural and caloric sweetener, activates different neural pathways than does an artificial and non caloric sweetener, such as sucralose. Indeed, Frank et al. (2008) observed that, while sucrose as well as sucralose induced activation of the primary taste pathways, sucrose elicited more activation than sucralose in the anterior insula, frontal operculum, striatum and anterior cingulate.

A study of evoked brain activity, by means of EEG and MEG, in response to a salted water solution in subjects aged 25-30 years, has yielded three gustatory components, namely: P1, N1 and P2 (Mizoguchi, 2002). Furthermore, Anninos et al. (2006) observed, using MEG, differentiated brain activation patterns in response to a sweet taste and a salted taste in subjects of mean age 35 in that the sweet taste induced low signal frequencies and the salted taste higher signal frequencies.

On the other hand, a natural sour liquid food stimulus –lemon juice-, as well as a natural sweet liquid food stimulus –chocolate solution- have been confirmed to induce activation of the orbitofrontal and insular cortices in subjects aged 22-35 years (Smits et al. 2007).

There are at least two studies examining brain activations in response to water, and therefore non pure taste but instead tasteless gustatory stimuli, in developing populations through fMRI. In the first (Zald & Pardo, 2000b), bilateral activations in the insula, the frontal operculum, the rolandic operculum and the cerebellum were found in 18-38-years-old subjects, in response to deionized distilled water. The second (Veldhuizen, Bender, Constable & Small, 2007) found activations in the insula and operculum in 26.2 ± 3.0-years-old subjects. Activations in the OFC were not found in either study. Both of these studies have demonstrated that the brain areas usually activated in response to taste stimuli, such as the insula and the operculum, are robustly involved in taste detection.

5.1.2.3. Brain activations involved in the hedonic value of gustatory stimuli irrespective of the motivational state in developing populations: is there any brain asymmetry?

The hedonic value of a food or tastant refers to the subjects' subjective sensation of pleasantness or aversion for that food or tastant. Brain representations of this kind of subjective sensation have also been examined in developing populations in several studies, by requesting participants explicitly to rate that subjective pleasantness, or aversion-related sensation, once they have tasted the tastant. In some studies, brains have been scanned prior, during and after the act of tasting while in others, only during this act, depending on the experimental design. Brain activations have then been statistically contrasted with subjects' pleasantness-unpleasantness ratings.

A body of evidence supports the claim that taste-related affective information processing in developing populations is brain lateralized, in that "good" tastes (i.e. sweet) are processed in the left brain hemisphere and the "bad" tastes (sourness and bitterness) are processed in the right brain hemisphere, thus coinciding with Gray's theory of brain lateralized emotional processing, which proposes that positive and negative affects are processed in the left and right hemisphere, respectively (Gray, 1987). For example, higher left than right hemisphere activity has been registered by means of EEG in human newborns of 2-3 days of age, when they were administrated a sweetened solution with sucrose –a positive stimulus-, compared to distilled water –a neutral stimulus- and to a citric acid solution –a negative stimulus- (Fox y Davidson, 1986). Likewise, Small et al. (2003) found an activation in the right caudolateral OFC, which was specifically involved in the bitter or aversive taste processing, whereas a left dorsal anterior insular and left operculum was specifically involved in the sweet or good taste processing in subjects of mean age = 31.5. In addition, they found dissociated neural representation for intensity and hedonic information of taste. Specifically, the anterior insula, frontal operculum, and OFC responded to the hedonic value of tastes. Brain regions specifically activated in taste intensity have been found to be the cerebellum, pons, middle insula and amygdala. However, in 7-day-old newborns, higher right than left frontal activity was registered by means of EEG, when they were presented a water solution followed by a heelstroke, whereas those newborns, who were presented sucrose before the same negative event didn’t show any EEG change from baseline to the post-heelstroke phase (Fernández, Blass, Field, Diego, et al. 2003).

5.1.2.4. Brain activations in response to gustatory stimuli, as a function of motivational state

The subjective sensation of pleasantness in response to gustatory stimuli appears to be modulated by whether the subjects are in a hungry or satiated motivational state. Specifically, the pleasantness sensation of the taste of a food is enhanced if an individual is hungry, with this effect being more pronounced in women than in men (Stoeckel, Cox, Cook & Weller, 2007). On the contrary, as long as the individual becomes satiated during consumption of the same food, its taste may become gradually neutral (Rolls, 2005) or even unpleasant (for example see Small et al. 2001). Reward value of a food is a term commonly used for designating the resultant quality of the hedonic value of a food, either attractive or aversive, as a consequence of being hungry or satiated. These subjective changes in the hedonic value of foods, which take place as a function of the motivational state, correlate with changes in brain activation patterns in gustatory areas (Rolls, 2007).

5.1.2.4.1. Under hungry conditions

There is consistent evidence showing that human neural activity, as reflected in the BOLD signal, in response to gustatory stimuli under hungry conditions tends to be higher than that in response to the same stimuli under the satiety-related condition. For example, Porubská et al. (2006) found activation increases in the left operculum, right putamen and bilateral insula in fasted 27.17±5.36-year-old participants in response to food images. Furthermore, a gender effect was found by Uher et al. (2006) when they examined motivational modulation of young adults' (age range = 18-45 years) brain activation patterns in response to food-related images (i.e. hamburger, chocolate cake) as well as to the act of tasting food stimuli (i.e. chocolate milk and chicken broth) under fasting, and thus hungry conditions. Women who had fasted showed a greater activation in the bilateral fusiform gyrus and the left anterior insula in response to visual and gustatory food-related stimuli than men who had fasted. A subsequent ERPs study (Stockburger et al. 2009) found a negative potential at occipito-temporal and a positive potential at centro-frontal sensor locations from young females (mean age = 23.3) in the time window 300-360 ms, in response to food images under deprivation conditions. In addition, in a later time window (450-460 ms), the deprivation-related condition elicited greater amplitudes of the positive potential at centro-frontal sensor locations. Finally, a fMRI study conducted in 19-22-years-old subjects (Haase, Cerf-Ducastel & Murphy, 2009) showed greater activation in the insula, thalamus and substantia nigra in response to different aqueous taste solutions (sucrose, caffeine, saccharin and citric acid) under deprivation conditions. However, a recent study by Siep et al. (2009) did not find any motivational modulation in brain activity in response to either high calorie (i.e. pizza) or low calorie (vegetables) food images by means of fMRI in a female sample aged 19.03±0.9. In this study, the left amygdala as well as the medial OFC were equally activated under both conditions (hungry vs. satiety).

5.1.2.4.2. Under satiety conditions

Unlike the hungry motivation state, human neural activity in response to gustatory stimuli under satiety conditions tends to both increase and decrease in various parts of the brain. Evidence supporting this motivational modulation in taste processing is found in the study from Small et al. (2001), in which rCBF changed as 18-45-years-old subjects rated the taste of chocolate at eight consecutive times. This procedure is assumed to yield participants' satiation with chocolate. The rCBF changes refer basically to increases in the caudolateral OFC and bilateral decreases in the insula. Subsequently, Smeets et al. (2006) observed a gender effect on brain activations occurred by satiation with chocolate in subjects of mean age = 20.5±1.4 years in which men showed increased activity more in the left than right hemisphere. Specific areas in which this increased activity was found were the left ventral striatum, left precentral gyrus, DLPC, left putamen, anterior insula, OFC and anterior cingulate. Men also showed decreased activity in several brain regions, including the inferior and superior parietal lobes and medial PFC. Women, in turn, showed greater activity in the right than left hemisphere, as increases were found in the bilateral but more pronounced right precentral gyrus, right superior temporal gyrus. Decreased activity in the hypothalamus and amygdala was observed in women.

In another study (Wagner et al. 2006) 28.6±6.75-years-old women showed different brain activation patterns in response to repeated administrations of water and sucrose solutions, a procedure assumed to lead to satiation, as a function of how it was administered. Within the pseudorandom setting, reductions in the activations were found in the bilateral amygdala, hippocampus, insula and caudal anterior cingulate cortex, while no reduction was found in response to sucrose. Within the sequential blocks, repeated exposure to both stimuli yielded decreased activations in those target regions. Haase et al. (2009) found decreased activation in the parahippocampus, amygdala and anterior cingulate under satiety condition, in response to different aqueous taste solutions (sucrose, caffeine, saccharin and citric acid) in a 19-22 years old subject sample.

5.1.2.5. Cognitive modulation-related effects on neural activity in response to gustatory stimuli in developing populations

Different cognitive aspects, such as attention focus, taste expectation, and even language have been observed to elicit changes in the neural responsiveness to gustatory stimuli in young adults. For example Grabenhorst & Rolls (2008) have shown that brain activation patterns in young subjects –aged 21-35 years- differ as a function of the task to which subjects had to pay attention. The medial OFC and the pregenual cingulate cortex were activated when participants were instructed to rate the intensity of a taste sitmulus –an aqueous solution flavored with 0.1 M monosodium glutamate-, while the insula and mid-insula were activated when the same participants had to rate the pleasantness of the same stimulus.

The expectation of receiving a gustatory stimulus elicits different brain activations from those activated by its receipt. Indeed, O'Doherty et al. (2002) found that subjects aged 18-35 years showed activation in the dopaminergic midbrain, posterior dorsal amygdala, striatum and OFC when they could see a visual cue that indicated the presentation of a sweet solution (1 M glucose), while only the OFC was activated during the direct taste receipt. Similarly, only the OFC was activated when participants received an unpredicted taste stimulus, in contrast to the activation of the insula and the operculum in response to trying to detect the presence of a taste in a tasteless solution, in a study of subjects aged 26.2 ± 3.0 years (Veldhuizen et al. 2007).

The influence of linguistic processing on brain representations of taste pleasantness has been also examined using fMRI (Grabenhorst, Rolls & Bilderbeck, 2008). In this study, a flavor stimulus (a MSG taste solution with added vegetable odor) was paired with different word descriptors that were either positive, such as “rich and delicious flavor”, or neutral, such as “boiled vegetable water”. Participants (young adults aged 21-35 years) were asked to first rate the pleasantness and then the intensity of these stimuli, once they saw the word descriptor, while brain scans were conducted. Positive correlations were found between the rated pleasure of the stimuli and the affective quality of the word descriptors with which stimuli were paired. Furthermore, activations in the OFC but not in the insular cortex were found to be correlated with pleasantness ratings and cognitively modulated by the word descriptor. This region exhibited more activation to the positive word descriptor than to the neutral word descriptor, while activations in the insular taste cortex, but not in the OFC, were found in response to the intensity ratings.

Finally, taste imagination, a pure cognitive activity has been also studied using fMRI, although possible cognitive modulation-related effects derived from this activity on brain representation of taste are yet to be studied. For example, Levy et al. (1999) observed, for the first time, that activation in the PFC, cingulate, insula and OFC occurred when participants, aged 22-35, were asked to imagine the tastes of salt and sweet, which indicates human brain representation of taste imaging. In the case of the insular cortex, its right side was more activated than the left (Levy et al. 1999). Later, with more sophisticated gustatory imagery paradigms, Kobayashi et al. (2004) observed more left than right activation in the insular cortex, the putamen, the orbitofrontal gyrus and the frontal gyri when participants aged 21-31 years imagined sweet, salty, bitter and sour tastes. Research on food craving, or intense desire to eat a specific food that is difficult to resist (Martin et al. 2008), which requires participants to imagine their favourite foods, resulted in activation in the hippocampus, the insula and the caudate (Pelchat et al. 2004).

5.2. Reviewing neuroimaging studies on olfactory system in developing populations

5.2.1. The orthonasal vs. retro nasal input entry-related specificity of olfactory representations

As we mentioned in the introduction, the sense of smell is involved in the perception of two kinds of olfactory stimuli, namely those derived from the external world via orthonasal stimulation and those derived from the oral cavity via retro nasal stimulation (Auvray & Spence, 2008; Rozin, 1982). A common phenomenon concerning this retro nasal olfactory stimulation is that people usually confuse taste and odor during retro nasal smelling, and think they taste when they really smell (Rozin, 1982). It has been suggested that this perceptual illusion may be due to the activation of the insula cortex that takes place as a consequence of repeated pairing of odors and tastes (Small, 2008). Neuroimaging studies have demonstrated that this dual sensory system also finds a dual cortical representation pattern of neural responsiveness in humans, which allows the inference that the input entry of olfactory stimuli determines olfactory perception. Indeed, Cerf-Ducastel & Murphy (2001) found activation in the right piriform cortex, right parahippocampal gyrus, right amygdala and left hippocampus as well as bilateral activation in the insula, the temporal operculum and the rolandic operculum in response to retro nasal presentation of two odorants -amyl acetate and ethyl butyrate-, in comparison to an orthonasally presented stimulus –amyl acetate- in 23-35 year old subjects.

On the other hand, it has been shown that the input entry-related specific neural response to olfactory stimuli may be modulated by whether an odor represents a food. For example, Small, Gerber, Mak & Hummel (2005) found activation in the insula/operculum, thalamus, amygdala, hippocampus and caudolateral OFC only in the retro nasal presentation of a chocolate odor, as opposed to its orthonasal presentation, which caused activation in the medial OFC and cingulated cortex. When compared with odors which did not represent a food, such as lavender, butanol and farnesol, the input entry-dependent neural response found for chocolate was not found. Subsequently, Bender, Small, Hummel & Negoias (2009) found that repeated presentation of a known odor in 19-29 year old subjects, via a different route from the route through which that same odor was previously presented, induces an increase in the salivary response in contrast to the usual decrease found with repeated presentation of the same odors. Furthermore, they found that this effect is specific to food odors.

5.2.2. Brain lateralized processing of the hedonic value of olfactory stimuli

There is evidence for the existence of cortical lateralization of neural activity in response to olfactory stimuli in newborns. The direction of this lateralization, as in the case of taste processing, appears to depend on the affective quality of the stimuli (pleasant or unpleasant) coinciding likewise with Gray’s theory of brain lateralized emotional processing (Gray, 1987). Bartocci et al. (2001) found cortical lateralization in processing an unpleasant olfactory stimulus (a disinfectant) in preterm neonates (gestational age = 30-37 days and mean postnatal age = 12.5 days) through NIRS. Specifically, the majority of babies showed a greater right than left brain hemisphere decrease in oxygenated haemoglobin (Hb O_2) and total haemoglobin (Hb tot) in the anterior OFC after the stimuli presentation. Previously, Bartocci et al. (2000) observed, with NIRS, a greater increase in Hb O_2 in the left side of the same brain area in newborns in response to pleasant odors (colostrum, the mother's milk odor and vanilla). The exposure to colostrum also gave an inverse correlation between the magnitude of activation and participants' postnatal age.

An fMRI-based study by Henkin & Levy (2001) found that young adults (aged 22-44 years) show greater left than right hemisphere activation in response to pleasant odorants, namely amyl acetate and menthone, and that this brain lateralization was more pronounced in women than men. In contrast, men exhibited a greater right than left hemisphere activation in response to an unpleasant odorant (pyridine).

On the other hand, Sanders et al. (2002) compared EEG activation asymmetry shifting from baseline to stimuli exposure between young adults (mean age = 30.95) and full-term neonates (mean age = 19.9 days), using lavender and rosemary oils as pleasant olfactory stimuli. Most of adults showed a lateralized activation shift from baseline to odor exposure, in that they showed greater relative left than right frontal activation in the odor exposure-related condition. Full-term neonates however, showed no significant shift in asymmetry from baseline to aroma exposure, but when data from these newborns were grouped according to the brain side of activation at baseline (right or left), infants showed the same shift pattern as the adult group.

This brain asymmetry has also been observed to be present in response to smell imagination in young adults (aged = 22-44 years) by Henkin & Levy (2001). Concretely, higher left than right hemisphere brain activation was found in response to the act of imaging pleasant odorants (banana and peppermint), with this brain lateralization being higher in women than men.

5.2.3. Cognitively-modulated brain activations in response to olfactory stimulation

De Araujo, Rolls, Velazco, Margot & Hobden (2005) conducted a study to examine the role of linguistic information in the brain representation of the hedonic value of odors presented orthonasally in 20-35-years-old participants using fMRI. They found that the rostral anterior cingulate/medial OFC was more strongly activated when a given odor (isovaleric acid + cheddar cheese flavor) was associated with the word descriptor “cheddar cheese” than when the target odor was associated with the word descriptor “body odor”. Participants also evaluated the target odor as significantly more unpleasant when that odor was paired with the descriptor “body odor” than when it was paired with the descriptor “cheddar cheese”.

Olfactory memory has also been studied in young adults using fMRI, although its possible modulation in the brain representation of olfaction is yet to be examined. Indeed, Cerf-Ducastel & Murphy (2006) scanned 20-25-years-old subjects while they were solving a cross-model olfactory recognition memory task three times. Subjects had to decide if certain words corresponded to names of odors previously presented or to odors not previously presented. Brain areas in which activation during this task was found were the hippocampus, amygdala, OFC, the cingulate cortex, superior temporal gyrus, cerebellum and parietal lobe. Furthermore, significant greater right than left hemisphere brain activations were found. However, this activation progressively decreased between runs 1 and 3, and was attributed by the authors to a greater familiarity with the words with repeated exposure.

5.2.4. ERPs-related studies on neural activity in response to olfactory stimulation

Age-related changes on ERPs in response to different odorants have been found although results regarding the direction of those changes (increases vs. decreases) are conflicting. For example, in the study by Hummel et al. (2007), event-related potentials (ERPs) were recorded and the components P1, N1 and P2 analyzed, while two groups of children (aged 3-5 and 6-10 years) were exposed to an unpleasant odorant (hydrogen sulfide, H_2S). A P2 latency increase between both age ranges was found. Hummel et al. (1998) measured amplitudes and latencies of P1, N1 and P2 in response to two odorants (ethyl-vanillin and H_2S) and to a trigeminal stimulant (carbon dioxide, CO_2) in three different age-related subject samples (15-34; 35-54 and 55-74). The between-group comparison revealed age-related changes. In general, the younger the subjects, the largest responses to the three stimulants were produced. For the N1P2 component, amplitudes corresponding to the three stimulants decreased significantly with age, with CO_2 producing the largest response, while responses to vanillin and H_2S showed the same magnitude. N1 amplitude also showed a mean decrease with age, but this was not statistically significant. P2 amplitude exhibited similar changes as N1P2 for stimuli. N1-related latencies increased with age and CO_2 produced the shortest responses. The paper provides no details about N1P2 and P2 latencies. However, decreased amplitudes of N/P components in response to olfactory stimulation with increasing age has been also found in several studies, in which brain behavior of aging participants has been compared to that of young adults (Murphy et al. 1994; Thesen & Murphy, 2001). This decreased brain activity in older subjects has also been observed through fMRI in several olfaction-related regions, such as amygdala, OFC, insula (Cerf-Ducastel & Murphy, 2003) and cerebellum (Ferdon & Murphy, 2003).

Gender-related differences in odor perception have also been examined in young adults using ERPs. Specifically, Oloffson & Nordin (2004) observed that amplitudes of P1, N1 and P2/P3 were greater, and the corresponding latencies shorter, in women of mean age = 27.2 than in men of mean age = 25.6. Moreover, amplitudes were greater and latencies were shorter with increases in the concentration of the odorant (pyridine).

Stimulus duration has been reported to impact the resulted ERPs in response to olfactory stimulation (phenyl-ethyl-alcohol and H_2S) in young adults (age range = 20-30 years), in that the longer the stimulus duration, the larger the amplitude of NIP2 (Frasnelli, Wohlgemuth & Hummel, 2006).

Finally, it has been reported that the resulted ERPs in response to an odorant (Mint tea) in adults in their early twenties depend on how early they begun to have experience with this target odor, in that "Algerian-French" subjects, who had been familiarized earlier with that odor than the "European-French" subjects, showed a longer P2 latency in ERPs in response to exposure to the Mint tea than this last subject group (Poncelet, Rinck, Bourgeat, Schaal, Rouby, Bensafi & Hummel, 2010).

5.3. Neuroimaging of flavor representation in the developing human brain

The integrated processing of taste along with olfactory stimuli generates flavor sensation (Rolls, 2005). This integration starts in the processes of food and drink intake. The action of chewing food and swallowing drink releases tastants and odorants within the oral cavity. These are mixed with saliva and the odorants spread through the environment of the oral cavity and are perceived retro nasally (Negoias et al. 2008).

Taste and smell interact producing several effects, including the intensity enhancement of odors produced by tastes and *viceversa*, especially if the combination of both kinds of stimuli is congruent due to its repeated pairing (i.e. lemon odorant + citric taste of the lemon fruit) (Lawrence et al. 2009; Noble, 1996; Small et al. 2004) and the odor-taste synaesthesia phenomenon, which refers to subjects' ability to describe odors using taste-related qualities (i.e. sweet odors) (Stevenson & Boakes, 2004). This taste-smell relationship has its own specific neural representation (See Verhagen & Engelen, 2006 for a review) so we will next describe reported brain activation patterns related to combined taste and olfactory processing, and therefore flavor processing in developing populations.

An interesting study on flavor processing conducted with PET in 22-41 year old participants (Small et al. 1997) showed significant rCBF decreases in bilateral anterior insula, frontal operculum and in the right caudolateral OFC in response to simultaneous presentation of congruent combinations of odorants and tastes, such as bitter with coffee, and sweet with strawberry in comparison to the independent presentation of the same stimuli. De Araujo, Rolls, Kringelbach, McGlone & Phillips (2003) observed, using fMRI in 20-year old participants, a greater activation in the left anterior OFC in response to the taste/smell combination of sucrose with strawberry than when activations in response to the independent presentation of each of these stimuli were summed. Significantly greater ratings of pleasantness in response to the combined sensory test than the sum of ratings of pleasantness in response to the unimodal presentation of stimuli were found as well. The same super additive effect was found, with fMRI, by Small et al. (2004) in women of mean age = 26 years in response to a congruent taste-odor pair of vanilla with sweet, when compared with the sum of its parts, that is, exposure to vanilla and sweet separately or to a non-congruent taste/odor pair, namely vanilla with salty. Taking these data as a whole, it can be concluded that flavor processing is not a product of the mere convergence of tastes and odorants. Furthermore, the work of Small et al. (2004) has demonstrated the high-experience-dependence of neural response to flavor perception.

6. Conclusions and future research

The principal aim of this review was to identify the evidence for the way in which developmental plastic changes, such as myelination and synaptic pruning, within the taste and olfactory systems have been reflected in signals obtained through neuroimaging techniques, with special emphasis on identifying sensitive periods of gustatory and olfactory postnatal and later development. We addressed this aim by reviewing the literature concerned with functional imaging signals obtained by means of neuroimaging techniques, such as fMRI, PET, etc., and following developing populations', namely newborns', infants', children's, adolescents' and young adults', exposure to gustatory and olfactory stimulation. In some studies, only gustatory stimulation was applied, in some others only olfactory stimulation was applied, while in the remainder, combinations of both kinds of stimulation were applied. The review was also intended to elucidate possible development-related changes in brain-related functional imaging signals responding to stimulation and its link to identification of development-related sensitive periods of flavor/odor learning and food/odorant preferences.

The review has identified three obstacles that have partially limited achieving the objectives. The first is that information regarding brain activation patterns in response to the target stimuli in newborns, infants, children and adolescents is scarce.

This finding is in contrast to the number of studies of both the visual and auditory systems in early stages of development –a few postnatal weeks- (Bortfeld, Wruch & Boas, 2007; Dehaene-Lambertz et al. 2006; Konishi, Gentaro, Yamada & Hirasawa, 2002; Morita et al. 2000), as well as in childhood (Burgund et al. 2006; Mosconi et al. 2005) and even in adolescence in the case of the auditory system (Chou et al. 2006). In the case of young adults, the state of the art is quite different. Indeed, the major proportion of empirical data obtained through neuroimaging techniques related to the target sensory systems, which have been found in light of the present review, concerns young adulthood. Thus, further research on developmental brain mapping of the taste and olfactory systems in the youngest age groups is required to obtain data on gustatory and olfactory-related neural activity and the changes associated with development.

The second limitation refers more specifically to the methodological designs of the available studies in which neural activity in response to gustatory and olfactory stimuli, either combined or not, has been examined in young adults. Practically all of them are cross-sectional between-subject studies which makes it difficult to observe subtle brain changes, either structural or functional, related to development. Observation of such changes could provide a more accurate picture of structural and functional brain development, which suggests the value of longitudinal within-subject study designs to allow extraction of those subtle brain changes (Blakemore & Choudhury, 2006; Durston et al. 2006). Two studies illustrate this. Sowell et al. (2004) found a GM thinning in the right dorsolateral frontal, bilateral occipitoparietal and anterior and posterior inferior temporal cortices with increasing age between the first and the second time 5-11 years-old subjects were scanned (the first scanning session took place at the mean age of 6,7 years and the second one at the mean age of 9). Durston et al. (2006) found that activity in many regions, including the DLPC, decreased between the first and the second scans of children who were carrying out a target detection task (the first scanning session took place at the age of 9 and the second at the age of 11). These changes were not observed using cross-sectional between subject studies when 9-year-old children were compared with 12-year-old children (Durston et al. 2006). Thus, further developmental research based on longitudinal designs is needed to contribute to elucidation of subtle brain changes.

The third limitation is the necessity of understanding the relationship between the effects of development-related neuronal events, in general, and those of neuronal events that regulate the action of sensitive periods of development such as synaptic pruning, in particular, and imaging signals. We also need to know how to differentiate these effects from effects of learning-related neuronal events, which are effects related to learning that typically occurs in the natural daily life of mature individuals without any *ad hoc* training in gustatory or olfactory skills. Indeed Poldrack (2000) stated that the biophysical impact of plastic neural changes associated with learning and development on functional imaging signals was yet to be identified. Nine years later this issue has not yet been resolved although some progress has been gained, as several authors have suggested possible relationships between some of the mentioned neuronal events and some imaging signals. For example, Morita et al. (2000) attribute the typical signal change –from BOLD increase to BOLD decrease- that has been observed to take place at approximately 8 postnatal weeks in the occipital cortex in response to photic stimulation (Konishi et al. 2002; Morita et al. 2000; Muramoto et al. 2002) to rapid synaptogenesis. A prominent indication regarding the usefulness of taking into account brain-related functional imaging signals in response to olfactory stimulation and in identifying sensitive periods of odor learning has been also obtained, at least by Poncelet et al. (2010), as they found a differentiated pattern of ERPs in response to an odor (Mint tea) as a function of how early participants have had experience with this odor in their lives, Specifically, young adults of an “Algerian-French-culture” origin, who have had early experience with the target odor showed longer P2 latencies than “European-French” individuals, who have not had such an early experience with the target odor. The questions then to be answered in future research would be: is there a specific sensitive period within early life, during which exposure to Mint tea would induce such a brain activation pattern in young adulthood? For providing an answer to this question, it would be necessary to vary the timing of the exposure to the target odor and to compare the resulted P2 latencies in young adulthood. Furthermore, would the resulted pattern of the P2 latencies in response to Mint tea in young adulthood be permanent throughout life span? For providing an answer to this question, it would be necessary to compare the resulted pattern of the P2 latencies in response to the same target odor later, during middle adulthood, for example. Then, existence of a sensitive period of learning about Mint odor could be confirmed.

Despite these limitations, this review has revealed interesting insights into gustatory and olfactory function in developing populations. Conclusions that can be drawn from this review are primarily related to young adulthood because the majority of empirical data extracted through neuroimaging techniques regarding the target sensory systems are from this developing group. For example, we have found that young adults, specifically aged around 18-34 years, are the only developing population in which brain activations in response to the act of tasting gustatory stimuli has been studied ad hoc. Therefore every conclusion about this issue may be applied only to that population. When the act of tasting gustatory stimuli is examined regardless of the emotional state (hunger vs. satiety), a robust overlapping brain representation of the well known basic five tastes has been found. Furthermore, brain activation patterns in response to these five basic tastes increase equally. Specifically, the insula and operculum region are always activated whenever young adults taste any gustatory stimulus, independently of the taste quality (De Araujo et al. 2003a; Kringelbach et al. 2004; Ogawa et al. 2005; Schoenfeld et al. 2004) and including water, which is a tasteless gustatory stimulus (Veldhuizen et al. 2007; Zald & Pardo, 2000b). Furthermore, the OFC has been shown to respond robustly to MSG, salty, sour and sweet tastes (De Araujo et al. 2003a; Kringelbach et al. 2004; Smits et al. 2007), but not to water (Veldhuizen et al. 2007; Zald & Pardo, 2000b), while the amygdala has been shown to be activated in response to the bitter and sweet tastes (Zald et al. 2002). Finally, DLPC has been shown to be activated in response to tasting the salty and sweet tastes (Kringelbach et al. 2004). However, when motivational state is taken into account, differentiated brain activation patterns are observed in response to gustatory stimuli in young adults. Brain activation increases have been observed in several regions of the taste system, such as the insula and operculum in response to gustatory stimuli under food-related deprivation conditions (Haase et al. 2009; Porubská et al. 2006). Food-related satiety conditions, in contrast, lead to both brain activation increases and decreases in taste-related brain regions (Small et al. 2001; Smeets et al. 2006; Wagner et al. 2006).

Brain activations in response to the hedonic value of foods have been observed in newborns (Fox & Davidson, 1986) and young adults (Small et al. 2003), and appear to indicate that there is a brain asymmetry with higher left than right hemisphere brain activation in response to pleasant tastes, such as the sweet taste and the contrary pattern for bad tastes such as sourness. This is not surprising, given the evidence that this brain asymmetry pattern is associated with approach-related positive and withdrawal-related emotions, respectively (Coan & Allen, 2004; Davidson, 1998; Davidson, 2000; Gray, 1987), and that taste stimuli can produce both emotions (Ganchrow et al. 1983; Rolls, 2005; Rosenstein & Oster, 1988; Steiner, 1979). This brain asymmetry is also present in emotional processing in mature subjects with positive emotions having been associated with higher left than right frontal brain activity and the contrary pattern for negative emotions (Davidson, 2000; Rohlfs & Martín-Ramírez, 2006).

Another interesting insight refers to the cognitive modulation of neural activity in response to taste stimuli in young adults. Three specific cognitive modulations have been found in the literature. Firstly, activation of different brain regions of the taste system may depend on the taste-related task to which subjects have to pay attention. While the medial OFC and the pregenual cingulate cortex are activated by rating taste intensity of gustatory stimuli, the insula and mid-insula are activated by rating pleasantness (Grabenhorst & Rolls, 2008). Secondly, activation of different brain regions of the taste system may depend on whether participants are given a cue that leads them to expect that they will receive a taste solution or they receive the actual taste. Specifically, expectation of receiving a gustatory stimulus is characterised by greater cortical activation than its reception. Thirdly, the strength of the activation in the OFC in response to rating the pleasure of flavor stimuli may be influenced by linguistic processing, as it has been found that this region is more strongly activated when the action of tasting MSG is paired with a pleasant word descriptor, than when it is paired with a neutral word descriptor (Grabenhorst et al. 2008). Several studies have examined brain representation in response to the act of imagining tastes (Kobayashi et al. 2004; Levy et al. 1999; Martin et al. 2008; Pelchat et al. 2004), although the mechanism of modulation of taste imagination in the area of the brain responsible for the representation of taste is yet to be elucidated.

Neural activity in gustatory-related brain areas in response to visual presentation of gustatory stimuli appears to change as a function of age, at least in female subjects.

There is a decrease in neural activity in the cingulate cortex in response to high-calorie food images between late childhood and middle adolescence but between middle adolescence and young adulthood, neural activity in the same brain area may increase in response to the same stimuli (Killgore & Yurgelum-Todd, 2005). Furthermore, neural activity in response to low-calorie food images increases progressively in the temporal lobe from late childhood through middle adolescence to young adulthood (Killgore & Yurgelum-Todd, 2005). Similarly, visual presentations of food-related utensils elicit a progressive increase of neural activity in the frontal lobe from late childhood to young adulthood (Killgore & Yurgelum-Todd, 2005). Furthermore, irrespective of the food-calorie-content, neural activity in response to images of vegetables has been shown to differ as a function of age. While these images elicited activation in the hippocampus in the female child/adolescent subjects in the study by Killgore & Yurgelum-Todd (2005), activation in response to images of vegetables was found in the insula/opercular cortex in the young adult subjects in the study by Porubská et al. (2006). In both studies, the OFC was activated by images of vegetables.

When considering olfactory representations in developing populations, the first conclusion that this review has revealed is that brain representations may differ as a function of the input entry (orthonasal vs. retro nasal) (Cerf-Ducastel & Murphy, 2001) and that the input entry-related specificity of olfactory brain representation may be modulated by whether an odorant represents a food (Small et al. 2005). A second conclusion refers to the observations of different brain-lateralized activations as a function of an odor's hedonic value. As with the case of taste stimuli, newborns show brain lateralized processing of affective responses elicited by olfactory stimuli, in that they exhibit higher left than right brain activations in response to pleasant odors, such as colostrum (Bartocci et al. 2000), and higher right than left brain activations in response to unpleasant odors, such as a disinfectant (Bartocci et al. 2001). This brain activation pattern appears to remain during young adulthood, at least in the case of pleasant odorants (Henkin & Levy, 2001; Sanders et al. 2002). Indeed, higher left than right hemisphere brain activation has also been observed when young adults imagine pleasant odorants (Henkin & Levy, 2001). Olfactory stimuli are similar to taste stimuli in that they produce positive and negative emotions (Rolls, 2005), which explains the brain asymmetry pattern. Furthermore, and also similarly to the findings in studies on taste, high-order processing, such as linguistic processing, has been observed to modulate brain representation of olfaction. De Araujo et al. (2005) found that the rostral anterior cingulate/medial OFC was more strongly activated when the target odor was associated with a specific word descriptor than when it was associated with another word descriptor. Olfactory memory has also been studied in young adults using fMRI, although its possible modulation in the brain representation of olfaction is yet to be elucidated (Cerf-Ducastel & Murphy, 2006). Finally, flavor processing from a combination of odors and tastes have been found to elicit brain activations in the insula, frontal operculum and OFC that differ from the independent presentation of individual odorants and tastes (De Araujo et al. 2003b; Small et al. 1997; Small et al. 2004).

In this review we have identified, as far as it has been possible, sensitive periods of gustatory and olfactory development by analyzing brain activation patterns of taste and olfactory systems that have been measured through neuroimaging techniques. This review has identified clear evidence indicating that brain activation patterns in response to gustatory and olfactory stimuli do, indeed, change across development of the taste and olfactory systems, on the one hand as well as evidence indicating the usefulness of taking into account brain-related functional imaging signals in identifying sensitive periods of odor and probably taste learning, on the other hand. The principal contribution of this review is to enhance awareness within the scientific community of the need to conduct further developmental research on the taste and olfactory systems in order to examine sensitive periods of gustatory and olfactory development, as well as the physiological impact of the imaging signals and their interrelationships in greater depth. A more thorough understanding will enable the identification, and therefore predict the course, of different sensitive periods of sensory (gustatory and olfactory) development from brain activation data.

CHAPTER 4

EFFECTS OF EXPERIENCE ON THE DEVELOPMENT AND ACQUISITION OF FLAVOR (TASTES AND ODORS) AND FOOD PREFERENCES IN CHILDREN: AN UPDATE

Abstract

Different experiences with flavors across development favor shaping of young and older children’s preferences for flavors, foods and drinks. On the basis of these experiences, operation of different mechanisms, such as flavor transmission via amniotic fluid and neonatal feeding regimen (breastfeeding and formula milk-based feeding), mere repeated exposure, Pavlovian or evaluative conditioning, specific parental strategies and food management in the school meals can be identified. Operation of these mechanisms is age-dependent but may act parallel to each other. Essential conditions for operation of these mechanisms are exposure to flavors and foods, which requires previous adults’ decisions about the foods and flavors to select for that exposure, thus guaranteeing cultural transmission of gastronomic habits. Promoting healthy patterns of food consumption, such as one rich in vegetables, in children requires careful manipulation of these mechanisms. The flavor, food and drink preferences developed by young and older children remain stable in later life phases. The lactation period has been here identified as a clear sensitive period of flavor preference development. Specific issues regarding the mentioned mechanisms have been here likewise identified as requiring further research, in order to get a better understanding of the development of food preferences in children.

Keywords: exposure to flavors, children, food preferences, parental influence and sensitive periods.

1. Introduction

Flavor is the most easily perceptible feature of foods and beverages for humans and its perception results from the interaction and integration of two kinds of chemical information present in foods and beverages, tastes and odorants, besides other sensory cues, such as temperature and texture (Small & Prescott, 2005; Beauchamp & Mennella, 2009). While there are five well-established basic tastes (sweetness, bitterness, sourness, salt and umami) (Mojet, Christ-Hazelhof & Heidema, 2001) and two still remaining controversial tastes (calcium and fatty) (Beauchamp & Mennella, 2009), the quantity of odorants has been estimated to be approximately around half a million (Kringelbach, 2007). Combinations of basic tastes and odors build, then, the global flavor of a food or beverage.

Flavor liking have been observed to be the most determining factor of food preferences and therefore food consumption in young and older children and even adolescents (Noble, Corney, Eves, Kipps & Lumbres, 2003; Burguess-Champoux, Marquart, Vickers & Reicks, 2006; Mennella & Beauchamp, 2010), although food preferences of these two last individual groups have also been observed to be influenced by other determining factors. This issue will treated later again within this introduction section, when we deal with cognitive development. On the contrary, adults tend to consider health-related aspects of nutritional habits, besides the flavor liking, when it comes to selecting foods or reporting food preferences (Pérez-Rodrigo, Ribas, Serra-

Majem & Aranceta, 2003; Navarro-Allende, Khataan & El-Sohemy, 2008). Preference for and intake of vegetables especially ilustrates this age-related differentiated determining factor of food preferences and intake, by extension. Vegetables, especially green vegetables, such as spinach, broccoli and Brussels sprouts are typically rejected by children and are their least preferred food mainly because of the unpleasant bitter taste of vegetables (Harper, 1963; Cashdan, 1998; Rasmussen et al, 2006; Wardle, Sanderson, Gibson, & Rapoport, 2001; Havermans, 2010). Furthermore, children's vegetable consumption rate does not meet the national recommendations (Krebs-Smith et al. 1996; Johnson & Kennedy, 2000; Yngve et al. 2005; Lorson, Melgar-Quinonez & Taylor, 2009). Vegetable intake has been observed to increase as individuals age due to assimilation of health-related beliefs that are shaped during the course of years of the life cycle (Navarro-Allende et al. 2008), however. Instead of vegetables, a kind of food considered as healthy because of its richness in antioxidant properties and its cancer-related preventive effects (Mikkilä, Räsänen, Raitakari, Pietinen, & Viikari, 2004; Ness et al., 2005; Číž, Čížová, Denev, Kratchanova, Slavov & Lojek, 2010), young children prefer, among others, snack foods, which are rich in fats and sugars that can lead to childhood obesity (Skinner, Bounds, Carruth, Morris, & Ziegler 2004; Knai, Pomerleau, Lock, & McKee, 2006; Warren, Parry, Lynch, & Murphy, 2008), one of the most serious public health problems throughout the world (Weker, 2006; WHO, 2009). Therefore, while *liking* and *preference* may not be necessarily synonymous terms (Rozin & Vollmecke, 1986) for adults, in the case of children they may be.

Some differences between infants and young children and adults have also been observed regarding the showed repertoire of food preferences, besides their determining factors. For example, infants easily accept milk formulas that are high unpalatable for older children and adults (Mennella & Beauchamp, 2005). Children aged between 5 and

9 years prefer the sourest gelatins over gelatins with lower sour taste concentrations, a preference that was not present in any of the adult participants (Liem & Mennella, 2003). Children also show a heightened preference for sweet foods and foods with added sugar, in comparison to adults (Zandstra & De Graaf, 1998; Mennella, Pepino & Reed, 2005), this difference diminishing in the adolescence (Popper & Kroll, 2005). A child's most preferred level of salt has also been shown to be quite higher than that of adults (Cowart & Beauchamp, 1986; Beauchamp & Cowart, 1990).

Such differences in the repertoire of and determining factor of food preferences between adults and the former young individuals may reflect development-related cognitive and sensory differences as well as differences likewise attributable to development-related differences regarding the way in which experience (contact with/exposure to) with foods and flavors (tastes + odors) impact their food preferences. Regarding cognitive differences, the study of Bahn (1989), for example, observed, on the basis of Piaget's theory of child cognitive development (Inhelder & Piaget, 1958) that children from 4- to 5-year-old (preoperational children) based their preferences for beverages on perceptual attributes, such as sugar content and affective appraisals, such as liking the taste, while children from 8- to- 9-year-old (concrete operational children) based their preferences on cognitive attributes, such as healthiness, besides affective appraisals. Furthermore, Zeinstra, Koelen, Kok, & De Graaf (2007) revealed also from a Piagetian perspective that children from 4- to 5-year-old (preoperational children) cannot yet categorize products correctly into healthy and not healthy as well as they cannot yet argue the underlying reasons for the healthiness of certain "healthy" foods that they are able, in turn, to name, both of these abilities emerging in later childhood – from the 7th year on-, which agrees with Contento's conclusion that preoperational children do not differentiate between foods and snacks, while concrete operational children do (Contento, 1981). Snacks are considered as unhealthy foods because of their high sugar and fat content (Warren et al. 2008). The ability of reasoning the appropriateness of a food on the basis of its nutritive content and health-related effects on the body requires exactly understanding of the effects of food on the body and the implications of supplying the body with nutrients, abstract concepts, of which understanding emerges when abstract thinking is more developed, that is, in the formal operational stage of development (Contento, 1981). A subsequent study (Fallon, Rozin & Pliner, 1984) observed in 3.5-12-year-old children that the displayed criterion for rejecting a food resulted to be age-dependent. Specifically, the youngest children based their food rejections on the disgusting taste of foods; older children considered harmful postingestive consequences of eating a food for rejecting it and the oldest children considered the contamination of physical chemistry of solutions. A posterior study (Nu, MacLeod & Barthelemy, 1996) observed that after the puberty, individuals begin to like certain foods, they did not like in younger life stages, authors arguing that individuals are able at puberty to understand relationships between food consumption and health, health being an important factor of food consumption for adolescents, and that that ability emerges once individuals have reached enough heights of cognitive development. «Cognitive development refers to changes in knowledge and in the use of knowledge that occur as a human ages» (McNeal, 2007, p. 123). All these studies have been developed in the theoretical frame of Piaget's theory of child development[1] (Inhelder & Piaget, 1958). The biologist and psychologist Jean Piaget built his theory of

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[1] Piaget's theory of child cognitive development is the most used theory when studying different aspects of human cognitive- and brain development, from disordered cognitive development (i.e. Torres, Olivares, Rodríguez, Vaamonde & Berrios, 2007) to normal (disease-free) neocortical maturation (i.e. Mukherjee & McKinstry, 2006).

child cognitive development around his observations that the operations of the child's mind differed markedly from those of adults (Pulaski, 1997). Piagetian theory proposes that each child develops across a series of stages that impact his cognitive development (see figure 1), the child passing gradually from a more primary and concrete- to a more abstract thinking (Flavell, 1963).

Table 1: stages of intellectual development proposed by Piaget and adapted from the reformulation by Pulaski (1997). It is to highlight that not every adult reaches the fourth stage, but scientists, for example (Pulaski, 1997).

Stage of development	**Age range**	**Main characteristics**
Sensory-motor	0-2 years	Behavior based on innate reflects, such as suction Infant's world is based on pure sensory-motor experiences No intentional mental activity
Preoperational	2-7 years	Pre-logical reasoning Use of symbolic representation Learning based on trial and error
Concrete operational	7-12 years	Use of logical thinking Ability to classify objects into categories Intellectual development sharply upward
Formal operational	12-	Ability to generate hypotheses Use of deductive, inductive and abstract thinking Ability to handle large amounts of data

Therefore, infants and young children appear to be equipped with flavor as the only criterion for preferring and selecting foods during infancy and early childhood, while other "tools", such as causal health-related attributions are available to them as they progress cognitively (Piaget, 1974). Adults, in turn, tend to appreciate other aspects different from or besides liking the flavor, such as the consequent health-related effects of eating a food, when it comes to select an item and to report food preferences, due to assimilation of health-related beliefs that are shaped across life span (Navarro-Allende et al. 2008). Regarding sensory differences, we know that infants' and young children's sense of taste differ markedly from that of adults, in that the sensitivity to tastes of the two former subject groups suffers certain changes that are attributed to development, and therefore are not present in mature individuals (Mennella & Beauchamp, 1998a). Specifically, at birth newborns are able to feel the sweet, sour and the bitter tastes and sensitivity to umami is showed, if it is diluted in a fluid, such as soup (Mennella & Beauchamp, 1998a), Sensitivity to salt, in turn, emerges around the 4-6 postnatal months, when the peripheral and central nervous system is mature enough to enable infants to feel that taste (Beauchamp, Cowart & Moran, 1986; Beauchamp, Cowart, Mennella & Marsh, 1994; Blossfed, 2006). Young adults (18-30 years), in contrast, are able to perceive the five basic tastes –sweet, sour, bitter, salty and umami- (Mojet, Christ-Hazelhof & Heidema, 2005; Hong et al, 2005) as also do middle-aged adults (30-50 years) (Cowart, 1981). Taste sensitivity of older adults (from 65-years old on), in turn, has been observed to suffer a progressive decline throughout aging, as they need higher taste concentrations to identify and discriminate among them (Murphy & Withee, 1986; Cowart, Yokomukai & Beauchamp, 1994; Schiffman, Sattely-Miller, Zimmerman, Graham & El-sohemy, 1994b; Schiffman, 2008; Navarro-Allende et al. 2008). Thus, it appears reasonable to think that the age-related changes in the ability to detect the different tastes may impact the extent to which the taste-related information is useful for determining food preferences and food choices across different life phases. Olfactory sensitivity to odorants, similar to sensitivity to some tastes is present at birth (Steiner, 1977) but, in contrast to tastes, a progressive development of sensitivity to different odorants has not been reported. This could be due to two main reasons, either it has not been found any evidence about such a progressive development, or the topic has not been researched enough, whatever the reason. Regarding experience’s impact on food preferences status, it is to say that experience with foods do not affect developmental and mature individuals equally. For example, while consumption of sweet orangeade during eight consecutive days has been shown to lead to an increase in the preference for this sweet drink in children, the same consumption does not increase the preference for the drink in adults (Liem & De Graaf, 2004). This kind of evidence leads to the conclusion that experience with gustatory stimuli shapes children’s preferences for flavors, foods and/or drinks through experience-expectant plasticity, which is considered to be present only in immature individuals (Greenough, Black & Wallace, 1987; Toga, 2006).

The present review is an attempt to summarize the published evidence accumulated up until now that explains how different experience-related mechanisms shape infants’, young children’s and older children’s preferences for flavors (tastes and odors), foods and/or drinks and the published evidence indicating that the flavor and food preferences developed during infancy and childhood are associated with later food or flavor preference status, in order to identify sensitive periods of development of flavor (taste and odors) preferences. Sensitive periods can be defined by restricted periods of time within development, during which there is a biological display of an extreme neural sensitivity to the storage of experience-driven (sensory = gustatory and olfactory) information, which promotes an individualized design of the shape and function of the neural circuits, which is directed to the individual’s survival, and thus, safeguards the normal development (disease-free) of sensory systems (Hensch, 2004; Spolidoro, Sale, Berardi & Maffei, 2009) –the taste and olfactory systems-. Sensitive periods are reflected in behavior (Knudsen, 2004), probably such as the fact of reporting flavor (odors + tastes), foods or drink preferences. For those aims, we have reviewed published experimental and review research on effects of developing individuals' exposure to gustatory (tastes, foods and drinks) and olfactory stimuli (odors, foods and drinks) on gustatory and olfactory preferences, as both senses –taste and smell- are required for flavor perception. On the other hand, as there is evidence that infants at birth are equipped with some inborn taste preferences, its prior summary is here presented as well.

As readers will see, one of the main theses of the present review is that passive exposure to chemical stimuli is the main factor contributing to development of flavor, food and drink preferences. The term passive exposure refers to the fact that developing individuals, such as neonates, infants, young and older children are usually submitted to adults' decisions about the kinds of foods, they have to be exposed to and have to eat. Furthermore, the present review tries to present some of the questions that require future experimental examination, in order to obtain explaining knowledge. The global aim is to get a better understanding of the origin of developing individuals' flavor preferences. This better understanding might help to generate effective strategies focused on increasing children's healthy food intake patterns, that is, rich in vegetables, for example. The importance of promoting healthy food intake patterns in children derives from the available evidence indicating that childhood, especially young childhood, is the life phase in which preferences for foods, including vegetables and eating habits are most likely to be established, these food preferences and eating habits tracking into later life phases, (Nicklaus, Boggio, Chabanet & Issanchou, 2004; Nicklaus, Boggio, Chabanet & Issanchou, 2005a; Pearson, Biddle & Gorely, 2009; Kimura et al. 2010).

2. Innate flavor preferences

It is widely accepted that infants and young children are naturally predisposed to accept and prefer sweet and salty tastes over the bitter and sour basic tastes, which tend to be avoided (Kajiura, Cowart & Beauchamp, 1992; Mennella et al. 2005a; Mennella & Beaucahmp, 2009). The biological function attributed to these innate flavor preferences as an evolved function concerns ensuring an enough calorie intake in order to avoid malnutrition-related pernicious effects derived from food shortage as well as protection against potential toxic poisonings, respectively (Drewnowski & Rock, 1995; Glendinning, 1994; Birch, 1999; Hladik, Pasquet & Simmen, 2002). Indeed, Cahsdan (1998 p.618) has reported that poisonings derived from ingestion of houseplants are the primary cause of 6- to 18-month-old infants needing medical attention at the Utah Poison Control Center. That neonates and young children are innately predisposed to accept certain tastes and reject others derives mainly from observational research that has elucidated the quality of facial expressions, either positive, negative or neutral that have been expressed by preterm and full-term newborns, neonates with anencephaly and hydro-anencephaly, severe malformations of the central nervous system, as well as older infants, in response to different tastes (Steiner, 1979; Fox & Davidson, 1986; Mennella & Beauchamp, 1998a; Steiner, Glaser, Hawilo & Berridge, 2001). Based on these studies, facial expressions have turned into an objective indicator of the subjective sensation of pleasantness either liking or disliking that is generated when tasting gustatory stimuli of different qualities. Indeed, newborns' facial expressions appear to be specific of the taste and constitute the so called gusto facial response (Steiner, 1977; Steiener, 1979). For example, the sweet taste elicits facial relaxation, smiles, sucking, tongue protusions; the sour taste elicits lip pursing and face grimace; the bitter taste induces depressed mouth angles, facial grimace and nose wrinkling (see figure 1). Salt, in turn, gives rise to no distinctive facial expressions (Nowlis & Kessen, 1976; Steiner, 1979; Ganchrow, Steiner & Daher, 1983; Rosenstein & Oster, 1988; Mennella & Beauchamp, 1998a; Zeinstra, 2010) (see figure 1), which is reasonable, as liking and preference for the salt taste appears to emerge later, at the age of 4-6 months and may continue until two years of age (Beauchamp et al. 1986; Beauchamp et al. 1994). These facial expressions are assumed to have been efficiently designed through the evolution course to communicate food acceptance or rejection to caregivers, as newborns cannot yet use verbal language (Erickson & Schulkin, 2003; Greimel, Macht, Krumhuber & Ellgring, 2006). Facial expressions in response to basic tastes have been less studied in children. Specifically, there is one study that has tried to determine if the analysis of facial expressions is a useful and objective parameter to measure preference (liking or disliking) in primary school children (age = 5-13 years) (Zeinstra, Koelen, Colindres, Kok & De Graaf, 2009a). The authors concluded that the analysis of facial expressions is not a suitable method for discriminating children's liking but disliking. With the exception of the study of Steiner (1979), studies on infants' and children's facial expressions in response to different quality-related odorants are hardly to find. Steiner (1979) found nasofacial responses that were similar to the gusto facial responses in neonates.

1 2 3

Figure 1: neonates' facial expressions in response to sweet (1), sour (2) and bitter (3) tastes. Taken from the study by Steiner (1979)[2].

Apart from facial expressions, other parameters, such as consumption rate (Desor, Maller & Andrews, 1975), sucking and heart rate (Crook & Lipsitt, 1976) have been used as objective indicators of neonates' inborn innate preference for the sweet taste and rejection for bitter and sour tastes. Indeed, Desor et al. (1975) found that babies from 1- to 4-day-old babies drank a sucrose solution in a lesser extent when that solution was added citric acid, which tastes sour, than when the sucrose solution was offered without citric acid. However, the authors did not found a differentiated consumption pattern of the sucrose solution among neonates as a function of the addition of urea, which tastes bitter. Addition of sodium chloride neither induced changes in neonates' consumption of the sucrose solution. Crook & Lipsitt (1976), on their part, found higher sucking and heart rates in neonates, the sweeter was the solution offered.

Once we know that facial expressions, intake rate, etc. elicited by gustatory stimulation at birth are a reliable objective indicators of the innate origin of certain

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[2] This material has been included here with permission of Dr. Steiner.

human gustatory preferences, an interesting issue that has to be further investigated refers to the genetic basis of those innate preferences. In this regard, ascertaining the link between the genetically determined individual variation in gustatory sensitivity to the different tastes and taste preferences may be a promising research line to solve this problem. Relatively recent progress in this field has been made. While sensitivity to the bitter taste along with its determining gene -TAS2R38- and its associated polymorphism explain the (individually varied) natural rejection for bitterness and therefore bitter foods (Nicklaus, Boggio & Issanchou, 2005b), the genetic determination of sensitivity to sweet, salty, sour, umami and other possible tastes, such as calcium and fatty tastes and its possible varied polymorphism requires further research (Nicklaus et al. 2005b; Fushan, Simons, Slack, Manichaikul, & Drayna 2009).

Regarding odor preferences, the literature reflects the position that odor preferences are not innate, but learned already from the prenatal life phase, in which fragrant food particles that are present in the amniotic fluid and are retronasally smelled by fetuses (Mizuno & Ueda, 2004; Blossfed, 2006). However, chemicals present in the amniotic fluid have also been identified to stimulate fetuses' taste receptors (Mennella & Beauchamp, 1997a), so that experience with tastes takes place prenatally too, and subsequent research work discovered genetically determined individual variation in the bitter taste sensitivity, which confirmed genetic predetermination in subjects' preference or rejection for the bitter taste. Although the proportion of research work done within the olfactory domain is quite little, in comparison to that done within the gustatory domain, some evidence supporting individual variation in sensitivity to odorants has also been found, but the genetic origin of that individual variation in olfactory sensitivity has to be further investigated (see Bartoshuk & Beauchamp, 1994; Young, Endicott, Parghi, Walker, Kidd & Trask, 2008; Hasin-Brumshtein, Lancet & Olender, 2009 for comprehensive reviews).

3. Passive exposure-related mechanisms

Current published information let us know that the phenotypic expression of innate flavor preferences can be modified through different experience-related mechanisms during development that have to do with availability, but above all with a passive exposure to chemical stimuli. Specifically, and as we will ser here, flavor preferences are shaped following a development-related chronological order of experiences with olfactory and gustatory stimuli, starting these experiences in very early life and continuing across childhood. Therefore, there is not a unique experience-related mechanism favoring shaping of food, flavor or drink preferences (Rozin & Millman, 1987), although all of them share exposure to flavors, foods or drinks as well as previous adults' decision about the flavors, foods and drinks, infants and children will be exposed to as unconditional requirements for these experience-related mechanisms being operating. Operation of these mechanisms guarantees infants' and children's acceptation of the foods that are available for them in their unique context (Birch, 1999; Savage, Fisher & Birch, 2007; Zeinstra, 2010).

3.1. Early gustatory and olfactory exposure

There are three kinds of early experiences with chemical stimuli (taste + odors = flavors) that may lead to the modification of innate gustatory preferences during early stages of life and may constitute the basis for posterior eating habits (Forestell &

Mennella, 2007). These experiences occur during different ontogenetic phases of human development that are followed one by one, the prenatal gestation stage, infancy and early childhood and may cause a gustatory and/or olfactory imprinting, these experiences affecting later flavor, food or drink preference and/or acceptance status. Furthermore, the early life phases in which that imprinting may occur might constitute sensitive periods of flavor (tastes + odors) preference-related learning because as we will see here the gustatory preferences that have been learned within each of these ontogenetic phases endure throughout later stages of development, although further research is needed, in order to obtain confirmatory evidence for existence of those sensitive periods. We will discuss this issue again in the conclusions section of the present review.

3.1.1. Flavor transmission through the amniotic fluid (AF) during prenatal stage of development

The first of those experiences is lived antenatal, in utero. At this moment, fetuses are exposed to chemical compounds (tastes and odors) derived from food particles of the mothers' daily food consumption that are spread through the AF within the placenta and are swallowed by fetuses (Mennella & Beauchamp, 1997a; Beauchamp & Menella, 1998; Mennella & Beauchamp, 1998a). Indeed, the chemical constitution of the amniotic fluid has been shown to change throughout pregnancy, thus reflecting the mother's diet pattern during pregnancy (Mennella, Johnson & Beauchamp, 1995). There is also evidence indicating that fetuses show different drink patterns depending on the taste quality of the specific substance injected into the AF –sweet vs. bitter-, and that they prefer the sweet substance over the bitter one (De Snoo, 1937; Liley, 1972).

Therefore, humans experiment their first different gustatory and olfactory sensations at the prenatal stage via AF, those chemical sensations being equivalent to the women's unique diet that she decides to consume during her pregnancy.

3.1.1.1. Link between prenatal experience with flavors and later food preference and acceptance status

A body of evidence indicates that these prenatal experiences with chemicals induce a facilitation of food and flavor preference and acceptance that is visible in subsequent life phases, such as weaning or even young adulthood. For example, Mennella, Coren, Jagnow & Beauchamp (2001) found that 5.7±0.2 months old infants whose mothers repeatedly drank carrot juice during pregnancy showed less negative facial expressions while feeding a carrot-flavored cereal relative to the plain cereal at weaning and compared to infants that were not previously exposed to carrot juice in utero. An interview-based study (Mennella, Turnbull, Ziegler & Martínez, 2005) extracted a body of data relating the kind of foods eaten by infants at weaning to the kind of foods eaten by their mothers during pregnancy in Mexico. Crystal & Bernstein (1995) found that young adults (aged = 20 year old) whose mothers suffered moderate to severe vomiting during pregnancy showed greater preference for snack foods with the highest level of salt, in comparison to young adults whose mothers suffered no or mild vomiting. These data specially support the claim that the prenatal development stage might constitute a first sensitive period of gustatory learning, as they evidence that prenatal experiences with chemicals contained within the AF may determine stable food preferences, lasting these food preferences at least until young adulthood. A subsequent study replied these results in 16-week-old infants. Specifically, infants whose mothers reported to have been affected by vomiting in a moderate to severe degree exhibited less number of negative facial expressions in response to the liquid solution with the highest level of salt, in comparison to infants whose mothers reported no or mild degree of vomiting (Crystal & Bernstein, 1998). Previous evidence showing that pregnant rats need to ingest high levels of sodium if they undergo routine episodes of vomiting due to its consequent physiological effects, principally dehydration of such pregnancy-related vomiting constitutes the main experimental antecedent of these human studies (Nicolaïdis, Galaverna & Metzler, 1990).

3.1.1.2. Link between prenatal experience with flavors and later olfactory preference status

Olfactory preferences have also been demonstrated to be susceptible to be learned in utero. For example, Varendi, Christensson, Porter & Winberg (1998) found out that full-term neonates exposed to the odor of their mothers' AF during 16-30 min immediately after birth cried significantly less when separated from their mothers than neonates exposed to the odor of their mothers' breast and neonates exposed to no odor. Moreover, it has been evidenced that prenatal experience with AF induces the acquisition of a preference for its odor over the odor of a formula milk and the odor of distilled water at the second and fourth postnatal days (Marlier, Schaal, & Soussignan 1998) and over a nonfamiliar AF and another control odor at the third postnatal day (Schaal & Marlier, 1998). Schaal, Marlier & Soussignan (2000), for their part, have demonstrated that in utero exposure to anise flavor derived from the mother's consumption of anise-flavored sweets leads to a stable preference for the anise odor at birth and at the fourth postnatal day. Faas, Spontón, Moya & Molina (2000) found significant higher rates of motor responsiveness in response to ethanol odor in 24- to 48h-old infants whose mothers reported to have been frequent drinkers during pregnancy, in comparison to infants whose mothers reported to have been infrequent drinkers during pregnancy. Mizumo & Ueda (2004) found higher rates of sucking pressure, efficiency and frequency when neonates were fed a formula milk in the context of a parallel exposure to the odor of the mother's milk, in comparison to the same feeding situation with a parallel exposure to the odor of formula milk and water and although no previous preexposure to the mother's milk took place but in utero preexposure to the mother's internal environment (amnion) of which odors may be reflected in the mother's milk.

3.1.2. Flavor transmission through the neonatal regimen feeding during the lactation period

Once the baby has born, postnatal experiences with flavors (tastes and odors) continue to take place and to induce acceptance of and liking and preference for flavors or foods. Indeed, several studies have shown that the lactation period, either based on breastfeeding or formula feeding, constitutes the second kind of experience, through which infants are exposed to chemical stimuli, these experiences therefore helping them to learn about which kind of flavors and foods are available to them within their environment during infancy and thus which kind of available flavors and foods to accept, to like and to prefer.

Studies on infants' breastfeeding point out that the mother's diet is transmitted to infants in form of flavors (tastes and odors) through her milk during breastfeeding and that diet induces a flavor and food-related imprint that remains visible during the weaning-related infancy life period. Preliminary evidence supporting that mothers' transmission of flavors to infants through her milk as well as infants' sensory awareness of the presence or absence of those flavors was revealed by Mennella & Beauchamp (1991a), in that they found that from 3- to 4- month-old infants spent more time attached to their mothers' breast and sucked more when the milk smelled like garlic after mothers' ingestion of garlic as compared to when infants fed mothers' milk that was not garlic-flavored. Subsequent studies obtained confirmation of these changes in infants' responsiveness to the sensory quality of the mothers' milk as a function of the presence or absence of a specific flavor associated with mothers' diet employing alcohol- and vanilla-flavored maternal milk (Mennella & Beauchamp, 1991b; Mennella, 2001; Mennella & Beauchamp, 1994; Mennella & Beauchamp, 1996).

Flavor transmission through formula-milk-based feeding has also been demonstrated by Mennella & Beauchamp (1996) to occur as well. In this study, it could be observed that infants of mean age = 3.2 months showed a differentiated pattern of responsiveness to the formula milk as a function of the presence or absence of the vanilla flavor in the formula milk, in that those infants sucked significantly more when feeding the vanilla-flavored formula, relative to the control formula, after a brief exposure to the vanilla-flavored formula. During a second and longer exposure (an entire feeding), infants fed longer when the formula was vanilla-flavored, relative to a control formula.

3.1.2.1. Food acceptance status at weaning and its link to flavor transmission through breastfeeding to infants

Evidence linking the flavor and food-related imprint generated in infants through their exposure to maternal milk to infants' eating behavior at weaning is found in the following body of research. For example, the already mentioned interview-based study by Mennella et al. (2005b) extracted a body of data which relate the kind of foods eaten by infants at weaning to the kind of foods eaten by their women during the lactation period in Mexico. That the emergence of such a link depends on the length of the time interval between the milk-related exposure and the test moment remains relatively unclear, given the conflicting results that experimental research on this variable has yielded, however. For example, Mennella & Beauchamp (1997b) found that 175.5±6.8 days-old infants showed higher rates of cereal consumption at weaning when the cereal was prepared with the mother's milk, to which infants were exposed previously during the lactation period, than when it was prepared with water, an effect that authors attributed to the prior exposure to the carrot flavor during the lactation period (preexposure effect). In this study, infants had been fed cereal for a short period of time, that is, an average of 12.9±1.5 days. However, a subsequent study (Mennella & Beauchamp, 1999) in which 3.4±1.0 months-old infants had been fed cereal for a short period of time, that is an average of 21.3±2.0 days, showed that infants consumed less carrot-flavored cereal than cereal prepared with water and spent less time feeding if they were exposed to the flavor of carrots in their mother's milk during the lactation period, in comparison to control infants. The authors attributed this effect to sensory-specific satiety (SSS) (Mennella & Beauchamp, 1999), the mechanism through which recent repeated exposure to the same flavor or food leads to a decrease in the consumption of that food (Rolls, Rowe & Rolls, 1982a). A subsequent study (Mennella et al. 2001) showed that infants of mean age = 5.7±0.2 months who were exposed to carrot juice during breastfeeding because the mothers were drinking carrot juice during the first two months of lactation enjoyed more the cereal prepared with carrot juice at 4±0.5 weeks of weaning, the same long period of time that infants had been fed cereal, than when they were fed plain cereal and more than did non previously exposed infants. The same preexposure effect was found by Forestell & Mennella (2007) in breastfed infants aged from 4 to 8 months that had been eating for a long period of time of 6.7±1.6 weeks when their intake rate of peaches and facial expressions were measured. Specifically, these infants ate more peaches than infants that were previously fed artificial formula-based feeding, a result attributed by authors to the high rate of fruit consumption of the mothers of the former group (Forestell & Mennella, 2007). Thus, it would be interesting to manipulate the length of the time interval between the exposure period and the test session as independent variable within the same experimental study, in order to examine if this variable determines the kind of the resulted subjects' intake pattern, either an intake pattern characterized by an effect of induced gustatory learning through early exposure to the flavor of the mother's milk or, in turn, of SSS.

3.1.2.2. Food acceptance status at weaning and its link to flavor transmission through formula milk-based feeding to infants

Effects of a gustatory imprint through exposure to artificial milk during the lactation period have also been observed in infants at weaning, although as in the case of the studies on infants' breastfeeding, the specific impact that the length of the time interval between the exposure period and the test moment could have on subjects' food acceptance pattern, either an impact associated with SSS, or at the contrary, a preexposure effect, remains relatively unclear. The study by Mennella, Forestell, Morgan & Beauchamp (2009) revealed that infants between 4 and 9 months of age that were fed hydrolyzed casein formulas (HCFs), which taste bitter, sour and are savory and have an unpleasant odor, during the first three months of life, ate more cereals characterized by these tastes and odor at ≥2 weaning weeks, a preexposure effect attributed to prior experience with the specific formula milk, than did infants fed bovine milk-based formulas, which present these tastes in a significantly lesser extent and infants fed breast milk, which tastes sweet. Mennella, Griffin & Beauchamp (2004) found that < 3 weeks-old infants fed a specific HCF (Nutramigen) during a seven months long period of time accepted another HCF (Alimentum) similar to the former in a higher degree, than control infants, who were fed a milk-based formula (Enfamil) during the same period of time; infants who were fed Nutramigen for 3 months and infants who were fed Enfamil for 4 months. In a subsequent study by Mennella & Beauchamp (2005), infants aged from 5 to 11 months preferred the HCF which they were being fed at the test moment, either Nutramigen or Alimentum, in comparison to infants that were being fed milk-based formulas, which rejected both HCFs. However, SSS emerged in the study by Mennella, Kennedy & Beauchamp (2006) when infants from 6- to 11-months-old, who were being fed a HCF that contains similar flavors with broccoli and cauliflower, had to consume pureed broccoli and cauliflower, as they consumed significantly less of these vegetables, relative to carrots and in comparison to infants that were being fed milk-based formulas. Thus, it would be also interesting to treat the time interval between the exposure period to formula milk and the test session as independent variable in future research for ascertaining which kind of effect emerges, either SSS or preexposure effect.

3.1.2.3. Link between food preference and food acceptance status in early childhood and beyond and flavor transmission during the lactation period

Imprinting effects associated with prior experience with flavors during the lactation period based on formula feeding, are not evident only in infancy, but in childhood and beyond, thus showing the long-lasting effects of very early experience with flavors. This claim finds support in the empirical evidence extracted by several studies that have showed flavor- and food-related prior exposure effects in children that are similar to those found in infants. For example, Mennella & Beauchamp (2002) reported that early experiences with specific formulas (milk, soy and HCFs) during the lactation period predicted the status of preferences for specific flavor-based juices in a 4- to 5-year-old subject sample. Specifically, children fed soy-based formulas, which taste sweet, sour and bitter and have a strong hay odor preferred significantly the bitter-flavored juice and children fed HCFs preferred the sour-flavored apple juice, in comparison to children fed milk formulas. Furthermore, the two former groups were more likely to prefer broccoli than the group fed milk-based formulas, as reported for their mothers. These results were replicated in another study, in which the age appeared to determine the level of flavor preference (Liem & Mennella, 2002). Specifically, the authors of this study found that 4-5-year-old children fed HCFs during the lactation period preferred apple juice with higher levels of citric acid, in comparison to the 6-7-year-old counterparts that also were fed HCFs. Likewise, Haller, Rummel, Henneberg, Pollmer & Köster (1999) found a positive correlation between early experience with vanilla-flavored formula milk and the preference for this flavor in a subject sample aged between 12 and 59 years, although the authors do not rule out the possibility that this effect could have been specific of other taste components of the formula milk, participants were fed during their lactation period, rather than vanilla. If breastfeeding can induce such long-lasting effects has to be further investigated.

Taken these data as a whole, we can conclude that the gustatory imprinting acquired by infants during the lactation period, independently on the feeding regimen, either breastfeeding or formula feeding, remains intact in the long term (early childhood and beyond), that is, several years after exposure, so that the lactation period might constitute a second sensitive period of gustatory learning that follows the stage of prenatal gestation. Although both fed regimen patterns have been empirically demonstrated not to differ from each other in their high effectiveness to induce the described preexposure effects, they do differ considerably from each other in the strength with which both of them facilitate infants' acceptance of new solid foods at weaning. Indeed, Sullivan & Birch (1994) exposed either breast-fed or formula-fed from 17- to 22-weeks-old infants that had been fed cereal during a mean period of time of 15 weeks at weaning to either pureed peas or green beans for 10 times on consecutive days and it was found that the breast-fed group consumed significantly more than did the formula-fed group after the repeated exposure period as well as one week later. The authors of this study attribute this result to the fact that breast milk is rich in a variety of flavors, while the flavor of formula milk is quite consistent across feedings, something that Mennella & Beauchamp (1991a) and Mennella & Beauchamp (1991b) have also argued. However, in the study by Sullivan & Birch (1994) no data on the lactating mothers' diet were recollected and it would be interesting to take this into account in future research.

3.1.2.4. Olfactory imprinting during the lactation period

Olfactory preferences are also well documented to be learned during early stages of postnatal development, besides during prenatal gestation and might constitute sensitive periods of olfactory learning. Indeed, one of the first odors, neonates learn soon about, concerns the natural odor of their mothers’ breast (Macfarlane, 1975; Russell, 1976; Sullivan & Toubas, 1998; Varendi, Porter & Winberg, 1994). Moreover, neonates are able to acquire an olfactory preference for this odor after repeated exposure to breastfeeding within the three-four postnatal days of life, as demonstrated by Varendi & Porter (2001), for example. In their work, a significantly higher number of full-term babies that had been fed breast milk in 6-24 occasions crawled towards the breast pad that the mothers wore during a mean period of 2.4h of the morning before the test and that smelled like the breast natural odor, in comparison to the number of babies that crawled towards a clean control pad. Breastfed neonates’ preference for an odor (i.e. chamomile) that has been previously added to their mothers’ breast and to which babies were repeatedly exposed whenever they fed maternal milk within their first 86h of life before the test session, has also been observed to be developed (Delauney-El Allam, Marlier & Schaal, 2006). Within this study, infants exposed to camomile spent significantly more time oriented towards the source of the camomile odor than to the source of control stimuli (Delauney-El Allam et al. 2006).

Olfactory preferences for odors, which do not emerge from the body, can also be developed early in life if infants’ early experiences with those odors take place. For example, Baloch & Porter (1986) induced an olfactory preference for an odor via mere exposure (mean period of 23.1h) in full-term female neonates at their first day of life (mean age = 12.0h). Specifically, females that were previously exposed, either to a cherry or a ginger odor spent significantly more time oriented toward the familiar odor than to the non-familiar odor after a temporal interval of a mean of 42.5 min between the olfactory exposure and the olfactory test. A subsequent study (Mennella & Beauchamp, 1998b) demonstrated that parental alcohol consumption duration over their lifetime as well as mother's frequency of vanilla- flavored foods consumption during lactation correlated significantly with infants' (mean of age = 7.5±0.2 months) behavior towards toys scented with ethanol odor and with vanilla odor, respectively, in that the longer was infants' exposure to alcohol via parents' long alcohol consumption, the higher was infants' rate of the mouthing response to the alcohol-scented toy, in comparison to infants' mouthing response rate to an unscented toy of identical appearance. Likewise, the more frequent was mothers' consumption of vanilla-flavored foods during lactation, the longer was the time infants spent looking at the vanilla-scented toy, in comparison to time spent by infants looking at the unscented toy of identical appearance.

The studies which have examined early acquisition of olfactory preferences by infants and which have been described up until now here have used experimental paradigms in which previous relatively long olfactory exposures to the target olfactory stimuli have been applied. However, several reports indicate that even a short exposure to odorants may induce such an early olfactory imprinting. In the study by Varendi, Porter & Winberg (2002), for example, a sample of full-term neonates delivered via elective cesarean section whose mothers suffered contractions before delivery and that were exposed during 30.5 ± 1.8 min to either the odor of cherry or to the odor of passion fruit at a mean age = 11.20 ± 2.15 min, showed a significant preference for the exposure odor, that is, they spent significantly more time oriented towards the source of this odor than to the source of the control odor, in comparison to neonates whose mothers did not suffer contractions before delivery, when neonates' preference for both odors was tested at a mean of 80 h of age after birth. Similarly, Romantshik, Porter, Tollmann & Varendi (2007) found preliminary evidence in favor of a sensitive period of olfactory learning at the perinatal time in full-term neonates. The authors exposed infants either to cherry aroma or mango aroma during 30 min at different mean postnatal ages, either 19.1 min (early exposure) or 12 h 02 min (late exposure) and then tested infants' olfactory preferences (see figure 2) at the mean age = 58 h 21 min. Only the early exposure group showed a significant preference for the familiar odor, in that this group spent more time oriented to the exposure odor, in comparison to a novel odor and an odorless stimulus. In a subsequent study (Romantshik, Tillmann & Varendi, 2008) it was observed that the olfactory preferences of 7-year-old children did not relate to the odor, to which participants had been exposed during 30 min within their first hour of life, however. The authors attribute this effect to an aversion originated from the early exposure to the, at that perinatal time unfamiliar odor that emerges in later stages of development. However, it would be interesting to replicate the study by Romantshik et al. (2008) in order to well-establish the direction of the predictive power that perinatal exposure to a specific odor may have regarding the status of olfactory learning in childhood, that is, if the perinatal exposure to that specific odor leads to a long-lasting preference for it or at the contrary the emergence of an aversion to it in later life.

Figure 2: unpublished picture that illustrates the olfactory preference test applied to one of the infants that participated in the study of Romantshik et al. (2007) as an example of the olfactory choice test devices that are currently used in research[3].

3.1.3. Effects of mere repeated exposure to foods at weaning and young childhood on food acceptance and food preference status

The third kind of experience is related to the repeated exposure to solid foods that takes place during weaning and young childhood. Specifically, "mere exposure" –without any reinforcement- to stimuli –words- was suggested by Zajonc (1968) as being a sufficient condition for liking those stimuli. When foods are taken into account, it has been empirically demonstrated that repeated mere exposure to novel foods, including vegetables, increases acceptance of these foods and other different new foods in infants during the transition from milk-based feeding to solid foods at weaning (Sullivan & Birch, 1994; Birch, Gunder & Grimm-Thomas, 1998; Gerrish & Mennella, 2001; Maier, Chabanet, Schaal, Issanchou & Leathwood, 2007; Mennella, Nicklaus, Jagolino & Yourshaw, 2008; Maier, Chabanet, Schaal, Leathwood & Issanchou, 2008).

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[3] This material has been included here with permission of Dr. H. Varendi, leader of the study of Romantshik et al. (2007). I am very grateful to her for this fact.

Furthermore, if children have been previously breast fed, the mere repeated exposure increases later acceptance of new foods significantly more than in the case of formula-based fed infants (Sullivan & Birch, 1994). Mere repeated exposure to a variety of flavors at weaning increases acceptance of new foods (puréed carrot and puréed chicken) two days later significantly more, in comparison to mere repeated exposure to just one flavor (Gerrish & Mennella, 2001) and the mere repeated exposure to a variety of new flavors, including flavors of green vegetables, at the start of weaning, in combination with previous history of breast-based feeding increases significantly acceptance of new foods, such as fish and meat, in comparison to control conditions, lasting this increase at least during two months (Maier et al. 2008). Repeated mere exposure to unfamiliar foods, including vegetables and its repetition (at least 8 exposures), tends to increase young children's liking and preference for those novel foods (Torrance, 1958; Rozin, 1979; Pliner, 1982; Birch & Marlin, 1982; Sullivan & Birch, 1990; Kern, McPhee, Fisher, Johnson & Birch, 1993; Gerrish & Mennella, 2001; Wardle, Herrera, Cooke, and Gibson, 2003a; Cooke, 2007; Gibson & Brunstrom, 2007; Williams, Paul, Pizzo & Riegel, 2008), besides infants' food acceptance. Therefore, mere repeated exposure to foods favors dissipation of neophobia, the natural response to potential unfamiliar foods characterized by a mixture of interest and fear (Rozin & Vollmecke, 1986). Neophobic reactions appear to take place between the second and the fifth years of life, in which children show resistance to try novel foods (Birch, 1979; Cashdan, 1998; Pliner, 2006; Nicklaus, 2009). An example of this phenomenon is the rejection for saline solutions relative to water that Beauchamp et al. (1986) found in 31-60 months-old children, in comparison to the high acceptance of saline solution of 4-24-months-old infants. What has been suggested and even demonstrated to be provided to children by mere repeated exposure to a novel food is the repeated experience that that food has no unpleasant postingestive consequences (Birch, McPhee, Shoba, Pirok & Steinberg, 1987; Birch & Fisher, 1998; Aldridge, Dovey & Halford, 2009), a process that Kalat & Rozin (1973) designated as “Learned Safety”, but see section of Pavlovian Conditioning (PC) for implication of other mechanisms in dissipation of neophobia. Furthermore, Cashdan (1994) has proposed a sensitive period of learning about what foods are safe to eat that coincides with young children’s (<2 years) high willingness to try new foods and older children’s (>4 years) refusing consumption of new foods, after carrying out a survey-based study on age-related changes in the degree, to which children are receptive to novel foods.

Apart from the enhancing effects that mere exposure as an independent mechanism has been here described to have on liking for and preference for foods, mere exposure can also produce no changes in food preference or decreases in food preference due SSS (Rozin & Vollmecke, 1986). Causes of such mere exposure- related differentiated effects have been attributed to the frequency of the exposure to the food. Specifically, if the exposure becomes an overexposure, then SSS will take place and otherwise, we will observe a preexposure effect (Rozin & Vollmecke, 1986). As we have earlier described, the length of the time interval between the exposure to the specific food and the moment in which the same food is eaten again may also have an impact on the kind of the effect produced by mere exposure to foods (Mennella & Beauchamp, 1999). On the other hand, repeated exposure to foods constitutes a critical condition that facilitates operation of other mechanisms that influence liking and preference (see section of PC).

The gustatory stimuli that have been used in mere-exposure studies are usually solid or semisolid, and thus it would be interesting to employ liquids in future studies as well. Nevertheless, due to the evidenced implication that both chemical systems (the gustatory and the olfactory systems) have in food- and fluid-intake regulation (Prescott, Young & O'neill, 2001b), it seems reasonable to think that the effects of mere exposure on development of food preferences described here may actually affect flavors (tastes + odors) regardless of the nature of the edible substance, either a solid or liquid and not only solid foods, in the real world.

It is also reasonable to think that the effects of repeated mere exposure associated with increases in the preference for foods also concern olfactory stimuli. Indeed, in the study by Mennella & García (2000), young children from 3.8- to 6-year old whose mothers, fathers or both parents reported to drink liked significantly more the odor associated with beer than children whose parents reported not to drink. However, among the children whose mothers, fathers or both parents reported to drink, preferences for the odor of beer were significantly related to parents' specific emotional situation in which they reported to consume alcohol, that is, children whose parents reported to drink to escape of disgusting mental or emotional states disliked significantly more the odor associated with beer than children whose caregivers reported not to drink to escape. This pattern of results was exactly replicated in a subsequent study (Forestell & Mennella, 2005) in children from 3- to 8-year-old regarding the cigarette odor. Although both of these studies did not examine effects or mere repeated exposure to odors on young children's olfactory preferences *ad hoc*, it is reasonable to think that the children who participated in both studies are repeatedly exposed to both respective experimental odors in their homes.

3.2. Acquisition of food preferences via exposure to foods in the context of Pavlovian conditioning (PC) or evaluative conditioning (EC) during childhood

An important mechanism through which children's experiences with foods and flavors induce acquisition of likes or dislikes for foods and therefore food preferences is PC or EC. Based on Rozin & Zellner (1985), we will define PC in the context of gustatory learning as hedonic changes in response or attitude to gustatory and/or olfactory stimuli resulting from their temporally and/or spatially contingent occurrence. Within the classical PC paradigm, a conditioned stimulus (CS), such as a light, is paired with a biologically relevant unconditioned stimulus (UC), such as a shock or food and whether appetitive or defensive preparatory responses to the CS change as a result of these pairings is explored (De Houwer, Thomas & Baeyens, 2001). Within an EC paradigm, in turn, a neutral stimulus is paired with an affective stimulus, either a positive (CS+), such as sugar or a negative (CS-) stimulus and changes in the valence of the neutral stimulus after these pairings are measured (De Houwer et al. 2001). Zellner, Rozin, Aron & Kulish (1983) provide us with a good example of EC. Furthermore, these authors studied EC with gustatory stimuli for the first time. In this study, participants were provided with two different kinds of flavored teas during the acquisition phase. While one of these teas was diluted in a sugar solution (CS+), the other kind of tea was diluted in plain water (CS-). The two different flavors used as the CS+ and CS- were counterbalanced across participants. During a subsequent evaluative test phase, in which both kinds of teas were presented in diluted plain water, participants showed a significant preference for the tea that was previously paired with sugar. Most authors (Rozin & Vollmecke, 1986; Baeyens, Eelen, Van den Bergh & Crombez, 1990, etc.) usually designate this process as PC, instead of EC. The most marked difference between PC and EC concerns the fact that within an EC-paradigm, acquisition of likes and aversions is explained in terms of the hedonic response system (Havermans, 2010). We want to make readers aware of the existence of those two different terms, but on our judgment, the terms PC or EC can be used interchangeable, at least when acquisition of flavor- or food preferences or aversions is taken into account. Empirical research has revealed several variants of the Pavlovian paradigm that induce children's acquisition of gustatory (food, drink or flavor) likes or preferences and aversions that will be described next. If dietary PC-based learning occurs automatically or within awareness is actually object of experimentation and great debate (Brunstrom & Fletcher, 2008), which is beyond the scope of this review, and readers are kindly invited to read comprehensive reviews on this issue, such as Brunstrom (2004; 2005).

3.2.1. Young children's conditioned preferences or aversions for gustatory stimuli based on associations between these stimuli and subsequent postingestive consequences

In a broad sense, the process involves ingestion of an edible substance under specific contingent circumstances that lead to a specific physical sensation, the postingestive consequence, it becoming the determining factor of either attraction or rejection for that edible substance. The two most well-known postingestive consequences that have been shown to condition young children's preferences and aversions for flavors, foods or drinks are the sensation of satiety –derived from the nutritive effects of ingested energy-, a positive reinforcer of those preferences (Birch, 1992; Birch, 1999) and the nausea and emesis –derived from the association of a food with a negative event that cause these reactions-, negative reinforcers of aversions (Rozin & Fallon, 1987; Birch, 1999), respectively. When the acquisition of flavor or food preferences is based on the pleasant nutritive effects of ingested energy, then the terms flavor-nutrient learning (FNL) or flavor-nutrient conditioning (FNC) are also used to designate this variant of PC (Appleton, Gentry & Sheperd, 2006; Mobini, Chambers & Yeomans, 2007; Zeinstra, Koelen, Kok & De Graaf, 2009b). Both, FNL and taste aversion learning (TAL) are two forms of conditioning because in either case the flavor or the food (CS) is paired with a physical sensation (US), either satiety, in the case of FNL, or nausea/emesis, in the case of TAL (Hermans, 2010).

3.2.1.1. The FNL mechanism as inductor of food preferences in children

It has been shown by at least two well-controlled studies that high energy-density novel flavored edible substances, that is, those which are high in carbohydrate or fat content, for example, are significantly more preferred by young children, after a series of repeated pairings of the flavored edible substance and the energy source have taken place, than the low-density flavored edible substances (Birch, McPhee, Steinberg & Sullivan, 1990) and (Johnson, McPhee & Birch, 1991). Additional data of both of these studies have led to the conclusion that young children are able to compensate their caloric intake at a meal, depending on the calories ingested previously, as it has been observed that they eat more food following consumption of the low- than the high-fat or high-carbohydrate-content stimuli, thus confirming young children’s responsiveness to the caloric density (Birch et al. 1990; Johnson et al. 1991). Authors attribute these results to the presence of positive postingestive consequences of calorie intake, thus arguing that this, in addition to learned safety, may contribute to reduction of neophobia

(Birch et al. 1990; Johnson et al. 1991). It is important to stress here the fact that young children's acquisition of gustatory preferences in the context of this conditioning paradigm is supposed to be facilitated by a repeated exposure to gustatory stimuli that, unlike the mechanism of mere exposure, is linked to the specific consequence of the positive nutritive effects of ingested energy. With the aim to determine robustly if this hypothesis could be confirmed a mere exposure condition, besides a conditioning condition was included in the study by Kern et al. 1993). Moreover, the children assigned to this last group were exposed to the conditioning intervention after an overnight fast, in order to test if preferences for flavors associated with caloric substances could be influenced by participants' hunger level, with the rationale that if preferences for flavors have been conditioned based on the positive nutritive effects of ingested energy, then the satiety/hunger state of participants should influence the expression of these preferences (Kern et al. 1993). The results yielded the conclusion that young children can learn to prefer flavors paired with the postingestive consequences of ingested energy from dietary fat, as only the preference for the high-fat-content edible substance increased after conditioning (Kern et al. 1993). Furthermore, the expression of the flavor preferences acquired during the conditioning intervention varied as a function of the young children's satiety/hunger state, as that preference for the high-energy-dense edible was most marked in the hungry than in the satiated state, while the condition based on mere exposure did not lead to a differentiated preference for flavors as a function of the fat content of the edible substance, or the satiety/hunger state (Kern et al. 1993). The studies described here, in which FNL has been evidenced to occur in young children, have employed liquid yoghurts, that is, fluids. It would be interesting to test this mechanism with novel solid foods. Young children's FNL has also been shown to occur regarding familiar foods (puddings) (Birch & Deysher, 1985; Birch & Deysher, 1986), besides novel foods, and with innately disgusting fruit juices because of the alike innately disgusting tastes, such as sourness (Capaldi & Privitera, 2008). In older children (8-10-year-old), however, FNL has not been shown to occur with the innately disgusting sour taste, but with the innately liked sweet taste (Liem & De Graaf, 2004). FNC has been suggested to be also potentially effective in increasing young children's liking for vegetables (Havermans & Jansen, 2007). Indeed, the survey-based study by Gibson & Wardle (2003), in which the correlation of young children's preference rates for different common foods, including vegetables, reported by their mothers, with the energy-density of these foods was calculated, fount that this variable predicted children's preference for vegetables. To our knowledge, there is no report testing the effects of the experimental manipulation of the energy-density of vegetables on preference for and/or vegetable consumption in young children, but in older children. Indeed, Zeinstra et al. (2009b) developed such approach in seven and half year-old children but did not find evidence for FNL as the mechanism responsible for preference for and/or vegetable consumption in those children. Nevertheless, it would be interesting to test if FNL is effective in increasing young children's preference for and/or vegetable consumption. FNL has been also shown to occur in the real world, under every day life conditions in adult humans, besides under experimentally well-controlled conditions (Appleton et al. 2006; Mobini et al. 2007). It would be interesting to test this with young and older children as well. The FNL mechanism shares with the innate preference for the sweet taste the biological function to ensure an enough intake of calories.

3.2.1.2. Children’s acquisition of taste aversions through TAL

Regarding learned taste aversions resulting from the pairings of nausea or emesis induced by a negative event with foods that have been observed in children, the supporting evidence has been extracted from pediatric cancer patients that have been subjected to druggist treatments (chemotherapy) for their recovery. While some druggist treatments result to be toxic for the gastrointestinal tract (GI) and are associated with moderate- to high levels of nausea and emesis, others do not produce such toxicity (Goodman & Gilman, 1975). In one of the few studies that have examined pediatric taste aversions associated with the kind of cancer-related treatment (Bernstein, 1978), it could be observed that patients with neoplastic disease from 2- to 16 year-old developed a taste aversion for a novel ice cream, that is, they were significantly less likely to choose this ice cream, when they consumed it before receiving a toxic chemotherapy, in comparison to patients who were being treated with a non toxic chemotherapy or any drug at all and to patients who did not consume the ice cream but were experiencing GI toxicity. One pairing of the ice cream (CS) with the GI toxicity (US) from the medical drug was enough for patients to form the taste aversion, which was expressed by them two weeks after that pairing, that is, after a relatively long time interval. A subsequent study (Bernstein, Webster & Bernstein, 1982) demonstrated that learned taste aversions can be developed by pediatric cancer patients not only regarding novel foods, but also familiar foods. Indeed, cancer patients from 2- to 18-year-old reported not to prefer longer or to dislike foods eaten after the beginning of the GI toxic chemotherapy that were frequently eaten by them during their usual diet before the treatment, in comparison to patients who were not receiving the GI-toxic treatment. Furthermore, aversions were significantly less apparent when patients were exposed to a novel ice cream before the beginning of the treatment, in comparison to control patients, indicating that the introduction to novel foods prevents or attenuates acquisition of aversions for familiar foodstuff (Bernstein et al. 1982). The authors of both of these studies attribute the anorexia and weight loss, typically developed by pediatric cancer patients (Van Eys, 1979), to these learned taste aversions, as one plausible origin. As we can see, in contrast to the learning paradigm that leads to FNL, in which normal (disease free) children were administered the source of the positive postingestive consequence of normal satiety in a direct way, that is, they were provided with foods which contained specific energy sources, such as carbohydrate or fat, the origin of the unpleasant postingestive consequence –nausea or emesis- in the TAL studies did not directly come from the food, but from a negative event that occurred after the food had been eaten. It is reasonable, however, to think that if the unpleasant postingestive consequence would have derived directly from the edible substance, TAL would have occurred as well. Therefore, every event or situation may act as a potential determining factor within the process of TAL in children, if any food or fluid is associated with potentially negative physical consequences of that event or situation. This claim may become especially relevant when childhood anxiety and childhood eating disorders, for example, are taken into account, at least at a speculative level. Moreover, there is evidence showing the co-occurrence of feeding problems, such as food refusal and eating disorders with anxiety-depressive symptoms and anxiety disorders in children (Timini, Douglas & Tsiftsopoulou, 1997; Chatoor & Ganiban, 2003; McDermott, Forbes, Harris, McCormack & Gibbon, 2006). Furthermore, children can feel nausea during stressful situations, which trigger high levels of anxiety (Pynoos, Steinberg & Piacenini, 1999). It would be interesting to examine the co-occurrence of eating disorders with anxiety in children, and to examine if the mechanism of TAL may be a contributing factor in childhood eating disorders that co-occur with anxiety or *viceversa* in future research studies. The biological significance of TAL lies on its effectiveness in preventing children from poisonings, as they learn to avoid foods with which they have had unpleasant experiences –illness- (Bernstein, 1999). Thus, the innate response of rejection for the bitter taste as well as TAL, and therefore nature and nurture, serve the same aim, that is, children's defense from dangerous edibles.

3.2.2. Young children's conditioned preferences based on flavor-flavor learning (FFL)

The FFL mechanism facilitates a conditioned increase or decrease in liking or preference for originally neutral flavors or foods that have been contingently paired with an already liked or disliked flavor or food that is not caloric in nature, this flavor or food acting as US (Baeyens et al. 1990; Birch, 1999). Occurrence of FFL in children has been examined mostly in regard to vegetable consumption. For example, Havermans & Jansen (2007) found that children of an average age of 5.2 years preferred significantly more a vegetable-flavored solution (CS), if repeated exposure to this solution with added dextrose (US) was applied, in comparison with a non-sweetened vegetable-flavored solution. This result has been replicated in older children's (8-10-year-old) in an unpublished study by Havermans & Jansen (see Havermans, 2010, p. 280). It would be interesting to examine if children's increase in preference for vegetables through FFL could be generalized to other types of foodstuff.

3.2.3. Flavor-related olfactory conditioning in children

As we have previously stated, perception of olfactory cues from edible substances are critical for experiencing its flavor (Prescott et al. 2001b; Bonfils, Avan, Faulcon & Malinvaud, 2005; Beauchamp & Mennella, 2009). Therefore, it is reasonable to wonder to which extent, does olfactory conditioning impact the development of food or flavor preferences during early life and childhood. To our best knowledge, there is no published report showing any indication regarding that impact, but it would be interesting to examine it, because as it is well known by scientific community, lack of evidence regarding a specific influence does not directly imply that this influence does not exist, but rather that either the needed methodology for its study is up until now unknown or that that influence has not yet been studied enough for other reason. In adults, in turn, a recent review (Yeomans, 2006) has identified evidence supporting the expression of the following olfactory conditioning-based phenomena: enhancements of the ratings of the sensory quality of the odors, after repeated exposure to pairings of those odors with sweet and sour tastes; increases in the liking and dislike for the odors, after repeated exposure to pairings of those odors with the sweet and the sour taste, respectively; SSS with food odors and modulations of the motivational internal state (sated vs. hungry) in the liking rates for odors, after repeated pairings of odors with sweet tastes. Given the evidence that children are not just adults in miniature, that is, their responses to stimuli differ markedly from those of adults' (Mennella et al. 2005a; Popper & Kroll, 2007; Chang, 2010), it would be interesting to examine the expression of the mentioned phenomena in children, in order to ascertain if these are marked by age-related differences or not, thus contributing to a better understanding of the development of flavor (tastes + odors) preferences.

3.2.4. Associations of foods with contextual stimuli

The context in which children eat foods can be made up of the social stimuli present during the meal, such as parents', teachers', other adults' and even peers' attitudes toward foods. Some authors consider approval or disapproval of elders, such as parents or teachers or even peers, that is, perception that such people value a food as positive or negative through the emission of either facial or verbal expressions as possible sources of enhancement of children's preferences and/or dislikes for foods, as those kinds expressions can become reinforcers of reactions or attitudes to foods in either direction (Rozin & Zellner, 1985; Rozin & Vollmecke, 1986). In this way, adults' and/or peers' facial and/or verbal expressions might be acting as US and the reactions or attitudes generated by associations of flavors or foods with those US may be conditioned (CS) by those US. On our knowledge, experimental research devoted to test this *ad hoc* is lacking. Alternatively to this PC-based explanation, adult or peer modeling may be the underlying mechanism for children's acquisition of likes or dislikes in presence of adults and peers (Highberger & Carothers, 1977; Rozin & Zellner, 1985; Romero, Epstein & Salvy, 2009). We will discuss operation of this mechanism in subsequent review sections. It is important to stand out here that presence of adults and peers during a meal can also occur through exposure to food-related commercial advertisements on the television (TV) and that this source of stimulation might also be part of a the child's social context of the meal. Therefore, acquisition of food preferences via PC and/or adult and/or peer modeling while watching TV might occur. It would be interesting to examine the influence of TV-driven adults' and/or peers' modeling on children's food and flavor preferences. Indeed, the study by

Borzekowski & Robinson (2001) revealed that young children from 2- to 6-year-old that had been exposed to a videotape interspersed with commercials were more likely to choose the edibles that appeared in commercials when they were asked to report their food preferences than children that watched the videotape without commercials. However, the report by Borzekowski & Robinson (2001) does not indicate if adults or peers appeared in the commercials, participants saw, so we do not know if this variable could have affected participants' food preferences or not.

The physical environment, such as that of the school canteen or that of surrounding food stores becomes part of the context in which children eat foods as well. In this sense, a recent review work (Stroeble & De Castro, 2004) has identified ambient temperature, lighting, time of the day and ambient sounds as factors that impact children's eating behaviors and it would be interesting to examine how these factors may contribute to shape young and older children's food and flavor preferences. Familiarity with the physical environment has been demonstrated to be a determining factor of children's food preferences, as it has been shown that they tend to prefer foods that are typically eaten in their familiar environments, that is, their homes, their schools and food stores visited by them (Birch et al. 1990; Story, Neumark-Sztainer & French, 2002; Van der Horst, Timperio, Crawford, Roberts, Brug & Oenema, 2008; Aldridge et al. 2009), and novel contexts tend to decrease young children's intake of even familiar foods (Birch et al. 1990).

3.3. Children’s exposure to flavors and foods in the specific context of parental influence

Research on pediatric nutrition has revealed the great impact that parents exert on the formation of their own children’s patterns of food intake, and food preferences. This impact derives from the fact that parents are the primary providers of foods for children, above all when children are young (Scaglioni, Salvioni & Galimberti, 2008). As parents decide which kind of foods shall be purchased and served in the household, parents modulate in this way the kinds of foods that are available for children, and to which children are exposed (Wardle, 1995). Several are the mechanisms that have been identified and through which parents develop that influence:

3.3.1. Parents’ transmission of their own food consumption patterns to their children via direct parental adult modeling

Hood, Moore, Sundarajan-Ramamurti, Singer, Cupples & Ellison (2000) observed that children from 3- to 5-year-old whose parents reported a high degree of disinhibition, that is, lability in eating behaviors and weight, coupled with dietary restrain, that is, conscious control of eating, showed a high body fat rate, suggesting that parents’ high disinhibited eating behavior coupled with a high dietary restrain promote an excess of body fat in their children through operation of parental adult modeling. Adult modeling has been shown to impact young children’s acceptance of novel foods. Indeed, Addessi, Galloway, Visalberghi & Birch (2005) found higher acceptance of novel foods in children from 2- to 5-year-old, if they saw adult models eating the same food, relative to a different food and to the presence of adults that were not eating at all.

Influence of parental adult modeling has also been shown to operate in older children. Indeed, Brown & Ogden (2004) observed that children from 9- to 13-year-old and their parents shared identical patterns of snack food consumption, which supports the theory of parental adult modeling.

A version of parental adult modeling is peer modeling, and its impact on young and older children's food intake has been shown to be similar to parental adult modeling (Birch, 1980; Romero et al. 2009), with the difference that instead of parents as being the figure driving that impact, children of similar age (peers) are who do it. Changes in food consumption rates by means of parental adult or peers implies that those changes are learned watching others eating the same food (Brown & Ogden, 2004), and that a learning by watching takes place. However, parents are authority figures and thus they may force some when a child to consume any kind of food (Batsell, Brown, Ansfield & Paschall, 2002), while peers are alike regarding authority. Therefore, it would be interesting to examine if parental adult- and peer modeling exert the same food consumption-related increasing effect in the same extent.

Parental adult modeling affects children's acceptance of new foods and food intake rates. If development of food preferences in children may be associated with parental adult modeling, has to be further investigated, however.

3.3.2. Parents' transmission of their own attitudes to foods and to eating behaviors to their children via direct parental adult modeling

Several authors have found correlations between mothers' ideology regarding food consumption and body weight and satisfaction and their daughters' eating-behavior-related health status and patterns of eating behavior. For example, Hall &

Brown (1983) found a correlation between mothers' degree of body dissatisfaction and incidence of anorexia in their daughters of mean age of 16.6 yeas, in that mothers of anorexia patients showed greater body dissatisfaction than mothers of girls who were not diagnosed from anorexia. Hill, Weaver & Blundell (1990), on their part, found correspondence of school-aged girls' degree of dietary restraint and that of their mothers. A recent publication (MacFarlane, Crawford & Worslet, 2010) indicates that adolescents from 12- to 15-year-old whose parents reported to be concerned with adolescent weight reported lower intake of energy-dense foods than adolescents of unconcerned parents. These studies have been developed, either with middle-aged female children or adolescents. It would be interesting to examine the possible transmission of mothers' worries about body satisfaction and dietary restraint to young female children as well, in order to ascertain if these attitudes to foods and to eating behaviors might be transmitted to female children in early childhood and if this early attitudinal transmission might have an impact on later eating behaviors. It seems logical to think of an affirmative answer, as it has been shown that weight concern, body dissatisfaction and high levels of dietary restraint among 5-year-old female children at risk for overweight are accompanied by greater weight gain from 5 to 9 (Shunk & Birch, 2004) and imprinting of expectancies about alcohol consumption that may impact alcohol consumption during adolescence have been argued to be developed in early childhood, specifically at the age of 6 (Miller, Smith & Goldman, 1990), but the long-term effects of impact of parents' concerns about weight or any food-related factor on children's food preference status have to be further investigated. In this regard, it is interesting to report that Francis, Hofer & Birch (2001) observed that mothers that were worried with their own weight and eating reported a higher degree of restricting daughters' intake in young female children (age = 5 years), but the long-term effects of this maternal influence on eating behavior are again to be elucidated. On the other hand, it would be interesting to test the hypothesis of an early imprinting of attitudes to foods and eating behaviors in young male children as well, in order to ascertain if male children respond in a similar way to maternal food-related attitudinal influence as females have been shown to do.

Women are specially pressured to keep a thin figure (Blowers, Loxton, Grady-Flesser, Ochipinti & Dawe, 2003) and men to show a strong appearance (Franzoi & Shields, 1984) and mothers have been argued to spend significantly more time with their children during familiar mealtimes, in comparison to fathers (Scaglioni et al. 2008), so that it seems reasonable to think that the style of parental attitudinal influence on children's food-related attitudes as well as children's response to that food-related parental attitudinal influence might be modulated by gender differences, although further research is needed for confirming or disregarding this.

On the other hand, as we have already mentioned in the previous review section, parents' own hedonic values of foods and/or eating behaviors might be also transmitted to children through verbal and/or non-verbal (facial) expressions, and therefore direct parental adult modeling (Highberger & Carothers, 1977; Rozin & Zellner, 1985), although further research is needed.

3.3.3. Parental specific child-feeding strategies

Certain parental strategies commonly used in daily life to regulate children's eating behavior have also been identified as exerting an important influence on children's eating styles, food choices and food preferences (Birch & Davison, 2001; Scaglioni et al. 2008). It is not surprising to state that parents try to regulate/control children's eating habits and patterns of food intake, in order to improve children's healthy patterns of eating behavior and to reduce harmful ones. An example of healthy patterns of food intake is one such that includes high rates of vegetable consumption, while a high intake of snack foods illustrates an unhealthy pattern of eating behavior because of snack foods' high sugar- and fat content (Warren et al. 2008). Parental influence on children's eating behavior can be positive or negative, depending on the concrete used strategy. For example, it has been shown that some strategies like making pressure to eat, restricting certain foods and employing instrumental feeding, that is, rewarding food intake with any prize or promoting children's pro-social behaviors with foods as prizes, even applied with best of intentions, do not reach the expected positive results of an intake increase, whenever an increase in the children's intake of a specific food (i.e. vegetables) is wanted by parents, but rather a decrease (Birch, Marlin & Rotter, 1984; Fischer & Birch, 1999; Reimer, Smith, Reicks, Henry, Thomas & Atwell, 2003; Brown & Odgen, 2004; Galloway, Fiorito, Francis & Birch, 2006; Zeinstra & De Graaf, 2008). Indeed, pressuring young children to eat vegetables results in a decrease in their preference for them (Fisher, Mitchell, Smiciklas-Wright & Birch, 2002; Wardle, Carnell & Cooke, 2005). Restricting children's access to foods, such as snack foods, in turn, increase children's wanting to eat them and their intake (Fisher & Birch, 1999), while "parental allowance", that is, parents permitting children to eat as much as they want, does not increase that wanting to eat those foods (Wind et al. 2006) nor vegetables (Brug et al. 2008).

Other kind of child-feeding strategies, like facilitation to eat a food (i.e. vegetables) via physical availability and accessibility to them, at the contrary, have been shown to correlate with a higher intake of that food in old children (Brug, Tak, Te Velde, Bere & De Bourdeaudhuij, 2008). Parents' provision with mere repeated exposure to vegetables has been shown to increase liking for previously disliked vegetables in young children (2-8-year-old) (Wardle, Cooke, Gibson, Sapochnik, Sheisham & Lawson, 2003b). The parental strategy based on overt control which can be detected by the child, as it implies to communicate clearly to the child how much the child should eat as well as the covert control strategy which cannot be detected by the child and which implies, parents not buying the foods that cannot be eaten by their children, for example, have been related to eating more fruits and vegetables in children from 4- to 7-year old (Brown, Ogden, Vögele & Gibson, 2008). Thus, parents' appropriate use of feeding strategies with their children may facilitate the establishment of children's healthy intake habits (Moore, Tapper & Murphy, 2007.

All these parent-triggered mechanisms may determine children's exposure to foods, and therefore, increases and/or decreases in preferences for foods and corresponding flavors might be modulated by them. We think that the best way in which parents can exert an effective influence on their children's eating behavior is selecting the child-feeding strategy that best adapts to the kind of food to be controlled, but as a first step parents need to know the great spectrum of different child-feeding strategies. Given the evidence regarding effectiveness of some parental strategies in regulating their children's food intake as well as the evidence regarding children's ability to self regulate food intake (Birch & Deysher, 1986), an equilibrium between external parental control of children's food intake and children's self regulation of food intake is here specially recommended.

3.4. Children’s exposure to flavors and foods at school

In Spain, young children from birth up until the age of 6 years have the possibility to visit schools specially designed for their early age (kindergarten[4]). This school period is called child education and is voluntary in nature (Spanish Department of Education, 2010a). Existence of Kindergarten in other countries, such as those forming the United States of America (Rimm-Kaufman & Pianta, 2000) is well known. Children from 6- to 12-year-old assist to the mandatory primary education (Spanish Department of Education, 2010b). It has been estimated that 20% of total children provided with schooling in Spain, regardless of the education grade and the school type, either public or private, receive their daily main mealtime, in Spain the lunch, in the school during 8 to 9 months, which is the yearly duration of a Spanish school period (Aranceta Bartrina, Pérez Rodrigo, Serra Majem & Delgado Rubio, 2004; Aranceta Bartrina et al. 2008). Therefore, Spanish children are subjected to food and flavor exposure in the school during a long period of time. In this sense, it is to highlight the fact that a shortage of vegetables in the Spanish school menus has been identified (Aranceta Bartrina et al. 2004; Aranceta Bartrina et al. 2008). Several other countries, such as United Kingdom, Ireland, Argentina, Sweden, United States’ countries, boast dining halls for children in the schools (Macairt & Perros, 1982; Briggs et al. 2003; Engström & Carlsson-Kanyama, 2004; Sosa & Hough, 2006; Moore, Murphy, Tapper & Moore, 2010). Therefore, a great proportion of children provided with schooling are yearly exposed to foods and flavors during the school period worldwide. Decisions

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[4] Kindergarten (in singular and plural) derives from the German language and signifies nursery school.

regarding foods and flavors that are present in the school meals are made by corresponding authorities, and, as in the case of the familiar context, are taken outside children's control. In this regard, we consider important to highlight the fact that, despite the importance of learning healthy patterns of food (vegetables) intake during young childhood, less attention has been focussed on this kind of learning within the scholar curricula regulated by applicable law for young children (age range 0-6 years) in the kindergarten, in comparison, for instance, to mathematical learning –at least during a first moment in Spain- (see Spain, LOE, 2006). Scholar curricula regulated by Spanish applicable law affect, among other aspects, the contents of teaching, with which children are provided (Spain, LOE, 2006). A subsequent applicable law (Spain, OECI, 2007) also dedicated to design scholar curricula for young children in the kindergarten repeatedly stresses the importance that young children acquire healthy eating habits but the specific food composition of these healthy eating habits is not specified and we think that this constitutes a legislative gap. The same legislative gap is found in the case of the applicable law for teaching contents for young children in the German Federal State of Berlin, for example (Dreier et al. 2004). Therefore, we can expect similar legal situations regarding emphasis of the importance of learning healthy patterns of food (vegetables) intake within scholar curricula in other European countries. The key question, to which the present review section is devoted, is: does this school-related exposure to gustatory stimuli shape children's, especially, young children's food preferences?

Experimental research on pediatric nutrition has revealed that exposure to the food provided by the schools' dining halls to children may impact children's eating behaviors in general and food preferences, in particular, in two ways. On the one hand, the provision to children with foods during the schools' routine mealtimes, that is, without implementation of especial intervention programs aimed to increase children's preference for and/or consumption of a target food, has been related, at least by a study, to children's increases in their preferences for those foods. Indeed, Baxter & Thompson (2002) found a significant increase in the preference for fruits and vegetables in fourth-grade children, that is, from 8- to 10-year-old, after authors had followed a systematic observation of the schools' mealtimes, which were rich in fruits and vegetables, during three consecutive years. Consumption of fruit and vegetables increased as well, and this increase was linked to the increased preference for these edibles (Baxter & Thompson, 2002). Long-term effects of this exposure on children's preference for vegetables are should be examined, however. It would be interesting to develop this study in young children, in order to ascertain if Baxter's and Thompson's results could be replicated in the young child population. Another study (Sepp, Abrahamsson, Junberger & Risvik, 2002) found that children of mean age = 4 years ate vegetables at least once a day during weekdays in the school, while at home the same children ate vegetables less than once a day. Data regarding the relationship between this pattern of vegetable consumption and children's preference for vegetable were not extracted, however, and it would be interesting to examine this relationship in future studies. Several other studies have studied the food composition of the meals with which children are provided in their schools (Lytle et al. 1996; Condon, Chepinsek & Fox, 2009), but again, its association with current children's food preferences and later status of food preferences has not been the study object of these studies and future research should take that association into account.

On the other hand, there are several reports showing the increasing effects that certain school-based intervention programs, taking advantage of the schools' dining halls or canteens and classrooms, and which have been specially designed *ad hoc* for increasing children’s food preference and or intake, among other variables, have reached on children’s food preference. Specifically, our review of scientific literature on this issue has identified nine published studies describing those effects. The majority of these school-based interventions have focused on fruits, but above all on vegetables as the target food stimuli, which is quite understandable, as it has been shown that vegetable consumption during childhood counteracts childhood overweight, one of the most worrying public health problems throughout the world (WHO, 2009) as well as health problems in the adulthood, such as overweight (Aranceta et al. 2007), hypertension, heart disease and cancer (Van Duyn & Pivonka, 2000; Maynard, Gunnell, Emmett, Frankel & Davey, 2003; Mikkilä et al. 2004), and that children’s, especially young children’s vegetable intake rate remains lower than national recommendations (Lorson et al. 2009; Yngve et al. 2005). Furthermore, six of the nine school-based programs identified here are concentrated on children from 6-year-old and older children, and just three have concentrated on young children, which is surprising, given the evidence that children’s patterns of food intake are linked to their food preferences (Baxter, Thompson & Davis, 2000; Jaramillo, Yang, Hughes, Fisher, Morales & Nicklas, 2006) and that young children’s food preferences track into later life, at least to adolescence and young adulthood (Nicklaus et al. 2004; Unusan, 2006; Kimura et al. 2010). These school-based interventions can be broadly classified into three different types according to its focus:

3.4.1. School-based interventions focused on nutrition knowledge

The best descriptor words for designating these school-based intervention programs are nutrition education programs and are mainly based on the provision to children with knowledge regarding healthy nutritional habits in the classrooms, and on organization of cooking workshops, where children can see and even exercise healthy culinary skills, these activities leading to learning about the importance of living of a daily healthy diet. Nutrition education programs are usually combined with other activities that are not strictly aimed to provide children with nutrition information. For example, in a nice study developed by Morris, Neustadter & Zidenberg-Cherr (2001) during ± 8 months, and aimed to increase young children's vegetable consumption, the integration of healthy nutrition-related lessons in the classroom and vegetable gardening activities within the school-based intervention yielded an increase in the young children's willingness to taste green vegetables, such as spinach and broccoli and others, such as carrots, although children's preference for these vegetables did not change. However, willingness to taste vegetables is a *sine qua non* condition in enhancing young children's preference for vegetables because young children's tasting-related experience is a previous essential requirement for changing food preferences (Birch et al. 1987). Furthermore, the resulted lack of increase in young children's preference for vegetables could have been due to the lack of experience with tasting the target vegetables within the intervention program. Thus, it would be interesting to include a vegetable-related tasting experience in combination with gardening activities within the nutrition education program in future studies, in order to examine possible changes in young children's preference for vegetables. Morris's et al's study was subsequently carried out again with older children, that is, from 9- to 10-year-old (Morris & Zidenberg-Cherr, 2002) during a year and adding a second experimental condition was added. Within this study, the combination of healthy nutrition-related lessons in the classroom and vegetable gardening activities (NG) as well as the nutrition-related lessons alone (N) improved children's preferences for carrots and broccoli in a significantly greater extent than did the control condition (C), which was based on no intervention. Furthermore, NG produced significant greater increase in children's preferences for peas and zucchini, in comparison to N and C. In addition, NG retained its difference for broccoli, peas and zucchini and N for carrots 6 months later. The intervention developed by Morris & Zidenberg-Cherr (2002) has been subsequently carried out again (Parmer, Salisbury-Glennon, Shannon & Struempler, 2009) with the same experimental and control conditions in children from 4- to 6-year-old and no changes in the preference for fruits and vegetables among groups were observed, after a 9-months-long school-based intervention focused on a nutrition education program. This could be attributed again to the lack of a fruit- and vegetable-related tasting experience. However, as in the study by Morris et al. (2001), the treatment groups showed a greater willingness to taste fruits and vegetables. A subsequent study developed in older children (age range = 6-12) that integrated fruit and vegetable taste tests, preparation of fruits and vegetables and gardening activities within the nutrition education program (Heim, Stang & Ireland, 2009) increased children's preferences for vegetables, while no changes in the preference for fruits was observed. However, another nutrition education program that involved the provision of knowledge regarding the physiology of digestion and the importance of consuming healthy foods by means of classroom lessons, videos, books and games during 12 weeks to children from 8- to 10-year-old did not increase participants' preference for fruits and vegetables (Tuuri et al. 2009). The last nutrition education program that we describe here (Reverdy, Schlich, Köster, Ginon & Lange, 2010) was mainly based on a series of schoolroom lessons regarding the five senses that included provision with senses-related vocabulary, gustatory and olfactory tasting, information regarding local gastronomic specialties and a cooking workshop during 4-6 months, and was applied to children from 8- to 10-year old. Reverdy et al. (2010) found that children exposed to this program increased their preference for more arousing versions of two of three food stimuli –potatoes and apple compotes-, and that this increase was observable only 10 months later but not just after the intervention.

3.4.2. School-based interventions focused on the schools' meals

The basis of this type of programs relies on modifications to the food composition of the schools' meals, such as additions of fruits and/or vegetables or to the conditions under which children have access to the foods in the school. Common manipulation of these independent variables and measurement of changes in children's preferences for those fruits and/or vegetables as the dependent variable are then carried out. In the study developed by Hendy, Williams & Camise (2005), children of mean age = 8.0 years were exposed to fruits and vegetables during 18 consecutive meals with token reinforcement, food choice and conditions that included peer modeling. A significant greater improvement in the preference for fruits and vegetables was observed in the children subjected to this multi-component school-based intervention, in comparison to children that were not exposed to the intervention two weeks after the end of the intervention but no differences between both groups were found seven months later. The solely provision with choice, that is, provision with the opportunity to select the item to eat among several options, in the context of school mealtimes to young children has also been shown to be effective in increasing Spanish young children's vegetable consumption in a recent unpublished study developed in 2009 in children from 2- to 6-year-old (Rohlfs et al. 2009), but not effective in increasing Duch young children's vegetable consumption (Zeinstra, Renes, Koelen, Kok & De Graaf, 2010a). Cultural and methodological differences between both of these two last studies have probably led to such a different result regarding the impact of providing choice to young children on their vegetable consumption. Regarding the effect of choice, it is to highlight that if children are given the possibility to choose between healthy foods (i.e. vegetables) and unhealthy foods (snacks), they use to choose these last options (Warren et al. 2008), so that the provision with choice to children must be among healthy options.

3.4.3. Mixed school-based intervention programs

These programs combine the two former mentioned types of intervention programs. The study by Wang et al. (2010) indicates that from 8- to 10-year-old children showed a differentiated level of preference for fruits and green vegetables, depending on the level of exposure to a multi-component program, in that the most exposed children (two-year-exposure group) showed a significant greater increase in their preference for fruit and green vegetables, in comparison to the less exposed children (one-year-exposure group). The multi-component program included changes in the foods provided to children in the school meals, gardening activities, cooking classes and provision with nutrition knowledge.

3.5. Evidence supporting tracking of preferences developed during young childhood into later life phases

Several authors have found that the food preferences developed during young childhood predict food preferences in later childhood and even young adulthood, whatever the experience-related mechanism/s that has been operating during that early stage of development. For example, Skinner, Carruth, Bounds & Ziegler (2002) found that food preferences of 8-year-old children were related to their food preferences at ages 2 to 4 years. Likewise, Nicklaus et al. (2004) found the same relationship between the status of food preferences of young children aged between 2 and 3 years from 1982 to 1999 and the status of food preferences of the same participants several years later, that is, at the ages between 12 and 22 years from 2001 to 2002. Another study (Skinner, Carruth, Bounds, Ziegler & Reidy, 2002) concluded that food-related experiences by children in the first 2 years of life predicted their diet variety at ages 6, 7 and 8 years. Young children's food-related behavior has also been reported to track into young adulthood, besides food preferences, in that the degree of food variety seeking of 22-year-old adults has been found to be related to the degree of food variety seeking of those adults at the ages of 2 and 3 years (Nicklaus et al. 2005a). That young childhood constitutes a sensitive period of food preference development requires further research, however. We will come back to this issue in the review section designated as conclusions and future research.

4. Conclusions and future research

The literature dealing with origin of infants', young children's and older children's gustatory preferences, that is flavor and food or drink preferences, indicates that that origin is innate and experience-related and that both factors, nature and nurture impact children's food choices and food intake. Indeed, although human beings are blessed with a genetic program that determines which gustatory stimuli to accept (sweet or salty cues) and which to reject (sour and bitter cues) (Kajiura et al. 1992; Mennella et al. 2005a; Mennella & Beauchamp, 2005), the fact is that prenatal and postnatal contact with different flavors derived from foods and/or drinks shape the degree, to which those innate preferences are expressed. The present review was aimed to summarize the accumulating evidence that explains how certain experience-related mechanisms operate leading to modifications in the expression of flavor, food and drink preferences that may be observable in later life phases, once contact with gustatory and olfactory cues (flavors) across development takes place, and to identify sensitive periods of development of flavor and/or food preferences. Additionally, we wanted to identify unclarified issues that, in the context of the indicated aims, would require future research. Therefore, in the present review section we will firstly enumerate the experience-related mechanisms through which children's preferences are shaped. Then, we deal with the issue of identification of sensitive periods, and finally, we will indicate the issues that, based on this review, we have identified as being issues that need further research.

The first of such experience-related mechanisms operated prenatally and refers to stimulation of fetal taste and olfactory receptors by its contact with tastes and odors that are spread through the AF because of the mother's diet of which volatile food particles reach the placenta (Mennella & Beauchamp, 1997a; Mizumo & Ueda, 2004; Blossfed, 2006). That this experience with chemical stimuli in utero induces changes in the preference level for those chemical stimuli, so that these changes are observable in later life phases, has been demonstrated regarding carrot juice (Mennella et al. 2001), sodium (Crystal & Bernstein, 1995), other edibles (Mennella et al. 2005b), and with certain odors, such as the odor of the mother's AF (Varendi et al. 1998; Marlier et al. 1998; Schaal & Marlier, 1998; Mizumo & Ueda, 2004), anise odor (Schaal et al. 2000) and ethanol odor (Faas et al. 2000). In all these cases, an increased preference for the flavors and aromas, including that of the AF to which fetuses had been exposed in utero was found, so that flavor imprinting may take place in very early life. That the prenatal phase might constitute a sensitive period of development of flavor preference, has to be further investigated. Furthermore, for considering the prenatal phase as such a sensitive period, longevity of the flavor preferences acquired prenatally has to be demonstrated in older subjects, besides infants and young adults. We will come back to this issue later again within this section.

The second experience-related mechanism concerns neonatal stimulation of taste and olfactory receptors by its contact with tastes and odors (flavors) that are dissolved in the milk, either breast milk or formula milk, with which infants are fed during the lactation period. Indeed, flavors derived from the mother's diet are transmitted to infants via breastfeeding, which has been demonstrated regarding the flavors of garlic (Mennella & Beauchamp, 1991a), alcohol (Mennella & Beauchamp, 1991b) and vanilla (Mennella & Beauchamp, 1996). That prior exposure to mother's milk-diluted flavors during the lactation period generates a flavor imprinting, thus observing an increased preference for those flavors in later life (i.e. at weaning) has been observed regarding the mother's milk (Mennella & Beauchamp, 1997b), carrot juice (Mennella et al. 2001), peaches (Forestell & Mennella, 2007) and a series of other foods (Mennella et al. 2005b). Flavor imprinting in infants via formula milk-based feeding and its consequent flavor preference-related increasing effects, which are observable at weaning have been likewise evidenced regarding the bitter and sour tastes (Mennella et al. 2009) and certain commercial formula milks, such as Nutramigen, Alimentum and Enfamil (Mennella et al. 2004; Mennella & Beauchamp, 2005). That that formula milk-driven flavor imprinting may be observable in childhood and beyond has been demonstrated by Haller et al. (1999), Mennella & Beauchamp (2002) and Liem & Mennella (2002). Both fed regimen patterns, breastfeeding and formula milk-based feeding have been empirically demonstrated to differ considerably from each other in the strength with which both facilitate infants' acceptance of new solid foods at weaning, however, in that breast feeding has been shown to be significantly more effective than formula milk-based feeding (Sullivan & Birch, 1994). It has also been shown that olfactory imprinting and its consequent olfactory preference-related increasing effects occur through stimulation of olfactory receptors during the lactation period regarding body odors, such as the odor of the mother's breast (Varendi & Porter, 2001; Delauney-El Allam et al. 2006) as well as other non-body-related odors (Baloch & Porter, 1986; Mennella & Beauchamp, 1998b; Varendi et al. 2002; Romantshik et al. 2007) has been also shown to occur.

The third experience-related mechanism operates when infants are introduced to solid foods and extends to young childhood when they are faced with new foods, and concerns mere repeated exposure. That mere repeated exposure to foods leads to an increase in the preference for those foods has been observed with several edibles, including vegetables, in young children (Torrance, 1958; Rozin, 1979; Pliner, 1982; Birch & Marlin, 1982; Sullivan & Birch, 1990; Kern et al. 1993; Gerrish & Mennella, 2001; Wardle et al. 2003a; Cooke, 2007; Gibson & Brunstrom, 2007; Williams et al. 2008). On the other hand, mere repeated exposure to foods leads to an increase in infants' acceptance of new foods at weaning (Sullivan & Birch, 1994; Birch et al. 1998; Gerrish & Mennella, 2001; Maier et al. 2007; Mennella et al. 2008; Maier et al. 2008).

Apart from mere repeated exposure, other experience-related and classical conditioning-based mechanisms, such as FNL have been shown to increase young children's preferences for novel foods (Birch et al. 1990; John et al. 199; Kern et al. 1993) and familiar foods (Birch & Deysher, 1985; Birch & Deysher, 1986). FNL has also been shown to increase preference for innately disgusting tastes, such as sourness in young children (Capaldi & Privitera, 2008) but not in older children (aged 8-10 years) (Liem & De Graaf, 2004). By means of TAL rejection for foods can be established in young and older children (Bernstein, 1978; Bernstein et al. 1982). FFL increases young and older children's preferences for foods (vegetables) (Havermans & Jansen, 2007; Harvemans, 2010, p.280). Children's conditioned dislikes or preferences for flavors or foods can be formed if they learn to associate those flavors or foods with social- and physical stimuli (Rozin& Zellener, 1985; Rozin & Vollmecke, 1986; Birch et al. 1990; Story et al. 2002; Stroeble & De Castro, 2004; Van der Horst et al. 2008; Aldridge et al. 2009).

Certain parental child-feeding strategies, such as mere repeated exposure favor an increase in the preference for foods (i.e. vegetables) (Wardle et al. 2003b), while others, such as making pressure to eat a food (i.e. vegetables), favor a decrease in the preference for that food (Fisher et al. 2002).

Exposure to foods during routine mealtimes in the school has been shown to increase middle-aged children's preference for fruits and vegetables (Baxter & Thompson, 2002), and it has to be examined if this result finds replication in young children. Several school-based intervention programs of the kind of nutrition education programs aimed *ad hoc* to increase children's preference for and consumption of fruits and vegetables have been shown to increase preference for these foods in middle-aged children (Morris & Zidenberg-Cherr, 2002; Hendy et al. 2005; Heim et al. 2009; Reverdy et al. 2010) but not in young children (Morris et al. 2001; Parmer et al. 2009), probably because the nutrition education programs that have been applied to young children have not included food tasting sessions, and Birch et al. (1987) already warned that young children have to taste the flavor or the food for inducing a change in their preference for that flavor or food. On the other hand, the recent study by Lumeng & Cardinal (2007) revealed that the provision with affectively positive information about a flavor while tasting it to children younger than 4.5 years does not change their hedonic ratings regarding their liking for that flavor but in children from 4.5- to 6-year-old, in agreement with at least one prior Piagetian studies indicating that young children are not yet cognitively developed enough to understand some kinds of information (Bahn, 1989). This leads to the question of if this implies that changing very young children's preference for a flavor or food requires acting directly on the taste –through repeated exposure, for example- of that flavor or food instead of acting on young children's knowledge of that flavor or food. Future research will ascertain the proper answer. School-based intervention programs focused on the school's meals have been shown to increase preference for fruits and vegetables in middle-aged children (Hendy et al. 2005) and vegetable intake in young children (Rohlfs Domínguez et al. 2009). Positive long-term effects of these school-based interventions have been observed to occur in middle-aged children (Morris & Zidenberg-Cherr, 2002; Reverdy et al. 2010), while these long-term effects have to be examined in young children. If these positive long-term effects derived from school-based interventions found in middle-aged children may remain invariable during adulthood has to be examined.

An especial issue, we want to discus here concerns existence of sensitive periods of development of flavor (tastes + odors), food and/or drink preferences. Although there is a vast body of evidence indicating existence of such sensitive periods, such as the reported by the numerous studies published by Mennella and collaborators regarding long-lasting effects of early feeding on subsequent food consumption and preference, it is necessary to demonstrate the longevity of the food and/or flavor preferences formed in early life (Aldridge et al. 2009) and therefore, their invariability in adult life

(Cashdan, 1994) for considering a certain time frame of life in a robust way as a sensitive period. In this sense, we know that young adulthood is a life phase in which individuals are still developing, as changes in the anatomical level of human high-order brain regions have been observed to occur (Sowell, Peterson, Thompson, Welcome, Henkenius, & Toga, 2003; Lebel, Walker, Leemans & Beaulieu, 2008), and these changes might affect the sensory systems, such as the taste and olfactory systems and might affect behavior, such as individuals' reports of flavor preferences, as it has been shown that high-order brain and cognitive functions modulate taste and olfactory processing (O'Doherty, Deichmann, Critchely & Dolan, 2002; De Araujo, Rolls, Velazco, Margot & Hobden, 2005). Furthermore, data derived from animal research in the visual system (Sale et al. 2007) have clearly shown that certain changes that were considered that could only occur during development, may also occur during young adulthood, if the surrounding environment is of such features that induce such changes. Specifically, amblyopia, an untreatable disorder of the visual system in adults, that affects visual acuity, was found to be eliminated in young adult rats (age = 70 postnatal days), when these rats were immersed in an environment of high sensory and motor stimulation, remaining visual acuity unaltered two weeks after the intervention (Sale et al. 2007). If the human taste and/or the olfactory systems may also display changes during young adulthood that are typically related to development, should be investigated. Thus, based on these evidences, we propose here that the longevity and invariability of the food preferences acquired in early life should be tested not only when subjects get young adulthood (age range = 18-30), but in older adulthood, that is, at least from the age of 35-year onwards. Longitudinal studies on development of food and flavor preferences might help to this purpose, although we are aware of the fact that the long duration and high costs of such studies may make its carry out difficult. To our knowledge, there is only one experimental study that has examined early experience with tastes in individuals aged within the age range, we recommend here. Indeed, the study by Haller et al. (1999) found a significant effect of early feeding history on preference for ketchup in a subject sample aged from 12- to 59-year-old, in that individuals' status of preference for a specific vanilla-flavored-flavored ketchup sauce was linked to the kind of feeding regimen, to which individuals had been exposed during the lactation period, that is, vanilla-flavored formula milk-based feeding, although that effect could have been due to a different taste component of this formula milk, rather than vanilla. Therefore, we can here conclude here that the lactation period may be a high-probability candidate to be a sensitive period of development of flavor preferences in humans (Haller et al. 1999). Furthermore, replication of the results obtained by Haller et al. (1999) would be very helpful, in order to consider the lactation period as a sensitive period of development of flavor preferences in humans robustly.

As we can see, the mentioned experience-related mechanisms may ensure cultural transmission of gastronomic preferences from one generation into the other, as the foods and flavors to which children are exposed, are mostly decided by adults of the preceding generation. Children, on their part, assimilate this gastronomic culture, similarly to other cultural aspects, and when children mature and become adults, they may transmit their learned food preferences and nutritional habits to their own children, so that culinary habits and preferences may remain stable along centuries of exercise of gastronomic customs. In this regard, it is to highlight that the decisions that adults make about the foods to which children have to be exposed at home and in the schools, especially during sensitive periods of development of flavor and food preferences, have to be made carefully.

Which issues require, on our judgment, being examined in future research work?

As prior exposure to flavor through either breastfeeding or formula milk-based feeding during the lactation period has been associated with increases in flavor and food acceptance, consumption and preference as preexposure effects (Mennella & Beauchamp, 1997b; Mennella et al. 2001; Mennella et al. 2004; Mennella & Beauchamp, 2005; Forestell & Mennella, 2007; Menella et al. 2009) but also with SSS at weaning (Mennella & Beauchamp, 1999; Mennella et al. 2006), the impact of the length of the time interval between the milk-related exposure and the test moment on determining emergence of both effects needs of further research for it being elucidated. This purpose would require manipulating the length of that time interval (long vs. short) within the same experimental design.

Young children's preferences for foods and drinks have been shown to be related to the kind of formula milk, those children had been fed during infancy (Mennella & Beauchamp, 2002; Liem & Mennella, 2002). Older subjects' flavor preferences have also been related to the kind of formula milk with which they have had experience in infancy (Haller et al. 1999). In the case of breastfeeding, in turn, its impact on later food consumption has been shown to be exerted only in infants at weaning (Sullivan & Birch, 1994; Mennella et al. 2005b), and therefore it would be interesting to examine if breastfeeding history impacts later status of food and/or flavor preferences beyond infancy.

Repeated mere exposure has been shown to increase infants'acceptance of new semi-solid foods (Birch et al. 1998; Gerrish & Mennella, 2001; Maier et al. 2008) and young children's preference for novel and familiar solid foods (Wardle et al. 2003; Cooke, 2007; Williams et al. 2008) and it would be interesting to test the effectiveness of repeated mere exposure in increasing infants' and young children's acceptance of and preference for fluids as well. FNL, in turn, has been shown to increase young and older children's preferences for fluids, such as liquid yoghurts and fruit juices (Lim & De Graaf, 2004; Capaldi & Privitera, 2008) and semi-solid foods, such as puddings (Birch & Deysher, 1985; Birch & Deysher, 1986). Thus, it would be interesting to test the same effectiveness of FNL with solid foods in young and older children as well as its effectiveness with vegetables in young children. Examination of FNL in the real world with young and older children is required as well.

Given the evidence for co-occurrence of feeding disorders and anxiety disorders in children (Timini et al. 1997; Chatoor & Ganiban, 2003; McDermott et al. 2006), it would be interesting to examine if TAL might be contributing to childhood eating disorders.

Young and older children's preference for vegetables have been shown to increase through FFL (Havermans & Jansen, 2007; Havermans, 2010, p.280). It would be interesting to test if young and older children's preferences for other foods increase through FFL as well.

Flavor-related olfactory conditioning has been demonstrated in adults (Yeomans, 2006), while its examination in children has not yet been carried out, and it would be interesting to carry out this examination in future research.

Children's perception of parents', teachers', other adults' as well as peers' values of foods has been suggested to increase or decrease children's preferences for foods as well as dislikes (Rozin & Zellner, 1985; Rozin & Vollmecke, 1986). Thus, it would be interesting to test this as well as the possible influence of TV-driven adults' and/or peers' influences on children's food and flavor preferences.

Stroeble & De Castro (2004) have identified several factors of the physical ambient in which children's meals take place as impacting children's eating behaviors, but it has to be further investigated, if these factors contribute to shape children's food preferences.

Parental adult modeling has been shown to impact young and older children's eating behaviors (Hill et al. 1990; Hood et al. 2000; Francis et al. 2001; Brown & Ogden, 2004) but its specific impact on young and older children's food preferences and associated long-lasting effects are have to be further investigated.

Routine exposure to foods in the school has been shown to increase food preferences in children from 8- to 10-year-old (Baxter & Thompson, 2002) while its effects on young children have to be examined. School-based intervention programs of the kind of nutrition education programs aimed to increase consumption of and preference for certain foods, such as fruits or vegetables, have been shown to be effective with children aged from 6-year-old and older children (Morris & Zidenberg-Cherr, 2002; Hendy et al. 2005; Heim et al. 2009; Reverdy et al. 2010), but not with young children (Morries et al. 2001; Parmer et al. 2009). Failure of these school-based intervention programs in increasing young children's preference for fruits and vegetables could be attributed to the fact that none of them included tasting-related experiences with the target foods, a condition that Birch et al. (1987) found to be essential for changing young children's food preferences, so that future school-based intervention programs should take this into account.

Finally, regarding existence of sensitive periods of development of flavor (tastes + odors) and/or food preferences, if prenatal, early and middle-childhood, adolescence and even young adulthood, besides the lactation period, may constitute sensitive periods of development of such preferences, has to be examined. The importance of examining this lies on the implications for national nutrition education policy as well as parental child-feeding regulation, as both should integrate information about sensitive periods of development of such preferences.

We hope having been able to contribute to a better understanding of how young developing populations' experience with flavors (tastes + odors), foods and drinks shape their gustatory and olfactory preferences and that the present review may inspire scientists and clinicians to develop new experimental designs for deciphering intriguing questions that remain still unclarified regarding young individuals' flavor preferences and to develop effective strategies focused on increasing children's healthy food intake patterns.

CHAPTER 5

PROVIDING CHOICE INCREASES CHILDREN'S VEGETABLE INTAKE[1]

Abstract

One hundred fifty children between 4 and 6 years old were studied to examine the effect of providing them a choice of vegetables on their vegetable consumption. Offering vegetable choice was expected to increase children's vegetable intake due to an increased personal autonomy. Children's possibility to choose the vegetables to ingest was varied across three different conditions. Within the discrete choice condition, children could choose the target vegetable at the beginning of the meal; within the continued discrete choice plus variety condition, children were exposed to a variety of vegetables (zucchini and green beans), so that they could choose the target vegetable whenever they made a bite during the whole meal. Within the no choice condition, in turn, children were likewise exposed to a kind of vegetable, so that no choice possibility was provided. Having children to choose the target vegetable in the discrete choice and the continued discrete choice plus variety conditions was associated with higher intake rates ($p<0.05$), in comparison to children of the no choice condition (47.86 ± 6.59 g and 43.25 vs. 22.36 ± 3.72 g, respectively). No significant differences were found between the discrete choice condition and the continued discrete choice plus variety condition regarding participants' total vegetable intake. These results demonstrate the enhancing effect of providing choice to young children in their vegetable intake. An increase in the

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[1] Although I am the first author of the present study, the following colleagues have also participated (alphabetical listing): De Graaf, K., Gámiz, F., Gil, M., Márquez, R., Moreno, H. & Zeinstra, G. I am very grateful to them all for their indispensable cooperation. De Brugada, I. & Gallo, M. have also participated as leaders of the study.

children's personal control over the food choice and consequent level of intrinsic motivation is hypothesized to underlie such effect of choice.

Keywords: young children, choice effect, school-based intervention, autonomy and motivation.

1. Introduction

Vegetable intake is essential for maintaining a good state of health and preventing diseases, in general (WHO, 2002; Dave, Evans, Saunders, Watkings & Pfeiffer, 2006; Steffen, 2009). Furthermore, vegetable consumption during the specific childhood life phase prevents the development of overweight (Aranceta et al. 2007), hypertension, heart disease and cancer in adulthood (Maynard, Gunnell, Emmett, Frankel & Davey, 2003; Mikkilä, Räsänen, Raitakari, Pietinen & Viikari, 2004). See Van Duyn & Pivonka (2000) for an in-depth review on this topic. Likewise, children's vegetable consumption counteracts childhood illnesses, like respiratory difficulties (Antova et al. 2003) and childhood overweight, one of the most serious public health problems throughout the world (WHO, 2009), and enhances children's cognitive development (Contento, Bronner, Lytle, Maloney, Olson & Swadener, 1995). However, vegetable consumption rates of young children –as being 6 years old or younger (Goldstein, Daum & Tepper, 2007)- do not meet the national recommendations in the United States (Krebs-Smith et al. 1996; Johnson & Kennedy, 2000; Lorson, Melgar-Quinonez & Taylor, 2009) nor Europe (Yngve et al. 2005). Two critical European examples of this childhood-related low vegetable intake are found in The Netherlands and Spain. While both lands' national guidelines locate an appropriate vegetable consumption for children between 4 and 6 years old in an average daily consumption of 150g of vegetables (The Netherlands' Nutrition Centre, 2008; Aranceta et al. 2008), the real vegetable consumption in this age group is 44g (Ocke et al. 2008) and 58g (Aranceta et al. 2008), respectively, and thus, very low.

What humans and specially children eat is mainly based on their liking for food tastes (Nasser, 2001; Sorensen, Möller, Flint, Martens & Raben, 2003; Zeinstra, Koelen, Kok & De Graaf, 2007; Brug, Tak, Te Velde, Bere & De Bourdeaudhuij, 2008). Most children show a natural rejection response to bitterness and sourness (Mennella & Beauchamp, 1998a). Indeed, the main reason, why children do not consume enough amounts of vegetables tends to be attributed to their bitter taste, in view of the data derived from research work conducted on the topic (Anliker, Bartoshuk, Ferris & Hooks, 1991; Gibson, Wardle & Watts, 1998; Blanchette & Brug, 2005; Bell & Tepper, 2006; Forestell & Mennella, 2007). However, early experiences with edibles, including vegetables, may induce and modify the establishment of stable food preference patterns and nutritional habits (Gibson et al. 1998; Birch, 1999; Menella & Beauchamp, 2002; Skinner, Carruth, Wendy & Ziegler, 2002; Mennella, Kennedy & Beauchamp, 2006), these habits lasting, at least, until young adulthood (Nicklaus, Boggio, Chabanet & Issanchou, 2004; Nicklaus, Boggio, Chabanet & Issanchou, 2005a). Thus, discovery of strategies which promote an increase of vegetable intake in young children are essential for reinforcing an everlasting healthy eating behavior.

Research on pediatric nutrition has identified the called parental child-feeding strategies, commonly used in daily life as a factor exerting an important influence on children's eating styles, food choices and food preferences (Birch & Davison, 2001; Scaglioni, Salvioni & Galimberti, 2008). It is not surprising to state that parents try to regulate children's eating habits, in order to improve children's healthy pattern of eating behavior and to reduce a harmful one. However, parental influence can be positive or negative, depending on the specific strategy used. For example, it has been shown that some strategies, such as making pressure to eat, restricting foods and the use of instrumental feeing, that is, rewarding children’s food intake with any prize or promoting children’s pro-social behaviors through provision with liked foods as prizes, even applied with best of intentions, do not reach the expected positive results regarding food intake (Fischer & Birch, 1999; Reimer et al. 2003; Brown & Odgen, 2004; Galloway, Fiorito, Francis & Birch, 2006; Zeinstra, Renes, Koelen, Kok & De Graaf, 2010a). Indeed, pressuring children to eat vegetables results in a decrease in their preference for them (Fisher, Mitchell, Smiciklas-Wright & Birch, 2002). Restricting children’s access to foods, in turn, increase children’s wanting to eat them and, therefore, their intake (Fisher & Birch, 1999), while “parental allowance”, that is, when parents permit children to eat as much as they want, does not (Wind et al. 2006). Other kinds of parental child-feeding strategies, such as facilitation to eat vegetables via physical availability and accessibility to them, at the contrary, have been shown to correlate with higher intake of vegetables in children (Brug et al. 2008). Thus, parents’ appropriate use of child-feeding strategies with their children may facilitate the establishment of different patterns of food intake in their children (Moore, Tapper & Murphy, 2007; Duijs, 2009).

Apart from parental influence, young children’s status of food preferences and food intake patterns may also be determined by exposure to the foods at school. On the one hand, the provision to children of foods during the schools’ routine mealtimes, that is, without implementation of especial intervention programs aimed to increase children’s preference for and/or consumption of a target food, has been related to increases in their preferences for and consumption of these foods. Indeed, Baxter &

Thompson (2002) observed that the provision to children between 8 and 10 years old of fruits and vegetables during the routine mealtimes at school was related to an increase in participants' preferences for these foods. On the other hand, school-based interventions conducted *ad hoc* to increase children's preference for and intake of vegetables and which have focused, either on the provision to children of nutrition knowledge regarding healthy eating habits, or on the school's meals, in which the food composition of the school's meals is modified as well as mixed school-based interventions, in which a combination of the two former strategies are integrated in the same school-based intervention (Rohlfs Domínguez, 2010), have also been shown to achieve that aim (see Heim, Stang & Ireland, 2009; Hendy, Williams & Camise, 2005 and Wang et al. 2010 for three examples, respectively).

Meiselman (2002) has identified that the fact of making choice is a determining factor of food acceptability. Similarly, it has been shown that making choice results in higher hedonic ratings, when subjects have to make food evaluations (King, Weber, Meiselman & Lv, 2004; De Graaf et al. 2005; Kin, Meiselman, Hottenstein, Work & Cronk, 2007; King, Meiselman & Henriques, 2008). Having choice within the context of food intake refers to have the possibility to choose the target food/s to consume between several options.

The effectiveness of offering choice to young and older children, together with other strategies, in increasing their food preferences and food intake has been explored in several studies. In one of them (Hendy, 1999), teachers offered choice to young children (mean age = 4,5 years) twice during the meal at school in the context of a three-day long repeated exposure to four new foods, including a vegetable (sweet red pepper, kiwi, chickpeas and fresh coconut), which were located together at the food table. Specifically, teachers ask each child regarding these four products the following question: “Do you want any of this?”. Taken all these foods as a whole, acceptance of new foods, measured by analyzing the number of eaten foods, number of meals in which children were present and number of bites, was higher under choice conditions, in comparison to a simple food exposure situation (when foods are just located on the lunch table). In a subsequent study (Perry et al. 2004), elementary school aged children ate more vegetables in the school lunch when the cafeteria staff asked them “Which vegetable would you like to have for lunch?”, besides encouraging them to eat fruits and vegetables and making these fruits more attractive (i.e. mixing fruits of different colors), in comparison to children that were not exposed to this intervention. In another study (Hendy et al. 2005), ± 8 years old children were randomly offered the possibility to choose the target vegetable to eat among three different kinds of vegetables (celery, baby carrots and grape tomatoes) and the target fruit to eat between different fruits during eighteen school lunch meals, besides encouraging them to eat some of these vegetables, and fruits; applying adult modeling and giving a price to the children, whenever they consumed 1/8 cup of any fruit and 1/8 cup of any vegetable during four meals. In comparison to control conditions, children subjected to both of these multi-component programs increased their fruit and vegetables consumption. Furthermore, in the study from Hendy et al. (2005), children’s preference for both of these foods remained enhanced two weeks later. Furthermore, Zeinstra, Koelen, Kok, Van der Laan & De Graaf (2010b) carried out a survey of the type of strategies used by parents to feed their children, in relation to fruit and vegetables and of their children’s fruit and vegetable intake. The analysis of the information extracted from that survey showed that providing choice to children of different ages (children between 4 and 5 years old; children between 7 and 8 years old and children between 11 and 12 years old) predicted preference for and intake of fruit and vegetables positively, and that children whose parents provided them choice with high frequency, ate daily an average of 40g more of vegetables and an average of 72g more fruits, in comparison to children whose parents used provision of choice with low frequency. Subsequently, a pilot study (Duijs, 2009) was aimed to sound out the opinion of children between 4 and 12 years old regarding the extent to which a child, who was visualized in four different vegetable choice situations via video recordings, liked his vegetables. In this study, the degree of choice provided to that child was varied among four different situations. In the first situation, the child could not choose the kind or the amount of the vegetables to eat and the mother would serve the vegetables on the plate; in the second situation, the child could choose two kinds of vegetables, but he could not the amount of these vegetables, the mother serving the vegetables on the plate. In the third situation, the child could not decide the kind of vegetables to eat, but he could decide its amount, the child serving himself the vegetable on the plate. Finally, in the fourth situation, the child was given the highest degree of choice because within this condition, he could choose and serve himself the kind as well as the amount of vegetables on the plate. The results showed that participants attributed the greatest appreciation for vegetables by the child visualized on the video recording, when this child was in the fourth choice-related situation. Finally, the effectiveness of providing only choice as a strategy to increase vegetable consumption in children between four and six years old has been recently tested as such for the first time in the context of the called KIK-study[2] in the Netherlands, although no choice effect on vegetable intake was found for the subject sample employed (Zeinstra et al. 2010a).

According to the Self Determination Theory (Deci, 1981), perception of having a choice increases the sensation of personal control and autonomy over a situation or

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[2] KIK results from the combination of the initials of the Dutch words Kinder (child) and Keuze (kick).

activity and the intrinsic motivation to carry out an activity (Zuckerman, Porac, Lathin, Smith & Deci, 1978; Iyengar & Lepper, 2000; Katz & Assor, 2007; Patall, Cooper & Robinson, 2008). These feelings are physically and psychologically beneficial for a general well-being state; they favor learning processes (Iyengar & Lepper, 1999; Chatzisarantis, Hagger & Smith, 2007; Patall et al. 2008; Ryan, Patrick, Deci & Williams, 2008) and are human needs (Zuckerman et al. 1978). If there is intrinsic motivation, there is self-determination (Iyengar & Lepper, 1999; Burón, 2000), and thus personal autonomy (Deci, Eghari, Patrick & Leone, 1994). Regarding food choices, young children are less autonomous than adults because parents and other adult caregivers choose the foods those young children will eat (Brug et al. 2008). However, it has been documented that young children would like to have more personal autonomy over decision making in relation to food choice (Hoerr, Utech & Ruth, 2005; Shepherd et al. 2006).

On the other hand, making a choice requires the involvement of an increased attention to the stimuli (King et al. 2008). Indeed, basic research on sensory perception has demonstrated that subjects give higher hedonic ratings to specific stimuli, when attention is paid to these stimuli, a factor which is present in choice situations (Prescott, 2005).

The provision to young children of choice might facilitate an increase of children’s vegetable intake because the perception of choice is congruent with the experience of personal autonomy, self-determination and an enhanced intrinsic motivation, this being the highest level of motivation (Lyengar & Lepper, 1999; Ryan & Deci, 2000). If we want to stimulate a person’s expression of a behavior and the permanence of that behavior along the time, an enhancement of that person’s autonomy and self-determination, when the target behavior is being expressed by that person, is needed (Gillison, Standage & Skevington, 2006). As we have previously pointed out, young children commonly reject vegetables. Therefore, we can conclude that they are not intrinsically motivated to consume vegetables. If we want to increase young children's vegetable intake, and to observe the continuance of this behavior along the time, an increase of children's self-determination of this behavior is needed (Ryan et al. 2008). Providing choice might be helpful for this purpose. Further, providing choice to children forces them to paid more attention to the vegetables and this fact might increase children's liking for and intake of vegetables.

Experimental research has also showed that the variety of flavors or foods increases food intake in adults (Norton, Anderson & Hetherington, 2006; Hetherington, Foster, Newman & Norton, 2006) and infants (Gerrish & Mennella, 2001; Mennella, Nicklaus, Jagolino & Yourshaw, 2008), while decreases in food intake rates have been demonstrated to occur in infants (Gerrish & Mennella, 2001), young children (Birch & Deysher, 1986) and adults (Rolls, Rolls, Rowe & Sweeny, 1981; Sorensen et al. 2003), if that variety is absent. These intake decreases, as a consequence of lack of food variety during a meal, has been explained through the sensory-specific satiation (SSS) mechanism (Rolls, Rowe & Rolls, 1982a). SSS has been defined as the progressive decline in liking for the flavor and the appearance of a specific food (satiation) as long as this food is consumed during a meal, in comparison to non-eaten foods (Rolls, 1985; Rolls, 1986). The occurred satiation has been suggested to be specific of the sensory characteristics of the food, because those changes in palatability have been shown to appear two minutes after the end of a meal, thus before absorption of foods and therefore satiety linked to postingestive consequences takes place (Rolls et al. 1982a; Hetherington, Rolls & Burley, 1989).

At least two published reports have demonstrated the increasing effect of the provision to infants and elementary school aged children of vegetable variety on their vegetable consumption, respectively. The study focussed on infants (mean age = 6,5 postnatal months) showed that the daily repeated exposure to a variety of vegetables (green beans and carrots) during eight days led to an identical tendency to consume more green beans as when a repeated exposure to only green beans was applied (Mennella et al. 2008). The study focussed on school aged children (Adams, Pelletier, Zive & Sallis, 2005) demonstrated a positive association between vegetable intake and the presentation of a variety of vegetables, independently of the kind of food serving (salad bar vs. pre-portioned serving schools). In addition, a tendency to consume more vegetables as long as the variety grew, independently on the kind of food serving, was observed as well (Adams, et al. 2005).

The present study was aimed to evaluate the effectiveness of the strategy of providing young children (age range = between 4 and 6 years old) a choice and variety of vegetables in increasing their vegetable consumption in the context of a school-based intervention focused on the meal provided to children at school. In contrast to past studies on choice and variety effects on young children’s food intake, the study described bellow is focused only on vegetables as food stimuli; on analyzing vegetable intake by weighing in grams the vegetables left on the plates by children; on the provision of only choice as strategy and on the provision of choice and variety within the same experimental design. Moreover, the present study has been conducted in the context of a continuation of the above-mentioned KIK study. In this sense, it is important to consider that there are several cultural differences, regarding eating habits between both lands (The Netherlands vs. Spain). For example, while the main meal in The Netherlands is the dinner, in Spain it is the lunch. Furthermore, children between 4 and 6 years old use to have their lunch at the dining halls of schools in Spain. In The Netherlands, in turn, they eat their lunch at home. Therefore, we needed to adapt the present study to those cultural differences (see the methods section). Our hypothesis was that providing children a choice and variety of vegetables would result in higher rates of total vegetable consumption than when children have no choice and variety. Our specific expectations were three: 1. That the provision to children of choice plus variety would lead to higher rates of total vegetable consumption than when children are not given any of these options. 2. That the provision to children of choice plus variety would lead to higher rates of total vegetable consumption than when children are provided just with choice. 3. That the provision to children of choice would lead to higher rates of total vegetable consumption than when children are not given any of the mentioned options.

2. Methods

The present study was approved by the Research Ethical Committee of Granada University. This study is naturalistic in nature because it was developed at the schools, during the children's main meal (the lunch), under real life conditions. The schools' psycho pedagogical team evaluated the study's suitability. All adults involved in the study (parents, schools' directors and the schools' psycho pedagogical team) were given the corresponding study-related informative document. Parents signed the informed consent.

2.1. Population under study

A total of one hundred fifty two healthy school-aged children (between 4 and 6 years old) separated in two age categories, that is, children between 4 and 5 years old and children between 5 and 6 years old of four public primary schools of the *Granada Educa Foundation* and their parents living in Granada (Southern Spain), took part in the study. Within each of these four schools, children are separated into two classes by age, so that children between 4 and 5 years old are seated together within a class and children between 5 and 6 years old are seated together within a different class. Thus, at each school, these age-related two classes participated in the study. The sex ratio was 80 females to 70 males. Parents filled out a screening questionnaire with the aim to assess their child's general healthy state and suitability for the study. Exclusion criteria were being vegetarian or showing vegetable allergies. Participants were blind to the hypothesis. An approximately equal number of children of both age groups were randomly assigned to the bellow described experimental conditions.

2.2. Experimental design

The present study was conducted over a period of two weeks and included two phases. During the first phase, parents were approached, children's familiarization with procedures took place and an evaluation of children's preference for six different vegetables was carried out. A total of ninety one children participated in this evaluation. During the intervention phase, a total of one hundred fifty children were exposed once to cooked vegetables and vegetable consumption (dependent variable) was compared among three different experimental conditions within a between-subject design.

Children’s possibility of choosing the vegetables to ingest (independent variable) was varied across conditions. Within the no choice condition, children (n = 44) received a previously and externally decided vegetable, either zucchini or green beans, so that they could not make any choice; in the discrete choice condition, children (n = 50) were allowed to choose the target vegetable to consume between those two specific options (either zucchini or green beans) once at the beginning of the meal, and thus they were given the possibility to making a choice of vegetables with low frequency. The term discrete refers to the fact that these options are finite and mutually exclusive and it is commonly used in market studies, in which humans’ choice behavior is examined (Train & Winston, 2007). Finally, in the continued discrete choice plus variety condition, a strategic combination of provision with choice and variety was provided to children (n = 56), that is, children were served both vegetables on the plate (zucchini and green beans). Previous research (Jansen & Tenney, 2001) has shown that application of a combination of different strategies leads to an increase in preference for tastes. Therefore, children of this last condition could decide which kind of vegetable to eat whenever they made a bite. Therefore, children were given the possibility to make a choice of vegetables with high frequency and they could enjoy vegetable variety during the whole meal. Furthermore, the present continuation of the KIK study was adapted to Spanish culture, leading us to introduce several changes in our experimental setting with regard to the original one from the KIK study. Specific changes made are shown in table 1.

Table 1. Main differences between the KIK study and the Grenadian study. The changes introduced into the present replication were aimed to adapt children's meal to Spanish meal characteristics, and to avoid disturbances in children's school rhythm and everyday life.

Experimental setting	**KIK study**	**The present study**
Meal place	Restaurant	Children's classrooms
Meal time	Dinner	Lunch
Vegetable presentation	Familiar (along with potatoes and canned sausages)	Non familiar (only vegetables with a bit oil and salt)
Parental presence	Yes (children ate with their parents)	No (children did not eat with their parents)

2.3. Procedures

2.3.1. Parents approach

After school directors' gave permission for carrying out the study, the researchers provided parents with an informative document. This document was given to teachers at first, then, teachers gave it to the children, and finally, the children gave it to their parents. This document was concerned with explanation of the main objective of the study (to increase young children's vegetable consumption), children's right to abandon the study, whenever they wanted, and the acquired benefits from their participation (extraction of readily applicable recommendations regarding daily child-feeding which promote children's vegetable consumption for parents and other adult caregivers, including personal stuff of schools). Likewise, parents were given the informed consent-related document to sign as well as a questionnaire about their children's familiarity with different kinds of vegetables to fill out.

2.3.2. Evaluation of Children’s preference for vegetables

This evaluation was conducted by several research team members for participants of both age groups at each of the four mentioned schools in their classrooms in order to select the target vegetables for the posterior intervention. Prior to the evaluation session, children got familiar with the preference-related test procedure, since the research team members explained this test through a game and adopting a language adapted to children between 4 and 6 years old. Preference for vegetables of a total of ninety one children, who were present at that day, could be evaluated.

2.3.2.1. Vegetable selection

We needed to select two vegetables, to which children would be exposed during the intervention. The two target vegetables selection was based on participants’ individual preferences for six vegetables (chard, spinach, zucchini, green beans, cauliflower and peas), tested at the classrooms by means of Birch’s methodology of assessing order of choice (Birch, 1979). Specifically, children completed a category-related ordered preference task for these six vegetables. Previous selection of these six vegetables was based on published reports concerning young children's frequency of vegetable consumption in Spain (Serra & Aranceta, 2002) and parents’ and cooks’ provided information, concerning children’s familiarity degree with them. It was important to control this variable because it has been shown that a low food-related familiarity decreases food intake (Wardle & Cooke, 2008). These six vegetables are very common within the Mediterranean diet, ensuring us that our participants would not reject them because of unfamiliarity-related reasons. We took into account the color of the vegetables as well because it has been shown that food colors influence flavor perception, food choice and food acceptability in humans (Clydesdale, Gover & Fugardi, 1992; Clydesdale, 1993). In the specific case of fruits and vegetables, its color has been shown to be one of the sensory properties, children tend to prefer (Burchett, 2003).Therefore, we decided to control this variable by selecting vegetables with the same type of colors, specifically cool-color vegetables, so that the color of vegetables did not differ from each other regarding brightness, and thus held constant across conditions.

2.3.2.2. Preference-level-related ordered ranking of vegetables

The ordered ranking of preference for vegetables was built showing *ad hoc* made pictures of all six vegetables to each child one by one, in randomly order, and asking the child to classify each vegetable, using a three-category facial hedonic scale. The scale consists of *ad hoc* made pictures of three kinds of emoticons, which correspond to three different liking-related categories. These categories were “I like it” (smiley face); “I neither like it nor dislike it” (neutral face) and “I do not like it” (frowning face) (See Table 2).

Table 2. Three-category facial hedonic scale based on our ad hoc made pictures of emoticons[3] .

Liking category	**Emoticon**
Positive	🙂
Neutral	😐
Negative	🙁

This tool has been shown to be valid for obtaining liking-related data from children aged ≥ 4 years (Chen & Resurrección, 1996). This tool allowed the researchers presenting the task in a play game manner that overcomes young children's limited linguistic skills, based on the rationale that young children deal more accurately with facial expressions than with complex words (Popper & Kroll, 2005). Furthermore, pictures are entertaining and thought to elicit closer attention to the task, thus overcoming difficulties derived from young children's short attention span (Popper & Kroll, 2005). Moreover, during the familiarization session, researchers explained to the children in a friendly and funny way that faces do not only represent emotions, such as happiness or anger, but also liking and disliking, thus overcoming possible confusions between both kinds of concepts, something that Cooper (2002) cleverly affirmed. Thus, each child had just to point at the picture of the specific emoticon which corresponded to his liking-related feeling elicited by the specific vegetable showed in each picture

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[3] The emoticons showed on table 2 are based on those used by Morris, Neustadter & Zidenberg-Cherr (2001, p. 44).

with his finger. Then, the child was asked to point to the vegetable liked the very best among the vegetables classified within the first category. When the child responded, the item was removed from that group of stimuli and this procedure was repeated with the whole stimuli left within the three categories, until an ordered succession of vegetable-related choices, ranging from the most to the least preferred vegetable was obtained. This method has been shown to discriminate suitably the level of preference for several food stimuli in young children, because it forces them to consider each food differently in comparison with the others (Birch, 1979). Moreover, this method has been shown to be valid and reliable when used with young children (Birch, 1980; Johnson, McPhee & Birch, 1991), indicating that children as young as 3 years old are able to provide reliable and consistent judgments about their food preferences (Kern, McPhee, Fisher, Johnson & Birch, 1993). Once preference for vegetables was measured for each participant, two equally preferred vegetables (zucchini and green beans) by all participants as an only group were selected.

2.3.3. Intervention

2.3.3.1. Social context and physical environment of the meal during the intervention

Children consumed the vegetables in groups, albeit separated by condition in their corresponding classrooms. In this way, possible effects of peer modeling were neutralized, as this factor held constant across the three conditions. Peer modelling in the context of food consumption refers to the specific social impact, which has been shown to have the presence of peers on young children's food acceptance, that is, children exposed to peers eating the same food as they eat, use to eat more of this food than when peers are eating a different food (Birch, 1980; Romero, Epstein & Salvy, 2009). Furthermore, as children consumed the vegetables in their own classrooms, thus providing them a familiar environment, the tendency of meals-related novel environments to restrict young children's intake of even familiar foods that has been observed by Birch and colleagues (see Birch, McPhee, Steinberg & Sullivan, 1990, p. 504) was minimized. Indeed, Zeinstra et al. (2010a) have speculated that their no found choice effect in children between four and six years old could have been due to an unexpected increased excitement felt by children because of being eating their dinner in a restaurant, a novel dinner-related eating setting, and recommend exploration of effects of choice-offering in more familiar meal settings.

One teacher, a teacher attendant and two researchers were present during the whole meal, but did not consume any food. In this way, possible effects of food-intake-related adult modeling did not operate in any of the three conditions. Previous early research has suggested that the probability, with which young children eat a food increases if they see an adult (a model) eating the same food (Highberger & Carothers, 1977). The adults that were present during the meal were instructed to not show any communicative sign of approval or disapproval regarding the hedonic value of vegetables, so that possible effects of social influence that has been observed to change food preferences in children (Birch, Zimmerman & Hind, 1980) could be avoided.

2.3.3.2. Vegetable presentation

The vegetable samples were cooked by the cooks of the schools and were weighed and placed in plain hard plastic plates that were arranged by the researchers for the children in a trolley. In all conditions, the vegetable samples were served in a mean of 149-g portions without any other food, just with a bit salt and olive oil as a first meal course. This is a new form of presentation of cooked vegetables, because participants use to eat them accompanied by meat or potatoes as garnish and as a second meal course following a salad as the first meal course and followed by a dessert.

2.3.3.3. Specific instructions provided to children

Children were instructed by the researchers to approach the trolley, one by one, and to take their plate of vegetables served by the researchers, and to eat from it as much as they wanted, without being necessary to eat the whole portion. They were also allowed to repeat as many portions as they wanted. Children were explicitly informed by the teachers about the degree to which they could choose the kind of vegetables. Specifically, depending on the specific condition, children were given a different instruction concerning their choice possibility. Within the no choice condition, children were transmitted the following sentence “Today, we have zucchini/green beans for lunch”; within the discrete choice condition, children heard “Today, we have zucchini or green beans for lunch; you can choose the vegetable, you want to eat”. Finally, the target sentence for the continued discrete choice plus variety condition was “Today we have zucchini and green beans for lunch; you will receive both vegetables in your plate; you can choose what you want to eat”.

2.3.3.4. Measurement of children’s total vegetable intake

After finishing the vegetable intake, children returned their plates to the teacher and the teacher gave them to the researchers, who weighed the plates again, in order to ascertain the consumed amount of vegetables in grams.

3. Data analysis

3.1. Preference for vegetables: rank order of children

Children’s vegetable-related liking data were analyzed with a one-factor ANOVA of repeated measures for the six mentioned vegetables (intra-subject factor), in order to ascertain if there were significant differences, regarding preference for the six selected vegetables. Then, we used a paired t-test for related samples in order to find two vegetables, which were equally situated in a medium preference level. Finally, we applied again the same one-factor ANOVA of repeated measures for those two the vegetables (intra-subject factor) and analyzed the interaction age x gender. All these and posterior analyses were done by means of SPSS V.15.0. A significance level of $p < 0.05$ was applied for all analyses.

3.2. Vegetable intake during the intervention

Two subjects were eliminated from the analysis because of their vegetarian condition. One-factor ANOVA with total consume as dependent variable and condition x school x age x gender as fixed factors was carried out, besides HSD de Tukey as post hoc test, were applied.

4. Results

4.1. Preference for vegetables

Significant differences in children's preference for the six differences were found, as the one-factor ANOVA carried out indicates [$F(1,89)=9.51$, $p<0.05$] (See Fig. 1).

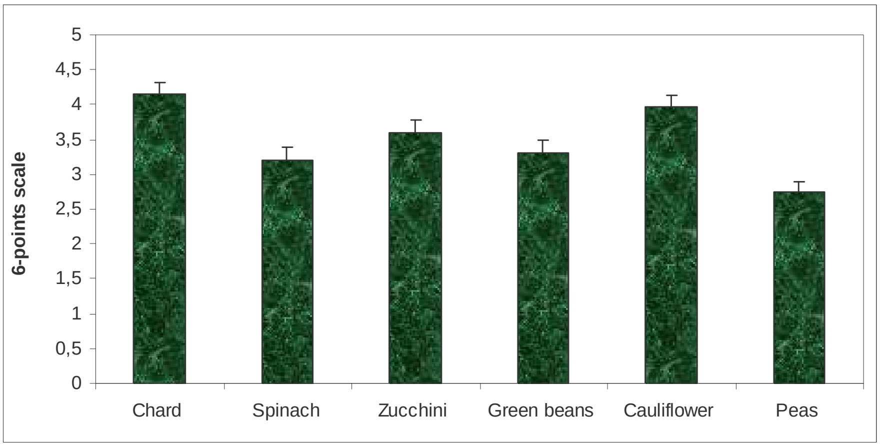

Fig.1. Children's means and standard error means of the preference for vegetables.

Furthermore, zucchini and green beans resulted to be equally preferred by children. Specifically, children's preference for these two vegetables was medium, as the paired t-test for related samples indicates. Therefore, no significant differences were found between zucchini and green beans by paired t-test for related samples ($p>0.3$), but between the two vegetables located at both extremes of the ranking –peas and chard-.

While peas, located at position 1 within the ranking, are the least preferred vegetable, chard, located at position 6, was the most preferred vegetable. Children's preference for zucchini and green beans is located in the middle of the ordered preference ranking (See Fig. 2.). Finally, no interaction effects (age x gender) nor main effects on children's preference for vegetables were found, based on the second applied one-factor ANOVA.

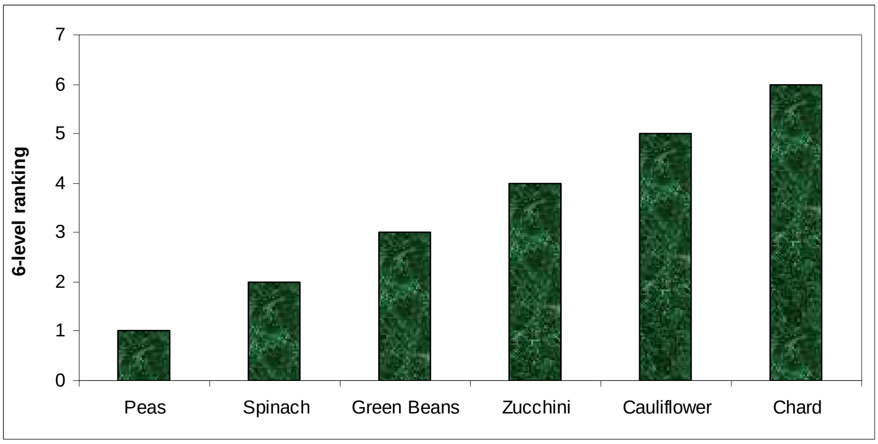

Fig.2. 6-level ordered vegetable-related preference ranking.

4.2. Intervention

A significant effect of condition x children's total vegetable intake, without any additional interaction effects (condition x school x age x gender) was found. Specifically, vegetable intake differed significantly between the no choice condition and the discrete choice condition as well as between the no choice condition and the continued discrete choice plus variety condition. There were no differences between the discrete choice condition and the continued discrete choice plus variety condition. Statistical confirmation of these results was found by means of the one-factor ANOVA and post-hoc analyses, which were made [$F(2,149)=5.19$, $p<0.05$] (See Fig. 3).

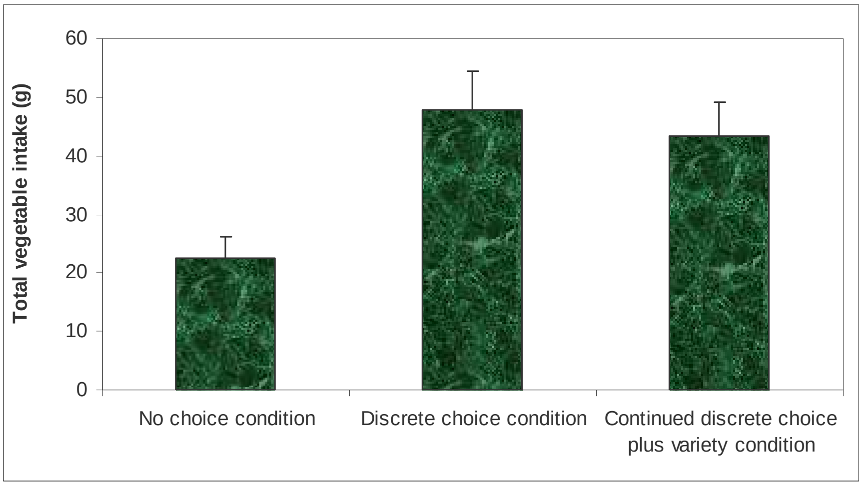

Fig. 3. Means and standard error means of the total vegetable consumption, including one or two vegetables, depending on the condition (*p*<0.05).

5. Discussion of results and future research

While a positive main effect was associated with characterising the meal served to the children as they having the possibility to choose the target vegetable to eat during the meal (discrete choice condition and continued discrete choice plus variety condition), in comparison to the situation in which that possibility was not available (no choice condition), it appeared that the presence of vegetable variety and a high frequency of choice during the meal (continued discrete choice plus variety condition) had no effect on children's vegetable consumption, as no significant differences between this condition and the discrete choice condition were found.

Irrespective of age and gender, our data show that children's intake was significantly higher when children could choose the target vegetable (discrete choice condition and continued discrete choice plus variety condition) than when they had no choice (no choice condition). This significant effect of choice on children's vegetable intake results to be in agreement with earlier research showing the increasing impact of choice on childhood’s food preference and food consumption (Hendy, 1999; Hendy et al. 2005; Perry et al. 2004). The increasing effect of choice on human behavior has been demonstrated with adults in several contexts as well, such as food acceptability (Weber, King & Meiselma, 2004; King et al. 2004; King et al. 2007), purchasing (Szrek & Baron, 2007) and physical activity (Chatzisarantis et al. 2007), yielding with an increased rate in relation to the target behavior under study.

One possible explanation for positive effect of providing choice to participants in the discrete choice condition and the continued discrete choice plus variety condition on their vegetable intake found within the present study might lie in the increased motivation, derived from that provision of choice, with which children ate their vegetables. Indeed, it has been observed that having choice increases personal control over the activity, and thus the intrinsic motivation for persisting at any activity (Deci, 1981; Iyengar & Lepper, 1999; Burón, 2000). Thus, children assigned to the discrete choice condition and to the continued discrete choice plus variety condition might have persisted at the activity of eating vegetables due to a choice-driven increased motivation that facilitated them to persist at that activity. Moreover, our experimental design gave children the opportunity to choose the specific vegetable to consume and thus, to increase their personal autonomy over food choice for their lunch.

Another explicative possibility is that children of the discrete choice condition and the continued discrete choice plus variety condition might have liked the served vegetables more than the rest of participants, since earlier research has shown that the possibility to choose personally the food is a determinant factor of food liking, leading to higher hedonic ratings within experimental contexts of food evaluations (Meiselman, 2002; King et al. 2004; De Graaf, 2005; King et al. 2007; King et al. 2008).

On the other hand, children of the discrete choice condition and the continued discrete choice plus variety condition had probably to attend more to the stimuli for making their choice, in comparison to children of the no choice condition. This increased attention on the food stimuli in the former two groups probably derived in an increase of vegetable acceptance, since Prescott (2005) demonstrated a direct link between an increase of attention to the stimuli under choice conditions and higher rates of food acceptance.

Furthermore, we provided participants a choice of vegetables in an explicit way, that is, we told participants literally that they could decide the target vegetable for their lunch. This probably helped to trigger the enhanced intrinsic motivation. Thus, we hypothesize that the explicit provision to young children of choice in our study had an enhancing effect on motivation to eat vegetables and their liking for them, because the fact of making their choice incited them to have more personal control over the situation, and to attend previously more to the stimuli.

Our data also indicated that no difference was found between the discrete choice condition and the continued discrete choice plus variety condition, when total vegetable intake was measured. We assumed at the beginning of the study that children of the continued discrete choice plus variety condition would consume more vegetables than children of the discrete choice condition, because children of the former group could choose the vegetable to eat, as many times as they made a bite during the whole meal, that is, with higher frequency than in the case of participants of the discrete choice condition, and because they would receive one kind more of vegetables, in comparison to children of the discrete choice condition, so that the former group would enjoy food choice plus food variety during the meal. As a consequence, we expected that they would show higher intake rates than children of the discrete choice condition due to an additive increasing effect on consumption derived from the combination of the increasing effect derived of each strategy, based on prior research showing such an additive effect (Jansen & Tenney, 2001). Children of the discrete choice condition, in turn, could choose their vegetables only once at the beginning of their lunch, that is, with lower frequency and would receive just one kind of vegetable, and thus, they would not enjoy variety, and therefore would show lower intake rates. However, our expectations did not fulfil.

One reason, our expectations did not fulfil might concern children’s choice frequency during the meal. It could be possible that children’s choice frequency itself has no effect on children’s vegetable intake and that the fact that children can choose the target vegetable to eat is a sufficient condition for increasing their vegetable intake. To our knowledge, the present study shows for the first time that the provision to young children of choice as a single strategy, that is, without adding any other strategy, may increase their vegetable consumption.

Another reason why children of the continued discrete choice plus variety condition did not eat significantly more vegetables than children of the discrete choice condition might concern the amount of vegetables served in the continued discrete choice plus variety condition. Previous findings from different studies indicate that the presentation of a variety of food stimuli, including vegetables, usually leads to an increased food intake during the meal due to the interruption of SSS in children (Adams et al. 2005; Mennella et al. 2008) as well as adults (Rolls et al. 1982a; Hetherington, et al. 2006; Brondel et al. 2009). In this sense, it is to say that children of the continued discrete choice plus variety condition probably suffered SSS in the same extent as children of the discrete choice condition did, and that the effect of variety on intake in the former group was not achieved enough to interrupt the natural SSS. This could be due to two reasons. First, the amount of vegetables, between which children could choose their target vegetable, was two –zucchini and green beans- in both choice-related conditions, so that the variety-related characteristic of the continued discrete choice plus variety condition of our study was probably not present. Moreover, the number of the items offered in the continued discrete choice plus variety condition was probably very small to interrupt the SSS. We base this speculation on previous findings that suggest that the simultaneous presentation of a variety of foods, three at least, leads to that intake increase, thus interrupting SSS (Pliner, Polivy, Herman & Zakalusn, 1980). However, we just presented two kinds of vegetables in the continued discrete choice plus variety condition. Alternatively, the successive presentation of a variety of foods, two at least, has been observed to have the same intake-related increasing effect (Rolls et al. 1981). However, our vegetable variety presentation was simultaneous. Nevertheless, it is important to stand out that in the studies, in which food variety has been applied, and therefore, an increased food intake has been found, the used foods were palatable and high-caloric-content foods, such as pasta (Rolls, Rowe & Rolls, 1982b), pizza (Pliner, Polivy, Herman & Zakalusn, 1980), cake, yoghurt and crispy snacks (Fuller, 1980). Vegetables, in turn, use to be disliked by children because of their bitter taste, so that it could be possible that offering vegetable variety to children has no increasing effect on children's vegetable intake. In addition, vegetables are low caloric content foods and children use to like high caloric content ones (Knai, Pomerleau, Lock & McKee, 2006). However, Adams et al. (2005) obtained a difference in vegetable consumption in elementary-aged children that was explained by the number of vegetables offered to participants (seven vs. four). Therefore, it is probable that a higher number of vegetables, that is, more than two vegetables are required to be offered to children, in order to obtain a vegetable-related variety effect on children's vegetable intake. Thus, consideration of the number of vegetables offered, as a function of the presence or not of variety as well as consideration of the kind of vegetable presentation –simultaneous vs. successive vegetable presentation- is required in future studies on the effect of choice on children's vegetable consumption.

In order to interpret our findings in a more comprehensive way, several limitations shall be considered as well. First, our data are transversal, so no conclusions can be established about the effect of choice on children's vegetable intake in the long term. Follow up- studies aimed to examine the maintenance of the choice effect across weeks, months or even years are warranted to elucidate that maintenance. Second, we tried to respect participants' ordinary teaching program rhythm during the whole study. After the lunch, participants use to continue with the teaching program in their classrooms. This circumstance forced us to renounce to take measures about participants' intrinsic motivation felt during the meal and about liking and preference for the target vegetables after the meal. Finally, technical obstacles prevented us of taking measurements of participant's attention focus while they were making their vegetable choice. It would be interesting to include these measures in future experimental works.

It is also important to take into account the existence of cultural differences, regarding children's level of intrinsic motivation at carrying out an activity, when choice is provided to them, as reported by Iyengar & Lepper (1999). Indeed, these authors demonstrated that Anglo American children, coming from a non-culturally interdependent background, showed more intrinsic motivation at carrying out word puzzles, if they personally could choose the category of anagrams, they had to work on. In contrast, Asian American children, whose background is interdependent, showed the opposite motivational pattern; they were more intrinsically motivated if the category of anagrams were chosen by others. Thus, the effectiveness of offering choice to children in increasing their persistence at any activity is probably culture-dependent. We recommend cross-cultural research work on the effect of choice on childhood's vegetable intake, in order to examine which cultures may take advantages of using the strategy of choice, when dealing with young children's vegetable intake.

Despite the limitations of the present study, the extracted data of the present study indicate that providing choice explicitly to young children, without any other additional strategy, may increase their vegetable intake. Thus, we recommend serving vegetables to young children under explicit choice conditions, which potentially increases their attention to vegetables and their intrinsic motivation to eat vegetables.

Finally, despite of the choice-related positive effects on young children's vegetable consumption found here, providing choice to children is not always a positive strategy for children's acquisition of healthy eating patterns. In fact, Warren, Parry, Lynch & Murphy (2008) have demonstrated that if children are given the possibility to choose between healthy (vegetables) and unhealthy foods (snack foods), children tend to choose these last options and even more when the mother, who has been reported to be the caregiver that significantly spends more time with the child, in comparison to the father, during familiar mealtimes (Scaglioni et al. 2008) is not present (Fisher & Birch, 1999). Thus, the mere fact of providing choice to children is necessary but not sufficient for the acquisition of a healthy eating pattern. The choice provided to children shall be among healthy options, such as fruits or vegetables.

CHAPTER 6

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The central objectives of this thesis were to investigate the factors that determine child vegetable consumption and to develop and evaluate the effectiveness of providing choices to young children to increase their vegetable consumption. A systematic literature review investigated the determining factors of child vegetable consumption. A school-based intervention program, which provided vegetable choices at lunch to young children, completed the second objective. Here, we discuss our general findings and offer an integrated model of child vegetable consumption.

1. Genetic variation in sensitivity to bitter taste

Our review shows that there is a positive relationship between individual variation in sensitivity to bitter taste—as indicated by PTC/PROP status or allele genotypification (or both) of the TAS2R38 gene—and consumption of bitter-tasting vegetables (i.e., spinach and broccoli) in young children. There is evidence that the more sensitive a child is to bitter tastes, the lower his or her preference will be for bitter vegetables (Anliker et al., 1991; Keller et al., 2002; Turnbull & Matisoo-Smith, 2002; Bell & Tepper, 2006). However, regarding raw broccoli, the results of Anliker et al. (1991), Keller et al. (2002) and Bell and Tepper (2006) differ markedly from those of Turnbull and Matisoo-Smith (2002). Turnbull and Matisoo-Smith did not find liking differences in raw broccoli as a function of PROP taster status. We speculate that these inconsistencies might be due to variable amounts of glucosinolates, Ca, or both in the vegetables used across the different studies. We base this speculation on the fact that different species of the same kind of vegetable may differ from each other in their bio-chemical composition (Dole Food Company, Mayo Clinic and University of California, 2002) and that many conditions affect plant development and therefore the taste of vegetables (see Mattheis & Fellman, 1999 for a review). Thus, the raw broccoli used by Turnbull and Matisoo-Smith (2002) might not have been bitter enough to elicit bitter taste sensitivity responses as a function of PROP taster status. The biochemical characteristics of the specific vegetables used in research must be taken into account in future research on the impact of genetic variation on young children's bitter taste sensitivity to vegetables.

On the other hand, based on the work by Tordoff and Sandell (2009), we speculate that sensitivity to Ca and glucosilonates—as indicated by PTC/PROP—impacts young children's vegetable acceptance. Ca content in vegetables is another source of bitterness detected by human adults and rats (Tordoff & Sandell, 2009); however, further experimental research is needed. For example, the Ca-related receptor gene needs to be further examined to assert that variation in sensitivity to Ca is genetically determined in humans. In addition, a causal relationship between variation in Ca taste sensitivity and young children's vegetable acceptance must be demonstrated. Chapter 2 also shows that the association between PTC/PROP taster status and food preferences is stronger in children than in adults (Mennella et al., 2005). This finding leads us to believe that genetic predisposition to vegetable acceptance, in absence of influences other than age-dependent ones, might be higher in children than in adults, although future studies should replicate this result.

The results derived from our review presented in chapter two do agree partially with the proposal by Kajiura et al. (1992) and Mennella & Beauchamp (2009), among other authors, regarding a general natural (innate) human rejection for bitter taste and a genetically determined variation in the bitter taste sensitivity. Both factors determine an individualized (and not general in the whole population) genotypic, and therefore phenotypic expression of the mentioned general natural (innate) human rejection for bitter taste. In this sense, we think that, although the facial expressions elicited by tastes in neonates and older infants (Steiner et al. 2001) have turned into an objective indicator of general human natural rejections for the bitter and sour tastes, as well as of general human natural attraction for sweet tastes, the proper way to obtain evidence regarding the innate taste preferences of a given individual is studying the individual genetic basis of taste preference status (likes as well as dislikes). Such evidence would allow to ascertain the link between that individual genetic basis of taste preference status (preference and/or intake), and the food acceptance (preference and/or consumption) status of a given individual (i.e. a given child).

Finally, as regards the relationship between PROP taster status and BMI in young children that we have additionally reviewed in chapter two, the results of the few published studies (Keller et al. 2002; Keller & Tepper, 2004; Lumeng et al. 2008; Goldstein et al. 2007) are inconsistent. Based on suggestions by Lumeng et al. (2008) and data of Baranowski et al. (2009), we speculate that this confused state of the art could be attributed to existence of one or more confounding factors that might be exerting an influence on this relationship, and that socioeconomic status (SES) might be one of those confounding factors, which should be determined in future research.

2. Sensitive periods for tastes and smells

Our review identified the breastfeeding period as a likely sensitive period for flavor preference development. To our knowledge, only Haller et al. (1999) demonstrated the invariability of a high preference for a flavor (vanilla) acquired during breastfeeding in mature adults. They concluded that exposure to vanilla-flavored milk may induce a vanilla preference. However, additional evidence that breastfeeding is a sensitive period is needed. Some data indicate that higher order brain regions are still developing during young adulthood (Sowell et al., 2003; Lebel et al., 2008). These developmental changes might affect gustatory and olfactory systems and thus flavor preferences (O'Doherty et al., 2002; De Araujo et al. 2005). Research on the visual system has discovered that certain developmental changes, such as amblyopia correction, may occur in young adulthood (Sale et al., 2007).

Flavor/food acceptance in young infants may also be related to prenatal experience with these items (Schaal et al., 2000; Mennella et al., 2001; Mennella et al., 2005). In general, although confirmatory evidence is needed, there are several indications that early childhood is a sensitive period for flavor/food preference development (Nicklaus et al., 2004; Skinner et al., 2002a; Skinner et al., 2002b).

Since Poldrack (2000) stated that the biological impact of plastic neural changes associated with learning and development on functional imaging signals has yet to be identified, some progress has been made in identifying the brain activation patterns of gustatory and olfactory systems through the use of neuroimaging and electrophysiological techniques. One of the most relevant contributions is Poncelet et al.'s (2010) study, which reported a differentiated pattern of ERPs in response to smelling mint tea in young adults as a function of how early in their life they experienced this odor. Specifically, young Algerian-French adults who had early experiences with mint tea showed longer P2 latencies than European-French participants with no such experience. However, to determine whether there is a specific sensitive period in which exposure to mint tea induces a particular brain activation pattern in young adults, the timing of exposure to the target odor must be varied and compared to P2 latencies in young and middle adulthood using a longitudinal design. Furthermore, because perception of flavor involves the integration of tastes and smells (Smith & Vogt, 1997), this demonstration should be extended to tastes. Chapter 3 also identifies the need to develop additional developmental brain mapping research in infants, children, and adolescents due to the fact that the majority of empirical data obtained through neuroimaging techniques are from young adults.

In summary, although there are behavioral and neuroimaging indications that support the existence of sensitive periods for flavor/food preference development, the examination of invariability regarding tastes, smells, flavors and foods acquired during development throughout adulthood using longitudinal designs should attempt to confirm this theory.

3. Hedonic value

Our review of literature that identifies brain responses to the hedonic value (pleasant vs. unpleasant) and emotional response (like vs. dislike) of gustatory and olfactory stimuli in developing populations indicates that the processing of this affective information is lateralized. Tastes and smells perceived as “good” in newborns and young adults tend to be processed in the left hemisphere while “bad” tastes and smells tend to be processed in the right hemisphere (Fox & Davison, 1986; Bartocci et al., 2000; Bartocci et al., 2001; Henkin & Levy, 2001; Sanders et al., 2000; De Araujo et al., 2003b; Small et al., 2003). This finding coincides with those that show positive emotions are associated with higher left brain activity while negative emotions are associated with higher right brain activity (Rohlfs & Martín Ramírez, 2006).

The relationship between food preference and emotion can be understood through Gray's theory of brain regulation of motivated behavior (Gray, 1987), the Behavioral Approach System (BAS) and the Behavioral Inhibition System (BIS). The BAS processes a pleasant taste or odor as a reward (Rolls, 2005) in the left hemisphere of the brain and elicits a positive emotion. BAS activation moves people to approach stimuli. Alternatively, the BIS processes an unpleasant taste or odor as a punishment (Rolls, 2005) in the right hemisphere and elicits a negative emotion. BIS activation induces a person to withdraw from contact with unpleasant stimuli.

This hedonic perspective helps to understand why young children may or may not eat vegetables. Young children will not eat vegetables if they find their tastes and odors unpleasant. Alternatively, if the flavors of vegetables reward young children, then the consistent activation of BAS might induce a rapprochement to vegetables. Therefore, the emotions elicited by the tastes and smells of vegetables constitute another relevant factor in explaining young children's vegetable intake.

4. The role of experience

Other factors may also determine whether children consume vegetables. Once they are mature enough to understand health concepts, health-related beliefs may be assimilated over time and overcome the genetic proclivity of vegetable rejection. Understanding health concepts begins to occur between 8 and 9 years of age (Bahn, 1989; Zeinstra, Koelen, Kok, & De Graaf, 2007). On the other hand, different experience-related mechanisms during development may impact vegetable acceptance. These mechanisms include (1) prenatal stimulation of gustatory and olfactory receptors through contact with molecules that derive from the mother's ingested foods and are diffused through the amniotic fluid (Mennella et al., 2001), (2) neonatal stimulation of gustatory and olfactory receptors through flavored maternal and artificial milk during the lactation period (Mennella & Beauchamp, 1991a), and (3) repeated exposure to new vegetables at weaning (Maier et al., 2007) and during young childhood (Gerrish & Mennella, 2001).

The flavor-nutrient learning (FNL) classical conditioning mechanism is ineffective at increasing school-age children's preference for vegetables (Zeintra et al., 2009b). The flavor-flavor learning (FFL) classical conditioning mechanism, however, is effective at increasing preference for vegetables in both young children (Havermans & Jansen, 2007) and school-age children (Havermans, 2010, p. 280). Some parent-child feeding strategies, such as the facilitation of eating vegetables, increase older children's vegetable intake (Scaglioni et al., 2008). Furthermore, overt and covert parental control is associated with an increase of vegetable intake in young children (Brown et al., 2008). In general, however, pressuring children to eat does not increase their food consumption (Galloway et al., 2006). Thus, we do not expect that this strategy would be effective in the case of vegetables.

On the other hand, exposure to vegetables during routine mealtimes increases vegetable intake in school-age children (Baxter & Thompson, 2002), and this strategy merits additional research in young children. School-based interventions such as nutrition education programs are effective in school-age children (Morris & Zidenberg-Cherr, 2002) but not in younger children (Parmer et al., 2009). This finding is probably because young children have to taste food to change their preferences (Birch et al., 1987) and their immature cognitive development limits them from understanding concepts such as the healthiness of a specific food (Bahn, 1989) or flavor-related affective information (Lumeng & Cardinal, 2007).

5. A new strategy: providing children the choice

School-based interventions may be efficient at increasing young children’s vegetable consumption if they change the conditions under which children are provided food rather than employ an educational strategy based exclusively on information (Hendy et al., 2005; Rohlfs-Domínguez et al., 2009). In fact, our study found that providing 2- to 6-year-olds with a choice during one school meal significantly increased their vegetable consumption compared to peers who were not provided with the same choice. We let participants decide between two different types of vegetables. Our results are congruent with data obtained in previous studies on the role of choice in vegetable intake at school with older children (Hendy et al., 2005). To our knowledge, however, our study is the first to demonstrate in a school-based school-meal intervention that choice alone leads to increase vegetable consumption in young children. Understanding the long-term effects of this study and generalizing these effects to contexts outside of school will require additional research.

Zeinstra et al. (2010) also examined the effect of providing 2- to 6-year-olds in the Netherlands with a vegetable choice; however, they did not find an increase in consumption. The fact that their participants ate vegetables in a non-familiar context might explain their negative results (Zeinstra et al., 2010). Indeed, novel contexts tend to restrict young children’s food intake (Birch et al., 1990). Cultural differences between Spanish and Dutch children may also be relevant. Iyengar and Lepper (1999) found that intrinsic motivation was culturally dependent in a study in which Anglo-American and Asian-American 7- to 9-year-olds solved word puzzles. In either case, school-based interventions may improve vegetable acceptance in young children.

Our results encourage us to examine whether educational processes aimed at increasing young children's preference for vegetable intake induce a long-term effect suggestive of a developmental sensitive period in future research. Furthermore, previous reports have argued that education affects neural plasticity and behavior depending on the type of stimuli to which children are exposed (Koizumi, 2004; Morrison, Smith & Dow-Ehrensberger, 1995). For example, some studies have shown that childhood mathematics education may impact adult mathematical performance (Korvorst, Nuerk & Willmes, 2007; Rohlfs Domínguez, 2008). Based on Koizumi (2004), we speculate that if we find such effects regarding cognitive functions (i.e., number abilities), we can expect to find similar effects in sensory functions. Thus, although speculative, we believe that to develop an interdisciplinary research approach that combines knowledge of sensory and cognitive function may help to advance knowledge about sensitive periods. Finally, our research also has other practical implications. For example, specific guidelines for healthy vegetable intake during childhood might be included in scholastic curricula and even put into law for children less than 6 years old.

In summary, our review and study indicate that, although there seems to be a general tendency to reject bitter taste, children differ from each other in the degree to which they reject bitter tastes from birth through infancy. From the prenatal stage onwards, brain maturation and numerous sensory experiences with tastes and smells as well as neural processes linked to cognitive development (e.g., understanding the concept of health) might moderate this genetic predisposition. In the following section, we propose a theoretical model to integrate all of these factors.

6. A proposed integrated model of child vegetable consumption

We conclude this thesis with a proposal for an integrated model of child vegetable consumption based on five determinants:

1. Genetic predisposition. Humans generally reject bitter tastes; thus, children are predisposed to reject vegetables at birth and through infancy.

2. Nervous system development concerning sensory function and cognition, including sensitive periods.

3. Variety of experience with tastes and smells (especially vegetables) during development in different contexts (e.g., home, school, and the grocery store).

4. Emotions and asymmetrical neural processing.

5. Applicable law that regulates scholastic curricula for children and thus determines teaching content, which may include aspects related to vegetable intake.

As Figure 1 illustrates, these factors interact with each other so that their respective forces can either offset or reinforce one another. However, there are still determinants of young children’s vegetable consumption that future research will have to resolve, as Figure 1 also indicates.

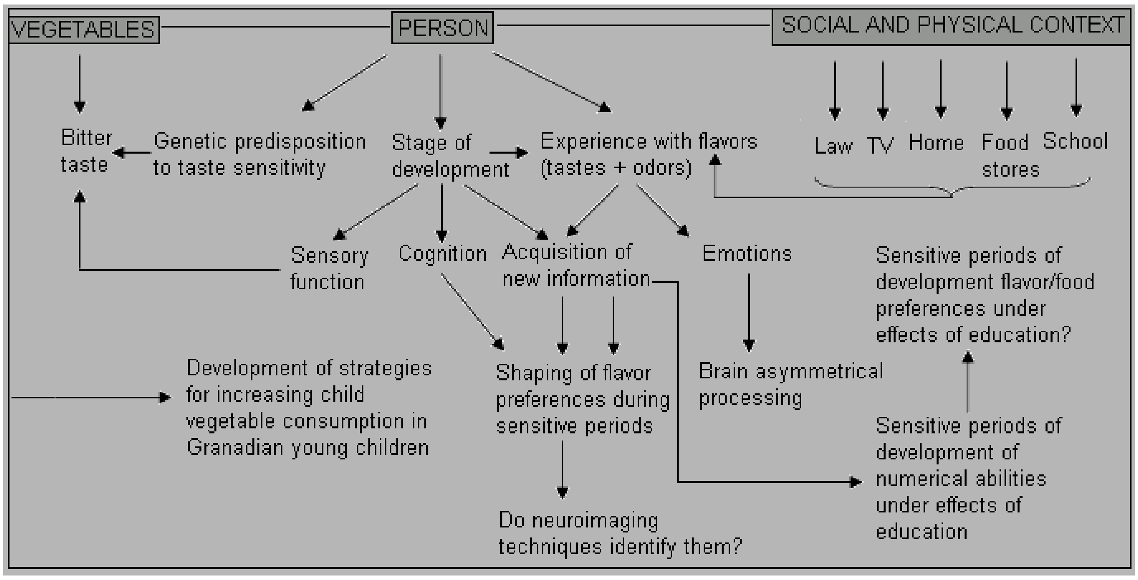

Figure 1: Schematic overview of the determining factors of young children's vegetable intake and their connections to each other. Question marks indicate prospects for future research.

The three basic elements of the model are the vegetables, the person in question and social and physical contexts.

Genetic predispositions interact with vegetables in a child who perceives the bitter taste of vegetables as a function of its glucosinate and (most likely) its calcium content. Developmental stages interact with the experience of the vegetable. In other words, this experience is age-dependent. Some types of experience with vegetables increase preferences at one age and not another. Developmental stages also interact with sensory functions and cognition. The stage of development combined with flavor experiences facilitates new information storage regarding flavor and thus shapes preferences during sensitive periods. In turn, this process may compensate or reinforce vegetable preferences. Social and physical contexts, the person, stage of development, and experience all interact with one another.

Indeed, a child will be exposed to foods in different physical and social contexts, and these different exposures will help shape their preferences. Adults (i.e., parents, school staff or educational policy makers) usually make decisions regarding the types of foods to which children are exposed. Cognition and emotion also affect flavor preferences. Cognition shapes food preferences during sensitive periods through the acquisition of new information (e.g., health concepts), and emotion shapes preferences through asymmetrical neural processing, hedonic flavor values, and approach/avoidance learning. When a child understands the healthiness of vegetables, he or she may make an effort to eat it despite the negative emotion derived from its taste.

This heuristic model facilitates future research by identifying areas with insufficient evidence on their effectiveness. For example, neuroimaging techniques clearly need more research on identification of developmental sensitive periods. Similarly, the effectiveness of structured education to provide ways to learn healthy patterns of eating, such as those based on daily consumption of the recommended amounts of vegetables during sensitive periods will also require further research.

7. Conclusions

The major findings of our thesis are summarized in the following statements:

1. Vegetable consumption of a given young child, may be determined by the following identified interconnected factors: individual genetic predisposition to reject and accept the bitter taste of the glucosinolate content of vegetables; early feeding history and the type of experiences with vegetables to which that child is exposed; brain maturation; level of cognitive development; and the emotion elicited by the vegetables.

2. The glucosinolate content of vegetables might not be the only source of the bitter taste perceived by young children, when they eat vegetables. The calcium (Ca) content of vegetables might also elicit young children’s bitter taste perception. Genetic

research shall search for the human Ca gene taste receptor and behavioral research shall examine causative relationship between Ca taste perception and vegetable acceptance (preference for and/or intake of vegetables) in young children.

3. The relationship between 6-n-propylthiouracil (PROP) taster status and body mass index in young children might be modulated by socioeconomic status (SES), which should be investigated.

4. There is inconclusive evidence that the prenatal life phase, lactation period and young childhood might be sensitive periods of development for flavors and/or food preferences. Further research is needed examining the invariability of the flavor/food preferences acquired during prenatal phase, lactation, and young childhood, in mature adulthood.

5. Possible changes in taste and olfactory systems in human young adulthood, as well as changes in the repertoire of food preferences, should be investigated.

6. The impact of educational process at school, in relation to food and eating habits during sensitive periods of development, on mature adults' food preferences and eating habits should be examined in future research.

7. Interdisciplinary research in order to obtain a better understanding of cognitive and sensory function development from a holistic approach should be encouraged.

8. There are some suggestions indicating the existence of a differentiated pattern of brain activation in young adults in response to an olfactory cue (Mint tea) as a function of how early participants have had experience with that odor. If there is a specific sensitive period within early life, during which exposure to Mint tea would induce such brain activation pattern in young adulthood, is yet to be determined. Such sensitive period should also be examined regarding tastes.

9. Further brain mapping research in newborns, infants, children and adolescents in the context of longitudinal studies are required, in order to identify sensitive periods of development of taste and olfactory function as well as flavor/food preferences.

10. Emotion influences food preferences probably via the Behavioral-Approach System (BAS) and the Behavioral-Inhibition System (BIS). If the emotion is positive - that is, if the child likes the food-, the BAS will induce the child to approach that food.

11. Prenatal experience with tastes and odors (flavors); experience with flavors (tastes and odors) through milk consumption during the lactation period; repeated exposure to new foods; certain paradigms based on classical conditioning, as well as parental and school influence, have been identified to shape human food acceptance (preference for and/or intake of foods, including vegetables) during development, thus modifying phenotypic expression of genetic determinations of that food acceptance. Effectiveness of these experiences in increasing child vegetable consumption is age-dependent. Specifically, prenatal exposure to flavors of vegetables as well as exposure to flavors of vegetables through milk consumption during the lactation period increases vegetable acceptance at weaning. Mere repeated exposure to new vegetables at weaning and during young childhood increases vegetable acceptance at these respective life phases. Flavor-flavor learning (FFL) increases vegetable acceptance in young and middle-aged children. Flavor-nutrient learning (FNL) does not increase vegetable acceptance in middle-aged children, and its effectiveness in increasing vegetable acceptance in young children should be investigated. Parental facilitation, as well as parental overt and covert control, increases vegetable intake in old children and young children, respectively. School-based interventions of the kind of nutrition education programs, aimed to increase child vegetable consumption, increase vegetable acceptance in middle-aged but not young children. School-based interventions that

focus on the food composition of the school meals increase vegetable acceptance in middle-aged children.

12. Long-term effects of the positive results derived from school-based interventions regarding vegetable intake in middle-aged children should be investigated.

13. School-based interventions of the kind of nutrition education programs should include tasting-related experiences with vegetables for increasing vegetable acceptance in young children, which should be examined *ad hoc*. Long-term effects of these interventions should be investigated as well.

14. The sole provision to young children living in Granada with vegetable choice, in the context of a school-based intervention, increases their vegetable consumption. Long-term effects of this intervention, as well as generalization to other contexts, should be examined in future research. Cross-cultural differences on the effect of vegetable choice in young children should also be investigated.

8. If the emotion is negative -that is, if the child dislikes the food- the BIS will induce the child to inhibit his approach to that food.

ANEXE: LIST OF PUBLICATIONS

1. Rohlfs, P. & Martín, J. (2006). Aggression and brain asymmetries: a theoretical review. *Aggression and Violent Behavior*, 11(3), 283-297. Impact factor = 1.6.
2. Rohlfs Domínguez, P. (2008). Estado actual de la actividad científica del grupo ed Aquisgrán sobre el procesamiento numérico. *Revista de Neurología*, 46(5), 299-304. Impact factor = 1.0.
3. Rohlfs Domínguez, P. (2008). Frequency of word-use predicts behavior in patients with Alzheimer disease. *International Journal of Psychology*, 43(3/4), 472. Impact factor = 0.8.

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